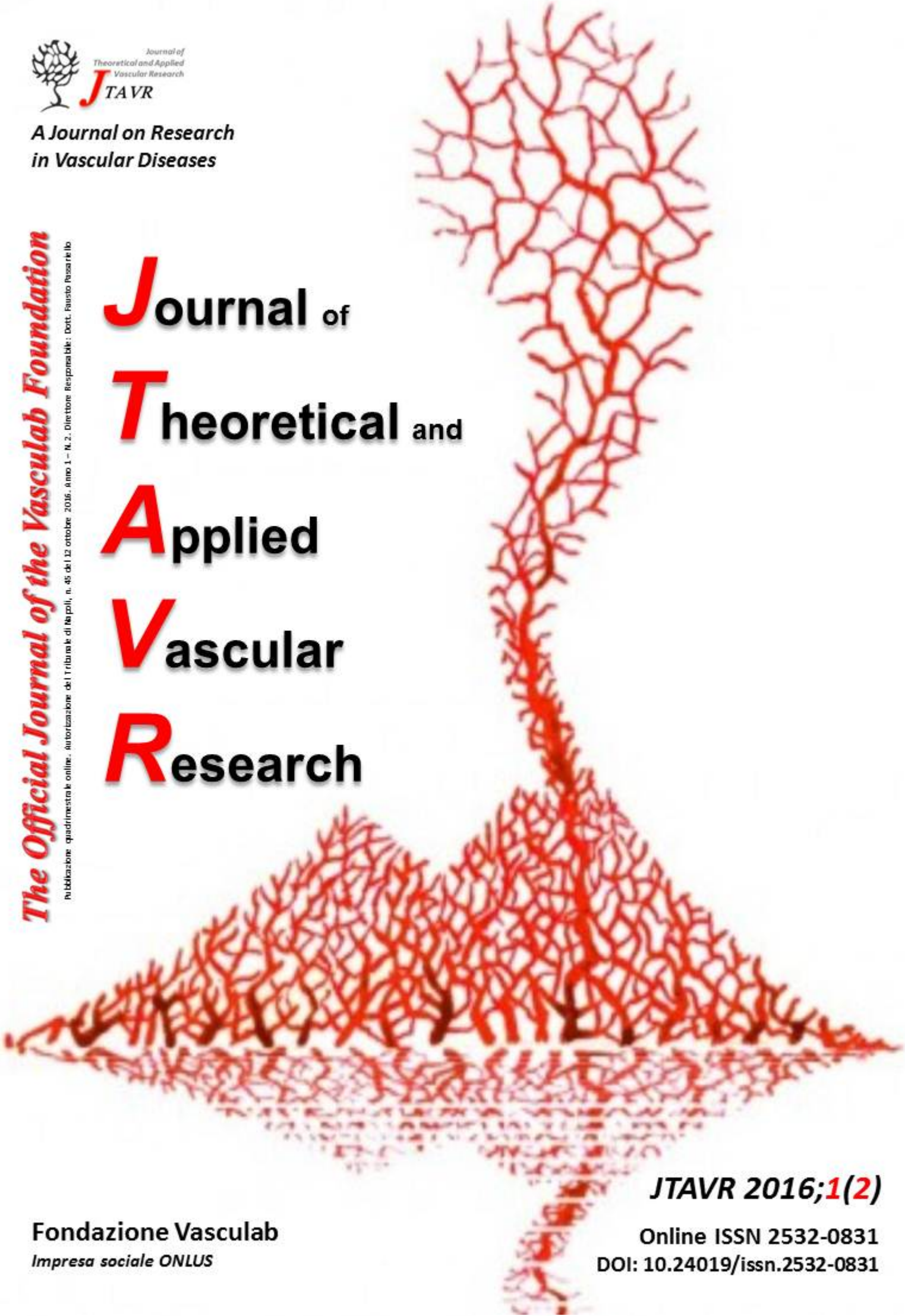
Journal of Theoretical and Applied Vascular Research
JTAVR

A Journal on Research in Vascular Diseases

The Official Journal of the Vasculab Foundation

Pubblicazione quadrimestrale online. Autorizzazione del Tribunale di Napoli, n. 45 del 12 ottobre 2016. Anno 1 – N. 2. Direttore Responsabile: Dott. Fausto Passariello

Journal of Theoretical and Applied Vascular Research



JTAVR 2016;1(2)

Fondazione Vasculab
Impresa sociale ONLUS

Online ISSN 2532-0831
DOI: 10.24019/issn.2532-0831

N. 02-2016 Nov, year 1

Journal of Theoretical and Applied Vascular Research

Online ISSN 2532-0831 DOI: 10.24019/issn.2532-0831

A Journal on Research in Vascular Diseases, published three times a year

The Official Journal of the Vasculab Foundation

Editor

Fondazione Vasculab impresa sociale ONLUS, Via Francesco Cilea, 280 - 80127 Napoli - Tel/Fax +39 081 7144110 - jtavr@vasculab.eu - www.vasculab.eu/jtavr.xml

Pubblicazione quadrimestrale online. Autorizzazione del Tribunale di Napoli, n. 45 del 12 ottobre 2016. Anno 1 - N. 1.

Direttore responsabile: Dott. Fausto Passariello

Fondazione Vasculab *impresa sociale ONLUS*

www.vasculab.eu

DONA IL TUO 5 PER MILLE

Sostieni le iniziative della Fondazione Vasculab ONLUS

- **Ricerca scientifica e divulgazione in Medicina**
- **Metodi alternativi alla sperimentazione animale**
- **Missioni mediche umanitarie all'estero**

Inserisci il Codice Fiscale della Fondazione

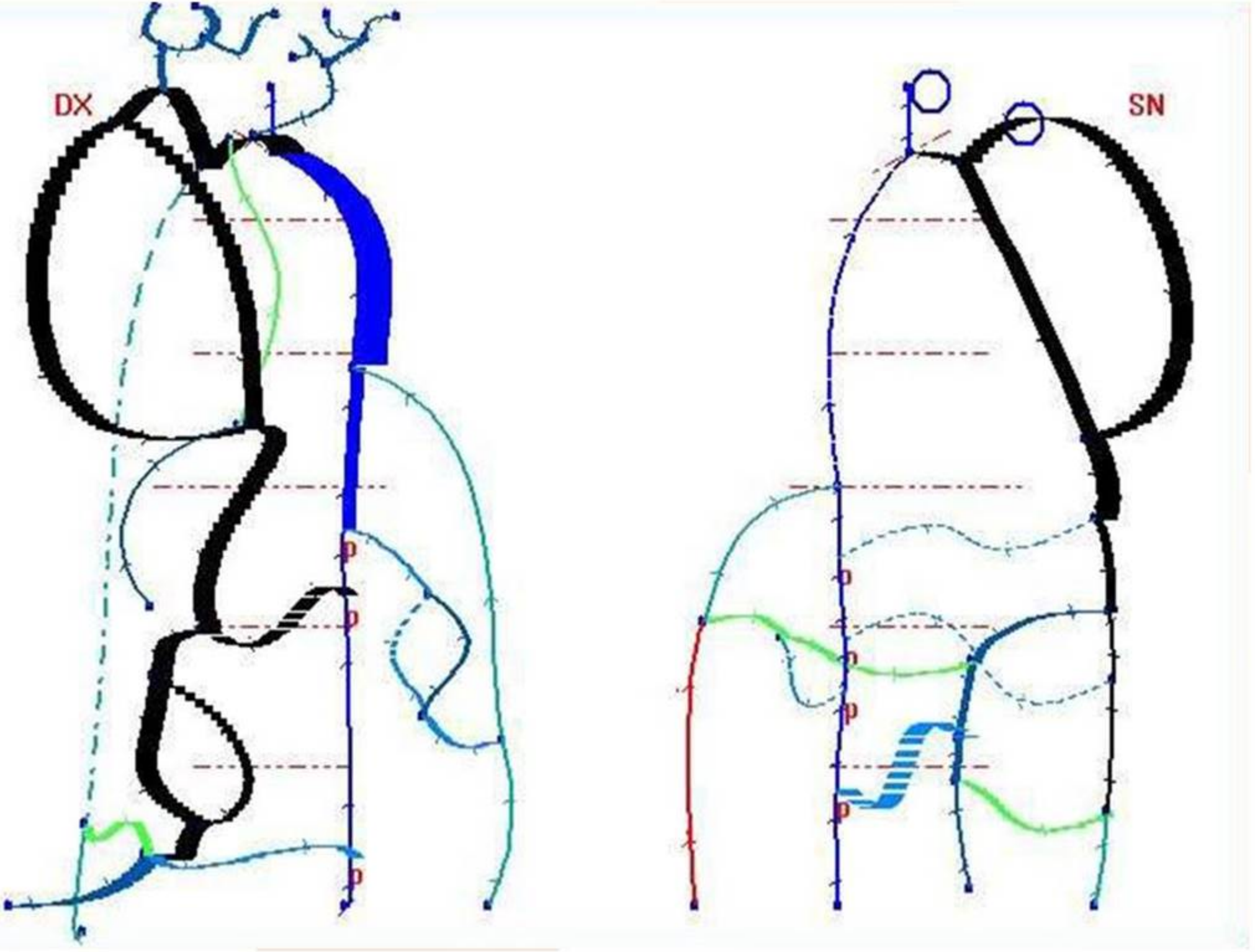
95218510634

nella dichiarazione dei redditi (Unico o 730)

nella sezione del *5 per mille*

Fondazione Vasculab impresa sociale (ONLUS)
Email fondazione@vasculab.it
tel/fax: +39 081 7144110 cell +39 3356250756

The Vasculab Foundation
Fondazione Vasculab


DX
SN

The Journal of Theoretical and Applied Vascular Research (JTAVR) publishes scientific papers on vascular diseases, biological research, history and philosophy of science.

Manuscripts are expected to comply with the instructions to authors which conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Editors by the International Committee of Medical Journal Editors (www.icmje.org/).

Submission of manuscripts

Papers should be submitted directly online to the Editorial Office at the Fondazione Vasculab ONLUS website: www.vasculab.eu/jtavr/submissions.htm

The journal adheres to the principles of the Helsinki Declaration (http://history.nih.gov/research/downloads/helsinki.pdf) about research concerning human beings and to the International Guiding Principles for Biomedical Research Involving Animals (http://cioms.ch/publications/guidelines/1985_texts_of_guidelines.htm) recommended by the WHO. In addition, the journal strongly supports alternative non-animal experiments, in order to Replace, Reduce and Refine (3Rs) animal experimental designs.

For complete information about publication terms please contact the Editorial Office of JTAVR, Fondazione Vasculab impresa sociale ONLUS, via Francesco Cilea 280 Italy - Phone +39-081-7144110 - E-mail: jtavr@vasculab.eu.

Open Access Publication

All manuscripts submitted to JTAVR are assumed to be submitted under the Open Access publishing model. In this publishing model, papers are peer-reviewed in the normal way under editorial control. Submission and reviewing process are not charged. When a paper is accepted for publication the author is issued with an invoice for payment of a publication processing fee (see www.vasculab.eu/jtavr.xml). Payment of this charge allows JTAVR to recover its editorial and production costs and create a pool of funds that can be used to provide fee waivers for selected authors, for instance for invited authors, authors of papers on history and philosophy of science and for authors from lesser developed countries (see below).

Free download

Published papers appear electronically and are freely available from our website. Authors may also use their published .pdf's for any non-commercial use on their personal or non-commercial institution's website.

Commercial use

No articles from the JTAVR website may be reproduced, in any media or format, or linked to for any commercial purpose (eg. product support, etc) without the prior written consent of JTAVR and payment to JTAVR of an appropriate fee.

Publication fees

Initial publications of JTAVR (up to presumably one year) are free of charge for invited Authors and for the members or supporters of the Vasculab Foundation. For the Vasculab Foundation membership see www.vasculab.eu.

Article types

Editorials, original articles, review articles, systematic reviews and meta-analyses, randomised controlled trials, research protocols, case reports, therapeutical notes, letters to the Editor, guidelines, special articles (like history and philosophy of science), invited sessions, reprints of historical papers of actual interest.

In order to submit an article online, follow the step by step instructions at www.vasculab.eu/jtavr/submissions.htm

Preparation of manuscripts

Footnotes or endnotes

JTAVR does not encourage the use of footnotes. Generally, they are not used in medical journals, but they are tolerated, especially in articles in the field of history and philosophy. Footnotes or endnotes must be quoted in Low Caps Romans in rectangular brackets (example: [iv] and cited as[iv]).

References

- Only cited references can be included in the bibliography. They must be numbered in Arabic numerals, in the exact sequence as they are firstly cited (example: "1)").

- Bibliographical entries in the text should be quoted using superscripted Arabic numerals (cited as[1]).

- References must be set out in the standard format approved by the International Committee of Medical Journal Editors (ICMJE), as described in the document Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals http://www.icmje.org/icmje-recommendations.pdf.

A simplified but comprehensive list is given in www.nlm.nih.gov/bsd/uniform_requirements.html.

Citation examples

Standard journal article

List the first six authors followed by et al.

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.

As an option, if a journal carries continuous pagination throughout a volume (as many medical journals do) the month and issue number may be omitted.

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347:284-7.

Books and Monographs

Author(s) and editor(s)

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Electronic materials

Homepage/Web site

Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Vasculab mailing list

Provided you know the number '#' of the message, the format of the citation here follows, where the date of the last access is required (following the Vancouver style) and the symbol '#' must be replaced with the effective number of the message:

Author(s) name(s). Vasculab Yahoo Groups. The Vascular List. Message '#'. https://it.groups.yahoo.com/neo/groups/vasculab/conversations/messages/# Accessed on line on 'date of last access'. A (free) subscription to Vasculab is required.

Historical monographs

The format will be specified in next future.

File of tables

Each table should be submitted as a separate file. Formats accepted are .doc and .rtf. Each table must be numbered in Roman numerals and accompanied by the relevant title. Notes should be inserted at the foot of the table and not in the title. Tables should be referenced in the text sequentially.

File of figures

Each figure should be submitted as a separate file. Formats accepted: JPEG set at 300 dpi resolution preferred; other formats accepted are TIFF and PNG. Figures should be numbered in Arabic numerals and accompanied by the relevant title. Figures should be referenced in the text sequentially.

Histological photographs should always be accompanied by the magnification ratio and the staining method.

Color illustrations

Open Access papers appear electronically. As no printed issues of JTAVR are produced there are NO additional charges for color illustrations.

However consider that many people will print them in black and white. Thus for a better result in communicating your data, test also the black and white printing when choosing colors.

EDITORIAL

Never never land

A Passariello[1,2]

[1]PhD candidate, Philosophy Department, Sapienza University of Rome

[2]Assistant Editor of JTAVR, History and Philosophy of Vascular Medicine, Fondazione Vasculab ONLUS

submitted: Apr 27, 2017, accepted: Apr 27, 2017, EPub Ahead of Print: Apr 28, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.10 - Corresponding author: Dr. Alessandra Passariello, alessandra.passariello@uniroma1.it

Dear Readers of JTAVR,

the second issue of the *Journal of Theoretical and Applied Vascular Research* is on-line.
As you already know, JTAVR is the *Official Journal of the Vasculab Foundation* and, as such, it is primarily focused on scientific and medical issues dealing with vascular research. Since vascular periodicals of very high quality are already quite a lot , you might want to know which is the specificity and, admittedly, the urgency of JTAVR. In other words, its *raison d'être*.
Resorting to a catchphrase, I would say that JTAVR bets on the fertility of a *no man's interdisciplinary land*.
Interdisciplinary lands are not common lands, which can be objectively described and praised. Neither a shared methodology to produce knowledge nor common criteria to evaluate it exist at the crossroads between disciplines.
Every wayfarer can pass through this land just with his own scientific background and contribute to build more or less robust bridges, together with others like him/her.
I admit it is not a really fascinating prospect to be part of an interdisciplinary team: no recipes to build these connections are provided nor their usefulness is even secured.
It is not my aim here to give you recipes and guarantees. I have none myself , but I will try to provide them. More humbly, I can tell you how JTAVR was born, coming out of one among those unstable bridges in the no man's land and how we hope, as Editors, it will get more and more stable by building new connections with future wayfarers.
JTAVR was founded in July 2016 and its foundation is the result of the innumerable and sometimes "Babel like" conversations between, on one side, a mature physician and physicist and, on the other side, an aspirant philosopher and historian of science.
I don't need to be so mysterious: it is just two common people, father and daughter, who appreciate themselves a lot but speak different languages: mathematics, informatics, physics, medicine and surgery on one side and history and philosophy on the other. I have the feeling that speaking together has been so fruitful and at the same time so hard that we were able to do it only in small doses.
Here is my first recipe: *interdisciplinarity is good but in small doses!*
Coming back to my tale, after many years, conversations became easier and we noted that both the historically and philosophically minded physician and the physically informed philosopher of science were not the same physician and philosopher they were before.
In this case, *interdisciplinarity had been difficult but in the end it was worth doing!*
JTAVR is nothing but our attempt to enhance this connection between medicine, history and philosophy of science at the broader level of the communities we belong to: scientists on one side, historians and philosophers of sciences on the other. Authors' participation and the great Readers' interest towards the first issue of JTAVR gave us an extremely positive feedback and we hope JTAVR will be able to accommodate an increasing number of *no man's land wayfarers*.

Alessandra Passariello

Assistant Editor, History and Philosophy of Vascular Medicine

HUMAN-ANIMAL RELATIONSHIP BOOK REVIEW

Do monkeys tell themselves? Passions and doubts of ethology

L Zaietta[1]

[1]PhD candidate in Philosophy. Consortium Philosophy North West Italy [FINO] | Université Paris 1 Panthéon-Sorbonne

submitted: Mar 22, 2017, accepted: Apr 14, 2017, EPub Ahead of Print: Apr 20, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.13 - Corresponding author: Dr. Lucia Zaietta, luciazaietta@gmail.com

What is a primatologist?
A zoologist first and foremost?
An anthropologist interested in early man?
A socio-biologist following selfish genes?
A psychologist?

Bruno Latour

Keywords epistemology, ethology, animal-human relationship, anthropomorphism, science's narratives

In the '70, the well-known psychologist Gordon Gallup proposed a test to a chimpanzee called Sarah. Sarah was not an 'ordinary' chimpanzee, because she had learned to communicate through sign language. Gallup gave her some pictures representing human beings (men and women known by Sarah) and others chimpanzees Sarah lived with. Sarah was asked to separate humans from animals. She did it without hesitation: on the one side, she put all her animal companions and, on the other side, she put all the humans, including herself (Picq *et al.* 2003[1]). Sarah seemed to consider herself as a *human*. Maybe, it's us that made her human.

To this day, the boundaries between human and animal beings have never been so nuanced. Above all, when it comes to primates. Primatology has produced essential results in recognizing incredible abilities to chimpanzees, macaques, gorillas and so on: intelligence, sociality, cooperation and a sort of primordial technology are already present in primates' behaviour. Thanks to primatology, we got an extensive knowledge of the common ground between primates and us. And yet, there is another way to think about the boundaries between *what we call* 'human' and 'animal'. This other manner lies in the boundary itself, and it concerns the way we, humans, look at animals: "what was my impression looking into the eyes a monkey for the first time? ". The same question goes for scientific gaze: which kind of look characterizes science? Is it an objective and neutral gaze? And what about primatology?

This kind of questions are at the heart of Augusto Vitale's book: *Le scimmie si raccontano? Passioni e dubbi dell'etologia*[2] (Do monkeys tell themselves? Passions and doubts of ethology) (Figure 1). For one thing, this book arises from different needs: first of all, the need to stop and consider what the encounter with an animal's gaze can tell us and, at the same time, what our human gaze can reveal about animals.

It's a matter of *contamination*: Vitale's book concerns precisely the grey area of intersection and overlapping between the stories of the one who looks at a behaviour and the stories of the one who is the lead of that behaviour (Vitale 2016, p.12).

This book has also to do with questions: with the essence of the question of life science and with the *right* question of ethology (See for example Despret 2014[3]). Science, and ethology most of all, is based on questions and questions are always contextualized and theory-based. The theory at the heart of the scientific question concerns a specific and scientific vision as much as the social, cultural and personal context. As we will see, science inaugurates new paradigms just when it changes questions.

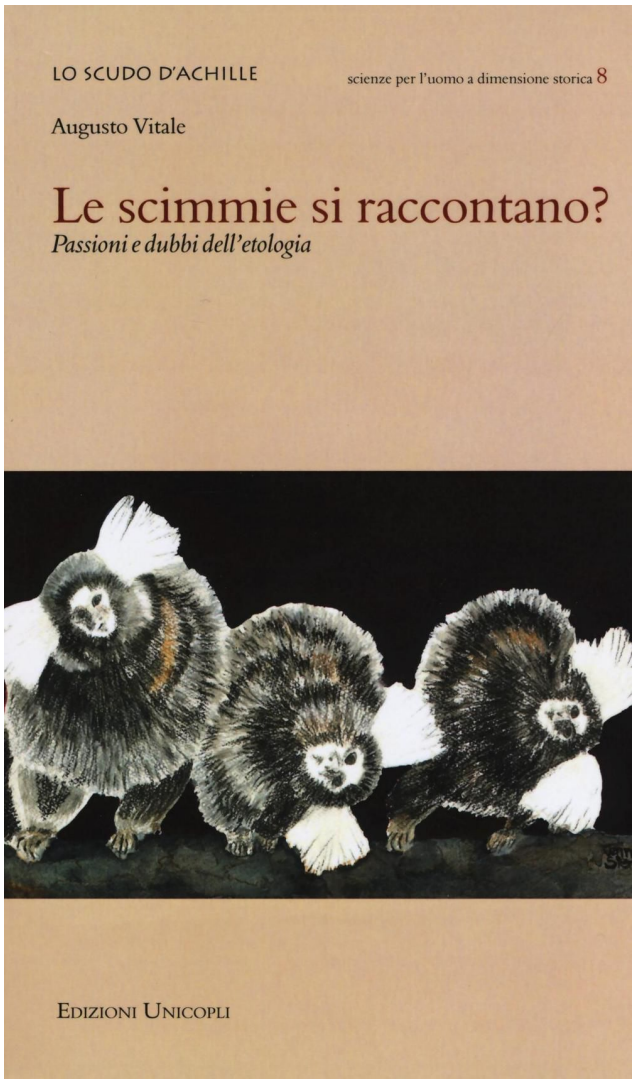


Figure 1 - Augusto Vitali. Le scimmie si raccontano ? Passioni e dubbi dell'etologia.

Furthermore, Vitale's book is a novel. And it is in a very peculiar way: it is a sort of meta-novel. Through the history of ethology and primatology, as much as through his personal experience as researcher, the author tells us the narrative nature of science, or better it tells the way science tells nature. As well as the way monkeys tell themselves.

The overlapping of all these levels should not confuse: the main thrust of Vitale's book is very clear and it concerns the classical problem of the relationship between subjectivity and objectivity in science. That is, more precisely, the problem of anthropomorphism in ethology or, more radically, if anthropomorphism is a problem or not for ethology. In a nutshell, we can define 'anthropomorphism' as the tendency to interpret the physical and animal world in analogy to our inner experience. As humans, we have a specific way to live, to perceive and to understand the world, and the scientific inquiry is a part of that. For this reason, anthropomorphism is strictly connected to science and to the role of human subjectivity in it. This is most apparent in the field of ethology, that is the study of the behaviour of animal beings. Is it truly possible a purely objective ethology? What is the role of the scientist's subjectivity? Can we assume an anthropomorphic principle as a heuristic and useful research tool?

Le scimmie si raccontano is divided in four chapters, that represent four different approaches to the issue. The first chapter is a quick but exhaustive look-back over some highlights of the history of ethology in the light of the relationship between animal and human beings. It immediately emerges the anthropomorphic 'problem': why ethological research prefers certain animals? What about the criteria on which this preference is based? Is ethology immune to anthropomorphism? Is it legitimate to consider the animal as subject, by adopting qualitative criteria? Is it legitimate to consider the animal as equipped with personality, temperament and, in a word, singularity? The same questions characterise the second chapter, that is focused on primatology.

Here, Vitale meditates on scientific models used in primatology and, specifically, on the way in which models change according to the questions preceding and the results following an ethological study. By comparing the most exciting and influential researches on sociality in primates' worlds (De Wall, Schino, Aureli, Tomaselli and Visalberghi, to name a few), what emerges is a wide variety of ethological narratives: these studies have profoundly changed our vision on primates, as much as the way we tell them. Behind each research and each result, in fact, we find the world of the observers, a world made of questions, motives and passions. The third chapter of Vitale's book is precisely devoted to this 'scientific backstage' (Vitale 2016, p. 76) of the history of primatology.

Actually, there is no one primatology, but *different primatologies*, each with their own specificity. Vitale wants to bring out the reasons why we have come to study certain aspects of primates' behaviour: has primatology always studied sociality and altruism? Has it always asked the same questions? And what about the impact of prominent scientist on primates' science? In this chapter, the narratives succeed one another: "there is no one history of primatology, but many histories for many primatologies" (*Ibidem*, p. 79). Haraway's *Primate visions* (Haraway 1989[4]) and Strum and Fedigan's *Primate Encounters* are the reference books (Strum and Fedigan 2000[5]). Two examples are given to illustrate how love, power, and science intertwine in the constructions of nature in the late twentieth century (Haraway 1989).

The first example shows the differences between Japanese primatology and the western one (Vitale, p. 79-94). Vitale tells us the great adventure of Imanishi, Itani and Nishida (to name a few), emphasising the specificity of

Japanese primatology. Governed and subjective at the same time, Japanese primatology is not familiar with the dualism human/non-human and neither with *either*-or fallacy. This enables a specific vision on primates' capacities, that is captured in all its significance by the notion of *kyokan* (Kawai 1969[6]).

This word means literally "feel-one" and it indicates the sympathetic and, finally, anthropomorphic method adopted by Kawai (and to a lesser extent by Japanese primatology). This notion brings out an interesting revision about the classical western distance between subjectivity and objectivity. In the words of Kawai, "that by positively entering the group, by making contact at some level, objectivity can be established. It is on this basis that the experimental method can be introduced into natural behaviour study and which makes scientific analysis possible. […] It is probably permissible to describe the method of the Primates Research Group as 'the new subjectivity'" (Kawai, in Asquith 1981, p. 346[7]. See also Haraway 1989).

The second example concerns the role and the revolution of women's gaze in primatology. The references are clearly Jane Goodall, Diane Fossey and Biruté Galdikas, as well as Jeanne Altman, Shirley Strum, Linda Fedigan and Thelma Rowell. The role of these women has been crucial in the deconstruction of the androcentrism that characterised primatology prior to the 1970's. As Vitale underlines (Vitale 2016, p. 96), it's not about a gender battle, it's about the contribution a minority can make with regard to a vision monopolized by a majority (Tang-Martinez 2000[8]).

These two examples, Vitale explains in details, highlight a crucial aspect of primatology (and life science in general): on the one hand, a primate behaves in the same way and he'll keep on; on the other hand, the way we look at this behaviour changes according to the geographic, social and cultural context. In a word, according to the worldview of the observer (Vitale 2016, p. 97). This brings us to the four chapter, in which Vitale collects his conclusions, his *right questions*. Science tells nature, it tells what happens "out there" (Hinde 2000[9]). Is the narrative character of life science a limit for the rigour that is requested to? Vitale rightly stresses the separation between data and interpretations.

The latter is not a neutral and independent process: it arises from historical, cultural and personal circumstances and it follows predictions and hypotheses. In the words of Latour, "*Facts* are circulating entities" (Latour, 2000[10]). It is important to underline that is not a distortion from the outside. Life sciences, and primatology most of all, have to do with narratives, metaphors and feelings: they have to do with human language.

It was Adam who named animals, after all. Augusto Vitale offers a well-balanced point of view on the intertwining of stories and narratives characterising life sciences, and offers and interesting approach to accept and include a *good anthropomorphism* in ethology. A wide debate is at work: starting from Lorenz to Jay Gould and Bekoff. Maybe, it is precisely by recognising a certain amount of anthropomorphism that an unjustifiable anthropocentrism can be avoided. Even if they are frequently lumped together, anthropomorphism and anthropocentrism are not at all synonymous.

This is the opinion of Viveiros de Castro, for example: the human projection is not necessarily a symptom of anthropocentrism. As Viveiros de Castro shows through the study of Amazonian perspectivism, anthropomorphism and anthropocentrism refer to cosmological attitudes that are radically opposed. On the one hand, anthropomorphism relativizes the human exceptionality, that is the main feature of anthropocentrism, by attributing humanity to the other non-humans. On the other hand, anthropocentrism radicalises human boundaries, elevating human to the status of a special and exceptional being (Viveiros de Castro 2015[11]).

Then again, the dichotomy anthropomorphism VS science is counterproductive, especially when it comes to ethology and to the study of primates' behaviours. It is a question of language and of its limits: the way human beings describe behaviour is limited by the language they use, namely the human language. When dealing with animals' behaviours, feelings or emotions, the anthropomorphic language can make other animals' worlds accessible to humans. As Bekoff claims: "Using anthropomorphic language does not have to discount the animal's point of view. Anthropomorphism allows other animals' behavior and emotions to be accessible to us. Thus, I maintain that we can be *biocentrically anthropomorphic* and do rigorous science" (Bekoff 2000[12]).

An acknowledgement of a multifactorial background, constituted by stories, visions, questions and bias, does not entail a confusion between subjectivity and objectivity and it does not menace the scientific value, which is the increase of knowledge. Maybe - and it is Vitale's argument - this kind of acknowledgement improves the scientific methodology, at least in respect of primatology. To a certain extent, the human and personal background of the scientist is unavoidable and it should be taken into account. Or even, it should be used as a heuristic strategy.

In this regard, the study of Thelma Rowell concerning the behaviour of sheep is inspiring in this regard. The peculiarity of this study relates to the original - and revolutionary - point of view assumed by Rowell: she has studied sheep asking different questions, or better by treating them as chimpanzees. As reported by Latour (and

Vitale 2016, p. 123), Rowell wanted to give her sheep "the opportunity to behave like chimps, not that I believe that they would be like chimps, but because I am sure that if you take sheep for boring sheep by opposition to intelligent chimps *they would not have a chance*". In this context, Latour underlines the subtle but crucial difference between a bias and an opportunity. As he affirms, "A whole new philosophy of scientific practice resides in this extraordinary statement: 'to give the opportunity to behave' is not the same thing as 'imposing a bias onto' animals that cannot say a thing" (Latour 2000). Precisely by a deliberate decision, precisely by an artificial and anthropomorphic collage between 'charismatic' chimpanzees and 'boring' sheep, Thelma Rowell has been able to reveal what *sheep really are* (Latour 2000).

Augusto Vitale's book is a useful and compelling instrument to call into question what we think ethology is and what ethology really is. Namely, an intertwining of different stories developing along different narrative levels: the narrative of ethology and ethologist, the evolutionary narrative, the narrative of the specific population of a specific study, the narrative of the social relationships into a group, the narrative of the individual member. Finally, the narrative of the observer, of course. These are the layers of the single and exciting history of ethology and these are the steps Vitale masterfully retraces.

References

1) Picq P, Michel S, Jean-Didier V. Qu'est-ce que l'humain?. Paris: Le Pommier;2003.

2) Vitale A. Le scimmie si raccontano? Passioni e dubbi dell'etologia. [Do monkeys tell themselves? Passions and doubts of ethology] Milano: Unicopli. Lo scudo di Achille; 2016. ISBN 8840019006, 9788840019000.

3) Despret V. Que diraient les animaux, si on leur posait les bonnes questions ? Paris: La Découverte;2014.

4) Haraway D. Primate Visions: Gender, Race, and Nature in the World of Modern Science. New York - London: Routledge;1989.

5) Strum SC, Fedigan LM. Editors. Primate Encounters: Models of Science, Gender, and Society. Chicago: The University Chicago Press;2000.

6) Kawai M. Life of Japanese Monkeys. Tokyo: Kawade Shyoho Shinshya;1969.

7) Asquith PJ. Some Aspects of Anthropomorphism in the Terminology and Philosophy Underlying Western and Japanese Studies of the Social Behaviour of Non-human Primates. Oxford: Oxford University; 1981.

8) Tang Martinez Z. Paradigms and Primates: Bateman's Principle, Passive Females, and Perspectives from Other Taxa. In: Strum SC, Fedigan LM, editors. Primate Encounters: Models of Science, Gender, and Society. Chicago: The University Chicago Press;2000, p. 261-274.

9) Hinde R. Some Reflections on Primatology at Cambridge and the Science Studies Debate. In: Strum SC, Fedigan LM, editors. Primate Encounters: Models of Science, Gender, and Society. Chicago: The University Chicago Press;2000, p. 104-115.

10) Latour B. A Well-articulated Primatology: Reflection of a Fellow Traveller. In: Strum SC, Fedigan LM, editors. Primate Encounters: Models of Science, Gender, and Society. Chicago: The University Chicago Press;2000, p. 358-381.

11) Viveiros de Castro E. Cosmological Perspectivism in Amazonia and Elsewhere. In: Viveiros de Castro E. editor. The Relative Native. Essays on Indigenous Conceptual Worlds. Chicago (IL): HAU Books;2015, p. 191-294.

12) Bekoff M. Animal Emotions: Exploring Passionate Natures. BioScience. 2000;50:861-70.

HISTORY AND MEDICINE EMBRYOLOGY

The Pricked Embryo in the Medieval Tradition

C Beneduce[1]

[1]Radboud University, Nijmegen (NL)

submitted: Jan 11, 2017, accepted: Mar 7, 2017, EPub Ahead of Print: Mar 10, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.16 - Corresponding author: Dr. Chiara Beneduce, c.beneduce@ftr.ru.nl

Abstract The medieval tradition transmitted the idea that an embryo, pricked with a needle in an early stage of its development, moves and shows a certain sensation activity. This article traces the history of this *topos* in the Middle Ages and up to William Harvey. The image of the pricked embryo was transmitted within three main frameworks: the discussions on the faculties of the soul, the problem of the localization of the sense of touch, and the issue of the corporeal localization of the common sense. The pricked embryo is a case in point to show the legacy of Aristotelian cardiocentrism well past the Middle Ages

Keywords Pricked embryo, Albert the Great, William Harvey, Aristotle, cardiocentrism.

I. Introduction

William Harvey (1578-1657), the physician famous for being the first to have accurately described the circulatory system, wrote a text on embryology and reproduction entitled *Exercitationes de generatione animalium*[1] . In a passage of this work, he points out a physical 'paradox' according to which blood is formed in the embryo, moved, and 'soaked' with vital spirits before the formation of any organs apt to producing blood or movement. He also adds and specifies that sensation and movement are present in the fetus before the formation of the brain. In fact the fetus moves and contracts before the brain is visible, which proves that sensation and movement do not entirely originate in the brain[i]. Harvey also remarks that the embryo moves and senses before the formation of the brain or of other corporeal members because, if the embryo is slightly pricked ("*leviter pungatur*"), it moves and squirms[ii].

The historian of science Walter Pagel (1898-1983) was the first to point out that "Harvey's method of demonstrating tissue irritability as independent of the brain by pricking the embryonic *anlage* with a needle was foreshadowed by an observation of Albertus Magnus in human foetuses …" (Pagel 1966, p. 410)[2] . In other words, Pagel underlined that Harvey's image of the pricked embryo is already in Albert the Great († 1280) who seems to be the first to have introduced this image (*Ibidem*, pp. 410-411). Most importantly, he remarked that "it is not unlikely that Harvey was familiar with Albertus' text …" (*Ibidem*, p. 411) since on the whole "…we have every reason to believe that Harvey was well acquainted with scholastic commentators of Aristotle …" (Ivi).

In linking Harvey with Albert, Pagel referred to a passage of Albert's *De animalibus* that is couched in a broader discussion of abortion. In this passage, Albert points out that a certain movement can be observed when an embryo, aborted on the fortieth day and expelled from the mother's body, is pricked with a needle, thus showing that the fetus is animated at this early stage of development (Albert The Great 1916, lib. IX, tract. 1, cap. 3, ll. 18-21, p. 698)[3] . As Pagel wrote, this passage is in turn based on Aristotle (384-322 BC) who describes not the image of the pricked embryo but the fact that the embryo aborted on the fortieth day is of a certain size (that of a large ant) and shows the presence of certain organs (limbs, penis, and eyes) (Aristotle, Hist. an.)[4] . It is exactly on this basis that Pagel observed that Harvey's 'pricked embryo' is already in Albert, although "[i]n significance and purpose Albertus' observation is … far removed from Harvey's ideas…" (Pagel 1966, p. 411) and "neither the experimental conditions nor the biological conclusions [of the two] are comparable" (Ivi), also because Albert deals with "… a

much later stage in foetal development" (*Ibidem*, p. 410) than Harvey.

Against the background of Pagel's remark, I want to show more details of the tradition on the image of the pricked embryo in the late Medieval thought. This could also shed more light on the use of the image of the pricked embryo made by Harvey.

II. The Pricked Embryo in the Medieval Tradition

Besides Albert's passage in the *De animalibus*, there is a conspicuous set of late medieval texts (all later than Albert's) presenting the image of the pricked embryo and all in different contexts. This image seems to have been transmitted under three frameworks: the discussions on the faculties of the soul, the issues concerning the sense of touch, and the problem of the localization of the common sense.

2.1 The Faculties of the Soul

The first framework transmitting the image of the pricked embryo are the discussions on the 'parts' or faculties of the soul: vegetative, sensitive, and rational. The image is found in different types of texts, both theological and natural-philosophical (especially commentaries on the *De anima*), addressing those topics. More specifically, the image is found in a variety of 'classic' medieval problems on the soul, such as 1) whether the nutritive, sensitive, and rational powers (of the soul) should be considered as one soul or three distinct souls; 2) the way and the chronology according to which the faculties of the soul are 'produced' and embodied; and 3) the ontological status of the human being before he acquires the rational soul[iii]5 .

The first example is in Albert the Great's *De anima* in a section where he shows that the vegetative, sensitive, and rational 'parts' of the soul are not three *distinct souls* (or three *different souls*). Among the arguments brought against this position, Albert explains there is one claiming that since the faculties of the soul are settled chronologically one after the other, it is not possible to consider all of them together as one substance. The pricked embryo is an example for this claim: the pricked embryo moves due to the sense of touch (namely, to the sensitive soul) before the rational soul is active[iv]6 .

The image of the pricked embryo in the discussions on the faculties of the soul also appears in the *De anima* of Roger Bacon († 1294), more specifically in a section devoted to the 'production' of the 'parts' of the soul. Bacon supports the idea that only the intellective soul is created, while the sensitive and nutritive souls are just naturally (*per viam naturae*) produced (*producantur*) from the potency of matter (*de potentia materiae*). The image of the pricked embryo is used to show that the nutritive and the sensitive souls function *before* the intellect is created. This means that the vegetative and the sensitive souls are not created *at the same time as* the intellective soul, otherwise we would have a duplication of the non-intellective parts of the soul: 1) a vegetative and a sensitive soul created *together* with the intellective soul and 2) a vegetative and a sensitive soul produced by the potency of matter *before* the creation of the intellective soul[v]7 .

A third example is from the *De anima* of Matthew of Aquasparta († 1302). He attempts to determine whether the human being, before the infusion of the ration soul, is 'human' according to another type of form, namely a non-rational form. His answer is negative. The image of the pricked embryo is inserted in one of the arguments listed in favor of the positive answer to the question: the embryo is animated and has the sense of touch, which is proved by pricking it. This makes him an animal (the sense of touch, in fact, according to Aristotle characterizes animals), but not a human being. Therefore before acquiring the rational soul, the embryo is in some not-yet-human species and is constituted by some not-yet-human form[vi].

The last example is found in Giles of Rome's *Quodlibet*. Giles († 1316) asks whether the human being, before the infusion of the rational soul, should be considered to belong to some (non-human) animal species. Giles' answer is positive. In his *quaestio*, he incidentally mentions the image of the pricked embryo in a complicated and technical digression on the issue of the plurality or unity of the soul[vii]8 . The pricked embryo appears again in a passage of Giles of Rome's *Sentences* commentary where he explains that the pricked embryo moves only when it is provided with the sensitive soul, while it does not move when it has only the vegetative soul[viii]9 .

This list of texts shows that the image of the pricked embryo, used in different types of texts and for different purposes, had a certain fortune in the late medieval discussions on the faculties of the soul. It is relevant to notice that two of the examples listed above (Roger Bacon and Matthew of Aquasparta) explicitly refer to Aristotle as the source for the image of the pricked embryo[ix]. This is especially evident in Matthew of Aquasparta's passage. In the Aristotelian works we do not find the image of the pricked embryo, but just the idea that the embryo possesses nutritive and sensitive functions in the early stages of its formation[x]10 , and that the fetus is able to sense thanks to the heart and before the formation of the other corporeal organs[xi]11 . Despite the fact that the pricked embryo is nowhere to be found in Aristotle, we should take into account that at least some of the medieval authors transmitting the Albertinian image of the pricked embryo directly cited Aristotle as its source.

2.2 The Sense of Touch

Two texts of the previous group connected the pricked embryo with the sense of touch[xii]. In fact, the image of the pricked embryo can be also found in medieval issues concerning this sense. The main medieval questions concerning the sense of touch were: 1) what is the corporeal localization of touch; 2) in which medium does it perform its activity (and, more radically, whether or not touch needs a medium to function), and 3) to which of the four elements (air, water, earth, and fire) is touch more naturally connected. In medieval treatises of natural philosophy the five senses were in fact often paired with the four elements.

The first example in this conceptual framework is in the *Parva naturalia* of John of Jandun († ca. 1323) in a question discussing the connection between the sense of touch and the element of earth. In order to prove this connection, he shows that the sense of touch is corporeally located in the heart, which being very solid in order to bear the heat is dominated by the terrestrial element. Therefore, touch is dominated by earth, too. The image of the pricked embryo is used to show that touch is actually located in the heart since the embryo performs tactile sensation after the formation of the heart[xiii]12 .

Even though our knowledge of late medieval commentaries on the *Parva naturalia* is still limited, it may be safe to generalize that the image of the pricked embryo was present in other medieval discussions on the sense of touch as they were addressed in those commentaries.

A second example is highly relevant. The pricked embryo - more precisely a pricked heart in a stage of foetal development - also appears in the *De anima* of John of St. Thomas (1589-1644), a contemporary of Harvey. In the section of his work on 'the potency, the act, and the medium of touch', he presents the Aristotelian idea that touch is localized in the heart, a position he ultimately rejects. In this framework, he presents an argument in favor of the Aristotelian position that runs as follows: the heart is formed in the living being before the brain and is immediately able to sense; this is proved by the fact that it palpitates and, if pricked, moves; therefore, the sense of touch is in the heart[xiv]13 .

We can therefore find the image of the pricked embryo within medieval discussions on touch and in later natural-philosophical treatises even contemporary to Harvey.

2.3 The Localization of the Common Sense

The third framework transmitting the image of the pricked embryo is found in the questions on the localization of the common sense in late medieval commentaries on the *De anima* and, above all, on the *Parva naturalia*. These questions were especially meant to solve the controversial issue on the corporeal localization of sensation; the '*sensus communis*', in fact, according to the Aristotelian and Scholastic tradition, is the ultimate perception ability whose primary role is to coordinate and organize the perceptual elemental stimuli coming in from the external world to be used for higher internal mental processes. This issue opposed the Aristotelian-philosophical tradition to the Galenic-medical tradition that located the common sense, respectively, in the heart and in the brain. The solution of this problem, among both philosophers and physicians, was mostly oriented at reconciling the two traditions.

In this framework, the image of the pricked embryo occurs several times in the texts of the philosophers commenting on Aristotle's natural philosophy, especially the *De anima* and the *Parva naturalia*. They most often insert the image when listing the arguments in favor of the Aristotelian cardiocentric position, the one they ultimately support. In fact, the Aristotelian commentators argue that sensation cannot be localized in the brain, since the pricked fetus moves and senses before the formation of this organ. The embryo shows sensation abilities because of the heart, which is the first organ to be formed in human beings. In chronological order, we find the image of the pricked embryo in a set of questions on *De iuventute et senectute*, *De morte et vita* not safely ascribed to Siger of Brabant († 1284)[xv]14 15 , in Simon of Faversham's († 1306) *Parva naturalia* (especially *De somno et vigilia*)[xvi]16 , in John of Jandun's *Parva naturalia* (again *De somno et vigilia*)[xvii]17 , and in John Buridan's († ca. 1360) *De anima*[xviii]18 .

As in the case of the sense of touch, the image of the pricked embryo used in the discussions on the localization of the common sense seems to have had a special circulation in the tradition of the commentaries on the *Parva naturalia*. We can likely expect to find more examples of the use of this image in that tradition.

III. Conclusions

The image of the pricked embryo clearly had a wide circulation in the Middle Ages. Albert the Great is the first author in which we have been able to find this image, but the main inspiration was undoubtedly Aristotelian. Based on the examples provided, two clear and influential points from Aristotelian natural philosophy appear to have persisted throughout the Middle Ages: a) the general idea that the embryo is able to perform vegetative and sensitive functions in the early stages of its formation and b) the more specific idea according to which sensation is located in the heart given that the embryo shows sensory abilities before the formation of the brain when only the heart is formed. This Aristotelian background clearly explains why the image of the pricked embryo had such fortune when medieval authors considered the Aristotelian cardiocentrism about

the localization of the sense of touch or the localization of the common sense. Moreover among all the textual traditions, the commentaries on the *Parva naturalia* seem to have been the most important vehicle for the transmission of the image of the pricked embryo. These commentaries spread the positions both on the localization of the sense of touch and on the localization of the common sense. However, the image of the pricked embryo is also present in texts addressing other medieval topics related to the 'science of the soul' - here, more theoretical than biological - such as the formation of and the relationships between the faculties of the soul.

We can safely state that the image of the pricked embryo is an actual *topos* of medieval philosophy that was transmitted later on to the early-modern period, both to philosophers and physicians of the sixteenth century, as the texts of John of St. Thomas and William Harvey testify. Harvey's passage in the *Exercitationes*, then, has to be contextualized in a broader and long-standing tradition that persisted well into his own times. More specifically, Harvey did not necessarily have the passage from Albert's *De animalibus* in mind, but he most likely included in his text a common and shared *topos*[xix]. We cannot even exclude that Harvey read about the image of the pricked embryo from one of his contemporaries perhaps in a philosophical treatise of his time.

More generally, the case of the pricked embryo testifies to the *longue durée* of medieval natural-philosophical topics into the Modern Era, especially to life of discussions on Aristotelian cardiocentrism, a core-aspect of medieval biological thought which lasted well past the Middle Ages.

Acknowledgments

I am grateful to Frederik Bakker and Elena Nicoli for their help with the Latin texts.

Endnotes

[i] "Videtur praeterea *paradoxon*, sanguinem fieri et moveri, spirituque vitali imbui; antequam ulla organa sanguifica, vel motiva existerint [exstiterint *ed.*]. Nec minus novum, atque inauditum, inesse sensum ac motum in foetu, priusquam cerebrum exstructum fuerit. Movetur enim fetus, contrahit et explicat sese, cum pro cerebro adhuc nihil conspicuum est, praeter aquam limpidam" (Harvey 1662, p. 243). "Moreover, it seems to be a paradox that blood is formed, moved, and imbued with a vital spirit before the formation of any organs apt to producing blood or movement. Nor is it less strange or unheard-of that sensation and movement are present in the fetus before the formation of the brain. For, the fetus moves, contracts, and unfurls itself when in the place of the brain nothing yet is visible except for clear water". All translations of the Latin passages are mine. When necessary, I modified the punctuation of the Latin text.

[ii] "… cumque cerebrum nil aliud, quam aqua limpida est; si modo leviter pungatur, instar vermis vel erucae, sese obscure movet, contrahit, et contorquet; ut sentire ipsam evidenter pateat" (Harvey 1662, p. 245). "… when the brain is nothing but clear water, if [the embryo] is only slightly pricked, it vaguely moves, contracts, and squirms like a worm or a caterpillar, so that it is clearly evident that it feels".

[iii] The following examples (in this first group of texts) have been collected by A.-J. Gondras in his edition of Matthew of Aquasparta's *De anima* (Matthew of Aquasparta 1961, footnote 'm', p. 77).

[iv] "Probant autem hoc ex eo quod embria prius tempore trahunt nutrimentum ex sanguine menstruoso, quam sentiant. Trahens autem nutrimentum et convertens in speciem nutriti, non est nisi anima vegetabilis. Similiter autem embria puncta contrahuntur, quod non fit sine sensu tactu …" (Albert the Great 1968, libr. 3, tract. 5, cap. 4, ll. 23-29, p. 248a). "However, they prove this by the fact that embryos take nutriment from the menstrual blood before sensing. But taking the nutriment and transforming it into the species of what is nourished, that cannot happen without the vegetative soul. However, in the same way, the embryos contract when pricked which would not happen without the sense of touch …".

[v] "Item, arguunt per experienciam. Nam embrio ante infusionem anime racionalis nutritur et crescit, et si pungatur sentit, et hoc sciunt mulieres ex parte in talibus, et Aristoteles hoc vult in libro *De animalibus*, et aliis auctores concordant. Manifestum est igitur quod anima vegetativa et sensitiva sunt in embrione hominis antequam intellectiva producatur". (Bacon 1911, pars 4, dist. 3, cap. 1, ll. 16-22, p. 283). "In addition, they argue on the basis of experience. For the embryo, before the rational soul is poured in, nourishes itself and grows, and, if it is pricked, it feels [it]. And women know this partly in such circumstances, and Aristotle implies this in the work *On Animals*, and other authoritative sources agree. It is evident therefore that the vegetative and sensitive souls are in the human embryo before the intellective soul is produced".

[vi] Matthew does not better specify what he means by the "not-yet-human" species and form; "Item, secundum Philosophum, II *De anima*, tactus est primus sensus per quem animal est animal; ergo omne animatum, in quo est sensus tactus, est animal; sed embryo est animatus et habet sensum tactus; ergo est animal; sed non est homo; ergo est in aliqua specie constitutus per aliquam formam.

Quod autem in embryone sit tactus, [manifestus est, quia] dicit Philosophus: si pungatur, contrahitur" (Matthew of Aquasparta 1961, q.5, p.77) . "Moreover, according to the Philosopher, in the second book of his *On the Soul*, touch is the first sense thanks to which an animal is [qualified as] an animal; therefore, every animated being in which there is the sense of touch is an animal; but the embryo is animated and has the sense of touch, therefore it is an animal; but it is not human; therefore it is constituted in a certain species by means of a certain form. That in the embryo there is touch [clearly appears since] the Philosopher says: if it is pricked, it contracts".

[vii] "Respondeo dicendum fuisse opinionem quorumdam in embrione hominis non esse substantia animae sensitivae vel vegetativae ante infusionem animae rationalis. Quod autem ibi oporteat opera vitae, quando embrio ante infusionem animae rationalis augmentatur vel etiam quando apparent ibi opera sensus; quandoquidem embrio ante infusionem animae si pungatur se retrahat, (ut dicunt) hoc esse per virtutem vegetativam, vel sensitivam, absque substantia sensitiva vel vegetativa" (Giles of Rome 1946, I, q.14, p. 29). "I answer that it must be said that some people were of the opinion that in the human embryo there is no substance of a sensitive and vegetative soul before the rational soul is poured in. But [that], because life's operations must [be] there, since the embryo, before the rational soul is poured in, grows, and also since sense's operations are manifest there - for the embryo, before the soul is poured in, if it is pricked, pulls back, this is (as they say) because of the vegetative or the sensitive virtue, without the sensitive or the vegetative substance".

[viii] "… embrio hominis primo vivit vita plantae et est ibi essentia animae vegetativae similis animae plantae et sunt ibi potentiae illius quia nutritur et augmentatur embrio hominis sicut nutritur [nutritivus *ed.*] et augmentatur planta et quandiu vivit vita plantae, si pungeretur, non sentiret, sicut nec sentit planta. Postea post vitam plantae incipit vivere embrio vita animalis, et incipit habere animam sensitivam, nec habet propter hoc duas animas quia adveniente anima sensitiva cedit anima plantae … cedente illo primo vegetativo, et introducto sensitivo, hoc sensitivum secundo introductum dabit embrioni quicquid dabat primum vegetativum et adhuc amplius … quod dabit ei quod sentiat ut ex tunc si pungeretur sentiret et retraheret se" (Giles of Rome 1581, dist. 19, q.1, art. 4, p. 128b). "… the human embryo first lives the life of a plant and the essence of the vegetative soul is there, similar to the soul of a plant, and the capacities of that [i.e., of the vegetative soul] are there, since the human embryo nourishes itself and grows, just as a plant nourishes itself and grows, and as long as it lives the life of a plant, if it is pricked, it does not feel [it], just as a plant does not feel. Then, after the plant's life, the embryo starts living the life of an animal, and begins to have a sensitive soul, and yet does not, for this reason, have two souls, since, when the sensitive soul comes, the plant's soul goes away. … Once that first vegetative [principle] is gone, and once the sensitive [one] is introduced, this sensitive [principle] introduced afterwards will give to the embryo everything the first vegetative [principle] used to provide and even more … [the sensitive principle] will give to it [i.e., to the embryo] the capacity of sensing so that from that moment, if it is pricked, it would pull itself back".

[ix] See endnotes [v] and [vi].

[x] See Arist., De gen. an., II, 3, 736a29-736b2. See the translation in Barnes' edition: "[it is also necessary to decide *CB*] concerning the soul in virtue of which an animal is so called (and this is in virtue of the sensitive part of the soul) - does it exist originally in the semen and in the embryo or not, and if it does whence does it come? For nobody would put down the embryo as soulless or in every sense bereft of life (since both the semen and the embryo of an animal have every bit as much life as a plant), and it is productive up to a certain point. That then they possess the nutritive soul is plain (and plain is it from the discussions elsewhere about soul why this soul must be acquired first). As they develop they also acquire the sensitive soul in virtue of which an animal is an animal …" (Aristotle 1984, pp. 1142-1143).

[xi] See Arist., De part. an., III, 4, 666a16-22. See the translation in Barnes' edition: "Again, as neither the blood itself, nor yet any part which is bloodless, is endowed with sensation, it is plain that that part which first has blood, and which holds it as it were in a receptacle, must be the primary source. And that this part is the heart is not only a rational inference, but is also evident to the senses. For no sooner is the embryo formed, than its heart is seen in motion as thought it were a living creature, and this before any of the other parts, it being, as thus shown, the starting-point of their nature in all animals that have blood". (Aristotle 1984, p. 1038).

[xii] See endnotes [iv] and [vi].

[xiii] "Item probatur aliter illud dominium quia nos videmus quod organum tactus est circa corpus, immo etiam in corde est organum tactus quod probatur per embrionum formationem, qui sentiunt solo corde formato et si pungatur retrahit se et dilatatur, …" (John of Jandun 1557, q.15, f. 9ra). "Moreover, this *dominium* is proved in another way because we see that the organ of touch is around the body or, even better, that the organ of touch is in the heart, which is proved by the formation of the embryos. [The embryos can] feel when only the heart is already formed and, [if the heart] is pricked, pulls itself back and dilates itself …".

[xiv] "Est tamen pro Aristotele argumentum, quia cor prius formatur in animali quam cerebrum et statim sentit, quia palpitat, et si ibi pungatur, se retrahit; ergo sensus tactus originatur a corde. Similiter decapitato homine adhuc

cor sentit et brevi tempore palpitat et si pungatur, sentit. Ergo sensus tactus radicatur in corde" (John of St. Thomas 2008, vol. III, pars. IV, q. V, art.6, p. 163a). "Nevertheless, there is an argument in favor of Aristotle because the heart is formed in the animal before the brain and it immediately feels, since it palpitates and, if it is pricked there, pulls itself back; then, the sense of touch originates from the heart. In the same way, if a human being is decapitated, the heart still feels and, for a short time, palpitates, and, if it is pricked, it feels [it]. Therefore, the sense of touch takes root in the heart".

[xv] The questions have been ascribed to Siger of Brabant by F. Van Steenberghen (Van Steenberghen 1931). On these questions and their doubtful attribution to Siger of Brabant, see P. De Leemans (De Leemans 2011, esp. p. 920). Van Steenberghen offers a summary of q.4 (*Utrum sensitivum commune sit in corde*), found at f. 72rb of the ms. München, Bayerische Staatsbibliothek, Clm. 9559. The relevant part of his summary runs as follows: "Le sens commun se trouve premièrement dans le coeur, car c'est là que se manifeste la première activité sensitive (dans l'embryon), alors que les autres organes ne sont pas encore formés: '*quoniam … si pungatur, retrahit se*'" (Van Steenberghen 1931, p. 265).

[xvi] See q. 5 (*Utrum sensitivum primum sit in corde*): "Dicendum est ad hoc quod sensitivum primum est in corde. Et ratio huius est, sicut Philosophus dicit primo *De morte et vita*, <quod> secundum eandem partem animal est animal <atque> primo vivit et nutritur. Et ratio huius est quia nos videmus quod quaedam animalia decisa vivunt … Tertio hoc determinatur sic: animal est animal per hoc quod habet [[hoc]] animam sensitivam; … Ex hoc arguitur: animal est animal per hoc quod habet animam sensitivam, sed anima sensitiva non invenitur sine sua virtute, et virtus sensitiva non reperitur sine primo sensitivo; ergo animal est animal propter sensitivum primum; nunc autem primum sensitivum in animali est ipsum cor, cuius ratio est quia formato corde non formatis aliis partibus ipsum retrahit se si pungatur, et hoc non esset nisi sensitivum esset in ipso; sed ideo etc." (Simon of Faversham 2013, esp. pp. 113-115). "On this, it must be said that the first principle of sensing is in the heart. And the reason for that is, as the Philosopher says in the first section of his work *On Death and Life*, that thanks to the same part due to which the animal is an animal, it lives and nourishes itself. And the reason for this is that we see that some animals, when cut, [can] live … Third, this is proved in the following way: an animal is an animal due to the fact that it has a sensitive soul … from this it is said: an animal is an animal since it has a sensitive soul, but the sensitive soul is not found without its virtue, and the sensitive virtue is not found without the first principle of sensing; therefore an animal is an animal thanks to the first principle of sensing; but, now, the first principle of sensing in the animal is the heart itself; the reason being that when [only] the heart is formed but the other [corporeal] parts are not [yet] formed it [i.e.; the animal] pulls itself back if it is pricked, and this would not happen if the principle of sensing would not be in it. But for this reason etc.".

[xvii] See q. 9 (*Utrum sensus communis sit in corde*): "Dimissis opinionibus aliorum, dico breviter quod sensus communis est in corde quia nullus sensus potest esse sine sensu communi et quicquid sentit potest iudicare se sentire illud quod sentit et cognoscere ad minus quo ad suam sensationem. Sed cor primo formatum nullo alio membro formato sentit, sicut patet per experientiam, si pungatur, retrahit se, ergo saltem habet tactum et sic oportet quod habeat sensum commune; et sic sensus communis est in corde quia si esset in cerebro, ut in suo proprio subiecto et organo, tunc cum ipsum cerebrum non est formatum, non sentiret cor, quod patet esse falsum" (John of Jandun 1557, q.9, f. 37ra). "Setting aside the opinions of others, I briefly say that the common sense is in the heart because no sense can be without the common sense and everything that feels can judge itself to be feeling what it is feeling and know at least as far as its sensation [goes]. But the heart, formed first, when no other member if formed yet, [can] feel as is evident from experience, [because] if it is pricked, it pulls itself back, [and] therefore, at least, it has [the sense of] touch and so must have the common sense; and so the common sense is in the heart, because if it were in the brain, as in its proper place and organ, then, when the brain itself is not formed, the heart would not feel anything, which is patently false".

[xviii] See q. 24 of the second book in the third version of Buridan's commentary (*Utrum organum sensus communis est in corde vel in cerebro*): "Item alia experientia est quod in formatione embrionis prima pars apparens nobis formata est cor, quod iam ante apparentem formationem aliorum membrorum habet vitam et sensum, nutritur enim et augetur. Et si pungatur, commovetur …" (John Buridan 1984, II, q. 24, p. 395). "And another experience is that in the formation of the embryo the first part that appears to us to be formed is the heart, which, already before the visible formation of the other members, has its own life and sense, nourishes itself and grows. And, if it pricked, it moves …".

[xix] We can then scale down Pagel's claim that Albert deals with "… a much later stage in foetal development" than Harvey. Harvey could have had the passage from Albert's *De anima* in mind, instead of that from the *De animalibus*. See endnote [iv] and reference 3.

References

1) Harvey W. Exercitationes de generatione animalium. Amsterdam: Ioannes Ravesteynius; 1662.

2) Pagel W. Harvey, Foetal Irritability - and Albertus Magnus. Medical History. 1966; Oct;10(4):409-411.

3) Albert the Great. De animalibus libri XXVI. Stadler H, editor. Münster: Aschendorff; 1916.

4) Aristotle, Hist. an., VII, 4, 583b15-20.

5) Matthew of Aquasparta. Quaestiones diputatae De anima XIII. Gondras A-J, editor. Paris: Vrin; 1961.

6) Albert the Great. De anima. Stroick C, editor. Münster: Aschendorff; 1968.

7) Roger Bacon. Liber primus communium naturalium. In: Steele R, editor. Opera hactenus inedita Rogeri Baconi. Oxford: Oxford University Press; 1911.

8) Giles of Rome. Quodlibeta. Leuven: Hieronymus Nempaeus; 1646.

9) Giles of Rome. In secundum librum Sententiarum quaestiones. Venice: Franciscus Zilettum; 1581.

10) Aristotle, De gen. an., II, 3, 736a29-736b2. Aristotle. Generation of Animals (translation), In: Barnes J, editor. The Complete Works of Aristotle, vol. I. Princeton: Princeton University Press; 1984, pp. 1142-1143.

11) Aristotle, De part. an., III, 4, 666a16-22. Aristotle. Parts of Animals (translation), In: Barnes J, editor. The Complete Works of Aristotle, vol. I. Princeton: Princeton University Press; 1984, p. 1038.

12) John of Jandun. De sensu et sensato. In: Quaestiones super Parva naturalia. Venice: Hieronymus Scotus; 1557.

13) John of St. Thomas. Corpus Philosophicus Thomisticus. Reiser B, editor. Hildesheim: G. Olms; 2008.

14) Van Steenberghen F. Siger de Brabant d'après ses oeuvres inédites, vol. 1: les oeuvres inédites. Institut Supérieur de Philosophie: Louvain; 1931.

15) De Leemans P. Parva naturalia, Commentaries on Aristotle's. In: Lagerlund H. editor. Encyclopedia of Medieval Philosophy. Philosophy between 500 and 1500. Dordrecht: Springer 2011; pp. 917-923.

16) Simon of Faversham. Quaestiones super librum De somno et vigilia. Ebbesen S, editor. Simon of Faversham, Quaestiones super librum De somno et vigilia. An Edition. Cahiers de l'Institut du Moyen-Âge grec et latin, 2013;82:90-145.

17) John of Jandun. De somno et vigilia. In Quaestiones super Parva naturalia. Venice: Hieronymus Scotus; 1557.

18) John Buridan. Quaestiones De anima, tertia lectura. In: Sobol P, editor. John Buridan on the Soul and Sensation. An Edition of Book II of his Commentary on Aristotle's Book on the Soul with an Introduction and a Translation of Question 18 on Sensible Species. Unpublished Ph.D. thesis. Indiana University; 1984.

REPORTS VASCULAB DEBATES

Risk Assessment in Venous ThromboEmbolism

A Puskas[1], F Lurie[2], F Passariello[3]

[1]Angio Center-Vascular Medicine, Targu Mures, Romania

[2]Toledo, Ohio (MI, USA). Adjunct Research Professor, University of Michigan. President at American Venous Forum Foundation.

[3]Fondazione Vasculab ONLUS, via Francesco Cilea 280 - 80127 Naples, Italy

The official report of the VTE_Risk Vasculab Debate, held on the Internet, Vasculab List, on Jan 10-31, 2016 (unmoderated session: Feb 1-10, 2016. Discussant: Fedor Lurie, Moderator: Fausto Passariello.
submitted: Feb 5, 2017, accepted: Feb 19, 2017, EPub Ahead of Print: Apr 3, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.12 - Corresponding author: Dr. Fausto Passariello, afunzionale@tiscalinet.it

Abstract Clinical pre-test probability scores are used to guide the subsequent steps in the diagnosis and therapy of venous thromboembolism. However, often there is resistance in accepting formal and standardized procedures as a substitute of expert judgements. A review of the available tools as well as of the laboratory and imaging techniques is presented, together with the detailed report of a comprehensive debate held on the Vasculab Mailing List. Several unusual topics came to attention during the discussion: as the validation of scores, limited to a few contexts and populations; the over-utilization of venous duplex ultrasound and the rational use of resources; how to choose the steps, managing the amount of time waiting for the results of a test; the scarce attention given today to the long term complications, like the chronic pulmonary embolism, the pulmonary hypertension and the post-thrombotic syndrome. A lot of open problems of course remains, the report being witness of the value of a free style atypical discussion, as generally occurs on Vasculab.

Keywords Venous thromboembolism, pre-test probability scores, duplex ultrasound, D-Dimer, sP-selectin, chronic thromboembolic pulmonary hypertension.

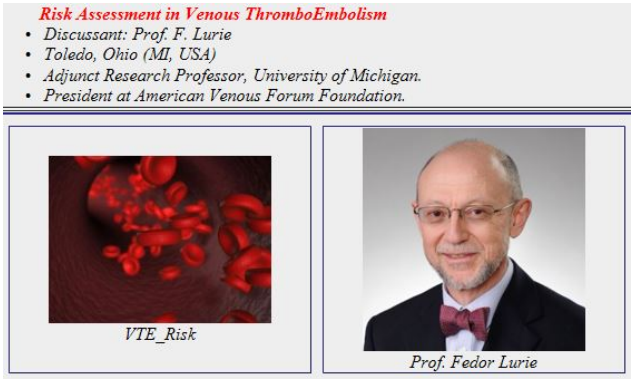


Figure 1 - The VTE_Risk webpage.
DOI: 10.24019/2016.VTE_Risk

Introduction

Venous thromboembolism (VTE) has gained an increased attention in the last years, owing to our better diagnostic capability and to the availability of new therapeutic choices. Most used acronyms are listed to insure a better comprehension (Table I).

The most common symptom of calf pain has been reported to have sensitivity between 75% and 91%, and specificity between 3% and 87%. The reported sensitivity of calf swelling for Deep Veins Thrombosis (DVT) diagnosis ranges from 35% to 97%, and its reported specificity ranges from 8% to 88%. In part, such variability is due to the high prevalence of the same signs and symptoms in patients without DVT[1,2].

Swelling and generally signs of lower limb thrombosis are not the main clinical presentation of VTE, which instead can present itself as a chest pain or a primary

respiratory failure with hypoxia, which can or cannot be associated to a lower limb thrombosis.

Interestingly, the idea of using risk assessment as the first step in the diagnosis of VTE was developed and promulgated when general consensus was that clinical presentation is unreliable.

The approach was initially developed for symptomatic outpatients, and most frequently used pre-test probability (PTP) instruments are validated only in restricted environments and their application remains uncertain for other patient populations, such as pregnant and post-partum women. Instruments that are designed for in-patients are designed for prevention, not for diagnosis of VTE. In addition, between inpatients the greater frequency of DVT is given by adverse effects in medical patients (like for instance post ictus and myocardial infarction), greater than the rate of the well-known VTE in post-operative period (especially in orthopaedic and gynaecologic surgery).

The incidence of VTE changes according to the clinical environment where the patient comes to our observation. Outpatients have a different prevalence of DVT and pulmonary embolism (PE), compared to inpatients and to emergency patients.

Occurrence of provoked VTE now encompasses clinical scenarios that we did not have 20 years ago. For example, the shift is towards seeing more VTE in intensive care units, where the average stay has increased and patients are maintained on life support longer. Unprovoked VTE on the other hand surely is seen more than before probably due to better access to ultrasound. We are probably at a point where studies on current VTE incidences may have to be repeated.

These facts, some of them reported only in a qualitative way, constitute a stimulus to look at VTE as an interdisciplinary pathology, which changes its presentation as soon as you change your point of view, i.e. your working environment.

Applicability of the entire approach as well as of the adopted instruments to other patient populations remains questionable.

The components of diagnosis

Though the availability of many clinical signs for DVT-PE, the expert-based diagnosis of VTE is considered unreliable[3,4]. Underdiagnosed cases can erroneously attach a DVT-PE label to a patient and be the premise of a low quality prevention and treatment of any future thromboembolic adverse effect.

PTP tools, **laboratory assays** and **imaging techniques** are the main components of diagnostic VTE algorithms.

Acronyms in use in VTE disease	
CTEPH	Chronic Thrombo-Embolic Pulmonary Hypertension
CUS	Compression UltraSound
DUS	Duplex UltraSound
ER	Emergency Room
HASBLED	(H)ypertension, (A)bnormal Renal or Liver, (S)troke history, (B)leeding (L)abile INRs, (E)lderly, (D)rugs
MDCT	Multi Detector Computed Tomography
NICE	The National Institute for Health and Care Excellence
PERC Rule	Pulmonary Embolism Rule-out Criterion
PESI	Pulmonary Embolism Severity Score
sPESI	Simplified PESI
PIOPED	prospective investigation of the pulmonary embolism diagnosis
TAPSE	Tricuspid Annular Plane Systolic Excursion
TTE	Trans-Thoracic Echocardiography
TEE	Trans-Esophageal Echocardiography
V/Q scan	Ventilation-Perfusion scan
VTE	Venous Thrombo-Embolism

Table I - Glossary.

PTP tools

VTE risk is dependent on the duration of inactivity: induced (anesthesia, surgery) or forced (coma, life-support, paresis, life-threatening illnesses and so on). Most risk assessment scores now take this into consideration.

Several scores are available for VTE (Table II). In order not to ingenerate any confusion, it is worth to describe them shortly.

The most used tools for the assessment of pre-test probability (PTP) in venous thromboembolism (VTE) are: Wells DVT score[5,6] (Table III), Wells PE score[7] (Table IV), Revised Geneva score[8] (Table V) and the pulmonary embolism rule-out criteria (PERC rule)[9,10,11,12] (Table VI).

Other scores are not for diagnosis. The Caprini[13] and Padua[14] (Table VII) scores quantify the risk of thromboembolism and are useful only for VTE prevention among in-patients. The PESI score[15] (Table VIII) and its simplified form sPESI score (Table IX) stratify the risk of outcome and death at 30 days in patients suffering for a

PE episode. The HASBLED score[16] (Table X) quantifies instead the risk of bleeding, when the patient undergoes oral anticoagulation.

The idea of risk stratification (or pre-test probability) in Wells DVT score was based solely on the population of symptomatic ambulatory patients. Wells PE Score, Geneva and Revised Geneva scores were designed instead for the emergency room (ER).

PTP Tools

Scores	Environment	Use
Wells DVT	outpatients	stratify DVT risk
Wells PE	emergency room	stratify DVT risk
revised Geneva	emergency room	stratify DVT risk
PERC	emergency room	exclude pulmonary embolism
Padua	inpatients	stratify DVT risk
Caprini	inpatients	stratify DVT risk
PESI	inpatients	stratify outcome risk in pulmonary embolism at 30 days
sPESI	inpatients	stratify outcome risk in pulmonary embolism at 30 days
HASBLED	any	stratify bleeding risk in anticoagulated patients
Villalta	any	stratify risk in VTE patients for post-thrombotic syndrome

Table II - List of the most known scores, their working environment and notes on their use

However, apart of a paper about Wells DVT score in the elderly[17], attempts to do the same for other populations (pregnant and post-partum, cancer, recent trauma or surgery, obesity etc) either failed or have not been suggested.

It is worth reminding once and forever that **the post-operative period is not the main cause of VTE, which is much more frequent in the medical department than in the surgical one.**

Some of the listed tools are generally not well known by physicians and are also used in an inappropriate way. Indeed, scores used alone have generally no diagnostic value. They serve instead to classify the patient into risk classes. Subsequent diagnostic choices depend on the selected class.

The Wells DVT score

Clinical characteristic	Score
Active cancer, (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery, within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

Table III - The Wells DVT score is used for out-patients in the Ambulatory for the quick computation of the pre-test probability for DVT, as a hint to suggest humoral and/or instrumental investigations.

Wells DVT Score is designed and validated to be used only in ambulatory outpatients. When VTE is suspected at the visit, the score is computed: if low, ask for a D-Dimer assay; if otherwise it is high, prescribe a Duplex UltraSound (DUS). The patient goes home and comes back (if not lost), generally in 7-15 days with the results. The physician waits a so long time for a diagnostic assessment and only the ambulatory environment can justify it, because the patient generally has no urgent symptom. The tree-like hierarchy of the algorithm can be explained only by the ambulatory environment. Wells DVT Score cannot be applied and is not validated in the ER , where a D-Dimer can be obtained in 1-2 hours following traditional laboratory methods, but also in 5'-20' using specialised bedside assays which are not so rare nowadays.

ERs use instead the Geneva[18] or the Wells PE score for people suspected for an important VTE, which can have life-threatening consequences. In addition, the PERC rule (Pulmonary Embolism Rule-out Criteria) is often used, which has the advantage of being simple and quick. If all the listed items in PERC are satisfied, pulmonary embolism is ruled-out. In addition, the efficiency of the PERC rule can be improved introducing also the *Gestalt*, i.e. the personal intuition of the operator about the presence/absence of PE.

Thus personal feelings together with a satisfied PERC Rule are very effective to exclude PE (not DVT) in the ER.

The Wells PE score

Variable		Points
Predisposing factors		
	Previous DVT or PE	+1.5
	Recent surgery or immobilization	+1.5
	Cancer	+1
Symptoms		
	Haemoptysis	+1
Clinical signs		
	Heart rate > 100 beats/min	+1.5
	Clinical signs of DVT	+3
Clinical judgement		
	Alternative diagnosis less likely than PE	+3
Interpretation		
Clinical probability (3 levels)		Total
	Low	0-1
	Intermediate	2-6
	High	>=7
Clinical probability (2 levels)		
	PE unlikely	0-4
	PE likely	>4

Table IV - The Wells PE score is used in the Emergency Room for the quick computation of the pre-test probability for pulmonary embolism, as an alternative to the revised Geneva score.

Discussion

*Very often it is not possible to find the embolism origin in PE: whether you use DUS, CT or MRI it is not important, very often PE seems isolated (**F Passariello**, **M Patel**). The origin can be elsewhere than in lower legs (everywhere in oncologic and rheumatic patients, right ventricle infarct, pelvis veins, and so on). Even in the legs, thrombi can hide in the calf and it can be difficult to detect them.*

*There is a great resistance among physicians to adopt PTP scores (the best known PTP score in this discussion is Wells DVT score but it is rarely utilized). Some people in the debate consider scores only as simple tools for family practitioners (**A Pieri**), whilst specialists' in the field can practically ignore them, owing to their competence (**D Casian**, **Z Lazarashvili**). This point of view is misleading, as scores were effectively introduced as tools to bypass the uncertainty of the clinical diagnosis and to avoid the so called Expert Opinion, which is non-standardisable and not useful for comparisons.*

*Other physicians participating in the debate recognize the clinical value of scores, but prefer to be non-methodical in their practical use, i.e. they don't use written forms, but declare to compute the scores mentally (**H Schlup**). This is questionable, because nothing guarantees that the mental procedure was effectively complete, as its details are not shared.*

*An extreme position in this debate is to assign a great value to DUS as screening investigation, i.e. applied to every people suspected for VTE (**D Casian**, **A Puskas**, **H Schlup**, **PL Antignani**, **A Pieri**, **Z Lazarashvili**). This seems an example of bad use of resources. Imagine what could happen in a high number access hospital with a small number of DUS specialists'. Even in private practice this is not an appropriate behaviour, as it increases costs. Cost is not only money, but also time to wait for the examination and time and the amount of work to perform it.(**F Passariello**, **G Stansby**, **M Schul**)*

Another respectable position is to use a low PTP threshold to ask for a DUS or to perform it directly in the ER. Well, if the DUS expert is available (or if you are the DUS expert), this behaviour is comprehensible, though it cannot be shared. Consider the case when you have a lot of concurrent requests in your work and you have to assign a priority. For instance, 10 patients need a DUS evaluation for a suspected VTE, but they have different PTP scores. Will you perform the DUS without any order or will you satisfy the requests according to their priority ? This is the meaning of a rational use of resources, which becomes more and more important as long as ER services become more widely spread.

The problem of over-utilization of DUS and other resources is well-known[19] and we will come back to it later. At the moment, it is useful to anticipate that the appropriate use of diagnostic resources must be guided by a reliable algorithm.

Laboratory assays

Laboratory assays are useful as the clinical signs and symptoms of VTE are nonspecific, the accuracy of clinical diagnosis being less than 50%. It would be useful to use biomarkers that enable early identification of patients at high or low risk of primary and recurrent VTE. Several established and new biomarkers associated with VTE have been investigated with regard to their potential for predicting primary or recurrent VTE, for facilitating the diagnosis and for optimizing the clinical management of VTE.

D-Dimer

D-Dimer[20,21,22] is used as an initial screening test in the ER to diagnose patients who have signs, or symptoms suggestive of VTE. Before ordering the D-dimer test, it is essential to assess the patient's clinical probability for VTE, for instance by means of the Wells score. D-dimers are degradation products formed when cross linked fibrin contained within a thrombus is proteolyzed by plasmin. D-dimers may be produced in many diseases and conditions associated with thrombosis and thrombolysis. Thus, although presence of D-dimers is specific for degradation of cross-linked fibrin, cross-linked fibrin is not specific for VTE. Being ubiquitous, D-dimer is not generally useful in confirming a diagnosis of VTE.

Clinicians must be aware that D-dimer is increased in many conditions. Physiologic causes of D-dimer elevation include pregnancy and puerperium, increasing age (>65 years), Afro-American heritage, cigarette smoking, recent trauma, and the postoperative period. Pathological causes for elevated D-dimer levels are: VTE, arterial thrombosis, atrial fibrillation, liver disease, renal disease, infections, malignancy and its treatment, chronic inflammatory disease, etc. High-PTP patients should not be tested for D-dimer because the post-test probability for a D-dimer >500 µg FEU/l has a poor positive predictive

value for VTE. However, a negative D-dimer is useful in ruling out VTE in low-PTP patients. The cutoff threshold may differ over age groups, for instance in the elderly an increased value of >750 µg FEU/l was proposed. Many factors play a key role in changing the sensitivity and specificity of D-dimer testing, including the extent of thrombosis and fibrinolytic activity, duration of symptoms, anticoagulant therapy, comorbidity due to surgical or medical illnesses, inflammatory diseases, cancer, elderly age, pregnancy and the postpartum period, and previous VTE.

Many studies have shown that the D-dimer test is highly sensitive (>95%) in acute deep venous thrombosis or pulmonary embolism, usually with a cut-off value of 500 µg FEU/l, which reasonably rules out acute VTE in low-PTP patients. Patients with high D-dimer levels upon presentation may prompt a more intense diagnostic approach, irrespective of pretest probability. Studies performed after a negative D-dimer for 3 months proved the high negative predictive value (NPV) of D-dimer testing in low-PTP patients with suspected VTE. The combination of the D-Dimer and Wells criteria can in significantly reduce the number of patients referred for venous Duplex ultrasound. In unselected inpatients, D-dimer testing has limited clinical utility because of its poor specificity. D-dimers are detected by immunoassays using monoclonal antibodies specific for the cross-linked D-dimer domain in fibrinogen. Commercially available assays include latex agglutination, immunoturbidimetry, and enzyme-linked immunosorbent assay (ELISA). Efforts made to standardize D-dimer results have not been successful thus far, because the D-dimer analyte is not uniform across the different assays[23].

sP-selectin

Soluble P-selectin[24,25] (sP-selectin) is a member of the selectin family of cell adhesion molecules and is primarily stored in the alpha granules of platelets and the Weibel-Palade bodies of endothelial cells. After activation of platelets and endothelial cells, P-selectin is translocated to the cell surface and in part released into the plasma in soluble form. P-selectin acts through binding to its main counter-receptor, the P-selectin glycoprotein ligand-1 (PSGL-1), located on leukocytes. P-selectin is an important molecule in hemostasis and thrombosis. The P-selectin receptor, PSGL-1, is also expressed on platelets and mediates platelet-endothelium interaction and supports fibrin formation and thrombus growth. The interaction of P-selectin and its receptor leads to several mechanisms that induce a pro-coagulant state. Studies have demonstrated the clinical significance of P-selectin for thrombosis, and elevated sP-selectin has been implicated as a risk factor for venous thromboembolism. sP-selectin levels have been observed to increase during an acute event of VTE. There is growing evidence that platelet activation results in higher levels of sP-selectin, and it can be assumed that sP-selectin is mainly platelet-derived and reflects platelet activation.

Plasma levels of sP-selectin are elevated in acute DVT. Further, high levels of sP-selectin were recently associated with an increased risk for recurrence of DVT and in cancer patients, high plasma levels of sP-selectin were predictive of VTE. In one study soluble sP-selectin in combination with the Wells score, established the diagnosis of DVT in lower limbs with a specificity of 96% and a positive predictive value of 100%. Another recent study showed that when Wells score >2, sP-selectin is an excellent biomarker to rule in DVT in lower limbs. D-dimer and a Wells score <2 was most sensitive at excluding a diagnosis of DVT. However the clinical applicability of sP-selectin measurements to assess the risk of VTE needs to be standardized and investigated in greater extent in interventional trials.

Oximetry and Acid Base Balance

Essentially, PE affects the oxygen transport and changes can be detected by means of the following measurements: oximetry, with detection of low peripheral oxygen saturation (SpO_2) and Acid Base Balance (ABB). As regards the ABB, there are 3 parameters:

ABB parameters and PE

- 1. Hypoxia (low arterial pO_2) and hypocapnia (low arterial CO_2);
- 2. Increased alveolar(A)-arteriolar(a) difference(Δ) of oxygen ($\Delta_{A\text{-}a}O_2$);
- 3. Increased ventilation/perfusion ratio ($\frac{V}{Q}$).

The first two ABB parameters can be measured with in an arterial/capillary sample, whilst the third one requires an arterial and a central venous sample[26-28]. Though very informative of the severity of pulmonary embolism, AAB parameters are not included in any officially recognized diagnostic algorithm for PE. Apart of measurement errors, a general relationship should generally hold:

$$S_aO_2 >= S_pO_2 >= S_vO_2$$

where SO_2 is the oxygen % hemoglobin saturation and the subscripts a, p and v mean arterial, peripheral and venous respectively.

The revised Geneva score

Variable		Points
Predisposing factors		
	Age > 65 years	+1
	Previous DVT or PE	+3
	Surgery or fracture within 1 month	+2
	Active malignancy	+2
Symptoms		
	Unilateral lower limb pain	+3
	Haemoptysis	+2
Clinical signs		
	Heart rate	
	75-94 beats/min	+3
	>=95 beats/min	+5
	Pain on lower limb deep vein at palpation and unilateral oedema	+4
Interpretation		
	Clinical probability	Total
	Low	0-3
	Intermediate	4-10
	High	>=11

Table V - The revised Geneva score is used in the Emergency Room for the quick computation of the pre-test probability for pulmonary embolism, as an alternative to the Wells PE score.

Discussion

F Lurie *states that D-dimer is the most frequently used test and many aspects of its utilization are well-known. The issues are a) variability in the diagnostic properties among different assays, b) low positive predictive value, and c) an established cut-off is missing in some populations of patients (pregnant and post-partum, post-surgical, trauma etc.). On the contrary, there is a general consensus that the sensitivity of D-dimer is high, though in literature it ranges from 60% to 96%. Similar to clinical evaluation, use of D-dimer as a single diagnostic tool may result in inadequate management of more than 15% of patients with suspected DVT.* ***A Puskas*** *states that the D-dimer is useful (good sensitivity but low specificity) to rule out DVT only when the Wells probability score is low.* ***G Stansby's*** *opinion is that we don't have to consider D-dimer separately, on the contrary what is required is an algorithm that incorporates a clinical prediction score, D-dimer and imaging. As such D-dimer would usually precede any other decision about ultrasound investigations.* ***F Passariello*** *argues that the reported use of D-Dimer together with the Wells score was validated only in an ambulatory setting.* ***M Patel*** *considers G Stanby's opinion most valid which means clinical scoring, laboratory test and imaging all in combination in case imaging creates a doubt.* ***M Boucelma*** *uses also D-dimer as a help in taking decisions when the clinical probability is mild and no thrombosis is evident in US and or scanner, she writes.*

F Passariello *argues that D-Dimer has no useful value in high-PTP patients. In synthesis, he tells that D-Dimer must be used as a rule-out criterion ONLY in low risk patients. Special bedside D-dimer assays are not so rare nowadays making possible their use in the ER.* ***M Patel*** *summarizes that the most reliable way of detecting DVT is based on 1. Clinical scoring 2. Duplex scanning with or without CT pulmonary angio 3. D-dimer test.* ***F Passariello*** *would like also to add CUS and sP-selectin to be included into a diagnostic algorithms for VTE.* ***M Boucelma's*** *opinion is that concentration of P-selectin and D-dimer after acute DVT may be a predictor of recurrent venous thromboembolism, and P-selectin inhibition promotes resolution better than enoxaparin. This biomarker may be included in thromboembolism algorithm, though almost all laboratories are not organized to measure it, replies* ***F Passariello****. He states that sP-selectin is validated to confirm VTE in high risk (high pretest score) patients, while it has a limited value in low risk ones.* ***S Szarka's*** *algorithm starts from D-dimer. In his practice all patients suspected for VTE receive a D-Dimer test and then based on clinical pre-test probability the patient may or may not get an ultrasound examination.* ***H Schlup*** *informs us that the price of a D-dimer test is 25$ in Brasil and it takes 3 days for the result while a DUS costs 45$ and is quickly available. After the DUS we probably don't need D-dimer but after D-dimer we probably will ask for DUS. In private practice usually the doctor doesn't have time to wait, he argues, thus the question arises why not asking directly for DUS.*

In conclusion almost all discussants agreed with the utility of biomarkers, especially of D-dimer in the diagnostic algorithm of VTE in combination with a clinical probability score and an imaging method (ultrasound and/or CTPA).

Available imaging methods

Ultrasound

TTE

Trans-Thoracic Echocardiography (TTE) can add useful information. Right heart chambers dimensions can increase considerably their diameters in acute PE. The pulmonary artery tension can be non-invasively estimated from right chambers velocimetry and inferior vena cava caliber and pulsatility. In addition, the **Tricuspid Annular Plane Systolic Excursion (TAPSE)** can evaluate the diastolic function of right heart chambers. These observation can help in assessing patients with PE or chronic thromboembolic pulmonary hypertension (**CTEPH**) and can match the corresponding changes in the electrocardiogram, which however are more reliable in chronic pulmonary hypertension (**CPH**).

DUS

Duplex ultrasonography (DUS) is a recognized ultrasound diagnostic tool in vascular diseases and of course in venous pathology. A training period (at least 2 years) is required to prepare a skilled ultrasonographer. Owing to its complexity DUS cannot be described here, thus we refer to any available educational text.

The pulmonary embolism rule-out criteria (PERC rule)
Age < 50 years
Pulse < 100 bpm
Pulse oximetry > 94%
No unilateral leg swelling
No hemoptysis
No surgery or trauma within 4 weeks
No prior DVT or PE
No oral hormone use

Table VI - The pulmonary embolism rule-out criteria (PERC rule) is used in the Emergency Room for the quick exclusion of pulmonary embolism. It works better when associated to the personal feelings of the operator (Gestalt).

CUS

Compression ultrasonography (CUS) may be proficiently learned in <2 hours. It was developed as a quick and simple emergency tool, in order to give reliable results in cases of suspected DVT[29-33]. It requires only a simple BMode scan of groin and popliteal region (2-points ultrasonography), where observation can be extended to the 3rd order confluence of anterior and posterior tibia and peroneal veins. This extension however is debated, because it is a more difficult manoeuvre which requires a longer training period.

Simple BMode scanning is used to look at the saphenous-femoral junction (SFJ) and saphenous-popliteal junction (SPJ), which can just visualize the thrombus inside the lumen, so providing the diagnosis.

A soft compression of the cited veins with the echo probe can show the flexible state of their wall. When the vein is compressible, CUS is negative, when the vein is rigid CUS is positive. In almost all cases compressibility implies patency, while rigidity implies occlusion. In several cases, it's possible to get intermediate results, i.e. partially compressible, which means partial thrombosis or recanalization of a vein.

There are false positive cases, due to tissue sclerosis, because veins are inside a not easy compressible compartment. However, this does not occur in lymph diseases, because generally veins remain compressible even if inside a heavy altered tissue compartment. There

are also false negative cases (thrombosis is elsewhere, i.e thrombus localized above or below the junctions and therefore non affecting junctions compressibility).

The Padua score

Baseline features	Score
Active cancer*	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility †	3
Already known thrombophilic condition‡	3
Recent (>=1 month) trauma and/or surgery	2
Elderly age (>=70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI >=30)	1
Ongoing hormonal treatment	1

Table VII - The Padua score is used for the assessment of VTE risk in in-patients.
Risk assessment model (high risk of VTE: >=4)
**Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months.*
†Bedrest with bathroom privileges (either due to patient's limitations or on physicians order) for at least 3 days.
‡Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

Other difficult cases are the absence of the greater saphenous vein or of the shorter saphenous vein, as normal anatomy is changed.

CUS is a valid tool in proximal lower limb symptomatic DVT, with a sensitivity of 97% and specificity of 98%. In lower limb distal DVT results are conflicting.

When the pre-test probability is high or the clinical suspicion is important and CUS is negative, it is possible to use a second CUS at 1 week. This second look or serial CUS can be used also to monitor the patient (when symptoms persist or increase) or in the post-operative period in patient at high risk.

CUS is a separate exam, not a DUS, though this latter includes compression on veins. In addition, DUS can visualize the echogenicity of the venous thrombus, its adherence to the venous wall and its mobility inside the lumen (floating thrombus). DUS looks also at flow (absent / present) and at its changes during breathing and functional manoeuvres.

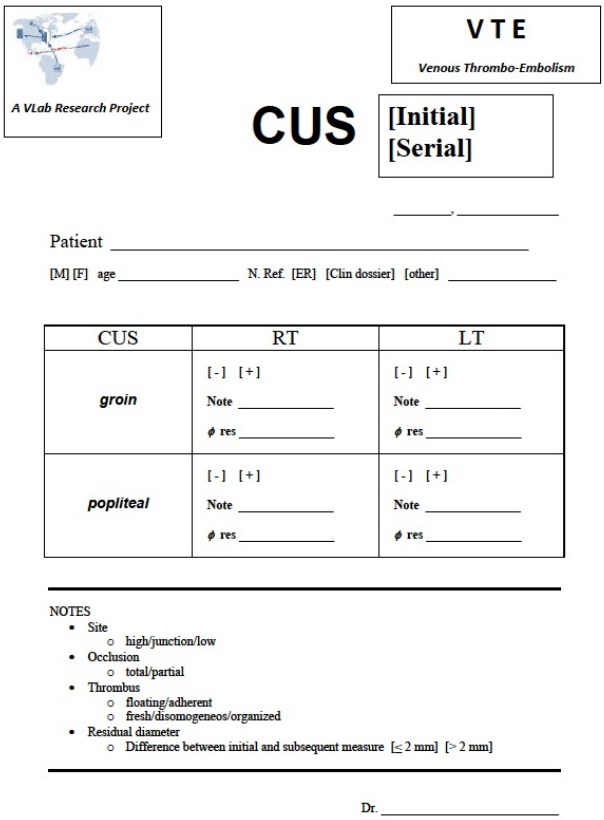


Figure 2 - The VLab CUS form for the Emergency Room

Patients with suspected DVT of the lower limbs are usually investigated with CUS or DUS. The latter approach has a much greater diagnostic capability, as for instance its ability to detect isolated calf vein thrombosis. However, it requires skilled operators and depends on the availability of an experienced ultra-sonographer mainly during the ordinary working hours. A prospective, randomized, multicenter study of consecutive symptomatic outpatients (n=2465) with a first episode of suspected DVT of the lower extremities shows that 2 diagnostic strategies (1. CUS+D-dimer when CUS is normal, 2. whole length DUS) are equivalent when used for the management of symptomatic

outpatients with suspected DVT of the lower extremities. Relevant features of this strategy are simplicity, reproducibility, and broad availability. There is the need to repeat the test within 1 week (serial CUS) in patients with normal findings at presentation and positivity of D-dimer. With DUS strategy color flow is exploited to enhance small vessel visualization, although vein compressibility still constitutes the main diagnostic criterion. The advantage of the DUS approach is the ability to exclude isolated calf DVT, allowing for 1-day low molecular weight heparin (LMWH) treatment of all patients, eventually stopping the therapy in case of negative DUS without any additional testing. Conversely, it needs top-quality ultrasound equipment and experienced operators; therefore, it is often unavailable after hours and during the weekends.

Other imaging techniques

The diagnosis of pulmonary embolism (PE) remains a common challenge confronting physicians in daily clinical practice. PE is considered in the differential diagnosis of many clinical presentations and in a wide variety of clinical settings. **Ventilation-perfusion lung scanning (V/Q)** has been the non-invasive imaging procedure of choice in patients with suspected PE for many years. However, a majority of patients with suspected PE undergoing a ventilation-perfusion scan have a non-diagnostic examination (low or intermediate probability of PE). **The prospective investigation of the pulmonary embolism diagnosis**[34,35] (**PIOPED**) study shows that clinical assessment combined with the ventilation/perfusion scan established the diagnosis or exclusion of pulmonary embolism only for a minority of patients-those with clear and concordant clinical and ventilation/perfusion scan findings. In PIOPED era the gold standard was pulmonary angiography. More recently, the **computed tomographic pulmonary angiography (CTPA)** has been introduced as an alternative non-invasive test. A CTPA provides a clear result (either positive or negative for PE) and possibly an alternative diagnosis to explain the patient's symptoms. Multiple-detectors CTPA have a higher sensitivity for PE as compared with single-detector CTPA. In particular, multiple-detectors CTPA allows better visualization of segmental and subsegmental pulmonary arteries. However, V/Q scintigraphy could have a similar or even higher sensitivity than CTPA in detecting CTEPH as a potential curable cause of pulmonary hypertension[36]. CTPA is now preferred as the first-choice test for PE by both scientific societies and practicing physicians. The increased sensitivity of CTPA may have a downside: the detection of emboli that are so small as to be clinically insignificant.

This phenomenon has been called "**overdiagnosis**", defined as the detection of an abnormality that will never cause symptoms or death[37,38]. Overdiagnosis matters because it can lead to iatrogenic harm. While a clinically non-significant PE is by definition not harmful, treating such an embolism can cause harm (e.g., bleeding from anticoagulation, which can in the worst case be fatal). On the other site of the coin is CTEPH as a consequence of repetitive emboli even if they are small. The judicious balance between these two ends of the spectrum of the disease needs further investigations. For certain patient groups, such as patients with contraindications to iodinated contrast media and young women (possibility of pregnancy) with a low PE-PTP, **magnetic resonance (MRI)** can be considered as a first-choice imaging tool for PE assessment. Recent technical developments have substantially improved the potential of MRI for PE diagnosis[39,40], as the development of short magnets and dedicated whole-body MRI systems together with the dynamic gadolinium enhancement, which allow a comprehensive evaluation of pulmonary embolism and deep venous thrombosis in a single exam. The introduction of parallel imaging has substantially improved the spatial and temporal resolution of pulmonary **MR angiography**. By combining time-resolved pulmonary perfusion MRI with high-resolution pulmonary MRA a sensitivity and specificity of over 90% is achievable, which is comparable to the accuracy of CTPA[41].

The PESI score

Age	+N. of years
Sex Male	+10
History of Cancer	+30
Heart Rate >= 110	+20
Systolic BP <100 mm Hg	+30
Respiratory Rate >= 30	+20
Temperature < 36°C / 96.8°F	+20
Altered Mental Status (Disorientation, lethargy, stupor, coma)	+60
O_2 Saturation <90%	+20

Table VIII - The pulmonary embolism severity index (PESI) is a 11 items score that predicts the outcome at 30 days in pulmonary embolism patients. Each item adds a value to the age of the patient. According to the total, the risk is considered very low <=65), low (66-85), intermediate (86-105), high (106-125), very high (>125)

The sPESI score

Age > 80 years
History of cancer
History of chronic cardiopulmonary disease
Heart rate >= 110
Systolic BP < 100 mm Hg
O_2 saturation < 90%

Table IX- The simplified PESI (sPESI) score uses a reduced set of items than PESI to predict the outcome at 30 days in pulmonary embolism patients. Low risk if all criteria are unsatisfied, high risk even if just one criterion is satisfied.

Discussion

***F Lurie** states that studies increasingly confirm that imaging methods are much less accurate than we think. A Puskas's opinion is that bilateral whole length DUS of the lower extremities (in laying, sitting and sometimes in standing position, including tibia/fibula/ gastrocnemius/soleus veins) has a very good sensitivity and specificity in DVT diagnosis. We perform it in every suspect patient, he says. It takes about 20 minutes but of course the accuracy is operator dependent and every center needs experienced specialists. In his opinion this specialist has to be a clinician (angiologist/cardiologist/ vascular surgeon/internist) rather than a radiologist. **M Patel and F Lurie** agree that it is not possible to look at all possible sources of emboli, so something is always missed. We all can see that occasional CT angiography of the chest shows PE when there is no DVT seen in the lower extremities. Another issue is that the false positive rate of DUS*

in low risk patients is about 4%, but the actual incidence is <1%. If you do ultrasound on all patients, and treat all positives, you uselessly treat at least 3 out of 100 patients. Is this an acceptable rate?-raises the question F Lurie. ***D Casian*** *says that his threshold for DUS is very low. If he has a minimal clinical suspicion of DVT, he performs DUS or at least 2 point CUS (popliteal and common femoral vein). In his institution the decision of the vascular surgeon usually is an empirical one, based on clinical experience.* ***A Puskas*** *emphasizes again that he performs in almost all cases CUS and DUS. This is whole length Duplex including tibia and fibula veins, especially in case of high Wells score. He mentions that his practice is an angiology ambulatory unit and patients come to him usually with leg symptoms.* ***PL Antignani***, ***H Schlup***, ***Z Lazarashvili*** *and* ***G Peruzzi*** *agree all with A Puskas' statement.* ***H Schlup*** *says that the DUS can be done immediately, while the D-dimer in Brasil takes some days. His sonographer is a doctor (not a technician) who does just DUS all the day.* ***Z Lazarashvili*** *states that DUS of the lower limbs is the first option not only for diagnosis of DVT, but also in ER when patient comes with suspicion on PE in combination with echocardiography. Only later it is possible to use other possible tools for diagnosis (D-dimer, CT-angiography, etc.). He thinks it is a right way to prevent repeated embolism.*

The HASBLED score

Hypertension	Uncontrolled, >160 mmHg systolic
Renal disease	Dialysis, transplant, Cr >2.26 mg/dL or >200 µmol/L
Liver disease	Cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal
Stroke history	
Prior major bleeding or predisposition to bleeding	
Labile INR.	Unstable/high INRs, time in therapeutic range <60%
Age > 65	
Medication usage predisposing to bleeding. Antiplatelet agents, NSAIDs	
Alcohol or drug usage history - >= 8 drinks/week	

Table X - The HASBLED score was introduced to evaluate the risk of bleeding in the treatment of atrial fibrillation. The score can be applied also to the treatment of venous thromboembolism. Each item is valued 1 point and the risk is high for a score >= 3.

F Passariello *points out that DUS and the CUS are different examinations and considering CUS as a simple manoeuvre performed during DUS, increases the confusion. He also states that very often it is not possible to find the embolism origin in PE whether one uses DUS or CT or MRI.* ***M Patel*** *thinks that over-treating is acceptable if a repeat DUS is carried out as a serial follow-up exam after one week. Anti-coagulation during that time is safe as complications of anti-coagulation are related mostly to duration. If the follow-up DUS is negative then anticoagulation should be withdrawn, he states.* ***G Stansby*** *replies that making DUS for everyone with suspected DVT is not a very resource efficient service.* ***F Passariello*** *completely disagrees with the great value assigned to DUS as a screening investigation, i.e. applied to every people suspected for VTE. This is an example of bad use of resources, he argues. CUS, D-Dimer and DUS must be used after a selection guided by scores. DUS is not CUS and vice versa, he states. Though he is a DUS expert, he must recognize that CUS in the ER is more useful, because it can be performed by a lot of operators, trained for CUS (1 morning), but not for echo Doppler (2 years). Having a lot of exams for a screening, even if not so precise, catches VTE better than a few precise examinations. In Moldavia, says* ***D Casian***, *DUS with well-trained specialist is available only in large hospitals (usually University or Research Center) and during the working hours. In rural area and small hospitals CUS (usually available 24/24) + clinical scores probably will remain the optimal strategy for DVT diagnosis. In Dr Casian's hospital he investigates suspected DVTs and experiments a low rate of DUS false negative, when the patient is referred by the Vascular Surgeon and not by another specialist.*

There are two weak points in this argumentation, replies ***F Passariello****. First of all what D Casian says can be true for lower limbs DVT, but is undoubtedly false for DVT-PE, as thrombosis can be everywhere and often the source of PE cannot be found, he argues. A consultation for a suspected DVT often is not a very urgent examination. People can wait one day or more for the exam, according to the availability of the specialist (for instance not at work now or in holidays). Try to apply this unavailability to a suspected PE, which can be a very critical disease (must enter or not ICU or coronary unit? must start a systemic thrombolysis ?). Time is a very high cost. F Passariello thinks that an always-available simple CUS can give a much better service than an inconstant DUS service on demand. Finally, he suspects also that D Casian's false negative rate is much greater for DVT-PE than for DVT only. Secondly though he is a Vascular Surgeon, he doesn't think that Vascular Surgeons are the best professional profile to put an indication to DUS for VTE (DVT-PE) patients. Generally Vascular Surgeons are not involved in the use of scores, CUS, DUS, D-Dimer, sP-selectin and so on. The danger is that the indication could be given following common opinions and not what is reported in the literature and the guidelines. VTE patients show a clinical presentation in a range from life-threatening cases (cardiac arrest, acute respiratory failure, hemopthysis) to no relevance ones, with only a few not important symptoms or no one at all.*

A Pieri *comes into the discussion arguing with the followings: PE is normally present (always) when one sees a DVT at any location (Angio CT scan always reveals small PE). Only clinically relevant PE needs hospitalization and rarely fibrinolysys. Fatal PE is fatal! Otherwise full dose subcutaneous Heparin treatment is enough, waiting for a "second degree" diagnosis. We only need to make a "correct" Color Duplex diagnosis. CUS is not a good diagnosis because Doppler investigation is not included and because upper limbs (subclavian DVTs) and distal DVTs are not considered. Distal DVT are often the marker of PE (residual DVT after embolisation). DUS investigation of abdomen can reveal iliac, renal, ovarian, etc. locations of DVT, CUS and probability scores would not be allowed, in his mind, in a great Hospital. CUS could even be DANGEROUS in cases of proximal floating DVT (femoral-iliac)! We have only to decide when a CT scan is needed and when to investigate patients for cancer !! D-Dimer false positive (trauma or surgical patients) give no value to this kind of investigation that must be avoided (obviously in his mind). Only negative D-Dimer tests are useful because they can exclude a recent DVT. By the same ultrasound device we can investigate the*

heart to visualize cardiac chambers, pleural or pericardial effusions. Clinically relevant PE can be diagnosed in few minutes. Color Doppler investigation can also offer alternative diagnosis.

***A Puskas** agrees with A Pieri's point of view regarding the better specificity and sensitivity of DUS and the potential risk of "aggressive" CUS as a cause of thrombus mobilization. **F Passariello** argues with the contrary: great hospitals SHOULD use scores and CUS, while avoiding them causes waste of resources. **D Casian** exemplifies different clinical scenarios (1. No symptoms of DVT + No symptoms of PE, 2. No symptoms of DVT + Symptomatic stable or unstable PE, 3. Symptomatic DVT + No symptoms of PE, 4. Symptomatic DVT + Symptomatic PE). These examples have as starting point mainly an already done diagnosis, while we are instead searching for a diagnosis, replies **F Passariello**. **D Casian** underlines that these clinical scenarios raise two questions: no routine screening for PE in asymptomatic patients and not to look for source of embolism in case of symptomatic PE and asymptomatic legs because patients in any case will be anticoagulated. In Scenario nr 4 D Casian's opinion is that confirmation of PE is required only if patient is hemodynamically unstable, because it will influence the decision to start the thrombolysis. In scenario nr 1 the investigation could be indicated only in high risk group. This could be achieved according to Caprini score, replies **A Puskas**. In scenarios nr 2 and 3 the imaging method will be selected to confirm DVT (DUS) or PE (CT angio) argues D Casian. **C Franceschi** agrees with D Casian's rational algorithm.*

BB Lee's opinion is that better to do PE study BEFORE one starts the anticoagulation based on pragmatic view because de novo PE development despite adequate anticoagulation is one of the indication for IVC filter placement. He also states that PE is NOT one shot episode. So anyone with PE, either hemodynamically stable or not, should have an assessment of 'current' PE status so that it will provide the BASELINE down the road for the future management, he argues. It is especially true for the DVT which is infrequently treated by the patient himself with a premature abandonment after a minimum due period. So proper assessment of PE with CTA at the beginning will provide a huge dividend with much reduced risk of a unique condition known as chronic thromboembolism (CTE) together with CTEPH, which is presumed to be due to recurrent pulmonary embolism-he comments. D Casian in his reply depicts the reality in Moldova: even in big hospitals the trombolysis is not available at all; actually for more than 5 years they have no any thrombolytic agents in their country; they have only one interventional radiology suite (not available 24/24) in their country; zero cava-filters were implanted during the last 5 years; CT-angiography is performed only occasionally due to high cost and low availability (just in private centers) - in his hospital (University Hospital) there was 1 case during the last 10 years.

*A Pieri says that indication of Cava filter is extremely rare nowadays. He states also that CUS is obviously included in DUS and that the first approach to DVT is heparin, then one can investigate for PE. **F Passariello** reminds the details of CUS and DUS (already outlined above in the text) and states that CUS is a separate exam and not a DUS. The latter of course includes compression of veins (everywhere and not only 2 points), but DUS does not consider venous compression as a step of a clinical algorithm. Thus though it uses compressions DUS does not include CUS. **M Schul** says that overutilization of CUS/DUS will be present until definitive guidelines will be established for DVT diagnosis and assessment. In his opinion CTA for PE investigation should be ordered on clinical basis alone. **C Franceschi** writes about plantar veins thrombosis as a possibility and this should be checked because it is rare but exists and can be efficiently assessed by DUS[42]. He also states that most of the time a false positive diagnosis regards the peroneal vein, because it is not easy to compress completely just with the probe. In that case, C Franceschi suggests an interesting and practical tip: a simultaneous additional compression with the free hand and/or the leg elevation more than 45% provides a complete vein collapse, when the vein is free of clot/thrombus.*

***A Puskas** calls for attention regarding the position of the patient during DUS examination which is crucial. For instance for the popliteal vein and below the best position is not in the ventral decubitus, but sitting at the free margin of the examination table, while the foot does not touch the floor. The examination is done from behind the knee and at the medial and lateral margin of the calf, internal malleolus and at the plantar level. In this way the calf is relaxed and the compression is easy to do with the probe and simultaneously with the free hand. Standing is also mandatory because sometime it is really a challenge to discriminate between chronic thrombus with partial reopening and acute recurrence on chronic thrombosis or in case of incomplete acute thrombus. Standing is the only way to detect reflux with provocative manoeuvres in diastole (Paraná). In the case of chronic residual thrombus the color filling is within the remnant/ residual thrombus which is "pierced" by the recanalization (A Puskas calles it the "cavernous" type), whilst in an acute incomplete occlusion the color flow is marginal and visible mainly in systole of the calf (Paraná). It is also true that recanalization can be "marginal" or "parietal" as he called in one of his paper but in this case the diastolic reflux is present at Paraná manoeuvre.*

***A Pieri** argues again in favor of DUS which is the method of choice in his opinion. It is very fast and safe to rule out DVT by complete DUS, he says. DUS also permit a possible differential diagnosis in approximately 90% of the cases with no need to access 3rd degree investigations which, in Italy at least, are much more expensive. **F Lurie** summarizes the discussion until this point as follows: this discussion confirms that the utility of any imaging technique depends on the practice settings, access to treatment options and local standard of care. For example, if thrombolysis is not available and is not a local standard of care all ilio-femoral DVTs will be treated the same as femoro-popliteal DVTs and the value of imaging ileo-caval segment is questionable. In other settings, when the catheter-directed thrombolysis is a standard of care for ilio-femoreal DVT, the ileo-caval imaging is absolutely necessary. **G Stansby** argues that CUS is the minimum and should be widely available and is very good for confirming proximal DVT. A venous specialist to see and investigate all potential DVTs with DUS would be ideal but that isn't the real world in most places, he writes.*

***BB Lee** emphasizes again that all the PE deserve to be clarified together with DVT as a part of VTE investigation when clinically suspicious enough to mandate further laboratory test. Whether the PE is small or large, and/or hemodynamically stable or unstable, the PE is a PE so that it has to be verified with appropriate measurement. Many institutes incorporated CTPA as a first-line imaging study in cases of 'suspected' acute PE. Traditional V/Q scintigraphy is no longer first option unless motion artifact of poor right heart function limits the quality of CTA or CTA is contraindicated due to the allergic reaction to radiographic contrast. The sensitivity and specificity of CTPA for diagnosis of acute PE have been reported to range from 53% to 100% and 67% to 100% respectively varying on the basis of patient selection, extent of thrombus, area of the vasculature imaged, interpretation criteria, and experience of the reader, he states. He also adds that modern MDCT or multi-detector CT (MDCT) scanners are an entirely different ball game in comparison to single-slice CT scanners we all are familiar with.*

The new one is able to deliver the images with sufficient resolution to delineate intraluminal filling defects with a sharp interface with intravascular contrast material. In chronic PE, for instance, it delivers clear evidence of recanalization, webs or flaps, and partial filling defects that form obtuse angles with the vessel wall. So common impressions on the CTA are often for old CT scanners while the new ones are quite different to provide proper differentiation of this unique

pathologic condition, whether acute or chronic, causing both partial and complete intraluminal filling defects in a variety of condition to assess properly, he argues. Regarding the 'asymptomatic' PE, found incidentally during the investigation of DVT or rather VTE he states as follows: I don't know whether this 'asymptomatic' PE should be considered same as so called 'unsuspected' PE but current guidelines from the American College of Chest Physicians clearly recommend same treatment like symptomatic PE in the absence of convincing evidence that anticoagulation can be safely withheld. Of course, I agree that the increasing use of CTA has led to the increased diagnosis of incidental 'asymptomatic' PE and/or small sub segmental PE (SSPE) which is not clear for its clinical relevance and the optimal therapy for SSPE is still on debating. Indeed, a single sub segmental defect probably does not have the same clinical relevance as a single segmental or lobar PE or multiple sub segmental PE. But, most experts agree such SSPE should be treated like symptomatic or large lobar PE especially when the risk factors for VTE persist, and there is concomitant DVT. Of course, the duration of anticoagulation in such cases should be individualized. Such sophisticated/advanced strategy would have not been possible without advanced MDCT and we would have not been able to reach this far in terms of future long term outcome.

He also says that in some countries, like China, the DUS is more expensive than CTA. In US the examination is heavily affected by the insurance payment system so that doctors simply endorse the DVT investigation algorithm based on DUS with not much appreciation on the CUS though its value has been acknowledged, not inferior to DUS. Nevertheless, CUS has been known for limited utility for the detection of isolated iliac vein thrombosis -failure to identify such thrombi may prove fatal-, and less sensitive for the detection of isolated calf vein thrombosis in symptomatic patients. Also, non-compressibility limited to the common femoral vein often does not represent venous thrombosis in patients with extensive pelvic disease (e.g., neoplasm or radiation). Indeed, when clinical suspicion is low or when circumstances favor a falsely positive CUS, he has no doubt a more aggressive diagnostic approach is necessary.

In such case, alternative approaches such as MRV/CTV would be needed together with standard DUS to confirm or exclude the diagnosis in his opinion. In spite of such disadvantages, many European physicians seem to use CUS as the initial diagnostic test for patients with symptoms or signs that suggest DVT based on well documented safety, accuracy and availability. And further they rely on negative CUS finding alone for decision to withhold anticoagulants on the day of presentation and again 5 to 7 days later. Indeed, combining D-dimer tests or clinical probability- low or moderate - with a single negative CUS exam seems to be safe for management of 'suspected' DVT among the patients. But in the U.S., CUS has been faded away from active leading role.

***G Stansby** replies with the statement that if the patient has a DVT and will be anticoagulated anyway a CTPA is not indicated if there is no clinical suspicion of PE. As a conclusion **BB Lee** emphasizes again that he does agree categorically with 'NO routine screening for PE on every DVT. But, when in doubt with a high suspicion, he would not hesitate to go beyond basic assessments of PE including Wells PE score and proceed with further solid/substantial assessment including the CTPA if feasible. That is my first message on the CTA involved to VTE assessment, he says. Second, he would like to caution on the statement: "Confirmation of PE is required only if patient is hemodynamically unstable". More we learned on the pathogenesis of CTEPH through the last decade, more we were surprised with its intimate relationship with chronic thromboembolism (CTE). So we know now clearly that CTEPH is presumed to be due to recurrent pulmonary embolism until proven otherwise. So he strongly advocates all the PEs, either hemodynamically stable or unstable, deserved to have proper assessment of the status of 'proven/confirmed' PE as the BASELINE evaluation for the future management. Indeed, appropriate assessment of the PE with CTA at the beginning will guide/ provide proper strategy to tackle with such unique condition of CTE/CTEPH. He strongly advocates the CTA on the management point of view as well but, ONLY when one have enough knowledge to imply its findings to proper treatment strategy to retrieve its benefit in maximum. Casual practice/commitment to CTA/CTPA without appropriate disposition should be discouraged.*

*In PE diagnostics CT angio has an edge over MR angio (**M Patel**, **N Labropoulos**). **M Patel** raises the problem of transportation of PE suspect patient. Transportation even within the hospital has been shown to be a risk factor, he continues. In fact many accidents occur while patients are transported. Unstable patients have to be diagnosed with whatever best the hospital has. Unfortunately treating such a patient in a place where diagnostic facilities are not optimum can lead to litigation. So transportation is required for diagnosis and be as safe as possible, he concludes. **G Stansby** agrees with him and says that for suspected PE patients usually it is best to start heparin immediately. If investigations (CTPA) are delayed then at least they are already covered by therapy. Another point for those without CTPA, V/Q spect is very promising as an alternative, he adds.*

*As regard to treatment options and for more aggressive thrombolysis indications **BB Lee** states that their standing policy is 'thrombolysis of any term, preferably PMT (percutaneous mechanical thrombectomy) unless otherwise indicated/contraindicated'. Even for the thrombus more than two weeks old, we do bend backward to try whenever the patient should give proper consent, he adds. Indeed, the 'limited' experience shows such flexible implication even to chronic thrombus is worthy with consideration of stenting, he continues. His personal feeling is that 'still better than nothing' as a believer of Tony Comerota's crusade despite persistently adamant ACP guideline. Regarding subsegmental PE (SSPE) he writes that the cumulative risks for VTE as well as death are in same ranges among the SSPE and proximal PE groups so that all PE, including SSPE, should be considered for anticoagulant therapy since its benefits outweigh the risks of complications. Hence, most of leading institutes advocate anticoagulant therapy to the symptomatic SSPE as long as there is no absolute contraindication or high risk factor of bleeding. We do have clear evidence to verify the effectiveness and safety of anticoagulation therapy versus no intervention on SSPE based on randomized controlled trial, he adds. Nevertheless, he mentions, that advanced CTPA revolutionized the diagnosis of PE including the smaller emboli in subsegmental pulmonary arteries so that it is able to diagnose relatively unimportant emboli for which the risks of anticoagulant therapy may not be warranted under the claim for persistent risk factors for recurrent VTE!*

*In his practice **M Patel** has very strict indications for use of an IVC filter. He uses it only when there is an absolute contraindication for anticoagulation. CTPA in India costs about USD 150-200 on a 64 or 128 slice CT scanner. We have to get maximum yield out of the test we order, he claims. For now, CTEPH will be a diagnosis based on high index of clinical suspicion and the scoring systems we are discussing on this board will throw more light on what should become standard procedure, he concludes. BB Lee comments that if the situation is serious enough to start the anticoagulation, it would be better to do PE study BEFORE starting the anticoagulation based on pragmatic view, because one of major indication for IVC filter placement is "de novo" PE development despite adequate anticoagulation! However, many, though mostly anecdotal, PEs were already there before one starts the anticoagulation so that belatedly found PE does NOT always means "de novo" as the outcome of anticoagulant failure to justify IVC filter, which was designed to reduce only the risk of 'fatal' PE and NOT for all the minor blood clots which continue to travel, he writes.*

F Passariello** introduces the discussion about a recently published clinical case of fatal endovascular thrombectomy[43]. **N

Labropoulos *comments that there are several methods for performing Pharmaco-Mechanical-Thrombectomy (PMT) in patients with PE and the presented case was not a real mechanical one.* ***M Simka*** *adds that this case was not a mechano-chemical but only chemical thrombectomy with the addition of an old-fashioned mechanical component. Currently, a real mechanical thrombectomy can be used for the treatment of critically-ill PE patients as a life-saving therapy. In addition, patients with sub-massive PE can also be managed in this way, but at the moment it is not a routine procedure in such cases - perhaps with more evidence it will be used more often, he argues.* ***F Passariello*** *completely agrees with M Simka about the old fashioned method used in the presented case. In addition, the rotational manoeuvre in the video lasts only a while, has no downstream protection and is not at first sight able to insure a result, comments. Actually PMT is not considered yet a primary tool in a very severe PE and guidelines should plan a more aggressive intervention when the clinical case requires it, he concludes.*

Algorithms

The British National Institute for Health and Care Excellence[44] (NICE) developed two important algorithms, the first for DVT, the latter for PE. Here we will take them just as an example of all the other existing algorhitms. Both are drawn for the ER or for a structure able to insure very quick evaluations. This is an important point, because the Wells DVT score is used in an ER environment, other than ambulatorial.

Both algorithms consider a **short term(4h) ultrasound availability**. DUS is not cited at all, while the term **proximal ultrasound** appears as a substitute for CUS.

In this regard several legitimate questions arise:

-is the proximal ultrasound term an analogous for a proximal CUS, i.e. performed only at the SFJ ?

-Is there an evidence-based medicine (EBM) available reference for the proximal CUS ?

-Is the proximal CUS documented to have the same sensitivity of a complete CUS.

-In addition, when time needed to get an ultrasound investigation is >4h and reaches 1 day or more, why not having a complete DUS instead of a CUS ? The same question holds if a repeated examination is needed one week later.

The reported flow charts are clear: **always perform a score**, there is no doubt about. However, scores are different for DVT and PE, though they are both Wells score. **Why Wells PE and not Geneva for PE ? Wells PE is more operator dependent**, because one of the items is subjective, exactly where the score asks if there is an alternative diagnosis. Geneva instead is operator independent and more repeatable. Interestingly, an interim treatment with heparin is always planned when investigations are not soon available. This feature means that NICE algorithms can be regarded as mixed ones, i.e. **diagnostic + therapeutic**. It seems that for the more urgent and life-threatening cases the diagnosis must be mixed with the therapy.

The PE NICE algorithm plans a reduced time threshold of 1h instead of 4h in order to choose between ultrasound and D-Dimer and introduces also CTA between diagnostic tools. In addition, the PE flow chart is **graphically redundant**, thus it could be **simplified** becoming more readable, but leaving the content unchanged.

Another last observation deals with the choice between these algorithms and the other ones we saw for the outpatients. In simple words, outpatients flow-charts should be modified to allow exiting with the urgent need of shortening the procedures, i.e. **sending the patient from the ambulatory to the hospital or to the ER**.

Conclusions

At the end of the discussion, the Moderator **F Passariello** tries to resume the still unclear and open points.

There are **two great approaches** in VTE diagnosis:

A. **The imaging techniques** are constituted in general by an anatomic and hemodynamic point of view, the detection of thrombosis being based definitely on its visibility In this group also the pressure evaluation is included (an endo-venous invasive measurement as well as a non-invasive one), as it deals with a mixed anatomical/ hemodynamic context. Examples in this group are: CUS, Duplex, phlebography, pulmonary angiography, CTA, MRA, V/Q scintigraphy, endo-venous catheter pressure measurement, non-invasive pressure measurements, etc.

B. **The statistical tools** include the scores and the biomarkers assays and clarify if thrombosis exists or not, but do not say nothing about its anatomical localization Examples are Wells (DVT and PE) scores, revised Geneva, PERC rule, D-Dimer, sP-selectin.

The contra-opposition is evident. The fans of the imaging methods will look with suspect at scores and biomarkers, asking instead "where" thrombosis is located and which are its features. On the other side, the fans of the statistical tools will criticise the negative findings of the imaging techniques, because very often thrombosis hides itself and it is very difficult to find it: if you are not able to see thrombosis, it doesn't mean that it is not there.

In addition, there are **two great styles** in VTE diagnosis:

a. **the expert opinion** which is more near to the clinicians' mind, with all the criticism which can be moved to it. Clinical judgements like the "Gestalt" associated to the PERC rule are included in this group. Also DUS (with the clinical and instrumental intuition associated to the use of

the "***III Chakra* Eye**" constituted by the ultrasound probe) gives the opportunity of expressing an expert opinion.

b. **The standard forms and procedures of the algorithms** pertain instead to another style, very near to EBM Medicine, which tries to limit as much as possible the role of the expert opinion in medical procedures.

Acknowledgements

The VTE_Risk Vasculab Debate was organized by the Vasculab List as an Online Debate. We thank all the participants for their contribute and especially for their active role: Pier Luigi Antignani, Benedetto Bernardo, Malika Boucelma, Victor Manuel Canata, Dumitru Casian, Tom Eaton, Khalil Fattahi, Francesco Ferrara, Carmine Finelli, Claude Franceschi, SB Gogia, Mitchel P. Goldman, Kuntelia, Nicos Labropoulos, Christopher R Lattimer, Zaza Lazarashvili, Byung Boong Lee, Fedor Lurie, Wademar Lech Olszewski, John Opie, Fausto Passariello, Malay Patel, Giampiero Peruzzi, Alessandro Pieri, Norma Poli, Attila Puskas, Cestmir Recek, Steve Szarka, Heraldo Schlup, Marlin Schul, Marian Simka, Gerard Stansby, Roy Varghese.

Finally, we thank Mrs. Iolanda Palma for her organizational efforts.

References

1) Haeger K. Problems of acute deep venous thrombosis. II. Mobilization and discharge of the patient. Angiology 1969;20:280-6.

2) Hull R, Hirsh J, Sackett DL, Stoddart G. Cost effectiveness of clinical diagnosis, venography, and non-invasive testing in patients with symptomatic deep-vein thrombosis. N Engl J Med 1981;304:1561-7. DOI: 10.1056/NEJM198106253042602

3) Oudega R, Moons KG, Hoes AW. Limited value of patient history and physical examination in diagnosing deep vein thrombosis in primary care. Fam Pract 2005;22:86-91. http://fampra.oxfordjournals.org/content/22/1/86.long DOI: 10.1093/fampra/cmh718

4) Anand SS, Wells PS, Hunt D, Brill-Edwards P, Cook D, Ginsberg JS. Does this patient have deep vein thrombosis ? JAMA 1998;279:1094-9. http://jama.jamanetwork.com/article.aspx?articleid=187418

5) Wells PS, Anderson DR, Bormanis J et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997;350:1795-1798.

6) Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J. et al. Evaluation of D-Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis. N Engl J Med 2003; 349:1227-1235September 25, 2003 DOI: 10.1056/NEJMoa023153

7) Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. ThrombHaemost 2000;83:416.420.

8) Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144:165-171.

9) Penaloza A, Verschuren F, Dambrine S, Zech F, Thys F, Roy PM. Performance of the Pulmonary Embolism Rule-out Criteria (the PERC rule) combined with low clinical probability in high prevalence population. Thrombosis Research 129 (2012) e189#e193. Available at the address http://www.thrombosisresearch.com/article/S0049-3848(12)00064-3/abstract at the date of Feb 8, 2017. 2012 DOI: 10.1016/j.thromres.2012.02.016

10) Schwartz DT. Problems With PERC. Available at the address http://www.annemergmed.com/article/S0196-0644(10)00487-7/fulltext at the date of Feb 8, 2017. DOI: 10.1016/j.annemergmed.2010.04.032

11) Kline JA. More on the PERC Rule. Available at the address http://www.annemergmed.com/article/S0196-0644(11)01441-7/fulltext at the date of Feb 8, 2017. DOI: 10.1016/j.annemergmed.2011.07.041

12) Hugli O, Righini M, Le Gal G, Roy PM, Sanchez O, Verschuren F, Meyer G, Bounameaux H, Aujesky D. The pulmonary embolism rule-out criteria (PERC) rule does not safely exclude pulmonary embolism. J Thromb Haemost 2011; 9: 300-4. Available at the address http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2010.04147.x/epdf at the date of Feb 8, 2017. DOI: 10.1111/j.1538-7836.2010.04147.x

13) Caprini JA. Risk assessment as a guide to thrombosis prophylaxis. Curr Opin Pulm Med. 2010 Sep;16(5):448-52. DOI: 10.1097/MCP.0b013e32833c3d3e.

14) Barbar S, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 2010;8:2450-7.

15) Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005 Oct 15;172(8)

16) Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov;138(5):1093-100

17) Tiganas D. Diagnostic value of the clinical probability score of deep venous thrombosis in the elderly . (French) La revue de médecine interne 26 (2005) 93-937. DOI: 10.1016/j.revmed.2005.08.010

18) The VLAB Geneva Form. Available at the address http://www.vasculab.it/VTE/Geneva.htm at the date of Feb 8, 2017.

19) Mousa AM, Broce M, Gill G, Kali M, Yacoub M, AbuRahma AF. Appropriate Use of d-Dimer Testing Can Minimize Over-Utilization of Venous Duplex Ultrasound in a Contemporary High-Volume Hospital. Ann Vasc Surg 2015;29:311-317. DOI: 10.1016/j.avsg.2014.07.032

20) Thachil J, Fitzmaurice DA, Toh CH. Appropriate Use of D-dimer in Hospital Patients. The American Journal of Medicine (2010) 123, 17-1.

21) Brotman DJ, Segal JB, Jani JT, et al. Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism. Am J Med. 2003;114:276-282. DOI: 10.1016/S0002-9343(02)01520-6.

22) Larsen TB, Stoffersen E, Christensen CS, et al. Validity of D-dimer tests in the diagnosis of deep vein thrombosis: a prospective comparative study of three quantitative assays. J Intern Med. 2002;252:36-40.

23) Pulivarthi S, Gurram MK. Effectiveness of D-Dimer as a Screening Test for Venous Thromboembolism: An Update. N Am J Med Sci. 2014 Oct; 6(10): 491#499. DOI: 10.4103/1947-2714.143278

24) Vandy FC, Stabler C, Eliassen AM, Hawley AE, Guire KE, Myers DD, Henke PH and Wakefield TW. Soluble P-selectin for the diagnosis of lower extremity deep venous thrombosis. JVS. 2013;April:117-25. DOI: 10.1016/j.jvsv.2012.09.001

25) Gremmel T, Ay C, Seidinger D, Pabinger I, Panzer S, Koppensteiner R. Soluble p-selectin, D-dimer, and high-sensitivity C-reactive protein after acute deep vein thrombosis of the lower limb. JVS. 2011;54(6 Supplement): 48S-55S. DOI: 10.1016/j.jvs.2011.05.097

26) Passariello F. La cascata dell'ossigeno al letto del paziente. [Bedside oxygen cascade]. Seminar. Napoli, Dec 16, 2014. DOI: 10.24019/2014.BO2C.

27) Passariello F. La cascata dell'ossigeno al letto del paziente. [Bedside oxygen cascade]. Presentation to the Meeting *Insufficienza respiratoria acuta su cronica. Nuovi modelli assistenziali dall'ospedale al territorio*. Napoli, Jun 5, 2015.

28) Passariello F, Angelini V, Bellinfante E, Curcio I, Helzel V. Stima del rapporto Ventilazione-Perfusione nel paziente critico con insufficienza respiratoria. [Estimate of the Ventilation-Perfusion ratio in the critical patient with respiratory failure]. Presentation to the X National Meeting of SIMEU (*Italian Society of Emergency and Urgence Medicine*. Napoli, Nov 18-20, 2016.

29) Cogo, A., Lensing, A.W.A., Koopman, M.W.M., Piovella, F., Siragusa, S., Wells, P.S., Villalta, S., (...), Prandoni, P. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: Prospective cohort study . (1998) British Medical Journal, 316 (7124), pp. 17-20.

30) Bernardi E et al. Extended Versus Rapid Analysis of the Leg Vein System: a Multicenter Ultrasound Study (The ERASMUS Study) - An Interim Analysis. Pathophysiol Haemost Thromb 2003; 33 (5-6), pp. 314-318.

31) Bernardi et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: A randomized controlled trial. JAMA 2008; 300 (14):1653-1659.

32) VLAB-CUS form (Italian). Available at the address http://www.vasculab.it/VTE/CUS_form.htm at the date of Feb 8, 2017.

33) VLAB-CUS form (English). Available at the address http://www.vasculab.it/VTE/CUS_form_en.htm at the date of Feb 8, 2017.

34) Worsley DF, Atavi A. Comprehensive analysis of the results of the PIOPED Study. J Nucl Med. 1995;36:2380-2387.

35) The PIOPED Investigators. Value of the Ventilation/ Perfusion Scan in Acute Pulmonary Embolism JAMA 1990;263:2753-2759.

36) He J, Fang W, Lv B, He JG, Xiong CM, Liu ZH, He ZX. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. Nucl Med Commun. 2012 May;33(5):459-63. https://www.ncbi.nlm.nih.gov/pubmed/22262242 at the date of Feb 8, 2017.DOI: 10.1097/MNM.0b013e32835085d9.

37) Hutchinson BD, Navin P, Marom EM, Truong MT, Bruzzi JF. Overdiagnosis of Pulmonary Embolism by Pulmonary CT Angiography. AJR Am J Roentgenol. 2015 Aug;205(2):271-7. DOI: 10.2214/AJR.14.13938.

38) Granovetter M. CTPA use reignites debate on overdiagnosis. The lancet Respiratory Medicine. 2013;1(6):436. DOI: 10.1016/S2213-2600(13)70168-1.

39) Hochhegger B, Ley-Zaporozhan J, Marchiori E, Irion K, Soares Souza A, Jr, Moreira J, Kauczor H U, and Ley S. Magnetic resonance imaging findings in acute pulmonary embolism. Br J Radiol. 2011 Mar; 84(999): 282#287. DOI: 10.1259/bjr/26121475

40) Revel MP, Sanchez O, Couchon S, Planquette B, Hernigou A, Niarra R, Meyer G, Chatellier G. Diagnostic accuracy of magnetic resonance imaging for an acute pulmonary embolism: results of the 'IRM-EP' study. J Thromb Haemost. 2012 May;10(5):743-50. DOI: 10.1111/j.1538-7836.2012.04652.x.

41) Schiebler ML, Nagle SK, François CJ, Repplinger MD, Hamedani AG, Vigen KK, Yarlagadda R, Grist TM, Reeder SB. Effectiveness of MR angiography for the primary diagnosis of acute pulmonary embolism: clinical outcomes at 3 months and 1 year. J Magn Reson Imaging. 2013 Oct;38(4):914-25. DOI: 10.1002/jmri.24057. Epub 2013 Apr 1.

42) Franceschi C. Thrombophlebite des veines plantaires. Actualités Vasculaires Internationales. 1997;47:29-39.

43) Oguzhan A. Percutaneous Rotational Pulmonary Thrombectomy. Images in Clinical Medicine. N Engl J Med 374:e1, January 7, 2016. Available at the address http://www.nejm.org/doi/full/10.1056/NEJMicm1415847?query=emergency-medicine at the date of Feb 08, 2017. DOI: 10.1056/NEJMicm1415847.

44) The National Institute for Health and Care Excellence (NICE). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. https://www.nice.org.uk/guidance/cg144

REPORTS VASCULAB DEBATES

A stepwise daily guide to the KTS Vasculab Debate

BB Lee[1]

[1]Professor of Surgery and Director, Center for the Lymphedema and Vascular Malformations, George Washington University, Washington DC, USA Adjunct Professor of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA Visiting Professor of Surgery, Johns Hopkins University School of Medicine, U.S.A. Emeritus Professor of Surgery, Georgetown University, Washington DC, USA

KTrenaunay Vasculab Debate, held on the Internet, Vasculab List, on May 1-21, 2016. (unmoderated session: May 22-28, 2016.). Discussant: Byung Boong Lee; Moderator: Fausto Passariello; Panel Experts: Miguel Angel Amore, Iris Baumgartner, NingFei Liu, Jovan Markovic, Raul Mattassi, Kurosh Parsi, Massimo Vaghi.
submitted: Mar 29, 2017, accepted: Mar 30, 2017, EPub Ahead of Print: Mar 31, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.15 - Corresponding author: Prof. Byung Boong Lee, bblee38@comcast.net

Abstract This paper gathers the suggestions of Prof. BB Lee, the Discussant of the Klippel-Trenaunay Debate, which came up daily beside the participants to help and clarify the issues which showed up during the Debate. The suggestions were provided as letters at each starting point of the Debate and as personalized answers to specific questions.

Keywords Klippel-Trenaunay syndrome; congenital vascular malformations; venous malformations; lymphatic malformations; capillary malformations; AV malformation; Parkes-Weber Syndrome; Hamburg classification; Hemolymphatic malformation; 'Extratruncular and Truncular' type

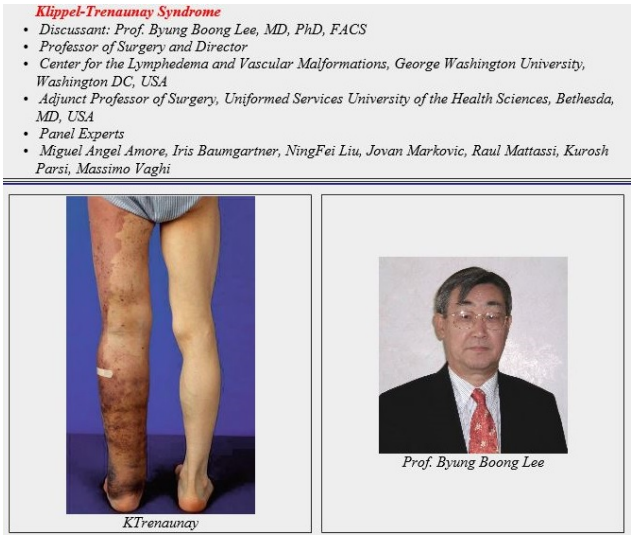


Figure 1 - The KTrenaunay webpage.
DOI: 10.24019/2016.KTrenaunay

Introduction - May 1

Dear Vasculab subscribers,

It is a great privilege for me to share our hard-earned knowledge not only on the Klippel-Trenaunay syndrome (KTS) but the congenital vascular malformations (CVMs) across the board through Vasculab.

I would like to thank first to Dr. Fausto Passariello, Moderator of this unique group/Vasculab, to giving us, myself and invited panelists, for this opportunity to present/discuss various issues involved to KTS despite the majority of this group/members has more interests on other popular venous issues.

Indeed, the major issue of KTS is venous disorders since various venous malformations (VMs) (e.g. marginal vein; femoral vein hypoplasia; iliac vein aplasia) are heavily engaged to such unique condition together with lymphatic malformations (LMs). But not many of phlebology

practitioners seem to be keenly aware how close their daily practice is to this potential risk, and inadvertently stepped in the middle of mine field of CVMs with surprise.

So we would like to support/guide you to get through this mine field, and further to show you how to defuse the mine safely if you wish. Hence, on behalf of the panel discussants, we wish you to bring up any issue, not only of the KTS but also all other CVMs so that we could share our humble experiences with you through this unique opportunity for the next three week period.

As Moderator Fausto already posted, we will arbitrarily divide three week period assigned for KTS to assign one topic for a week for convenience sake:

Topics in KTS Debate

- 1. Definition & Classification-anatomy, embryology, patho-physiology, hemodynamics, and genetics
- 2. Diagnostic Strategy including differential diagnosis
- 3. Management Strategy: Medical, endovascular and surgical management and its complications

For this unique group of Vasculab, we invited SEVEN experts on many different issues involved to KTS as our panelists: Drs. *Iris Baumgartner (Switzerland), NingFei Liu (China), Jovan Markovic (USA), Raul Mattassi (Italy), Kurosh Parsi (Australia), Miguel Amore(Argentina) and Massimo Vaghi (Italy).*

Indeed, we intentionally selected/invited only 7 among the colleagues with quite diversified background as well as specialty so that the discussion will become livelier. I am sure many of you know them well through their publications through the consensuses as well as the handbooks in this unique field of CVM. But I will make a brief introduction on seven stars.

Mme Iris Baumgartner of Bern Univ who is not only big chair of huge angiology department but also de facto leader to organizing the CVM session to set a new trend in Europe through Charing X Symposium every year. Currently, Iris works closely with Prof. Raul Mattassi and other senior experts of CVMs to strengthen her fantastic multidisciplinary team.

Mme NingFei Liu is current president of ISL (International Society of Lymphology) but known more as tough(?) plastic surgeon in Shanghai to lead a huge group/ department devoted to the lymphedema. Indeed, she is one of few lymphatic reconstruction surgeons in the world we all trust to providing reliable data. Besides, her pioneering work on MR lymphangiography to establish as a clinical tool is legendary.

Massimo Vaghi is rather better known for his enormous capacity/knowledge as an editor through 'Atlas of CVM and Hemangioma' he organized with Raul Mattassi. Now, he took over such prestigious Garbagnate program of CVM, Raul and Prof. Belov established many decades ago. He is a real expert to organize the group to lead the consensus and indeed, without his initiation/help, the IUA-ISVI Consensus for Vascular Anomaly many of you are familiar with would have not been completed.

Kurosh Parsi is a world renown dermatologic surgeon from Sidney, Australia as you all know, specialized in CVMs and hemangioma with enormous clinical and research background as well. I had a special privilege to take advantage of him as my right arm partner whenever I had to organize any big CVM project through years since he is a genuine perfectionist. He is now a vice president of IUP and will organize IUP World Congress in Melbourne in 2018 and would become de facto leader of the society with no doubt.

Jovan Markovic of Duke University is, as I teased, my most favorite young activist(?) with full of passion and enthusiasm, working with his chairwoman Cynthia Shortell as her right arm to lead famous CVM Center /program of Duke Univ. Jovan is the only person I envy most what Cinny has and I steal his experts especially his fresh idea whenever I have a chance.

Miguel Amore of Univ of Buenos Aires is one of few jewels I found among Latin American colleagues and I am trying to engage more actively in these days through a few joint projects with him. Miguel is a disciple of famous Prof. Ciucci and has simply fascinating cadaver lab no one I know of can match, with enormous data I try to introduce to Anglophone society now. He is currently works with his mentor, Cristobal Papendieck as future leader of CVM as well as lymphology field in Latin America. Indeed, Miguel is the only one young executive board member of ISL if I know correct as only hope for new young blood transfusion ISL needs badly.

Lastly, Raul Mattassi, my life time partner, would not need any introduction to make it redundant but Raul is one of legendary trio together with Dirk Loose and the late Prof. Stefan Belov to establish Hamburg Classification. Indeed, when I got the first 1 million US dollar grant from SamSung Conglomerate back in 1994 as the seed money(?) to organize CVM Center -as the price/compensation to organize American surgery program/system for Korean people through SamSung Medical Center as a joint project of SungKyunKwan Univ/Johns Hopkins Univ-, the first thing I requested was to travel to visit/meet this trio! Since then, Raul has remained as my loyal comrade with unlimited support for the last three decades.

So, we encourage Vasculab members to bring any question directed to any of the panelists if they would.

Indeed, we welcome any questions, requests, and opinions from the Members, including clinical cases.

Definition - May 1-8, 2016

We all agree that name-based eponyms like 'Klippel-Trenaunay Syndrome' or 'Parkes-Weber Syndrome' gave us a tremendous contribution to understand the bizarre nature of congenital vascular malformation (CVM) through the last century. Indeed, before the modern technology became available to identify complex nature of the CVMs involved, two French physicians, Maurice Klippel and Paul Trenaunay (1900) documented this unique condition for the first time ONLY based on available clinical findings/observation: port wine stain (capillary malformations) and soft tissue and bone hypertrophy, and atypical, mostly lateral varicosity, known as famous clinical triad of KTS. 'Klippel-Trenaunay Syndrome (KTS)' has become a hall mark of CVMs through the last century; it is still most popular 'name based' nosology among many similar syndrome-based descriptions of complicated birth defects involving the circulation system. However, such syndrome-based description has generated substantial confusion because name-based terminology as a "syndrome" *failed to differentiate various anatomo-clinical pictures with a proper definition of pathogenic role of the vascular abnormality, of its evaluation, and of therapeutic possibilities* as correctly pointed by Prof. E. Malan (1974). KTS, for example, failed to accommodate the lymphatic malformation (LM) condition which is an essential CVM component of KTS its initial document as well. And this LM condition was subsequently added to venous malformation (VM) and capillary malformation (CM) to complete its classical description as a syndrome. Besides, substantial confusion on the definition of KTS from the outset still remains with argument on vascular malformation components of the KTS, claiming for extending its vascular malformation component to AV malformation (AVM) as an extra component in addition to the classical triad of the CM, VM, and LM, despite orthodoxy interpretation of this condition as 'Parkes-Weber Syndrome (PWS). Indeed, as Prof. Raul Mattassi raised the questions on KTS versus PWS through previous workshop for the consensus we already published, there are quite a few questions remained to be answered for the further clearance;

KTS definition issues

- Only lower limbs or also upper one?
- Also other sites (head, thorax, buttocks.)?
- What about "incomplete cases": only 2 signs of the triad (no nevus, no limb overgrowth, no visible dysplastic veins)?
- Is lymphatic involvement mandatory?
- What about AV malformation without overgrowth or nevus?

However, we consider the definition of KTS by Mulliken et al (2005) as "A capillary-lymphatic-venous malformation associated with soft tissue/skeletal hypertrophy, usually to one or more limbs and sometimes the trunk" will be the most accurate interpretation so far. Therefore, previously crucial role of such name-based eponyms/ classification became obsolete now for the understanding of such complex nature of the CVMs, failing to meet the mandate as a new classification for contemporary concept of the CVMs and became the symbol of the old concept with the historical merit for the 'angiodyplasia' era. Although the old concept based on a name-based terminology still remains a significant source of confusion, a new concept based on the Hamburg classification cleared unwanted confusion generated by old concept and identified the vascular malformation components of KTS as a Hemolymphatic Malformation (HLM), providing proper etio-anatomo-pathophysiology of each CVM component to clear the inherent confusion. When the HLM is consisted of VM and LM in addition to CM, it would be interpreted as CVM component of KTS; when the HLM has AVM as one more vascular malformation component in addition to VM and LM, this condition is compatible to the PWS. Notwithstanding, it is still noteworthy to understand the exact nature of so called KTS because this unique syndrome represents a combined condition of CVMs as primary lesions and various abnormal conditions in the soft tissue, bone and/or varicose veins as 'secondary phenomena/ outcome of CVMs' in addition to defective development of other tissues/organs as well. I therefore, do NOT advocate total removal of good old term, KTS from our essential armamentarium to fight the CVMs but claim its 'discriminating' use. The term KTS per se is nothing wrong! Indeed, it accomplished wonderful mission through the last century, and we still need it to back up the current term whenever needed (e.g. easy start to communicate on the CVM issues with lay persons). I only wish to warn its *indiscriminating use would do more harm than good* since its critical role for the contemporary management of the CVMs is over. Such useless argument along the definition of various CVMs with name-based eponyms is futile for the modern concept, and discriminating use of this old term KTS versus PWS is advised.

Diagnosis - May 8-16, 2016

We spent one full week, enough time to touch many critical issues involved to Definition and Classification. Hope it helped you to clear much confusion if not all on the definition of KTS. Since such name-based eponyms always carry inherent confusion including KTS, we adopted a new name/classification for the condition as 'hemolymphatic malformation (HLM)' as one of combined form of the CVMs.

We once again uphold the general consensus on how to define inclusion as well as exclusion criteria for KTS

and indiscriminating use of this name based eponym was emphatically discouraged. Based on what we discussed through the week, we would like to proceed to the second phase for the diagnostic evaluation so that we could get to the final phase of the management a week later.

The diagnosis of this mixed bag of worms/CVMs is however, not so simple in comparison to one single condition of CVM as 'independent' lesion. But it is not complicated as a rocket science and you could reach the goal based on simple mathematic approach on each CVM component involved to KTS.

As discussed through the last week, we concur the majority of CVM specialists to agree that KTS should have THREE basic CVM components, that is, VM and LM as basic CVM components, and preferably CM as its third CVM. Indeed, we infrequently do bend backward to accommodating only two rather than all three components as KTS. Besides, we feel strong that additional findings along musculoskeletal as well as cutaneous-subcutaneous system, mostly as the secondary phenomena caused by their primary (CVM) lesions, would strengthen the diagnosis of KTS more although they are non-essential further to Gastrointestinal/Genitourinary findings.

Nevertheless, one crucial problem involved to KTS is 'VM and LM' present in TWO entirely different conditions, that is 'Extratruncular and Truncular' type in various combinations among four of them: extratruncular VM & LM and truncular VM & LM. All four conditions have completely different behavior as well as different prognosis due to their different embryological characteristics, which is extremely important to the clinicians who manage.

The 'extratruncular' VM/LM represents the group of birth defects as the outcome of developmental arrest affecting venous and lymphatic system during the 'earlier stage' of embryonic life while the vascular system is in the reticular stage. Therefore, extratruncular lesions, either VM or LM, retain the characteristics of the mesenchymal cells (angioblasts) as embryonic tissue remnants of mesodermal origin. It means, they retain the potential power to grow/ proliferate when the condition/milieu is right with sufficient stimulation, internally (e.g. menarche, pregnancy, and hormone) or externally (e.g. trauma, surgery). Therefore, all the extratruncular lesions of VM and LM carry a significant risk of recurrence, especially after suboptimal treatment.

Morphologically, extratruncular lesions present as either a diffuse *infiltrating or a limited* lesion in the form of amorphous vascular cluster with no direct involvement to named vessels; they cause a mechanical compression to surrounding tissues and organs/systems in addition to its hemodynamic impact.

On contrary, the 'truncular' VM/LM lesions are the outcome of developmental arrest during the 'later stage' of embryogenesis while vascular trunk is formed/matured. Therefore, truncular lesions no longer possess the potential power of the mesenchymal cells to grow and proliferate like extratruncular lesions. But, truncular lesions cause much more serious hemodynamic consequences since the lesions are directly involved to the (named) vessel trunk formation, resulting in defective vessel trunk, either partly (e.g. vein web/crest) or as a whole (e.g. venous aneurysm, hypoplasia/ aplasia). Besides, when embryonic vein should fail to take normal involution and remain through the birth as a persistent fetal remnant (truncal) vessel (e.g. marginal vein; sciatic vein), they will cause quite unique hemodynamic consequences due to coexisting avalvulosis (e.g. chronic venous insufficiency; intravascular/deep vein thrombosis and pulmonary embolism).

Morphologically, truncular VM lesions are further subclassified based on the degrees/extents of developmental defect either as an obstructive or dilated lesion with direct involvement to fully matured/ named vessel, ranging from incomplete or immature lesions (aplasia or hypoplasia) to overdeveloped lesions (hyperplasia) (e.g. agenesis/rudimentary deep vein).

Accordingly, clinical evaluation of this *combined form of CVMs* should start with careful and thorough history taking and physical examination to look for how many kinds of CVMs (CM, VM, and LM) as well as how many embryological subtypes (extratruncular and/or truncular) should coexist. Based on the clinical findings, clinical investigation should proceed to the next step to confirm and/ or rule out each lesion through due laboratory tests in proper combination.

However, diagnostic evaluation should proceed to identify the CVM components first and then to extend to the assessment of secondary phenomenon caused by primary lesion to establish proper linkage between them (e.g. limb length discrepancy caused by VM; chyluria by LM).

Investigation/confirmation of 'primary' pathology can be made mostly based on various combinations of non- to less-invasive tests. Selective invasive (e.g. arteriography) study is seldom needed for routine diagnosis of HLM but remains essential for the differential diagnosis to rule out an AVM involvement.

Primary pathology investigations

- I. Non-to less-invasive study - basic (standard)
  - T1 & T2 weighted MR image study
  - Duplex ultrasonography
  - Whole body blood pool scintigraphy (WBBPS)
  - RI lymphoscintigraphy

- II. Non-to less-invasive study - optional
  - CT and CT Angiography
  - Transarterial lung perfusion scintigraphy (TLPS)
  - MR venography and/or arteriography
  - MR lymphangiography
  - Ultrasound lymphangiography
  - Indocyanine Green lymphangiography
- III. Selective invasive study
  - Ascending, descending and/or segmental venography
  - Standard and/or selective arteriography
  - Percutaneous direct puncture phlebography
  - Percutaneous direct puncture lymphangiography

For the investigation of 'secondary' pathology, proper verification and assessment of the direct and/or indirect secondary effects of the primary pathology (VLM) to the various systems should be made;

Secondary pathology

- Gastrointestinal system (e.g. GI bleeding, chyloascites, malabsorption syndrome)
- Cardiopulmonary system (e.g. pleural effusion, chylothorax)
- Musculoskeletal system (e.g. long bone length discrepancy, scoliosis, pelvis tilt)
- Genito-urinary system (e.g. lymph leak: chyluria, chylorrhagia)

Accurate hemodynamic assessment of the deep venous system of the lower extremity is absolutely mandatory for the safe management of the VM component of KTS, especially before resection of a marginal vein.

Management - May 16-20, 2016

Today is the first day of the third, last part of KTS Session dedicated for its Management issue. Once again, I would like to thank to Fausto arranging such unique opportunity through Vasculab, sparing full three weeks for KTS alone.

The subject is relatively new to majority of Vasculab subscribers so that we tried hard NOT to waste your precious time for unnecessarily impractical issue but remain to deal with essential basic issues using various references to help better understanding through the week. Those references should be sufficient to give appropriate answer/ explanation on the questions/issues we could not respond enough. However, we are happy to keep the gate open to assist you even after the official three long week, dedicated for KTS.

In order to help you to help us to communicate better, I will duly provide the base/ground for your discussion though this third and last part of the session.

We will remain through the week for two-way communication with ample space to accommodate any input from the subscribers.

NOT ALL the CVM lesions involved to KTS (VM +LM+CM) are warranted for the (interventional) therapy. Indeed, NO therapy with 'close observation' should be considered as THE first option among many- AVM is an EXCEPTION as potentially life/limb threatening lesion but it doesn't belong to KTS as we repeatedly pointed out.

Indeed, absolute majority of VM and LM components of KTS are rarely life-or limb-threatening so that conservative treatments should remain as the first option and only when it is failed, invasive treatment modalities should be considered as next step. Hence, once the diagnosis is fully established including precise assessment of its extent and severity, the outcome of the evaluation should be reviewed by multidisciplinary team together and decide whether the patient should need the intervention or not based on the indications for the therapy.

Treatment Indication

- Hemorrhage
- Lymph leak with/without infection
- Acute venous thromboembolism
- Chronic venous insufficiency secondary to chronic venous hypertension
- Lesions located at life-threatening region (e.g. proximity to airway, etc.)
- Recurrent sepsis (local and systemic)
- Vascular-bone syndrome- secondary pathology
- Refractory phlebolymphatic ulcer- secondary pathology
- Disabling pain
- Major functional impairment by the primary lesion and/or its secondary impact
- Cosmetically severe deformity
- Lesions located at the region with potentially high risk of complication (e.g. deep vein thrombosis, hemarthrosis, and/or pulmonary embolism)
- Lesions combined with secondary pathology (e.g. GI bleeding; Chyluria)

Absolute indications for treatment include hemorrhage, infection, acute thromboembolism, and refractory venous ulcers. Relative indications include pain, functional impairment, chronic venous insufficiency, limb asymmetry due to vascular bone syndrome, and/or cosmetic reasons.

Once the treatment is decided with legitimate indications, the management of CVM lesion per se

is rather straight forward to go after individual CVM lesion belonging to four different types of VM and LM: Extratruncular VM, Truncular VM, Extratruncular LM, and Truncular LM in addition to CM. But the decision to choose which lesion should go first with priority remains a tricky issue since a variety of CVMs are involved in various extents/severities simultaneously.

Precise assessment of each CVM component is therefore essential not only for appropriate selection of the treatment modality but also for prioritizing treatment among the different CVM lesions.

Conclusion - May 20, 2016

It has been a quite unique experience for me as well as invited panelists to have such non-stop marathon session dedicated only for KTS issue for the last three week period. So I do sincerely thank to Fausto and Vasculab once again for this opportunity to discuss on this challenging issue of complex nature in depth to help better understanding.

Although Professor Olszewski pointed out 'Lack of even descriptive definition, no imaging helping to differentiate with other malformations and only marginal reports', we believe most of the literatures we provided as references - especially 5 world consensuses on various issues of CVMs- provided sufficient data/ information for 'descriptive definition' of KTS and also for 'differentiate with other malformations' through the first two weeks besides discussions mostly led by the panelists. We also dedicated this last third week for its management encouraging more active participation among the subscribers with their own KTS cases, based on various references we provided to meet most of your need.

We certainly hope our attempt to deliver the core issues of KTS has met its goal to make the subscribers feel comfortable to encounter this unique problem of KTS from now on. Indeed, its official session will be over through today, but by all means we are happy to get involved to this issue whenever the subscribers should need further assistance in future, either through Vasculab or my personal emails.

ADDENDUM - May 21-28, 2016

The Debate will be carried on through another week as Un-moderated session.

Acknowledgements

The KTrenaunay Vasculab Debate was organized by the Vasculab List as an Online Debate. We thank all the participants for their contribution and especially for their active role: Miguel Angel Amore, Pier Luigi Antignani, Iris Baumgartner, Jean-Paul Belgrado, Lena Blomgren, Alun H Davies, Tom Eaton, Stefano Ermini, Claude Franceschi, S B Gogia, Byung Boong Lee, NingFei Liu, Jovan N Markovic, Raul Mattassi, Nick Morrison, Tom O'Donnell, Waldemar L Olszewski, Sandeep Raj Pandey, Kurosh Parsi, Hugo Partsch, Fausto Passariello, Malay Patel, Sergio Pillon, Teresa Pintos Moreu, Cestmir Recek, Heraldo Schlup, Eva M Sevick, Natarajan Sekar, Gerard Stansby, Massimo Vaghi, David Wright. Finally, we thank Mrs. Iolanda Palma for her organizational effort.

References

1) Lee BB, Laredo J, Lee TS, Huh S, Neville R. Terminology and classification of congenital vascular malformations. Phlebology. 2007; 22(6):249-52.

2) Lee BB, Bergan J. Gloviczki P, Laredo J, Loose DA, Mattassi R, Parsi K, Villavicencio JL, Zamboni P: Diagnosis and treatment of venous malformations - Consensus Document of the International Union of Phlebology (IUP)-2009. International Angiology 2009 December; 28(6):434-51.

3) Lee BB, Villavicencio JL: Primary Lymphedema and Lymphatic Malformation: are they the two sides of the same coin? Eur J Vasc Endovasc Surg (2010) 39:646-653

4) Lee BB, Andrade M, Bergan J, Boccardo F, Campisi C, Damstra R, Flour M, Gloviczki P, Laredo J, Piller N, Michelini S, Mortimer P, Villavicencio JL : Diagnosis and treatment of Primary Lymphedema - Consensus Document of the International Union of Phlebology (IUP)-2009. International Angiology 2010 Oct;29(5):454-70.

5) Lee BB, Laredo J. Classification of congenital vascular malformations: the last challenge for congenital vascular malformations. Phlebology. 2012;27(6):267-9. http://www.ncbi.nlm.nih.gov/pubmed/22865415

6) Lee BB. Klippel-Trenaunay syndrome:is this term still worthy to use? ACTA PHLEBOL 2012;13(2):83-5

7) Lee BB, Andrade M, Antignani PL, Boccardo F, Bunke N, Campisi C et al. Diagnosis and Treatment of Primary Lymphedema. Consensus Document of the International Union of Phlebology (IUP)-2013. Int Angiol 2013;32(6):541-74

8) Lee BB, Antignani P.L. Not all the Vascular Malformations are AV malformation! Editorial, ACTA PHLEBOL 2014, 15: 1-2

9) Lee BB. New classification of congenital vascular malformations (CVMs). Reviews in Vascular Medicine. 2015;3(3): 1- 5

10) Lee BB, Baumgartner I, Berlien P, Bianchini G, Burrows P, Gloviczki P, Huang, Y, Laredo J, Loose DA, Markovic J, Mattassi R, Parsi K, Rabe E, Rosenblatt M, Shortell C, Stillo F, Vaghi M, Villavicencio L, Zamboni P. Diagnosis and Treatment of Venous Malformations Consensus Document of the International Union of Phlebology (IUP): updated 2013. Int Angiol 2015;34(2): 97-149.

REPORTS VASCULAB DEBATES

The Klippel-Trenaunay Syndrome

JN Markovic[1], BB Lee[2], F Passariello[3]

[1]Department of Surgery, Division of Vascular Surgery, Duke University Medical Center. Durham, NC 27710, USA. Office Phone: +1-919-681-2223

[2]Professor of Surgery and Director, Center for the Lymphedema and Vascular Malformations, Division of Vascular Surgery, Department of Surgery, George Washington University Medical Center, Washington, DC 20037, USA.

[3]Fondazione Vasculab ONLUS, via Francesco Cilea 280 - 80127 Naples, Italy

The official report of the KTrenaunay Vasculab Debate, held on the Internet, Vasculab List, on May 1-21, 2016 (unmoderated session: May 22-28, 2016. Discussant: Byung Boong Lee, Moderator: Fausto Passariello, Panel Experts: Miguel Angel Amore, Iris Baumgartner, NingFei Liu, Jovan Markovic, Raul Mattassi, Kurosh Parsi, Massimo Vaghi.
submitted: Jan 22, 2017, accepted: Mar 23, 2017, EPub Ahead of Print: Apr 22, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.11 - Corresponding author: Prof. Byung Boong Lee, bblee38@comcast.net

Abstract The Klippel-Trenaunay Syndrome (KTS) includes congenital, low flow vascular malformation(s) that leads to structural and functional anomalies of the vascular system characterized by variability of presenting symptoms and often unpredictable clinical course. Traditionally described pathognomonic triad of findings in KTS patients are capillary malformation, venous malformation, and bone and/or soft tissue hypertrophy. KTS frequently includes the presence of lymphatic malformation(s), as well. Historically, the management of KTS was hampered by the lack of understanding of underlying hemodynamics and pathophysiology responsible for development and progression of KTS symptoms, confusing nomenclature which characterized majority of the early literature discussing KTS, as well as by the absence of established guidelines for KTS management. A relatively recent advancement in the diagnostic and treatment modalities have resulted in better understanding of the pathophysiology and natural history of KTS and represents a fertile environment for improved management of these patients. Multidisciplinary approach and diagnostic algorithm utilized to distinguish vascular malformations from vascular tumors, arterio-venous lesions from low flow vascular malformations have been validated as clinically applicable for making an accurate anatomical and hemodynamic assessment of the lesions found in KTS and serve as a basis for proper treatment selection. It has to be emphasized that treatment of majority KTS patients is palliative and goal oriented. In this manuscript we describe diagnostic protocols and therapeutic algorithms which results in favorable outcomes with an acceptable complication rates in the management of this frequently challenging patient population.

Keywords Klippel-Trenaunay Syndrome, Congenital Vascular Malformations, Venous Malformations, Lateral Marginal Vein, Sclerotherapy

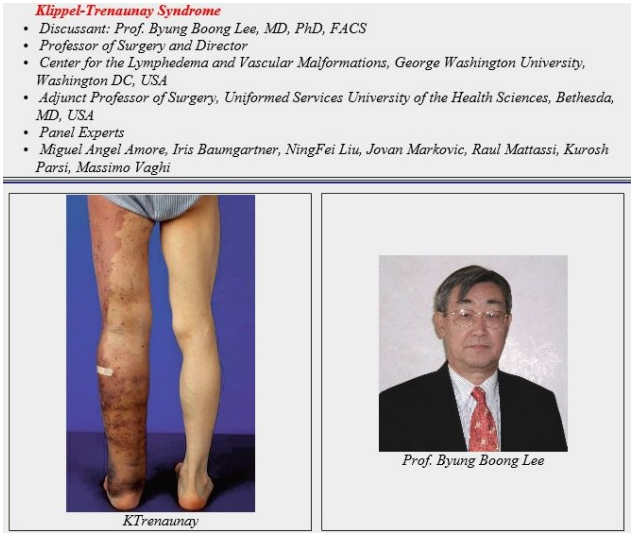


Figure 1 - The KTrenaunay webpage. DOI: 10.24019/2016.KTrenaunay

Classification	
KTS	Klippel-Trenaunay Syndrome
KTW	Klippel-Trenaunay-Weber syndrome (obsolete term)
PW	Parkes-Weber
PWS	Parkes-Weber Syndrome
VBS	vascular bone syndrome
CVM	Congenital Vascular malformation
AVM	Arterial-Venous malformation
CM	Capillary malformation or port wine stain
VM	Venous malformation
LM	Lymphatic malformation
FAVA	Fibro-Adipose Vascular Anomaly
HLM	Hemolymphatic Malformation
MV	Marginal Vein
GI	Gastro-Intestinal
GU	Gastro-Urinary
VLM	Veno-Lymphatic Malformation
CLOVES	CLOVES syndrome (representing each component) (C)ongenital, (L)ipomatous, (O)vergrowth, (V)ascular malformation, (E)pidermal nevus, (S)coliosis
ISSVA	International Society for the Study of Vascular Anomalies
IUP	International Union of Phlebology
LEC	Lymphatic endothelial cells
LIC	localized intravascular coagulation

Table I - Classification.

History

The Syndrome of Klippel-Trenaunay (KTS) was already discovered and described by Isidore Geoffroy Saint-Hilaire in 1832[1,2], a French Zoologue and teacher of Compared Anatomy, who studied the monstrosities in depth and was the founder of Teratology (the Science of monsters). He described a patient with concurrence of osteo-muscular hypertrophy and cutaneous vascular anomalies of the extremity. In the ensuing years other authors have described patients presenting with similar signs which included limb overgrowth and associated vascular anomalies.

In 1858, Adams published the first report in English language, where the author described a patient as "singular case of hypertrophy of the right lower extremity with superficial cutaneous nevus of the same side"[3]. This was followed by Trélat et al.[4] who published in 1869 a summary of 12 case reports of patients with the concurrence of osteo-muscular hypertrophy with unilateral cutaneous vascular nevus and varicose veins.

However, it was not until 1900's when two French physicians, Drs. Maurice Klippel and Paul Trenaunay, first recognized above mentioned concurrence of clinical findings as a separate clinical entity which they named "naevus variqueux osteohypertrophique"[5]when describing two patients with cutaneous vascular lesions of the skin that were associated with asymmetric soft tissue and bone hypertrophy, what is today known as Klippel-Trenaunay Syndrome (KTS).

In the following years various authors have proposed different definitions for this clinical entity. Most notably, in 1907 Parkes-Weber described a similar case that differed from KTS in the presence of arteriovenous malformations[6]. Unfortunately, subsequently several authors merged the two disorders together as the Klippel-Trenaunay-Weber Syndrome, which caused confusion that persisted through the 20th century with regards to classification and terminology, of these two distinctly different clinical entities. Today it is well established that KTS should be clearly distinguished from Parkes-Weber Syndrome (PWS) which is a high-flow vascular malformation characterized by arterio-venous shunting. Clinically this is of a paramount importance as clinical features, management and prognosis of these two syndromes are distinctly different.

KTS represents a complex congenital vascular disorder characterized by the pathognomonic triad of findings that include capillary malformation(s) (CMs), venous malformation(s) (VMs), and hypertrophy of affected extremity, with or without presence of lymphatic malformations(s) (LMs). (Figure 2) Congenital vascular malformation(s) (CVMs) associated with KTS patients are localized or diffused abnormalities in vasculogenesis and angiogenesis that arise by embryologic dysmorphogenesis without increased endothelial proliferation that causes true structural and/or functional anomalies of the vascular system[7,8].

These anomalies in turn can lead to variable clinical presentation and course (in both their extent and severity) what depends upon location, size and/or the type of vessel affected. Most frequently they cause discomfort, pain, hemorrhage, thrombosis, negatively affect patient's appearance, emotional well-being and can lead to a significant reduction in daily functional capacity and quality of life of patient.

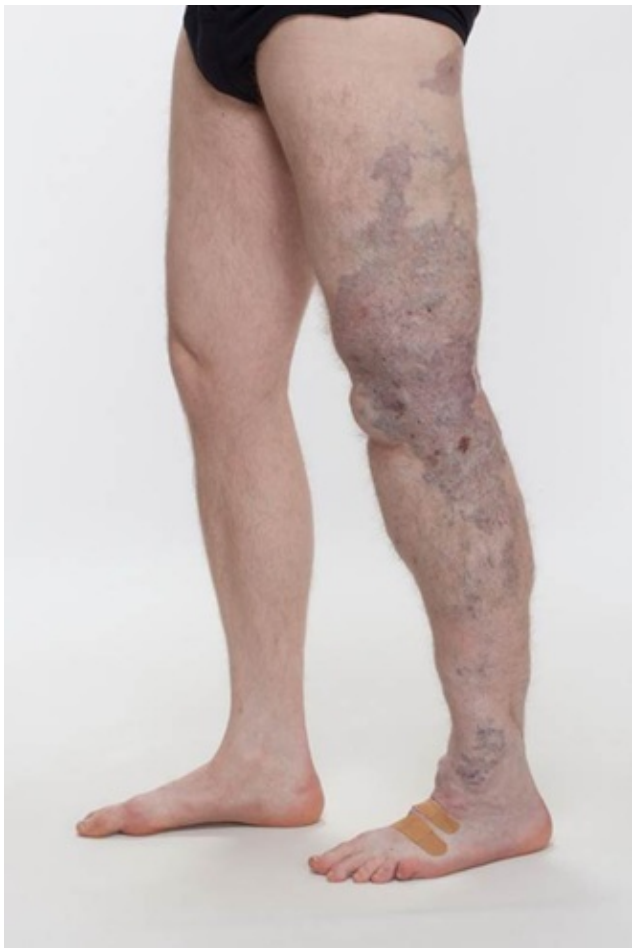


Figure 2 - A 32 year old KTS patient with pathognomonic triad of findings that include extremity hypertrophy, cutaneous capillary malformations and varicosities affecting the left lower extremity.

For most doctors - from primary care clinicians to subspecialists (including vascular surgeons and phlebologists) - management of KTS represents a difficult task and it is usually reserved for referral to specialized centers with expertise in this area.

Relatively low frequency at which KTS occurs, the confusing nomenclature which traditionally characterized majority of the early literature discussing KTS, overlap with other vascular malformation syndromes, such as PWS, Proteus Syndrome, and hemi-hypertrophy, as well as the absence of established guidelines for KTS management represents the main reason why expertise for diagnosis and treatment of KTS patients was most frequently centralized to major medical centers.

Consequently a significant number of KTS patients have been discouraged by the lack of correct diagnosis and proper treatment despite numerous visits to different clinics.

Relatively recently introduced concept of the multidisciplinary team approach, characterized by full integration of expertise of different medical specialists, combined with evaluation with modern diagnostic techniques and treatment with novel therapeutic modalities afforded the opportunity for the improvement in understanding of the pathophysiology and the management of KTS patients.

BB Lee *reminded all the participants that such dedication for full three weeks ONLY for the KTS issues is virtually impossible other society/congress activity can afford! Indeed, "Vasculab is the first one ever as I know of willing to spare/dedicate full three weeks to its subscribers for free exchange of their opinion on the KTS as you always wanted to know but afraid to ask… So please take advantage on this unique opportunity Vasculab provides through full three week period unconditionally no other group ever did.", he declared.*

BB Lee *added the following remarks about the history of KTS in the XX century.*

"I feel obliged to clarify on the dark side of the CVMs through the last century. That is WRONG prejudice against the CVM as a whole with truly biased opinion based on many hearsays. Indeed, during my residency days in Medical College of Virginia in Richmond, Virginia in early '70, the CVMs- in those days we called it angiodysplasia!- were 'a curse to the surgeons' so that we were warned to stay out whenever possible.

My mentor, the late David Hume - who missed Nobel prize to receive for his pioneering work on kidney transplant together with Joseph Murray due to his early death by airplane accident - often quoted Dr. Emerick Szilagyi, condemning the CVMs as a sort of four letter words to the surgeons.

Dr. Szilagyi at Henry Ford Hospital, Detroit in '60, who is a legendary vascular surgeon with his tremendous work as a pioneer on the developments of vascular surgery combined with transplant surgery, became more famous with his incredible joke to his disciples to using the CVM cases as the tool to ruin- 'get rid of'- competing surgeon based on his horrible experiences with CVMs/AVMs.

Indeed, through the last century, a cavalier approach to CVMs, mostly led by surgeons alone, often resulted in disastrous outcomes with high recurrence and high complication/morbidity due to then limited knowledge and experiences in this unique vascular disorder. They simply learned that CVM is a unique vascular disorder of extreme variety with stigma of ***totally unpredictable*** *behaviour. But then, they did not know it is due to its unique embryological characteristics.*

Therefore, CVM remained most difficult and confusing diagnostic and therapeutic enigma through the century with a wide range of the clinical presentation; unpredictable clinical course; erratic response to the treatment with high recurrence; high morbidity of conventional treatment; confusing terminology without proper information on etiology, anatomy, and pathophysiology.

*Such notorious reputation only added further confusion on the management of CVMs with erroneous prejudice as '****Enigma among the vascular disorders****' (Edmondo Malan)*[9]*. And recurrence became the trademark of CVMs.*

*Through last three decades, we learned a lot through many painful lessons! Yes, it is still one of '****ultimate challenge to the clinicians****' (Stephan Belov). But now we know how much we know and also how much we do NOT know on this unique embryological remnants. So we will be able to guide the colleagues through this mine field safely and further to teach how to defuse this mine: 'symbol of humiliation'".*

Etiology

The Klippel-Trenaunay Syndrome represents a rare congenital vascular disorder without gender predilection that occurs with estimated incidence of approximately one in 100,000 live births[10]. Most KTS cases are sporadic without identified pattern of inheritance; however, several studies have reported familial occurrence[7,11,12].Although the etiology of KTS still remains to be elucidated, data from molecular studies suggest that errors in embryonic development of the normal vasculature (which include angiogenesis, vasculogenesis and vascular remodeling) are responsible for development and progression of vascular malformations associated with KTS[13].

In summary, this complex biochemical process is regulated by different vascular endothelial growth factors (VEGFs). By binding to receptor tyrosine kinases (VEGF-R1 and VEGF-R2) VEGF modulates endothelial proliferation and vessel tube formation[14,15]. This process is significantly influenced by an antagonist, angiopoietin-2. VEGF also stimulate angiogenesis with the action of angiopoietin-1 and its receptor (Tie2). Berry et al. suggested that in KTS there is an alteration in vascular remodeling, most likely at the level of altered angiopoietin-2 antagonism[13]. Early genetic studies also showed contradictory data. Although majority of the earlier studies reported KTS patients to have normal karyotype, there were studies that contradicted these findings[8].

Specifically, Whelan et al. described a KTS patient who had a reciprocal translocation of chromosomes 5 and 11[16]. Chromosomal translocation was supported by Wang et al. who showed a balanced translocation involving chromosomes 8q22.3 and 14q13[17], as well as Timur et al. who reported a mosaic de novo supernumerary ring chromosome 18 in KTS patient18. Genetic susceptibility for capillary malformations, as one component of the clinical triad in KTS, was suggested by Eerola et al.[19] Authors of this study identified a large genetic locus, CMC1, on chromosome 5q and by using genetic mapping identified heterozygous inactivating RASA1 mutations in families manifesting capillary malformations. However in 2013 Revencu et al. published opposite data showing that germline RASA1 mutations are not associated with KTS[20].

More recent genetic studies suggest that underlying pathophysiologic mechanisms responsible for KTS development stem from mosaic activating mutations in the phosphatidylinositol 3-kinase catalytic (PIK3CA) gene and showed that several members of the PIK3/mTOR pathway have been implicated in the pathogenesis and progression of vascular anomalies[21]. Vascular endothelial growth factor (VEGF) is a key regulator in lymphangiogenesis and angiogenesis, and acts as both a potential upstream stimulator of, and a downstream effector in the mTOR signaling pathway[22].

mTOR is the abbreviation term for 'mammalian target of rapamycin' and its inhibitor (mTOR-I) has been used extensively for decades as immunosuppressive drugs as 'sirolimus and everolimus' largely in renal transplantation. Indeed, sirolimus was the first mTOR-I approved for use in renal transplant and its activity is based on its binding ability to the immunophilin FK binding protein-12 (FKBP-12) to halt T-cell progression from the G1 to the S phase(cell cycle) so that IL-2-induced protein synthesis and cellular proliferation can be inhibited.

But, lately mTOR-I was found to have antilymphangiogenic activity to induce the impairment on downstream signalling of vascular endothelial growth factor/VEGF-A through the inhibition of mTOR/p70S6K pathway in lymphatic endothelial cells (LECs). Further it was found to interfere with the intracellular pathway activation of LEC by VEGF-C, the main initiator of lymphangiogenesis[23]. In other words, mTOR inhibition impairs downstream signalling of VEGF-A as well as VEGF-C via mTOR to the p70S6 kinase in LECs. So, Rapamycin can inhibit VEGF-C driven proliferation and migration in concentrations as low as 1ng/ml.

In 2015, Luks et al. evaluated genetic aberration responsible for lymphatic pathogenesis in patients with lymphatic malformations (n=17) and/or syndromes in which lymphatic malformation is present including patient with CLOVES (n = 33), KTS (n = 21) and FAVA (Fibro-Adipose Vascular Anomaly[24]) (n=8). Data from this study showed that somatic mosaic mutations in PIK3CA[25] genetic locus represent genetic mechanisms underlying development of the above mentioned syndromes. However, it remains to be elucidated why the same genetic PIK3CA gene mutation causes an isolated malformation in one patient and a different syndrome associated clinical presentation in another patient. One of the explanations can be based on the stage of the embryonic development when the genetic mutation arises as well as the location of the first mutated embryonic cell and the stem cells that arise from that particular cell linkage.

Mammalian target of rapamycin (mTOR) is a serine/ threonine kinase regulated by phosphoinositide-3-kinase (PI3K). mTOR acts as a master switch of numerous cellular processes, including cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth and is becoming a target of relatively novel pharmaceutical agents being tested[26]. In 2016, in a study funded by National Institute of Health, Dimopoulos et al. performed genotyping of DNA from 17 KTS patients by using microarrays[27].

Authors identified 15 copy number variants in genes involved in chromatin modification, which is a key regulatory process of embryonic vascular development. Specifically, authors identified deletion in two cases within transcripts of histone deacetylase (HDAC9), which is essential for angiogenic sprouting of endothelial cells. One case had duplication upstream of a transcription factor essential for embryonic development (SALL3[28]), that inhibits DNA methyltransferase responsible for embryonic de novo DNA methylation (DNMT3A). Data of this study also showed that another patient had a duplication spanning ING5, a histone acetylation regulator which is active during embryogenesis. Although above referenced initial genetic data are promising, further studies (with ideally larger number of patients) are needed for the more accurate assessment of genetic aberrations responsible for pathogenesis of KTS. These findings have a potential to provide a fertile environment for development of novel genetic diagnostic, prognostic and therapeutic modalities.

Genetics	
CMC1	large locus on chromosome 5q
DNMT3A	DNA methyltransferase 3 alpha
FKB9-12	immunophilin FK binding protein-12
HDAC9	histone deacetylase
ING5	histone acetylation regulator
mTOR	mammalian target of rapamycin
mTOR-I	mTOR inhibitor drug, like sirolimus and everolimus
PI3K	phosphoinositide-3-kinase
PI3KCA	phosphatidylinositol 3-kinase catalytic PIK3CA
RASA1	p120-RasGTPase#activating protein
SALL3	salt-like 3 DNMT3A inhibitor
Tie2	angiopoietin-1 and its receptor
VEGF-R1	Vascular endothelial growth factor receptor-1
VEGF-R2	Vascular endothelial growth factor receptor-2
VEGFs	Vascular endothelial growth factors

Table II - Genetics

Discussion

***BB Lee** affirmed that marginal vein (MV) maintains embryonic venous structure with the lack of media, NO SMOOTH MUSCLE LAYER, besides NO VEIN VALVES!*

*According to **NF Liu**, lymphatic malformation is a common component, but have been underreported in many studies, in part because of difficulties in establishing a suitable proof of lymphatic involvement of KTS. It is not possible to directly observe the abnormal development of the lymphatic system in KTS patients until we have used the MR lymphangiography[29].*

*Not only lymphatic vessel is involved in KTS, the inguinal lymph node may also affected (including lymph node aplasia, hypoplasia or hyperplasia). Venous system and lymphatic system have close relationship during embryonic development, it may explain in part for the co-existence of the pathology of both systems in the disease. Recent studies have showed that genes that regulate development of venous system as VEGFs, Angiopoietins…, also show important effect on lymphatic development. These study may explain the clinic phenotype of co-involvement of the two system in KTS and primary lymphedema, added **NF Liu**.*

*But are those veins **really dysplastic** following the histological definition of dysplasia? Is there cytological atypia in biopsy samples with atypical nuclei OR are we looking at architectural abnormality which is not dysplasia? (asked **K Parsi**)*

***BB Lee** noted that histology says simply they are "dysplastic veins", but he was not very convinced about the usefulness of that data to define KTS.*

*The cause of Klippel Trenaunay syndrome is a cellular mosaicism. This mosaicism may be present in every cell or group of cells, argued **M Vaghi**.*

***BB Lee** remarked that in regard to the discrepancy between the LSG and ICG lymphangiography the lymphatic defects involved to KTS are closely linked to coexisting VM (rather than co-developed!) as a typical 'mosaic pattern' (as already noted by M Vaghi) so that its truncular form/primary lymphedema looks a lot different from independent lesion, **BB Lee** added. As **NF Liu** pointed out, MR Lymphangiography shows its dysplastic development as aplasia/ hypoplasia/hyperplasia is only a part of it along the collecting system but we do see many defects involved to lymph nodes. So **BB Lee** concurred with what Cristobal Papendieck claims as three separate groups to 'lymphangiodysplasia/ lymphnododysplasia/ lymphangio-adeno-dysplasia'.*

*We speculate this unique condition named as KTS as the outcome of multiple genetic mutations affecting not only vascular but also other organs/systems/tissues of mesodermal origin in particular, most probably as a 'mosaic' pattern. So musculoskeletal overgrowth remains to be assessed from this genetic mutation point of view as we previously pointed out. Indeed, so far up to Year 2015, we do NOT have any other clue and the VM as the culprit to cause abnormal long bone growth together with LM for KTS cases remained to be verified for this genetic mutation involved. In other words, there is no specific confirmed gene mutation identified yet for KTS altogether. So regretfully we do NOT have clear answer on "different therapeutic implications" and "Why some patients present with limb length and size overgrowth and others no if they all have VM and LM" , insisted **BB Lee**.*

*Nevertheless, a limb length discrepancy is one of secondary phenomena caused by the primary CVM lesion in its majority, we speculate the venous hypertension caused by (extratruncular) **VM lesions along the epiphyseal plate** as a major culprit of angio-osteo-hypertrophy. And when the VM, either extratruncular or truncular, is intervened on time, such progress of abnormal long bone growth can be arrested/corrected, pointed out **BB Lee**.*

***WL Olszewski** underlined the important point of aplasia of lymphatics and nodes. So far nobody proved and reported objective data on selected (from other coexisting developmental defects) lymphatic aplasia. The 1962 Kinmonths concept of aplasia based on unsuccessful lymphatic cannulation for lymphography is not more tenable, as biopsies showed normal lymphatic wall layers with lumen full of acellular amyloid-like masses. In the so called KTS he found normal collectors on lymphography, on ICG thousands of fluid lakes and on histology thousands of minute fluid cysts. Not to describe now*

the coexisting deformed blood vascular structure. Fluid lakes have no connection with collecting trunks."

***C Recek** added several intriguing questions: "The limb overgrowth in KTS is really the consequence of hemolymphatic malformation, how does that come about? Is there at all any causal relationship between the hemolymphatic malformation and the soft tissue and bone hypertrophy? Or are both released by unknown factors, e.g. epigenetically activated or suppressed genes? Anyway, the relationship between vascular malformations and congenital vascular bone syndrome (VBS) remains obscure. So, the enigma continues." In addition, he stated that it was not specified how the hemodynamic disturbance in KTS looks like.*

***BB Lee** answered that we only speculate the etio-pathogenesis of VBS and describe vaguely as the result of the stimulation to epiphyseal plate by the VMs nearby before the plate is closed. But we know the overgrowth of bones and soft tissues as well are closely related from changes in one or more genes that regulate the growth of blood vessels during embryonic development though no associated genes have been identified. Nevertheless, all the conditions of KTS we know of are almost always as the outcome of gene mutations that are not inherited, and all these so called 'somatic mutations' present only in certain cells - so far no associated genes have been found -, probably occurring very early in development, and explain why the conditions of KTS are often limited to specific areas of the body. Indeed, as you previously touched briefly, the final answer on this mixed condition of defective genes is the severity of 'mosaicism'- otherwise, embryo would not remain viable as a homozygous zygote.*

Classification

As mentioned earlier, historically numerous attempts have been made to properly classify congenital vascular malformations based on anatomic, clinical, and/or embryologic criteria and no real consensus existed regarding nomenclature and management of these lesions[30,31]. Based on a classification of "vascular birthmarks", initially proposed by Mulliken and Glowacki in 1982[32] the International Society for the Study of Vascular Anomalies (ISSVA) introduced a classification system in which all vascular anomalies were divided into two categories: vascular malformations and vascular tumors. The differentiation of vascular anomalies into tumors and malformations permitted more effective communication between different medical specialists.

Unfortunately, the eponym based terminology which characterized the ISSVA classification, as well as the lack of clinical applicability of this classification with regards to pretreatment planning, was believed by many to be the major limitation for widespread acceptance and utilization of this system. To address ISSVA classification limitations the authors of "Hamburg" and subsequently "Modified Hamburg Classification" developed a classification system by incorporating malformation flow characteristics (i.e. arterial, venous, capillary).

In addition, they defined vascular malformation based on the stage of developmental arrest during embryogenesis into truncular and extratruncular lesions which is important for treatment selection and prognosis of treatment outcomes as extratruncular lesions are associated with significantly higher recurrence rates and resistance to therapy, presumably because of their preserved mesenchymal characteristics of independent growth potential[33]. "Modified Hamburg Classification" system has been considered to be "a more clinician-friendly classification for vascular malformation management" as outlined in the 2009 Consensus Document for the treatment of venous malformations of the International Union of Phlebology (IUP)[34]. According to this classification KTS is a low flow vascular malformation, as it does not have an arterial component.

Discussion

The KTS Eponym

R Mattassi noted that Edmondo Malan from Italy, considered internationally one of the main pioneers in CVM, in 1974 reported about 460 cases of CVM (one of the main series of cases at that time). In his book[9] he wrote "the Klippel-Trenaunay-Parkes-Weber eponym is meaningless and should be abandoned". That because he found in the literature much confusion about.

Stefan Belov, another pioneer in CVM, described 11 different types of CVMs with the well-known triad of signs in cases defined as KTS. Also he was of the opinion that KTS is a confusing term to be avoided, because the same clinical picture may be originated by different malformations.

However, the use of KTS diagnosis is so diffuse that it is better to maintain it, just avoiding its incorrect use. That was done partially during the VM international consensus for IUP (Int Angiol, 2014)[31].

The intention of the KTrenaunay Debate was to improve the definition, maintaining the KTS eponym, as abolishing it seems impossible. KTS should only be used correctly and not as a general term for anomalous vessels, he concluded.

However, the eponym can have also advantages, as the description terms do not include all localizations and may not highlight complications in liver, lung and brain, noted **M Vaghi**. In addition, in Italy you can have some economical support for people affected by congenital vascular diseases, all classified with eponyms. Changing the nomenclature will automatically exclude these patients from the financial support, he added.

On the contrary in the USA, improper use of the term KTS would make the clinician legally liable, so that we urge the colleagues to use the term carefully especially on clinical document/ record, argued **BB Lee**, saying that they effectively replaced/renamed KTS to Hemolymphatic malformation (HLM) based on Hamburg Classification.

The difficulty of the matter is amplified by previous clinical nosographic classifications as Klippel-Trenaunay-Weber syndrome (KTW) or Parkes-Weber (PW) which are only the emerged part of the iceberg that the modern imaging is today showing. Maybe we should better retain the eponyms only for the history of medicine, noted **C Franceschi**.

BB Lee declared that he feels ISSVA led/opened Pandora's box! He was NOT talking about many legitimate syndromes like CLOVES syndrome which represents each components (congenital lipomatous overgrowth, vascular malformation, epidermal nevus, scoliosis), but

he was talking about illegitimate(?) NAME-based syndrome which represents NOTHING but the lists of the names of the person who documented first.

Definition

One of the main issues in the discussion was the identification of the primary and secondary defects in KTS, in order to achieve a better definition.

BB Lee reminded that AVMs are absent in KTS and can be found only in PWS instead.

R Mattassi reported about a recent ongoing statistic (46 cases, Castellanza, 2011 - 2015, later published on Phlebolymphology[35]), where all cases were studied with modern technology (Duplex scan, MRI, Lymphoscintigraphy). While only superficial dysplastic veins were present in all cases, other signs and vascular defects occurred in a lesser extent.

JN Markovic affirmed that giving a clear definition of KTS is a critical initial step. In his opinion, the definition should be based on clinical applicability and preservation of original findings described by M Klippel and P Trenaunay, allowing a certain degree of deviation.

As regards the clinical applicability, emerging novel therapeutics with preliminary data show that mTOR-I are effective in the treatment of pediatric patients only in KTS patients with LM component. Therefore, classifying a patient as KTS with OR without LM is clinically relevant, especially with regards to treatment planning.

The exclusion of the osteomuscular discrepancy from KTS definition could carry the risk of contradicting findings of the original authors and silencing the previous work that steamed from their discovery. He suggested the definition to incorporate osteomuscular discrepancy as a pathognomonic symptom and low flow hemodynamic characteristics (VM/CM +/- LM) as chief symptom. In his opinion deep venous system status should be incorporated in diagnostic work up of KTS rather than in the definition.

BB Lee added that LM is a possible component of KTS. That means we should not talk about KTS + LM but simply of KTS. As a part of primary criteria, he suggested to consider the fact that (anterior) lateral embryonic/marginal vein (MV) is ONE of unique truncular VMs as an embryonic tissue remnant which is supposed to be involute/ regressed on the birth, but remained through due to arrested/defective development in its later stage of embryogenesis to form the venous trunk.

Naturally there are other risks of truncular VMs directly involved to the (named) venous trunk like iliac vein aplasia/absence or femoral vein hypoplasia, either as an independent VM lesion if not combined with MV (in our series, over 25 to 30% were identified for 'coexisting iliac/femoral/ popliteal vein dysplasia).

For secondary criteria, he stated that in his personal perception it is hard to imagine KTS with NO port wine stain (Maurice Klippel included this as a triad, while LM which was added later by Paul Trenaunay). Hence, he once defined this unique group of VM + LM and no CM as 'veno-lymphatic malformation (VLM)' as per recommendation by his mentor, Leonel Villavicencio. But in order NOT to add more confusion, he stopped using this new term of VLM for more than a decade. So his personal feeling was we should stick to the original claim led by the late Stefan Belov of Bulgaria with all three components as mandatory CVM components of KTS.

F Passariello noted that using simply a description instead of using an eponym could be considered a solution, though it does not comply with the difficult and variable clinical picture of the syndrome. Furthermore, a good classification should be also extendible to the future. For instance, the original KTS definition by Klippel was later extended adding the lymphatic component. On the contrary, specifying in details the components in the definition blocks definitely any further improvement.

R Mattassi pointed out the question if limb overgrowth should be mandatory for KTS. Several patients have bilateral disease and combination of two or more vascular defects, but no limb length discrepancy. How to define them? Another point regarding limb shortening. Are these cases KTS or not? Some authors call them Servelle-Martorel syndrome. He declared that CM is not a mandatory requirement and certainly in his current paediatric list, CM is seen in less than 30%.

K Parsi intervened saying that what we really have to be careful about is having a circular argument. In other words, if some patients were excluded to start with due to the wrong definition, then all statistics will be wrong as the definition was wrong in the first place: in simple words, using a criterion to assess the diagnosis and then finding that item present in 100% of your sample.

This especially applies to dysplastic veins and limb length hypertrophy. He remarked that this needs to be put in the context, because in his paediatric population he observed that early intervention can slow down the growth. So, while limb hyperplasia should be considered a criteria, it is a dynamic concept and needs a further definition.

F Passariello observed that nowadays we have the old completely clinical KTS classification and the new diagnostic facilities, which recognize the presence of single components and needs sophisticated instrumental tools to assess (for instance deep veins occlusion/dysplasia) or exclude the components (for instance AV fistulas, which change the diagnosis towards Parke-Weber Syndrome).

The two approaches are completely different and no problem arises if we try to use them separately, while the problem arises in the attempt of calling KTS (old eponym) something which is investigated in each component, using modern tools.

I Baumgartner remarked that we need a clear definition, declaring that she does not treat the KTS, but individual problems existing in an individual patient so that the sophisticated semantic definition becomes less important. Open question for her is if LM is mandatory or NOT to define classical, complete KTS.

R Mattassi noted that the extension of the defect is important. KTS exist only if the whole limb is involved. CVM of just a limited part of the limb (foot, calf, thigh) is not KTS.

Anyway, the term/condition of KTS can be applied to any limb, upper or lower or both! "Involvement of other organs/systems is another issue for KTS!", argued **BB Lee**. Indeed, the vascular malformation can develop anywhere throughout the body where the arterial-venous-lymphatic circulations reach. Lower gastro-intestinal (GI) bleeding is one of the most common GI complications caused by the VM involved to the colon-rectum among KTS patients, and 'lymphorrhea' including 'chyloreflux' is also a common complication of the LM involved to KTS, with GI as well as gastro-urinary (GU) localizations[36,37].

The most notorious findings are the 'vascular bone syndrome'/ angio-osteodystrophy, secondary to VM+/-LM, GI bleeding secondary to VM and lymphorrhea and chyloreflux by LM. Regarding KTS and chylous reflux, this type of association is infrequent, while milky lymphorrhea can be found in Waldmann's disease, added **MA Amore**.

R Mattassi expressed the opinion that these locations without limb involvement cannot be defined KTS. Reason is that definition

of vascular defects is not possible like in the limbs: how can we establish truncular defects in an infiltrating VM or LM of the cheek or of the thorax wall? How can we find truncular LM in that defects? He proposed to exclude from the definition of KTS vascular defects of other parts of the body, without limb involvement.

Definition attempts

K Parsi proposed an interesting classification, based on primary and secondary criteria, as follows.

The K Parsi proposal
- Primary Criteria (both required)
  - 1. Presence of an embryonic Marginal vein or diffuse and dysplastic superficial veins of the anterolateral thigh venous system. Predominance of lateral pathology over medial (GSV) or posterior (SSV).
  - 2. Limb length or limb circumference hypertrophy
- Secondary Criteria (2 required)
  - 1. Ipsilateral lower limb, upper limb or head and neck truncular or extratruncular VM
  - 2. Ipsilateral lower limb, upper limb or head and neck truncular or extratruncular LM
  - 3. Ipsilateral CM

The primary and secondary components approach is nowadays common to several disciplines and the first similar classification dates to 1958 with the classification of rheumatoid arthritis from the American Rheumatic Association, based in the origin on 10 items, noted **F Passariello**. According to his opinion, the classification proposed by **K Parsi** was very interesting, but the criterion used to arrive to this discriminating tool was not declared.

M Vaghi proposed to define KTS as "truncular congenital venous anomalies associated with limb overgrowth". Other features like naevus, lymphatic disease may be added to the original nucleus. Given the complete classical picture (naevus, limb overgrowth, dilated veins), **I Baumgartner** added a rational scheme for classification as follows.

The I Baumgartner proposal
- KTS (complete classical picture; LM?)
  - *give involvement and main problem for patient*
  - *diffuse, dysplastic superficial veins, naevus, limb hypertrophy, /// (? LM needed to define complete classical picture ?)*
    - large marginal vein with localized intravascular coagulation (LIC) and orthostatic symptoms, aplasia of femoral vein
    - painful pelvic manifestation of VM
    - mild, clinically latent LM (stage I)
    - naevus (non disturbing)
    - limb length difference (< 2 cm)
- Incomplete KTS
  - *give involvement and main problem for patient*
    - But absence of one sign of the triad
    - But absence of LM
- No KTS / diagnosis is VM or LM
  - VM - *patients with a single type of VM (truncular defect, like MV or deep vein anomaly or extratruncular forms) alone. As these cases do not meet the mandate of "syndrome" they should not be defined as KTS*
  - VM & CM - *patients with a single type of VM and naevus without limb overgrowth and LM*
  - LM & CM - *patients with a single type of LM and with naves but no VM.*

R Mattassi stated that KTS is a Syndrome (combination of defects, not a single one!) and with diffuse, dysplastic superficial veins + other defects. In addition, he provided an exclusion criterion, as follows.

R Mattassi exclusion criterion. KTS is NOT
- 1- all cases with AVM
- 2- all cases without VM (truncular or extratruncular)
- 3- all cases with just lymphedema. (not necessary because included in point 2)
- 4- all cases with malformation just in one segment of the limb and not in the whole leg

F Passariello suggested to try a description based on something similar to the CLOVES description, based on the following items: (C)ongenital, (L)ipomatous, (O)vergrowth, (V)ascular malformation, (E)pidermal nevus, (S)coliosis. If better adapted to CVM, it could describe all the component combinations, without any need to rely to the old KTS eponym.

BB Lee intervened saying that it would be the most ideal way to describe KTS. Indeed, the IUP tried to organize it when starting the first VM Consensus in 2009[34] using the CLOVES Syndrome, though this fruitful way was later abandoned.

He underlined the need of classifying KTS as a Hemolymphatic Malformation (HLM) by Hamburg Classification, proposing the following definition: "KTS is a combination of truncular and extratruncular VM and LM which may originate secondary effects".

Possible vascular defects are 4: truncular and extratruncular venous and truncular and extratruncular lymphatic. A fifth defect can be added which is capillary malformation (CM) or cutaneous nevus flammeous.

Secondary lesions/conditions (e.g. leg length discrepancy; chyluria; hematochezia; pulmonary embolisms, etc.) can be present. Limb length discrepancy can be overgrowth or limb shortening. However, secondary effects are only the result of the vascular defect: there is no limb overgrowing without vascular defect. That means that the crucial point is the vascular defect and not the secondary effect. In his opinion, as limb length discrepancy is secondary and may not be present, it should not be included in the definition.

JN Markovic noted that at his Institution they define KTS as "Low Flow Vascular Malformation (VM/ CM +/- LM) + osteomuscular discrepancy". Defining KTS just as "combination of truncular and extratruncular VM and LM, with requirement that the existence of **two of the above** mentioned malformations **are enough** for definition of KTS, allows to define erroneously the combined extratruncular VM + extratruncular LM as KTS. These patients can be simply classified as combined CVM instead.

Furthermore, the definition of KTS as "combination of truncular and extratruncular VM and LM" is excellent, but it should be added "in patients with osteomuscular hypertrophy", he argued. In absence of hypertrophy, he would classify those patients as "Combined CVMs" instead, as proposed in IUP 2014. It should also be emphasized that we are not referring just to length discrepancy but also to circumference/ osteomuscular hypertrophy.

Clinical Presentation

Presentation of patients with KTS can range in severity from trivial, mild forms such as capillary malformations and few veracities of the affected extremity causing only cosmetic concern to life-

threatening, severe disability associated with massive limb overgrowths, chronic pain, infections, thromboembolism and/or hemorrhage from venous malformations[38-40]. As mentioned in the introduction, the classic triad of KTS findings include capillary malformation, venous malformation, and/or soft tissue or bony hypertrophy of affected extremity. In a significant number of KTS abnormalities of the lymphatic system are present either in form of primary lymphedema, cutaneous vesicles draining lymph fluid, cystic hygromas or lymphangiectasia associated with reflux of the chyle[41].

Patients with at least two of the three classic findings have been classified as incomplete KTS form[42]. Less frequently, a shorter and smaller limb may be present instead of hypertrophic extremity. With few exceptions, most frequently the presence of physical exam findings of the baby after birth will persist and will define the appearance of a patient. Some of the findings can worsen with triggering factors such are infection, injury, influence of hormones during pregnancy or puberty. Occasionally symptoms can worsen without identifying triggering factor.

A study from Mayo Clinic, that evaluated 252 KTS patients, showed that the capillary malformations, tissue or osteo-hypertrophy and varicosities or venous malformations were present in 246 (98%), 236 (94%) and 182 (72%) patients, respectively[43]. More frequently the lower extremity was involved (70%) and the malformation was unilateral in 81% of cases. Data from this study also showed that most common presenting symptoms included swelling (70%), hemorrhage (17%) and pain (7%). 15% of patients had a history of superficial phlebitis. 4% of patients had a history of deep vein thrombosis and the same percentage had pulmonary embolism. One pulmonary embolism was lethal. Lateral varicose veins, medial varicosities and suprapubic varicosities (due to iliac vein aplasia) were found in 56%, 19% and 1% of patients, respectively.

Presence of the lateral embryonic vein deserves special consideration since the hemodynamic alterations associated with blood stasis in these frequently valveless veins not only causes symptoms but is also associated with a high risk of venous thromboembolic events[44]. It has to be emphasized that there is inconsistent terminology that characterizes majority of the literature discussing persistent embryonic veins. The persistent lateral (marginal) embryonic vein and the persistent sciatic vein are the only two persistent embryonic veins found in KTS patients. The lateral marginal vein is a superficial vein although from the anatomical stand point the term "superficial" is a misnomer since this vein frequently penetrates the deep fascia and involves muscles of the deep compartment of the lower extremity. Persistent sciatic vein is part of the deep venous system.

Diagnostic Imaging

Historically, the diagnosis and treatment of KTS have been hampered not only by the complex nature of these vascular lesions, but also by the absence of defined imaging protocols and therapeutic algorithms. Multiple diagnostic modalities are used (alone or combined) to evaluate KTS and to confirm the initial clinical diagnosis including US imaging, CT scan, catheter based angiography, and MRI[45-47].

Diagnostics	
CHIVA	
CHIVA	cure (C)onservatrice (H)emodynamique de l'(I)nsufficense (V)eineuse en (A)mbulatoire [Hemodynamic Conservative cure of Venous Insufficiency in the Ambulatory]
CS	closed shunt
DPT	DUS Probe compression test
OVS	open vicarious shunt
ODS	open deviated shunt
MRI	
MRI	Magnetic Resonance Imaging
dceMRI	dynamic contrast enhanced MRI
STIR	Short Tau Inversion Recovery
T1	Short TE and TR weighted images
T2	Long TE and TR weighted images
TE	time to echo
TLPS	transarterial lung perfusion scintigraphy
TR	time to repetition
TREAT	time resolved echo-shared angiographic techniques
TRICKS	time resolved imaging of contrast kinetics
WBBPS	whole body blood pool scintigraphy

Table III - Diagnostics

Ultrasound

Physical examination is most frequently followed by detailed color duplex ultrasonography of the venous system of the leg. Ultrasonography is frequently utilized as it is non-invasive, widely available (including non-hospital settings) and inexpensive. Ultrasonographic evaluation is utilized to establish patency and to evaluate for any anomalies, including hypoplasia, aplasia and/or aneurysms of the deep venous system. Complete ultrasonographic evaluation needs also to include assessment for deep venous thrombosis and competence of deep, superficial and perforating venous systems. In addition to this, complete evaluation of lateral marginal vein is

performed as well. On duplex ultrasonography venous malformations demonstrate monophasic, biphasic and no detectable flow in 78%, 6% and 16% of cases, respectively[48].

Since the '90s, an increasing interest is seen towards the so called hemodynamic approach to vascular malformations, especially to KTS. This approach is derived from the CHIVA strategy for the treatment of chronic venous insufficiency. The French acronym CHIVA means *cure Conservatrice Hemodynamique de l'Insufficense Veineuse en Ambulatoire*[49] [Hemodynamic Conservative cure of Venous Insufficiency in the Ambulatory]. As CHIVA was treated extensively during the Debate, we will present it here its specialized ultrasound assessment.

The modified Perthes test

The deep veins occlusion/hypoplasia/agenesia (often femoral) and the superficial atypical venous conduct called Marginal Vein (MV) are two important components of the venous Malformation (VM) in KTS, though sometimes they can be absent.

The MV is an anatomic anomaly with variable functional impairments. This vein is sometimes totally or partially compensating a deep vein obstacle (open vicarious shunt or OVS), sometimes fed and overloaded totally or partially during the diastole by the deep veins (closed shunt or CS), sometimes a combination of both. In all the cases, the associated CM is aggravated by or totally due to the increased venous pressure due to the shunts and the residual pressure at its level is high, cause of the low resistance of its microcirculation[50-53]. A detailed venous mapping is required, with the detection of the systolic and diastolic reflux.

The role of MV can be contextualized by the study of the Systo-Diastolic reflux in the short saphenous vein (SSV) and MV (systolic and diastolic ultrasound venous carthography). A "Modified Perthes Test" can help in the selection of the patients and of the sites of surgical intervention. The test, proposed by C Franceschi[54], checks the delayed response of the limb exposed to a long lasting exclusion of the superficial network (including MV) . The test can be achieved also by an eccentric compression, just limited to the MV[55] and is useful in the selection of the patients for surgery and in the choice of the possible sites of surgical intervention.

N Morrison proposed a prolonged Perthes test with an associated huge effort (presented during the systo-diastolic event and also later on Vasculab[56]). However, during a hard exercise, after a few calf contraction there will be no additional appreciable ejection of blood. This fact can be easily seen in air plethysmography, where (whatever the manoeuvre) the leg volume reaches almost a plateau after a few repetitions. In other words, muscles during the exercise do not receive and do not expel much blood, like they were in anaerobe metabolism.

In addition, while the Morrison manoeuvre testifies the patency of the deep system, nevertheless if compared to the other variants of the manoeuvre it points only approximatively to the punctual sites for the MV interruption.

Recently, **C Franceschi** proposed a very promising variation of the Perthes test, the DUS probe compression test (DPT)[57] (KTrenaunay msg 11186[58]), achieving the same results of the modified Perthes test, but using a very quick procedure. The test has the aim of assessing a compensating vein, whether a varicose or a malformed vein, and is based on the compression by the ultrasound probe below a perforating vein, during the activation of the venous pump.

DUS probe compression test (DPT)

- The result can be
  - a venous collapse in case of closed shunt (open deviated shunt or ODS)
  - an unchanged calibre in case of deep venous incompetence (deep competitive reflux)
  - an increase of the tension of the venous wall in case of flow compensating a deep obstacle

The modified Perthes test (any of the above cited) can be effected before conservative procedures, showing to the surgeon (as well as to the patient) what can be expected from the disconnection at the compressed point.

In order to test the outflow capacity of the deep venous system, C Recek proposed to use the occlusive plethysmography, performed firstly with open MV and later with the compression of the MV (with a tourniquet or digitally) to assess how much it contributes to the outflow. The occlusive plethysmography is used in analogy to the work of Trendelenburg, who tested the patency and outflow capacity of deep veins in varicose vein patients using his reversed Trendelenburg test.

In the standing position, a tourniquet was placed in the thigh to compress the incompetent GSV. Then the patient laid down and elevated the limb. Varicose veins emptied through calf perforators and deep venous system, also not as quickly as through the incompetent GSV after releasing the tourniquet, Trendelenburg wrote. He insisted that both the normal test and the reversed one should be performed before ligation of the GSV. The same can be applied to the MV in KTS.

These investigations are not theoretical, because they help in understanding in a rational way "if" and "in which extent" the MV can be excised and in addition "how to deal with the naevus" and "if and where" to operate.

Other diagnostic Imaging

Plain X-rays of the bones (scanograms) are used as a routine radiologic test in patients with limb size discrepancy. X-rays are performed to measure bone length. Occasionally they will demonstrate phleboliths as well. Contrast-enhanced CT can identify the location of the venous malformation, bony involvement, vessel ectasia, and aneurysm formation[59]. True extent of the lesion into soft tissue, however, is underestimated as only contrast-enhanced vessels opacity. Although still frequently used US and CT scan provide variable degrees of diagnostic accuracy or frequently insufficient information with regards to pre-procedural planning. This is especially true for medical centers where treating physician does not perform diagnostic ultrasonography, as this evaluation is performed by a designated ultrasonographer.

Given the above mentioned limitations MRI became the imaging modality of choice in the evaluation of KTS in specialized centers. MRI gives a bright signal on T2-weighted spin-echo sequences for the parenchymal portions of vascular lesions which is not only useful to delineate the extent of the malformation throughout the involved tissues but it also allows for treatment planning and can be used for objective assessment of the treatment efficacy[60]. Full extent of tissue involvement is readily depicted when T1 and T2 or Short Tau Inversion Recovery (STIR) images are acquired.

Venous malformations associated with KTS have characteristically augmented intraluminal signal on T2-weighted images. There is frequently an intraluminal signal on the T1-weighted images as well. Low flow vascular lesions enhance with contrast and normally do not contain flow voids. If present, macrocystic lymphatic malformations are often differentiated from venous malformations by their predominantly cavitary, lobulated and septated appearance that is

characterized by hypointense signal on T1-weighted and hyperintense signal on T2-weighted and STIR images.

Distinct from venous malformations, macrocystic lesions do not enhance with an exception of "rings and arcs" appearance within cyst wall or septae. Macrocystic lesions are more likely to demonstrate fluid-fluid levels. Microcystic lesions are differentiated from macrocystic lesions by the absence of dominant cystic spaces and lack of contrast enhancement and this is used as criteria to differentiate them from venous malformations. High-flow vascular malformations typically do contain flow voids that can be identified on T1- and T2-weighted images.

This radiologic characteristic is used for excluding arterial flow, which is found in PWS. Conventional MRI was not used only for evaluation of a lesion but for the evaluation of deep venous system. This is very important as the prevalence of deep venous system anomalies is high in KTS patients and the status of deep venous system and its relation to the vasculature is used for treatment planning.

Although conventional MRI shows the lesion's flow characteristics, relation to normal circulation and provides good soft tissue definition it is frequently not adequate to provide hemodynamic data. In addition, many particulars can mitigate conventional MRI findings; for example: a blood vessel that courses within an imaging plane may produce an intraluminal signal despite fairly fast flow, falsely suggesting a low-flow malformation which can potentially lead to catastrophic side effects if the lesion is treated as low flow malformation. To avoid this, relatively recently dynamic contrast enhanced MRI (dceMRI) started to be increasingly used in highly specialized referral medical centers[61].

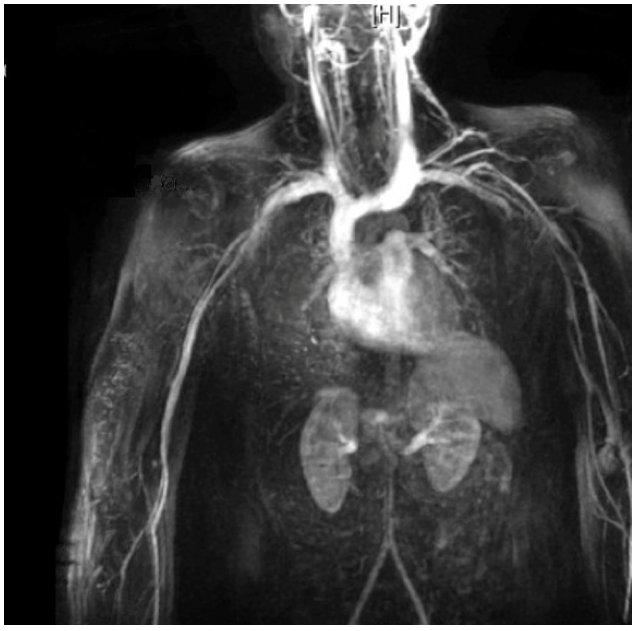


Figure 3 - dceMRI of the right upper extremity demonstrates absence of the appearance of the malformation during the arterial phase of the maximum intensity projection time-resolved imaging, which is confirmatory to exclude arterio-venous shunting. This is a critical step for treatment planning.

dceMRI can be used to more accurately assess flow within the lesion since it yields more information with regards to hemodynamic characteristics by utilizing time resolved imaging of contrast kinetics (TRICKS) and time resolved echo-shared angiographic techniques (TREAT) where images are acquired sequentially[63,64]. This dynamic image acquisition produces multiple image volume sets, each at a different time points that are subsequently converted to a maximum-intensity projection, which are displayed in a way that vessel and lesion enhancement are the only structures visualized.

This technique generates the appearance of dceMRI images that are analogous to a display of a conventional digital arteriogram with background subtraction. (Figure 3) In this way, main vascular components of the lesion are enhanced, which provides better definition and more accurate differentiation between high-flow and low-flow lesions than conventional MRI. In addition, dceMRI has the advantage of being able to detect dominant or multiple feeding vessels, what is critical for treatment planning.

Image acquisition extends from the arterial to the late venous phase using time-resolved imaging of contrast kinetics, time-resolved echo-shared angiographic technique, or time-resolved angiography with stochastic trajectories dynamic sequences. Besides defining the extent of the abnormality, dceMRI results interpretations includes information with regards to the type of vascular malformation as well as the flow velocity within the lesion. If the dynamic gadolinium-enhanced sequences identified flow within the lesion at or preceding the visualization of arterial flow within normal vessels, the lesion is considered to be a high-flow lesion and would exclude diagnosis of KTS. The presence or absence of early venous return from veins draining the lesion or true immediate arterial venous shunting (i.e., an arterial venous malformation) through the lesion is used to describe the flow characteristics.

If the lesion is not apparent on the dynamic gadolinium-enhanced images until the capillary phase, or more typically the venous phase, as determined by a comparison with visualization of normal vessels, the lesion is considered to be a low-flow. In 2002, Van Rijswijk et al. published data from a prospective study resulted from blinding two independent observers as they reviewed conventional MRI and dceMRI imaging performed on 27 patients with clinically suspected high-flow vascular malformations[64]. All patients underwent dceMRI as well as diagnostic angiography. Sensitivity of conventional MRI in differentiating venous and non-venous lesions was 100%.

However, data from this study showed an increase in the specificity of MRI from 24% - 33% to 95% with the addition of dynamic contrast-enhanced sequences. When dceMRI is not definitive in assessing flow status, arteriography is performed not only to confirm the diagnosis, but also to identify the communication pattern with the draining venous system and to provide an opportunity for treatment planning and/or intervention. Although highly specific, arteriography is limited in its ability to delineate a lesion relative to its adjacent anatomic structures. This is an important limitation as malformations can infiltrate muscle, encircle nerves and can invade adjacent vital tissues. In addition arteriography is considered an invasive technique as it carries significant risk for complications including groin hematoma, pseudoaneurysm, arteriovenous fistula, acute arterial thrombo-embolic events and infection. These complications have been reported in approximately 1.5-9% of patients[65,66].

The ability to use a single imaging modality to distinguish between high-flow and low flow lesions is essential when the goal is to avoid noncontributory and/or invasive imaging modalities, select proper treatment modality, avoid unnecessary invasive catheter-based procedures and to avoid potentially life threatening side effects. Although multiple imaging modalities are available for the management of KTS, dceMRI provides the most critical information. Above described diagnostic algorithm with novel imaging techniques

avoids non-contributory imaging and has been validated as clinically applicable for making an accurate anatomical and hemodynamic diagnosis and for treatment planning in majority of patients. In addition, it avoids unnecessary diagnostic arteriograms, in most of the cases, allowing a significant number of patients to be spared the expense, risk, and inconvenience of a catheter-based diagnostic study, as well as delayed or erroneous diagnosis. However it has to be emphasized that dceMRI adds to the cost of the treatment and is currently widely utilized only in high volume hospitals.

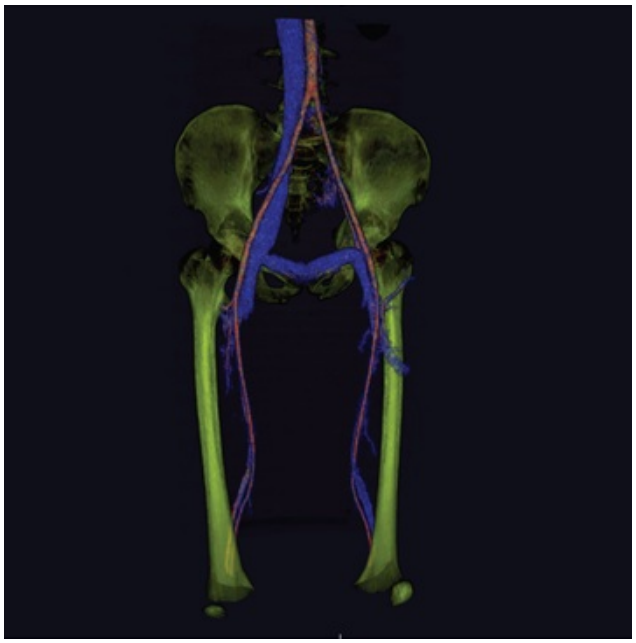


Figure 4 - 3-D MRI reconstruction of a 26-year-old male demonstrates aplasia of the left common iliac vein. Evaluation of patency and anatomical variations of the deep venous system is vital in all KTS patients prior to establishing a definite treatment plan, due to relatively high incidence of deep venous system anomalies.

Discussion

R Mattassi *said that the old triad of 1900, based only on clinical data, is old enough. Today we can perform a more precise diagnosis, which should be a step by step progression of examinations, starting from the less invasive, as following:*

Examination tools in KTS

- *step by step, starting from the less invasive*
  - *clinical examination: it is very important that the presence of the triad should NOT bring directly to the diagnosis but only to a suspicion*
  - *duplex scan*
  - *MRI: some specific settings for main veins demonstration are required*
  - *lymphoscintigraphy: to demonstrate main draining lymphatics. That exam should be done not in the standard manner but with separate morphological study of deep and superficial lymphatics*
  - *comparative bone X-Ray to measure limb length difference*
  - *other optional test*

BB Lee *noted that diagnosis to find out or exclude the AVM is based on clinical evaluation/physical exam, basic combination of non-invasive tests like DUS and MR especially when there are other CVMs as well. We postpone further evaluation of AVM with invasive test like arteriography till needed/indicated for the treatment but meanwhile, we do carry CTA and/or trans-arterial lung perfusion scintigraphy (TLPS)*[67-69]*, etc. to assess its progress, he added.*

In selected cases, the edema's composition of the foot could be analysed and might show chylous components or /and leaking skin vesicle, losing a milky lymphorrhea, argued ***JP Belgrado****.*

BB Lee *noted that 'Deep infiltrating veins/ Extratruncular VM' can be combined with Extratruncular LM. Indeed, in his experience, quite a few of extratruncular VM diagnosed with MRI with no contrast was subsequently confirmed, as either combined with extratruncular LM or pure extratruncular LM through MRI with contrast, which he confirmed by direct needle aspiration to check its contents.*

Treatment

The vast majority of practitioners consider hemorrhage, infections, acute thromboembolism and/or refractory ulcerations as absolute indication for treatment. Relative indications include pain, functional impairment, edema (secondary to chronic venous insufficiency), limb asymmetry and/or cosmesis[70,71]. Pretreatment planning for KTS patients is best done by a multidisciplinary vascular malformation team, when possible. Prior to treatment, every effort should be exerted to rule out the arterial component. This differentiation is of critical significance as treatment options for high flow and low flow malformations are significantly different as the presence of arterio-venous shunting represents an absolute contraindication for sclerotherapy due to increased risk of distal embolic events.

Pretreatment planning should routinely incorporate evaluation of patency of the deep and superficial venous system due to the high prevalence of the deep venous system anomalies in KTS patients. In a study of 392 patients Eifert et al. documented aplastic or hypoplastic deep venous trunks in 8% of vascular malformation patients[72]. The prevalence of deep venous anomalies is even higher (18%) in subgroup of patients with KTS. (Figure 4) This assessment needs to be included in the treatment planning since venous blood flow from the affected extremity may depend on the malformation vessels and obliteration or exclusion of the malformation from the circulation carries the risk of the impairment of venous return from the affected extremity. Surgical resection of dilated superficial varicosities in a patient with an absent or hypoplastic deep venous system is disastrous. The remaining venous collateral system is not adequate to drain the limb, and massive lower extremity swelling and ulceration can develop.

The treatment modalities utilized for the management of KTS can be conservative and interventional.

Compression therapy represents the mainstay for conservative treatment. Most commonly an elastic garment or graded compression stockings are used on the affected extremity, as this has been shown beneficial in managing both lymphedema and/or symptoms of chronic venous insufficiency. In patients with venous edema or chronic lymphoedema physical therapy including massage treatment and intermittent pneumatic compression therapy, has been used with good results.

In addition to this, conservative treatment can be supplemented with local wound care, special orthopedic footwear as well as with lifestyle modification, as these may be needed to improve daily functional capacity of a KTS patient. In addition to somatic symptoms, the psychological aspect of KTS pathology, caused by a visible deformity of the KTS should not be underestimated. Therefore, KTS patients should be offered a psychological counseling, if needed, as well as participation in the KTS support group(s)[42]. This participation should be offered to both patients and their families.

Only patients who are symptomatic or have absolute indications for the intervention (discussed above) that are refractory to conservative treatment should be considered candidates for therapeutic intervention, given the potential for additional morbidity related to any intervention. The treatment of KTS patients is characterized by multiple treatment sessions, in significant majority of patients, applying the treatment modality that is the most appropriate for the location, extent and morphology of the lesion(s).

The need for multiple treatment sessions should be discussed with a patient and their family (if applicable) prior to initiation of treatment to increase patient's compliance with the therapy. The possibility of recurrence following the treatment should also be discussed with the patient prior to starting the treatment to minimize patients' frustration in case of the recurrence. Goals of the treatment should be preset with each patient individually and successful accomplishment of preset goals marks the completion of treatment, as treatments are frequently palliative and goal-oriented, especially in extensive lesions.

Traditionally, surgical resection was effectively used for encapsulated and small lesions. However in patients with diffuse and multifocal lesions, the surgical debulking is relatively contraindicated as damage to surrounding anatomic structures and massive hemorrhage may ensue[73]. In 2016 Malgor et al. retrospectively evaluated long term outcomes of open surgical treatment in 49 patients (53 limbs) with KTS[74]. The great saphenous vein stripping, lateral embryonic vein, small saphenous vein and accessory saphenous vein surgical removal was performed in 17 (32%), 15 (28%), 10 (19%) and nine (17%) lower extremities, respectively. Data from this study showed that two patients developed DVT, one had pulmonary embolism, and one patient had peroneal nerve palsy.

Kaplan-Meier analysis demonstrated that freedom from disabling pain at one, three and five years was 95%, 77% and 59%, respectively. Respective rates for freedom from secondary procedures were 86%, 78% and 74%. In addition, at the last follow-up visit, the venous clinical severity score had decreased from 9.4 ± 3.27 to 6.0 ± 3.20 ($P<0.001$). Data from this study showed that surgical approach in patients with KTS is safe and durable. Although historically surgery has been used to treat vascular malformations associated with KTS over the last two decades, minimally invasive procedures have emerged as effective treatment options.

Sclerotherapy has been used as an effective alternative to surgery in the treatment of venous malformations. Traditionally, the most widely used sclerosant was ethanol. Although effective, data showed that ethanol sclerotherapy was associated with limitations and major complications (local and systemic), including severe pain requiring general anesthesia, ethanol toxicity, and localized tissue necrosis[75-77]. In a study of 87 patients with venous malformations treated with 98 sessions of ethanol sclerotherapy Lee et al. reported outstanding results with 95% initial success with no recurrence in 71 patients at a mean follow-up of 24 months[78].

Data from this study also documented complications in 26.7% of patients which ranged from mild to severe. There were nine cases with ischemic bullae, five with nerve palsy, four cases of transient pulmonary pressure elevation, two with tissue necrosis and tissue fibrosis, one with DVT and one with pulmonary embolism. Of the five nerve palsies, one (affecting the peroneal nerve) was irreversible. Other studies also reported major side effects following ethanol sclerotherapy including cardiac arrest and episodes of transient bradycardia. Ethanol sclerotherapy can also result in transmural vessel necrosis, massive swelling (sometimes resulting in compartment syndrome), depression of the central nervous system, hypertension and pulmonary vasospasm.

Burrows and Mason reported good to excellent results after serial sclerotherapy in 75-90% of patients with low flow vascular malformations and showed that ethanol injections should be avoided close to major nerves or cutaneous lesions[79]. There was a 12% complication rate per session and 28% complication rate per patient in this series, with at least some skin necrosis occurring in 10-15%. Given that liquid sclerosants become diluted by intralesional blood, the use of sclerosants in microfoam form significantly improves the procedure for venous malformations as the foam bubbles displace intralesional blood and prevent sclerosant from becoming diluted. Foam

bubbles achieve maximal exposure between the sclerosing agent and the endothelial lining of malformation and the echogenicity of the bubbles makes them visible on ultrasonography making the procedure more effective and easier to perform. (Figure 5)

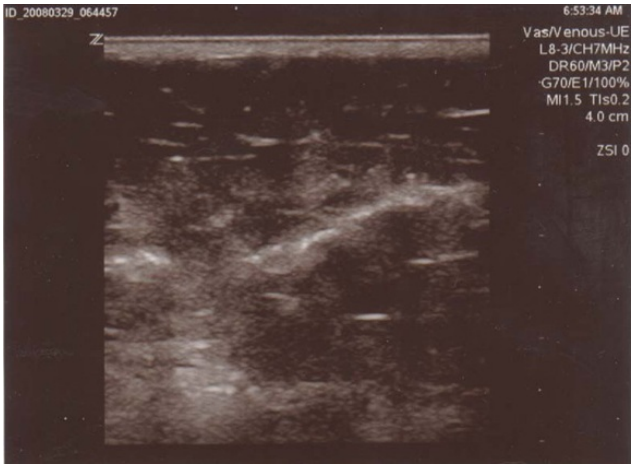


Figure 5 - Ultrasonographic findings during sclerotherapy treatment of low flow, venous malformation in a 21 year old female with KTS. The echogenicity of the bubbles makes them visible on US surveillance making the procedure easier to perform, which is one of the major advantages of foam sclerotherpay as compared to liquid sclerotherapy.

For these reasons foam treatments, in contrast to liquid sclerotherapy, can be performed on ambulatory basis under local anesthesia. In a prospective randomized clinical trial Yamaki et al. compared efficacy of ultrasound-guided foam sclerotherapy with ultrasound-guided liquid sclerotherapy in the treatment of 89 symptomatic venous malformations[80]. Data from this study showed that the amount of sclerosant required to treat the lesion was significantly smaller in patients who were treated with foam sclerotherapy. These properties of sclerosant in the form of microfoam make it possible to use smaller doses in small increments what reduces the risk of side effects and toxicity. Foam can be produced with different techniques that result in differences in bubble size, foam stability and reabsorption rates.

Most widely accepted method for producing stable foam is "Tessari method" first described in 2000[81]. The choice of foamed sclerosant is typically physician dependent. Currently the majority of venous malformations are treated with 0.5%-1% sodium tetradecyl sulfate or 1% polidocanol. Alternative sclerosants such as bleomycin or doxycycline may be used in special circumstances, including malformations with lymphatic component. The first large study of patients treated by foam sclerotherapy was published by Cabrera et al. This study included 50 patients (35 with venous malformations and 15 with KTS)[82]. Sclerotherapy was performed by ultrasound guided injection of 0.25% to 4% polidocanol microfoam.

Data from this study showed that the treatment was beneficial in 46 (92%) patients. Total disappearance of treated malformation, reduction in size of more than 50% and reduction in size of less than 50% was documented in 158, 15 and 13 patients, respectively. In subgroup of patient who presented with pain (n=39), 25 experienced total relief, and in the remaining 14 patients the pain was significantly reduced. There were no major adverse events. Skin necrosis developed in three patients and four patients developed skin hyperpigmentation that was transient.

Data from another perspective study that included 14 patients (eight with KTS) treated with 1% or 2% polidocanol, demonstrated that the use of polidocanol foam sclerotherapy was effective, and showed no major complications, no down time and no need for general or regional anesthesia. Although there is a significant amount of data that showed excellent results by evaluating safety and efficacy of the endothermal treatment either with radiofrequency ablation (RFA) or endovenous laser ablation (EVLA) in patients with chronic venous insufficiency caused by superficial venous reflux disease there are some limitations in KTS patients who have large incompetent superficial veins located immediately under the skin, as treatment of these superficial veins can lead to significant thermal injury.

Although this concern should not be underestimated data from several case reports and smaller case series showed that both RFA and EVLA were efficient and safe treatment for superficial incompetent veins in KTS patients. Frasier et al. showed that combined treatment (RFA and sclerotherapy) was associated with markedly decreased leg pain, edema, and varicose vein appearance in three female KTS patient that were previously unsuccessfully treated with the conservative therapy[83]. In 2014, Harris et al. showed that RFA can be safely and effectively used for obliteration of perforating veins in KTS patients. Data from this study showed a significant symptomatic improvement following staged and multimodal treatment of perforating veins that included RFA combined with sclerotherapy[84].

The specific indications for treatment of lateral embryonic vein are based on symptom severity and the status of the deep venous system. In symptomatic patients (i.e. hemorrhage, debilitating pain, and/or functional disability) with patent deep veins, treatment of the lateral embryonic vein is indicated for the elimination of altered hemodynamics without compromising lower extremity blood return. This also applies to a subgroup of patients with hypoplasia of the deep veins: in this case treatment of the lateral marginal vein will lead to spontaneous dilation of the deep veins, and therefore hypoplasia of deep veins

is not a contraindication for treatment. By contrast, aplasia of the deep veins does represent a contraindication for intervention, as the lateral embryonic vein serves as a major draining vein of the affected limb in these cases. A modified Perthes text could clarify the compensating value of the marginal vein, analyzing its exclusion at different levels. The result can suggest a local surgical therapy.

All patients with a lateral marginal vein should undergo a complete hypercoagulability workup (including measurement of D-Dimer and fibrinogen) and should be anticoagulated appropriately with weight adjusted dose (100 U/kg/d) of low molecular weight heparin periprocedurally[31]. Traditionally, as mentioned above, surgical resection of lateral marginal vein is preferred over endovascular treatment modalities as it is safe and durable and due to the superficial location of this vein and the fact that endovenous treatment modalities are associated with the risk of skin damage.

Discussion

A quarter or more of LM components of the KTS is extratruncular LM/lymphangioma alone as a constant source of lymph leakage especially after ill-planned excision of coexisting marginal vein (MV), where the complication seems to be the effect of the previous balance disrupted by the treatment, affirmed ***BB Lee****.*

MA Amore *declared that LM is often present in KTS, but we must take care in the treatment with the massive use of Rapamycin, owing to the Rapamycin associated lymphedema, lymphocele, chylous ascites… etc. as secondary effect. More interesting Rapamycin was the "STAR" of the last ISSVA meeting held in Buenos Aires one week before the KTrenaunay debate, with a lot of groups around the world with a high follow up of this drug.*

BB Lee *declared he was so disturbed by sudden enthusiasm on Rapamycin, that transplant surgeon are already fully aware of, about the risk involved with de novo swelling of the limb/lymphedema together with increasing risk of the lymphocele formation following kidney transplantation for many decades. Besides Rapamycin certainly increased delayed wound healing with higher risk of wound disruption in his personal experience.*

As regards the surgical treatment, ***F Passariello*** *reported that in selected cases the surgical therapy has a clear beneficial effect, for instance when an extrinsecal compression on the deep veins increases the symptoms of deep veins KTS hypotrophy. As suggested by Servelle[85], the resection of fibrous structures can improve considerably symptoms . Compression can be due to abnormal arterial branches or to fibrous arcs, as it occurs in the upper limb with the Langer axillary arc[85] or in the lower limb with a fibrous-muscular fiber between the two gastrocnemius muscles[86].*

The Chiva Strategy in KTS

The CHIVA strategy essentially separates the systolic reflux from the diastolic part. Only the diastolic component can be excised in order to preserve the compensating veins[87-89]. The study of the Systo-Diastolic reflux is essential to understand if there is a compensating pathway, which must be respected and if there is a diastolic reflux, which can be safely interrupted. The CHIVA strategy uses the modified Perthes test to select the level of interruption of the marginal vein and to achieve also a naevus reduction.

An accurate ultrasound mapping is performed, together with dynamic tests as Valsalva, Paraná and Perthes, in order to respect the compensating veins in an open vicarious shunts (OVS) and disconnect the diastolic overload of the closed shunts (CS). The surgery is mini-invasive, performed in one or more steps with 6 months interval (time needed to let the system to stabilize) with divisions and non-absorbable ligations at the disconnections sites. Surgery is planned without any excision in order to let the capillary malformation drain properly (reduced coloration) and paying careful attention to the uneasy haemostasis, due to fragile veins and capillary malformation.

The intervention tries to block the diastolic overload, pressures and flows while preserving the draining outflow, in order to ease the skin drainage as well as the reduction of the capillary skin malformation. These are the basics of CHIVA management, whatever the vessels anatomy and the cause of their dysfunction.

Such aimed punctual disconnections prevent large bleedings caused by extended phlebotomies, ease the skin drainage, improve the skin changes and prevent any recurrence. As regards the neavus reduction, it is worth noting that the CHIVA strategy is the first one which links the skin drainage as well as CM/port wine stain to MV drainage, as we know of. This observation/ hypothesis is certainly a new area to be included into future research projects together with unintentionally neglected CM altogether with microcirculation at tissue level.

Summary

Over the last two decades there has been a significant progress in the understanding of molecular and genetic mechanisms responsible for etiology and pathophysiology of KTS as well as significant improvement in the management of these patients. Data from numerous studies provide strong evidence that experienced providers working in the context of a coordinated and structured multidisciplinary vascular malformation team can offer the most efficient management of KTS patients. Diagnostic algorithm utilized to exclude presence of arterial flow is clinically applicable for making an accurate diagnosis and pretreatment planning in majority of patients. For most patients with minimal symptoms conservative treatment seems to be the best strategy. Patients with more severe symptomatic require treatment. Choice of treatment modality depends upon lesion's location, extent and morphologic as well as hemodynamic characteristics. This management algorithm for KTS results in favorable outcomes with reasonable complication rates in this

frequently challenging group of patients. New expectations come from the CHIVA approach to vascular malformations, which detects the systolic and diastolic components of reflux, in order to perform selective and short venous excisions. The method is considered an effective one, though an adequate training is required.

Acknowledgements

The KTrenaunay Vasculab Debate was organized by the Vasculab List as an Online Debate. We thank all the participants for their contribution and especially for their active role: Miguel Angel Amore, Pier Luigi Antignani, Iris Baumgartner, Jean-Paul Belgrado, Lena Blomgren, Alun H Davies, Tom Eaton, Stefano Ermini, Claude Franceschi, SB Gogia, Byung Boong Lee, NingFei Liu, Jovan N Markovic, Raul Mattassi, Nick Morrison, Tom O'Donnell, Waldemar L Olszewski, Sandeep Raj Pandey, Kurosh Parsi, Hugo Partsch, Fausto Passariello, Malay Patel, Sergio Pillon, Teresa Pintos Moreu, Cestmir Recek, Heraldo Schlup, Eva M Sevick, Natarajan Sekar, Gerard Stansby, Massimo Vaghi, David Wright.

Finally, we thank Mrs. Iolanda Palma for her organizational effort.

References

1) Geoffroy Saint-Hilaire I. Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux. 3 volumes + atlas. Paris, J.M.; Baillère édit., 1832-7. Available on line at the address http://www.biodiversitylibrary.org/item/106438#page/768/mode/1up at the date of Feb 8, 2017.

2) Morin A. 1996, "La tératologie de Geoffroy Saint-Hilaire á nos jours" [The teratology of Geoffroy Saint-Hilaire nowadays]. Bulletin de l'Association des Anatomistes, 80, 248:17-31.

3) You CK, Rees J, Gillis DA, et al. Klippel-Trenaunay syndrome: a review. Can J Surg. 1983;26:399-403.

4) Trelat U, Monod A. De l#hypertrophie unilaterale partielle ou totale du corps. Arch Gen Med. 1869;13:536 -538.

5) Klippel M, Trenaunay P. Memoires originaux : du naevus variqueux osteo-hypertrophique. Arch Gen Med. 1900;Tome III:641-672.

6) Parkes Weber F. Angioma formation in connection with hypertrophy of limbs and hemi-hypertrophy. Br J Dermatol. 1907;19:231-235.

7) Aelvoet GE, Jorens PG, Roelen LM. 1992. Genetic aspects of the Klippel-Trenaunay syndrome. Br J Dermatol 126:603-607.

8) Oduber CE, van der Horst CM, Hennekam RC. 2008. Klippel-Trenaunay syndrome: Diagnostic criteria and hypothesis on etiology. Ann Plast Surg 60:217-223.

9) Malan E. Vascular Malformations. Carlo Erba ed. Milan, 1974.

10) Lorda-Sanchez I, Prieto L, Rodriguez-Pinilla E, Martinez-ML. 1998. Increased parental age and number of pregnancies in Klippel-Trenaunay-Weber syndrome. Ann Hum Genet 62:235-239.

11) Jorgenson R, Darby B, Patterson R, Trimmer K. Prenatal diagnosis of the Klippel-Trenaunay-Weber syndrome. Pren Diag 1994;14:989-92.

12) Lindenauer SM. The Klippel-Trenaunay syndrome: varicosity, hypertrophy and hemangioma with no arteriovenous fistula. Ann Surg. 1965;162:303-314.

13) Berry SA, Peterson C, Mize W, et al. Klippel-Trenaunay syndrome. Am J Med Gen 1998;79:319-26

14) Hanahan D. Signaling vascular morphogenesis and maintenance. Science 1997;277:48-50.

15) Klagsbrun M, D#Amore PA. Vascular endothelial growth factor and its receptors. Cytokine Growth Factor Rev 1996;7:259-70.

16) Whelan AJ, Watson MS, Porter FD, et al. Klippel-Trenaunay-Weber syndrome associated with a 5:11 balanced translocation. Am J Med Genet. 1995;59:492- 494.

17) Wang Q, Timur AA, Szafranski P, et al. Identification and molecular characterization of de novo translocation t(8;14)(q22. 3;q13) associated with a vascular and tissue overgrowth syndrome. Cytogenet Cell Genet. 2001;95:183-188.

18) Timur AA, Sadgephour A, Graf M, et al. Identification and molecular characterization of a de novo supernumerary ring chromosome 18 in a patient with Klippel-Trenaunay syndrome. Ann Hum Genet. 2004;68:353-361.

19) Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet 2003;73:1240-9.

20) Revencu N, Boon LM, Dompmartin A, Rieu P, Busch WL, Dubois J, Forzano F, van Hagen JM, Halbach S, Kuechler A, Lachmeijer AMA, Lähde J, Russell L, Simola KOJ, Mulliken JB, Vikkula M. 2013. Germline mutations in RASA1 are not found in patients with Klippel-Trenaunay syndrome or capillary malformation with limb overgrowth. Mol Syndromol 4:173-178.

21) Vahidnezhad H, Youssefian L, Uitto J. 2016. Klippel-Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). Exp Dermatol 25:17-19.

22) Wullschleger S, Loewith R, Hall MN TOR signaling in growth and metabolism. Cell 2006;124:471-484.

23) Bessis D, Vernhet H, Bigorre M, Quéré I, Rössler J. Life-Threatening Cutaneous Bleeding in Childhood Klippel-Trenaunay Syndrome Treated With Oral Sirolimus. Jama Dermatology, published online May 11, 2016, E1-2, DOI: 10.1001/jamadermatol.2016.1008.

24) Fernandez-Pineda I, Marcilla D, Downey-Carmona FJ, Roldan S, Ortega-Laureano L, Bernabeu-Wittel J. Lower Extremity Fibro-Adipose Vascular Anomaly (FAVA): A New Case of a Newly Delineated Disorder. Ann Vasc Dis. 2014;7(3):316-319. DOI: 10.3400/avd.cr.14-00049.

25) Luks et al. Lymphatic and Other Vascular Malformative/ Overgrowth Disorders Are Caused by Somatic Mutations in PIK3CA. J Pediatr 2015;166:1048-54.

26) Vignot S, Faivre S, Aguirre D, et al. mTOR-targeted therapy of cancer with rapamycin derivatives. Ann Oncol 2005;16:525-537.

27) Dimopoulos A, Sicko RJ, Kay DM, Rigler SL, Fan R, Romitti PA, Browne ML, Druschel CM, Caggana M, Brody LC, Mills JL. 2017. Copy number variants in a population-based investigation of Klippel-Trenaunay syndrome. Am J Med Genet Part A 173A:352-359.

28) Shikauchi Y, Saiura A, Kubo T, Niwa Y, Yamamoto J, Murase Y, Yoshikawa H. SALL3 Interacts with DNMT3A and

Shows the Ability To Inhibit CpG Island Methylation in Hepatocellular Carcinoma. Molecular and Cellular Biology, 2009 Apr;1944-58.

29) Liu NF, Lu Q, Yan ZX. Lymphatic malformation is a common component of Klippel-Trenaunay syndrome. JVS. 2010 Dec;62(6):1558-63. DOI: 10.1016/j.jvs.2010.06.166.

30) Mulliken JB, Young AE, eds. Vascular Birthmarks: Hemangiomas and Malformations. Philadelphia: WB Saunders, 1988.

31) Lee BB, Baumgartner I, Berlien P, Bianchini G, Burrows P, Gloviczki P, Huang, Y, Laredo J, Loose DA, Markovic JN, Mattassi R, Parsi K, Rabe E, Rosenblatt M, Shortell C, Stillo F, Villavicencio L, Zamboni P. Guidelines: Diagnosis And Treatment of Venous Malformations. Consensus Document of the International Union of Phlebology (IUP). Int Angiol. Jun, 2014.

32) Mulliken JB, Glowacki J (1982) Hemangiomas and vascular malformations in infants and children.A classification based on endothelial characteristics. Plast Reconstr Surg 69:412-422.

33) Belov S. Classification, terminology, and nosology of congenital vascular defects. In: Belov S, Loose DA, Weber J, eds. Vascular Malformations. Reinbek, Germany: Einhorn-Presse; 1989:25-30.

34) Lee BB, Bergan J. Gloviczki P, Laredo J, Loose DA, Mattassi R, Parsi K, Villavicencio JL, Zamboni P: Diagnosis and treatment of venous malformations - Consensus Document of the International Union of Phlebology (IUP)-2009. International Angiology 2009 December;28(6):434-51

35) Mattassi R. Management of combined venous and lymphatic malformations. Phlebolymphology. 2016;23(2):112-20. Available at the address http://www.phlebolymphology.org/phlebolymphology-89/ at the date of Mar 23, 2017.

36) Blei F. Medical management (Chylorrea). In Lee BB et al. (eds.), Lymphedema, chapter 54, 449. Springer-Verlag London Limited 2011. DOI: 10.1007/978-0-85729-567-5_54.

37) Azizkhan RG, Taylor JA. Surgical Management (Chylorrea). In Lee BB et al. (eds.), Lymphedema, chapter 55, 455. Springer-Verlag London Limited 2011. DOI: 10.1007/978-0-85729-567-5_55.

38) Baskerville PA, Ackroyd JS, Lea TM, Browse NL. The Klippel-Trenaunay syndrome: clinical, radiological and haemodynamic features and management. Br J Surg 1985;72:232-6

39) Upadhyay H, Sherani K, Vakil A, Babury M. A case of recurrent massive pulmonary embolism in Klippel-Trenaunay-Weber syndrome treated with thrombolytics. Respiratory Medicine Case Reports. 2016;17:68-70. DOI: 10.1016/j.rmcr.2016.01.008.

40) Li T, Hu SY, Chen ZT, Chen ZQ, Zhi XT. Colorectal cavernous hemangioma in Klippel-Trenaunay syndrome: a rare cause of abdominal pain and hematochezia. Surgery. 2015;157(2):402-4.

41) Servelle M. Klippel Trenaunay syndrome: 768 operated cases. Ann Surg 1985;201:365-73.

42) Gloviczki P, Driscoll DJ. Klippel-Trenaunay syndrome: current management. Phlebology 2007; 22: 291-8.

43) Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc 1998; 73:28-36.

44) Garg L, Mittal UK, Puri SK, Rissam HK. Klippel-Trenaunay syndrome, an unusual association with persistent lateral marginal vein of Servelle: colour Doppler and 256 dual-source MDCT evaluation. BMJ Case Rep. 2015.

45) Bucek RA, Vavrik J, Minar E, Lammer J, Tscholakoff D. Images in cardiovascular medicine. Multimodality imaging of hemangiectasia hypertrophicans (Klippel-Trenaunay-Parkes-Weber syndrome). Circulation. 2004;110(10):e295.

46) Trapanotto V, Hamper UM, DeJong MR, Sheth S. Klippel-Trenaunay-Weber syndrome: three-dimensional sonographic imaging. AJR Am J Roentgenol. 1996;166(2):472.

47) Roebuck DJ, Howlett DC, Frazer CK, Ayers AB. Pictorial review: the imaging features of lower limb Klippel-Trenaunay syndrome. Clin Radiol. 1994;49(5):346-50.

48) Trop I, Dubois J, Guibaud L, et al. Soft-tissue venous malformations in pediatric and young adult patients: diagnosis with Doppler US. Radiology. 1999;212:841-845.

49) Franceschi C. Theorie et pratique de la (C)ure (H)emodynamique de l' (I)nsuffisance (V)eineuse en (A)mbulatoire. Éditions de l'Armancon, Precy-sous-Thyl, 1988.

50) Franceschi C. Le malformazioni vascolari congenite. Part II. p 161-192. In Angiodisplasie. Flebologia. 1997; VIII(3):137-192.

51) Franceschi C, Cappelli M, Ermini S, Gianesini S, Mendoza E, Passariello F, et al. CHIVA: hemodynamic concept, strategy and results. Int Angiol 2016;35:8-30.

52) Franceschi C, Delfrate R, Bahnini A, Laurian C, Bricchi M, Massoni Cl, Birsdorff A. Venous Malformation. Pathophysiology, hemodynamic assessment and treatment strategy. Part 1. Presented at the 1st International Haemodynamic Symposium on Venous Disorders. Milan, 2015.

53) Franceschi C, Delfrate R, Bahnini A, Laurian C, Bricchi M, Massoni Cl, Birsdorff A. Venous Malformation. Pathophysiology, hemodynamic assessment and treatment strategy. Part 2. Presented at the 1st International Haemodynamic Symposium on Venous Disorders. Milan, 2015.

54) Franceschi C, Zamboni P. Principles of Venous Hemodynamics. New York: Nova Science Publishers, 2009.

55) Systo-Diastolic. A Vasculab On Line Event (Jan 12th - 22nd, 2013). DOI: 10.24019/2016.Systodiastolic

56) Morrison N. [KTrenaunay Debate Vasculab Message Archive. May 1-28, 2016. DOI: 10.24019/2016.KTrenaunay] - Treatment of the Marginal Vein. Msg 11170, May 19, 2016. https://it.groups.yahoo.com/neo/groups/vasculab/conversations/messages/11170, May 19, 2016. Accessed on line on Mar 23, 2017. A (free) subscription is required.

57) Laaengh Massoni C, Betroune K, Laurian V, Paraskevas N, Bisdorff A, Franceschi C. Varicose veins and venous malformations of the lower limbs. Duplex US assessment of the venous drainage and compensatory veins test. Presented to the 50th Congrès du College Français de Pathologie Vasculaire, Paris 2016.

58) Franceschi C. [KTrenaunay Debate Vasculab Message Archive. May 1-28, 2016. DOI: 10.24019/2016.KTrenaunay] - Treatment of the Marginal Vein. . Msg 11186, May 20, 2016. https://it.groups.yahoo.com/neo/groups/vasculab/conversations/messages/11186, May 20, 2016. Accessed on line on Mar 23, 2017. A (free) subscription is required.

59) Rauch RF, Silverman PM, Korobkin M et al. Computed tomography of benign angiomatous lesions of the extremities. J Comput Assist Tomogr 1984; 8:1143-46.

60) Konez O, Burrows PE. Magnetic resonance of vascular anomalies. Magn Reson Imaging Clin N Am. 2002;10(2):363-88.

61) Van Rijswijk CS, van der Linden E, van der Woude HJ, van Baalen JM, Bloem JL.Value of dynamic contrast-enhanced MR imaging in diagnosing and classifying peripheral vascular malformations. AJR Am J Roentgenol. 2002 ;178(5):1181-7.

62) Markovic JN, Kim CY, Lidsky ME, Shortell CK. A 6-year experience treating vascular malformations with foam sclerotherapy. Perspect Vasc Surg Endovasc Ther. 2012;24(2):70-9.

63) Lidsky M, Spritzer C, and Shortell C. The role of dynamic contrast-enhanced magnetic resonance imaging in the diagnosis and management of patients with vascular malformations. J Vasc Surg. I 2011;53(1):131-137.

64) van Rijswijk CS, van der Linden E, van der Woude HJ, van Baalen JM, Bloem JL. Value of dynamic contrast-enhanced MR imaging in diagnosing and classifying peripheral vascular malformations. AJR Am J Roentgenol 2002;178:1181-7.

65) Lumsden A, Peden E, Bush RL, Lin PH.Complications of endovascular procedures. In: Vascular Surgery. Rutherford RB (Ed.). Elsevier Saunders, PA, USA, 809-820, 2005.

66) Nasser TK, Mohler ER 3rd, Wilensky RL, Hathaway DR. Peripheral vascular complications following coronary interventional procedures. Clin. Cardiol. 18(11), 609-614, 1995.

67) Lee BB, Choe YH, Ahn JM, Do YS, Kim DI, Huh SH, Byun HS. The new role of magnetic resonance imaging in the contemporary diagnosis of venous malformation: can it replace angiography? Jamcollsurg. 2004 Apr;198(4):549-558. DOI: 10.1016/j.jamcollsurg.2003.12.013.

68) Lee BB, Mattassi R, Kim YW, Kim BT, Park JM, Choi JY. Advanced management of arteriovenous shunting malformation with transarterial lung perfusion scintigraphy for follow-up assessment. International Angiology. 2005 Jul;24(2):173-84.

69) Chung HW, Choi JY, Kim YW. Diagnosis and Post-Therapeutic Evaluation of Arteriovenous Malformations in Extremities Using Transarterial Lung Perfusion Scintigraphy. Nucl Med Mol Imaging 2006;40(6):316-321.

70) Sung HM, Chung HY, Lee SJ, Lee JM, Huh S, Lee JW, et al. Clinical Experience of the Klippel-Trenaunay Syndrome. Arch Plast Surg. 2015; 42(5):552-8.

71) Lee A, Driscoll D, Gloviczki P, Clay R, Shaughnessy W, Stans A. Evaluation and management of pain in patients with Klippel-Trenaunay syndrome: a review. Pediatrics. 2005;115(3):744-9.

72) Eifert S, Villavicencio JL, Kao TC, Taute BM, Rich NM. Prevalence of deep venous anomalies in congenital vascular malformations of venous predominance. J Vasc Surg 2000;31:462-71.

73) Gloviczki P, Stanson AW, Stickler GB, Johnson CM, Toomey BJ, Meland NB, et al. Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. Surgery. 1991;110(3):469-79.

74) Malgor RD, Gloviczki P, Fahrni J, Kalra M, Duncan AA, Oderich GS, et al. Surgical treatment of varicose veins and venous malformations in Klippel-Trenaunay syndrome. Phlebology. 2016;31(3):209-15.

75) Villavicencio JL. Primum non nocere: is it always true? The use of absolute ethanol in the management of congenital vascular malformations. J Vasc Surg 2001; 33: 904-6.

76) Yakes WF, et al., Symptomatic vascular malformations: ethanol embolotherapy. Radiology, 1989. 170(3 Pt 2): p. 1059-66.

77) Yakes WF, Baker R. Cardiopulmonary collapse: sequelae of alcohol embolotherapy. Radiology 1993;189:145.

78) Lee BB, DI Kim, et al. New experiences with absolute ethanol sclerotherapy in the management of a complex form of congenital venous malformation. J Vasc Surg 2001. 33(4): 764-772.

79) Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. J Vasc Interv Radiol 2004; 15: 431-45.

80) Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T: Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations. J Vasc Surg 2008; 47: 578-584.

81) Tessari L, Cavezzi A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. Dermatol Surg 2001;27:58-60.

82) Cabrera J, Cabrera J, Garcia-Olmedo MA, Redondo P Treatment of venous malformations with sclerosant in microfoam form. Arch Dermatol. 2003;139:1494-6.

83) Frasier K, Giangola G, Rosen R, Ginat DT. Endovascular radiofrequency ablation: a novel treatment of venous insufficiency in Klippel-Trenaunay patients. J Vasc Surg. 2008;47(6):1339-45.

84) Harrison C, Holdstock J, Price B, Whiteley M. Endovenous radiofrequency ablation and combined foam sclerotherapy treatment of multiple refluxing perforator veins in a Klippel-Trenaunay syndrome patient. Phlebology. 2014;29(10):698-700.

85) Servelle M. Malformations congénitales des veines des membres. In "Pathologie Vasculaire. 2. Les Affections Veineuses." [Congenital Malformations of limb veins. In "Vascular Pathology. 2. Venous Diseases."] 1978. Masson. p. 23-109.

86) Tramontano R, Pane G, Gallucci A, Passariello F, Aliperta D. La sindrome di Klippel-Trenaunay-Servelle: Considerazioni su di un caso osservato. [The Syndrome of Klippel-Trenaunay-Servelle: Notes about a clinical case.] Presented to the 7th International Meeting of Phlebology (Copenhagen, 1980). La Riforma medica 1982 Sep;97(9):535-8.

87) Franceschi C. Les malformations vasculaires congénitales. [Congenital Vascular Malformations] In "Encyclopédie pratique d'échotomographie et de Doppler vasculaire". Paris, 1994. Editions LEN Médical, Paris. 1995.

88) Laurian C, Enjolras O, Bisdorff A, Franceschi C, Marteau V. Hémangiomes et malformations vasculaires [Hemangiomes and Vascular Malformations] - 21/03/14. EMC Encyclopédie Médico-Chirurgicale [43-265] - DOI : 10.1016/S0246-0459(14)67383-4.

89) Laurian C, Franceschi C, D Herbreteau D, Enjolras O. Traitement chirurgical des malformations vasculaires des membres [Surgical Treatment of Vascular Malformations of the limbs]. EMC - Encyclopedie Médico-Chirurgicale - Chirurgie. Paris, Apr 2004. 01/01/04 [43-260]

LYMPHEDEMA REVIEW

Italian Guidelines on Lymphedema: New public regulations 2017

S Michelini[1], M Cestari[2], M Ricci[3], A Leone[4], A Galluccio[1], M Cardone[1]

[1]San Giovanni Battista Hospital, Rome, Italy

[2]Vascular Public Consulting Room, Terni, Italy

[3]Rehabilitative Department Torrette Hospital, Ancona, Italy

[4]Carmide Hospital, Catania, Italy

submitted: Feb 08, 2017, accepted: Feb 27, 2017, EPub Ahead of Print: Mar 16, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.14 - Corresponding author: Prof. Sandro Michelini, s.michelini@acismom.it, sandro.michelini@fastwebnet.it

Abstract Lymphedema in many countries is still considered an "aesthetic" problem, even though a chronic, degenerative, and debilitating disease. After a long period of study with internal and external experts, the Italian Ministry of Health has implemented National Care guidelines for lymphedema and other related disorders. This Document represents a fundamental element with regards to diagnostic and therapeutic regulation procedures that satisfy the health needs of these patients. In this paper the description of the main constituents of the document that has revolutionized the possibility of access the best specialized care facilities situated in the country.

Keywords Lymphedema, Public Health System.

General considerations

The problem of classifying treatment of primary and secondary lymphedema in both the public and private sectors, derives from a series of considerations. First of all the fact that the same global guidelines of the principal scientific societies that are experts in the subject (i.d. Consensus Document of the International Society of Lymphology) [1,2,3] illustrate the opinions of the leading world experts of the field: some consider lymphedema as an alteration of the lymph transport linked to intrinsic or extrinsic dysfunction of the lymphatic system itself; others consider it a disease. In fact the World Health Organization in the International Classification of Diseases (version number 9-ICD9) recognizes the various forms of lymphedema as diseases and not as symptoms or clinical manifestations. They were also assigned specific codification for the disease: 457.0 Breast cancer related lymphedema and 457.1 for all the other forms of primary and secondary lymphedema.

For these reasons in many countries patients with lymphedema find enormous difficulties coping with their health problems. The confusion and inadequate information, even among clinicians, with regards to the disease discredits even the scientific societies and associations of patients that struggle to be valid advocators for a serious confrontation with politicians who have to decide on funding treatment. As a result of this situation in almost all of the countries in the world a lymphedema patient is obliged to bear high health care costs that only a minority of patients can sustain.

Considering this particular critical situation, in Italy in 2006 a Commission was appointed by the Ministry of Health to draft ministerial guidelines on the management of national public health care for patients affected from lymphedema and other related diseases (Lipedema). The workshop was concluded in 2016 with the publication of a document that stipulates a series of specific health care regulations that guarantee free treatment under the

Universal Public National Health Care system for these patients.

The highlights of the Document, officially made public on Sep 15th, 2016, are the following:

Primary and Secondary lymphedema are considered a chronic disease, naturally progressive and degenerative, subject to clinical complications and exacerbations, similarly to other chronic diseases [4,5,6]

In Italy there will soon be a National Register that will document all the patients treated for both forms primary and secondary. It is currently estimated approx. 450.000 clinical cases nationwide with a majority of cases of the secondary form [7,8,9]

Clinical complexity chart

Indicator name	N. of patients in day hospital setting	Setting	Rehabilitation medicine
Dimension	Process	Area	Volumes/Benefit
Data update	weekly/monthly/annually	Sources	Clinical records
Mathematical formula	N. of patients in treatment in DH/N. total patients seen with Lymphedema		
Expected standard	> 60%		
Regulation requirements			
Bibliography	*Although scientific literature does not provide evidence of a significant correlation between the activity volumes and the quality of the above procedures, it can be assumed that this relationship is a qualifying requirement for a Centre of Excellence*		

Indicator description
the indicator measures the N. of patients with a 'heavy' clinical picture being in charge to the Centre.
Indicator meaning
the indicator assesses the center's ability to manage complex patients.

Table I - Indicator of clinical complexity.

The primary forms of Lymphedema are included in the new Government Document for Essential Health Care Levels recognized in the category of 'rare disease' so that patients are identified with special classification codes that guarantees the patient specialized treatment, with respect to diagnostic testing clinical and instrumental, therapeutic cycles, as well as for the final elastic garments that are identified with specific codes by the National Health Care System.

All forms of the disease are considered: present at birth (connatal), appearing within the first decade of life (early) or later onset (second, third, fourth, fifth, decade of life); these are the most common forms.

Primary lymphedema can also be hereditary type (it is common that blood relatives are affected by the same disease), syndromic (this type of lymphedema is globally more complex, i.d. Klippel-Trenaunay Syndrome, the Ghoram Stout, the Noonan, the Hennekam ecc…) or sporadic (only one member of the family is affected and there is no presence of other blood relatives who have the same clinical problems) [10,11].

The diagnosis of lymphedema is clinical; in primary forms it is essential to perform a lymphoscintigraphic examination.

Other tests (i.d. High resolution echography, videofluoroscopy, lymphangio nuclear magnetic resonance, echo color Doppler) contribute to a better diagnostic evaluation and therefore, a more accurate definition of treatment program.

In the primary forms genetic testing is highly recommended to determine the presence and the type of mutation, also with regards to primary prevention for blood relatives of patient [12, 13].

Primary lymphedema (fig. 1) and Secondary (fig. 2), are subdivided, in accordance with the clinical stages indicated by the International Society of Lymphology, in 4 clinical stages:

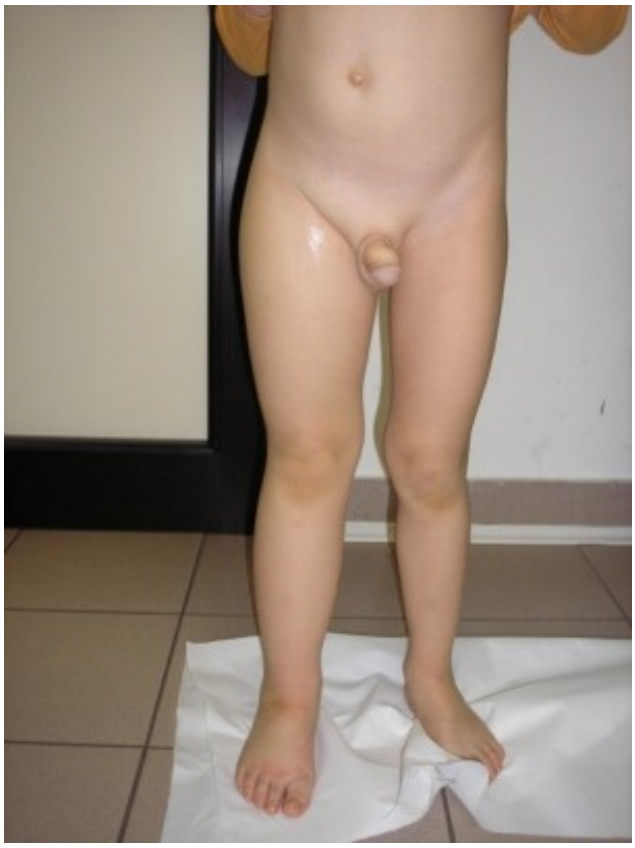


Figure 1 - Primary lymphedema of lower limb and genitalia.

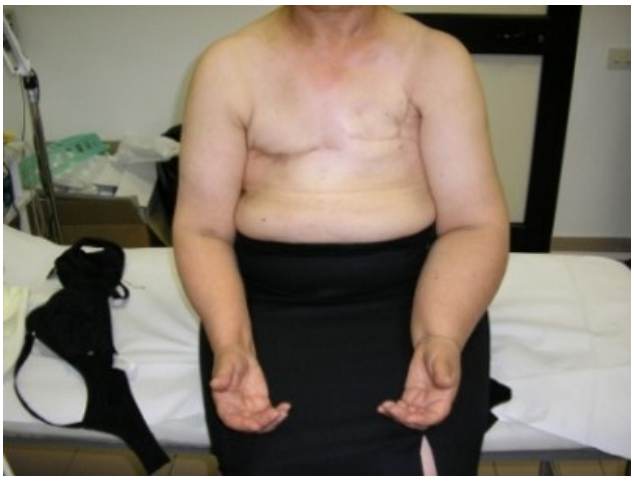


Figure 2 - Bilateral upper limbs secondary Lymphedema.

Stage 0: subclinical cases with possibility of developing edema (ex. Patients with mastectomy and axillary lymph node that present limbs apparently similar in volume and consistency).

Stage 1: presence of edema that shrinks partially with anti limb elevation and night rest;

Stage 2: uncomplicated elephantiasis

Stage 3: complicated Elephantiasis consisting of skin wounds, infectious, fungal, warty, ulcers, up until transformation linfosarcomatosa [3,4,7,10].

The National Health System provides treatment for these patients in various health care settings: outpatient services, day hospital or inpatient rehabilitation.

Outcome Indicator Chart			
Indicator name	N. of patients treated	Setting	Rehabilitative Medicine
Dimension	Outcome	Area	Volumes/Benefit
Data update	weekly/monthly/annually	Sources	Medical records
Mathematical formula	N. Lymphedema patients with clinical improvement (ROM, Barthel, Volume)/ total N. Lymphedema patients		
Lymphoscintigraphy	N. improved Patients/N. treated	Sources	Medical records
Expected standard		> 90%	
Normative requirements			
Indicator description *The indicator measures the N. patients improved with the received treatment* *Indicator meaning* *The indicator assesses the outcomes of the offered treatment and the fairness of procedures.*			

Table II - Outcome indicator.

The criteria that determines the care setting is essential based on the stage and the intensity of treatment after an accurate global evaluation of the needs of the patient taking into account also "social fragility", 'transportability' of patient and the necessity or not of medical assistance provided in an inpatient setting especially useful in the phase of the so called "attack Treatment"[14].

Every Italian Region has to organize regional observatory treatment Centers (Hub) which initially take into care and register patients in a Regional Register where periodically collected data is transmitted to the National Ministry of Health; the Center provides information and overall training programs.

The offered training programs are realized in collaboration with dedicated scientific societies. In these regional center it's possible to treat patients in 'outpatient', in Day Hospital, or 'inpatient' setting.

Each Region is requested to identify one or two reference hospitals for taking charge of clinical exacerbations or lymphangitis, ulcerative, trophic complications, even to the detriment of other organs or tissues. For maintenance treatment the organization provides various outpatient centers throughout the region to satisfy rehab needs of these patients. The treatment consists of combined physical therapy with at least manual lymphatic drainage, multilayer inelastic bandaging, physiotherapy under bandaging, ultrasound therapy and shock waves to be applied on fibrotic areas, linfotaping. Proscribed are 'monotherapy' (only lymph drainage, only physiotherapy etc.). Drug treatment is particularly indicated in early clinical stages of the disease: alpha and gamma benzopyrones constitute a therapeutic procedure that makes use of the proteolytic and pro-lymphokinetic and membrane stabilizers effects of such molecules. Surgical therapy uses techniques of reconstructive microsurgery and super-microsurgery; they must be carried out in highly specialized centers, by experienced staff certified by a recognized Masters degree, and are in synergy with the other treatment, since they cannot solve the problem in a definitive way in most cases. In case of lymphangitis, especially Erysipelas, is essential the use of broad-spectrum antibiotics (penicillin or macrolide), combined with anti-inflammatory drugs or cortisone. In cases (frequently in both primary and secondary forms) with repeated recurrence of infection it is recommended the use of penicillins for long periods (over the year), or desensitizing vaccines. The key issue is to control the obtained results by means the phase of major impact using physical treatment, by permanent elastic garment use (standard or 'tailored'); It is possible, to provide custom fit garments made of materials which permit the hold-up in certain anatomical regions in which the greater the tissue texture, major pressure effects by positioning 'thickness' that they are introduced in special 'pockets' pre-packaged [15,16,17,18,19].

They are provided, for patients with primary and secondary forms, elastic flat knitted garments that are replaced according to wear over time. These garments are identified with specific codes and are prescribable twice a year.

The Lymphedema reduces the quality of life; it is a disease that causes disability in patient. National Health System (in Italian Law 104/92) offers to the patients affected , and or family caregiver, special benefits (i.d. special work) and permits to allow patients to take time off work to do treatment or medical visits and for caregiver to accompany patients, temporary paid leave from work to take care of a family member who is ill, reduction of taxes on certain essential items ecc [20].

A special role is reserved for specialized voluntary Associations that advocate to control the implementation at local level of the procedures provided and pay particular attention to the quality of provided services.

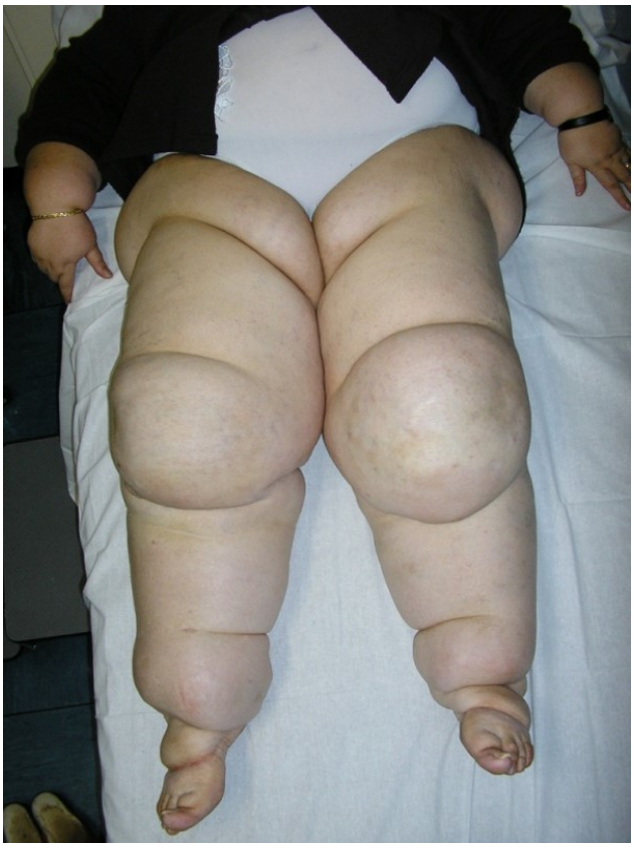


Figure 3 - Lower limb Lipedema.

The document also provides tools for the clinical and therapeutic outcome monitoring with specific scales that provide information on 'before' and 'after' treatment (Tables I and II).

Among the diseases related to Lymphedema, Lipedema (Fig. 3) is becoming more prevalent in the female population and often confused with Lymphedema, even by experienced clinicians. The disease affects the lower limbs; It can also be located in the upper limbs but spares always the distal portions of the limbs (hands and feet). The increase in volume is determined by the filing, under the skin, of large amounts of fatty tissue that does not respond to common adipose tissue self-regulation mechanisms and poorly to exercise. It is a stable clinical picture, not evolutionary, that does not come to infectious complications. It affects only women. It can give complications on the osteo-muscle-ligamentous structures (it is frequent Baker's cyst in the popliteal pit level for prolonged abnormal joint stress), and, lately, it can develop in Lipo-lymphedema for mechanical involvement of loco-regional lymph system. The treatment is absolutely symptomatic and aims to limit the mechanical obstacle and alleviate painful symptoms that frequently is one of the components of the clinical features [21, 22].

In view of an appropriate management of patients with lymphedematous disease, the following aspects are fundamental:

Recognized clinical experience of formal caregivers of the team (doctors, nurses and physiotherapists, orthopedic technicians, social workers);

Ability to work directly or with connected centers all the diagnostic tests needed to define the clinical picture (Lymphangioscintigraphy, high-resolution echography ultrasound, CT).

Possibility of execution, directly or by using approved genetic laboratory, the genetic test for the primary forms, exerting also through inter-regional agreements.

The very long (over ten years) and detailed discussion that has taken on the management of the disease, between Scientific Societies and patient Associations on the one hand and Government Structures on the other, has led to the final basic work for patients and as model for Health Care Systems, public and private, also of other countries. We hope that the final document produced and translated into legislation, inspired by international guidelines drawn up by leading experts, gives a basis for the resolution of support needs for about 300 million patients with primary and secondary lymphedema, identified by World Health Organization. With an adequate Training, incentive of professional caregivers and general practitioners, it will help pave the way to earlier diagnosis of the disease (with equally early Therapeutic management of the individual case) and improvement of primary and secondary prevention.

References

1) International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology. 2013;46:1-11.

2) Lee BB, Andrade M, Bergan J et al. Diagnosis and treatment of primary lymphedema. Consensus Document of the International Union of Phlebology (IUP)-2009. International Angiology 2010 October;29(5):454-70.

3) Lee BB, Andrade M, Antignani PL et al. Diagnosis and Treatment of Primary Lymphedema. Consensus Document of the International Union of Angiology (IUP). International Angiology. 2014;37:5-22.

4) Földi M, Földi E. Földi's Textbook of Lymphology for Physicians and Lymphedema Therapists. III ed. Elsevier. San Francisco; 2009.

5) Michelini S, Failla A. Linfedemi: Inquadramento diagnostico clinico e strumentale. Minerva Cardioangiologica. 1997;45(Suppl. I al n° 6): 11-15.

6) Michelini S, Failla A, Moneta G et al. Linee guida e protocolli diagnostico-terapeutici nel linfedema; Eur. Med. Phys 2008;44(Suppl. 1 to No. 3).

7) Michelini S, Campisi C, Cavezzi A et al. Epidemiologia del linfedema. Auxilia-Linfologia. 1998;1:22-25.

8) Michelini S, Failla A, Moneta G. Lymphedema : Epidemiology, disability and social costs. Lymphology. 2002;35:169-71.

9) Boccardo F, Michelini S, Campisi C. Epidemiology of Lymphedema. Phlebolymphology. 1999;26:24-8.

10) Cavezzi A, Michelini S. Il flebolinfedema. Edizioni P.R. Bologna; 1997.

11) Michelini S, Campisi C, Gasbarro V et.al. National guidelines on lymphedema. Lymphology. 2007;55:238-42.

12) Bourgeois P, Leduc O, Leduc A. Imaging techniques in the management and prevention of post-therapeutic upper limb oedemas. Cancer. 1998 Dec 15;83(12 Suppl American):2805-13.

13) Michelini S, De Giorgio D, Cestari M et al. Clinical and genetic study of 46 Italian patients with primary lymphoedema. Lymphology. 2012;43:3-12.

14) Ministero della Salute. Metodologia per la definizione dei criteri/parametri di appropriatezza ed efficienza dei ricoveri di riabilitazione ospedaliera. 2013 Febbraio.

15) Casley-Smith John. Modern treatment for lymphoedema. The Lymphoedema Association of Australia Inc. Adelaide. 1994.

16) International Lymphedema Framework. Best practice for the management of lymphoedema. 2nd Edition 2012 www.lympho.org.

17) Michelini S, Failla A, Moneta G et al. Shockwave therapy in lymphedema patients: preliminary study. Lymphology. 2007;55:235-7.

18) Casley-Smith John, Casley-Smith Judith. "High-Protein Edemas and the Benzo-Pyrones". Sydney J.B. Lippincott Company, 1986.

19) Michelini S, Failla A, Moneta G et al. Immunostimulation and reaction of infective complications in patients with lymphoedema. European Journal of lymphology and related problems. 2009;20(56):17-18.

20) Michelini S, Failla A, Moneta G et al. International classification of lymphedema functioning and disability evaluation. Eur J Lymphology. 2007;17(51):16-19.

21) Forner Cordero I, Szolnoky G, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome - systematic review. Clin Obes. 2012;2:86-95.

22) Schmeller W, Meier-Vollrath I. Lipödem: Ein update (Lipedema: an update) Lymphol Forsch Prax. 2002;

LYMPHEDEMA REVIEW

Mathematics of lymphedema

F Passariello[1]

[1]Fondazione Vasculab ONLUS, via Francesco Cilea 280 - 80127 Naples, Italy

presented to: the VIII theoretical and practical workshop. Diagnosis and treatment of (phlebo)lymphedema. Apr 23rd, 2006, Bologna, Italy
submitted: Mar 8, 2017, accepted: Mar 22, 2017, EPub Ahead of Print: Mar 23, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.19 - Corresponding author: Dr. Fausto Passariello, afunzionale@tiscalinet.it

Abstract Flow in the extracellular matrix can be the last available resource in advanced lymph dysfunctions. The ultrasound appearance of the subcutaneous tissue in lymph diseases resembles a desert of stones. Flow can be assimilated to the liquid flow through a porous medium. In hydrogeology these phenomena trace back to the Darcy law, by Henry Darcy, French engineer of the XIX century. In a porous medium the area available to flow is generally smaller than the area of the overall cross section and the underlying fluid dynamics occurs in a viscous regimen. The mathematical details of the Darcy representation are here reported. Apart of the general and theoretical interest, these information can be of practical use if they are linked to data coming from the ultrasound investigation of lower limbs.

Keywords Lymphedema, extracellular matrix, Darcy law, porosity, viscous forces, Reynolds number.

Introduction

The lymphatic circulation sustains side by side the venous drainage in the task of removing tissue catabolites. In details, the lymph system deals with the removal of the remains, non-efficiently taken away by the venous circulation.

The lymph system acts in a **much wider temporal scale** than the venous system, which is instead able to react in a quicker way to tissue metabolic changes.

The removal of the interstitial fluid occurs essentially by means of two pathways:

The lymph vessels, which originate from the initial lymphatics or pre-lymphatics, which are constituted by an endothelial layer with wide fenestrations; in lymph diseases they have a modified function, for instance cause of an obstruction or cause of their absence (agenesia).

The extracellular matrix (ECM), which can show several considerable modifications, being however always present and constituting the last resource in an advanced lymph disease[1].

Structure of the extracellular matrix

Shortly, the ECM is constituted by a structured space, which is placed between the connective cells and contains a colloidal solution, sometimes present as a "**sol**", sometimes as a "**gel**". **Fibres** originating from fibroblasts cross the matrix and link cells each other and to the lymphatic vessels and contribute to make the matrix a structure of constrained elements. Skin handling provokes the fibre strain and can ease or prevent fluid movement (**micro-reticulum**).

Matrix, porous media and porosity

The reticular appearance is emphasized in the advanced lymphatic disease, where ECM appears as a **reticular material**, often detectable in ultrasound images of lymphatic limbs. The sub-cutaneous tissue here is rendered as an image similar to a **desert of stones**, everywhere fragmented into **clamps** of several sizes. Hypo-echogenic spaces are placed between clamps of hyper-reflecting material, which is stored in the matrix (**macro-reticulum**)[2].

The Darcy Model

Flow through the matrix occurs in a bed, where several completely impenetrable structures (bones) are present as well as partially penetrable ones (muscles, tendons).

For this reason, ECM flow can be assimilated to the liquid flow through a porous medium. In hydrogeology

these phenomena trace back to the Darcy law, by **Henry Philibert Gaspard Darcy**, a French engineer of the XIX century[1] 3-7 (Figs. 1-3).

Figure 1 - Henry Philibert Gaspard Darcy. (Dijon 1803 - Paris 1858)

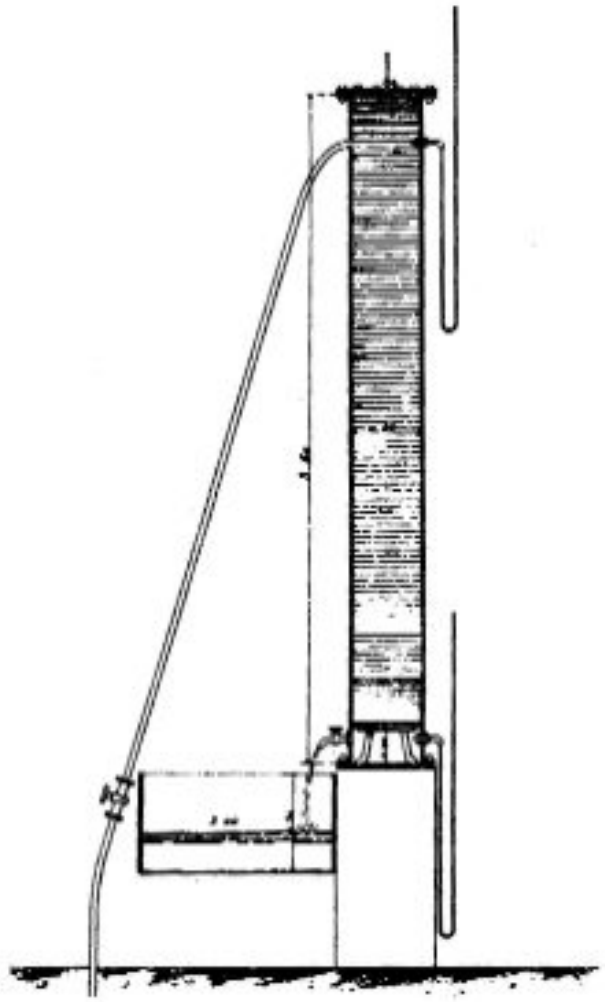


Figure 2 - Apparatus intended to determine the law of the water flow through sand. (Darcy, 1856)

Cross section available to flow

The reticular structure and the aggregation of the interstitial materials allows the similitude between the ECM and a **porous medium**, i.e. a medium where the fluid penetrates without occupying all the space, but only an available part.

The fluid enters a porous medium in the same way we can afford an obstacle pathway or a walk through the crowd. The space we can use is only the one placed between the obstacles. If someone would measure the crossing velocity, considering just the moment and the point of entry and exit and the distance between these points, he would measure a different velocity than the one experimented by a real traveller, kept busy in avoiding the obstacles encountered on the traveller's pathway.

Generally, the **pore velocity** (v_{bed}) is higher than the **upstream** or **Darcy velocity** (v_{up}) and their ratio is the same of the ratio between the **upstream area** (A_{up}) and the **porous area** (A_{bed}) or the area really available to flow. The **porosity coefficient** (n) can be defined:

$$n = \frac{V_{up}}{V_{bed}} = \frac{A_{bed}}{A_{up}};$$

where n <=1.

Shortly, the fluid enters the section A_{up}, but it flows really through a reduced section A_{bed} with a greater velocity v_{bed}. This is the concept of porosity.

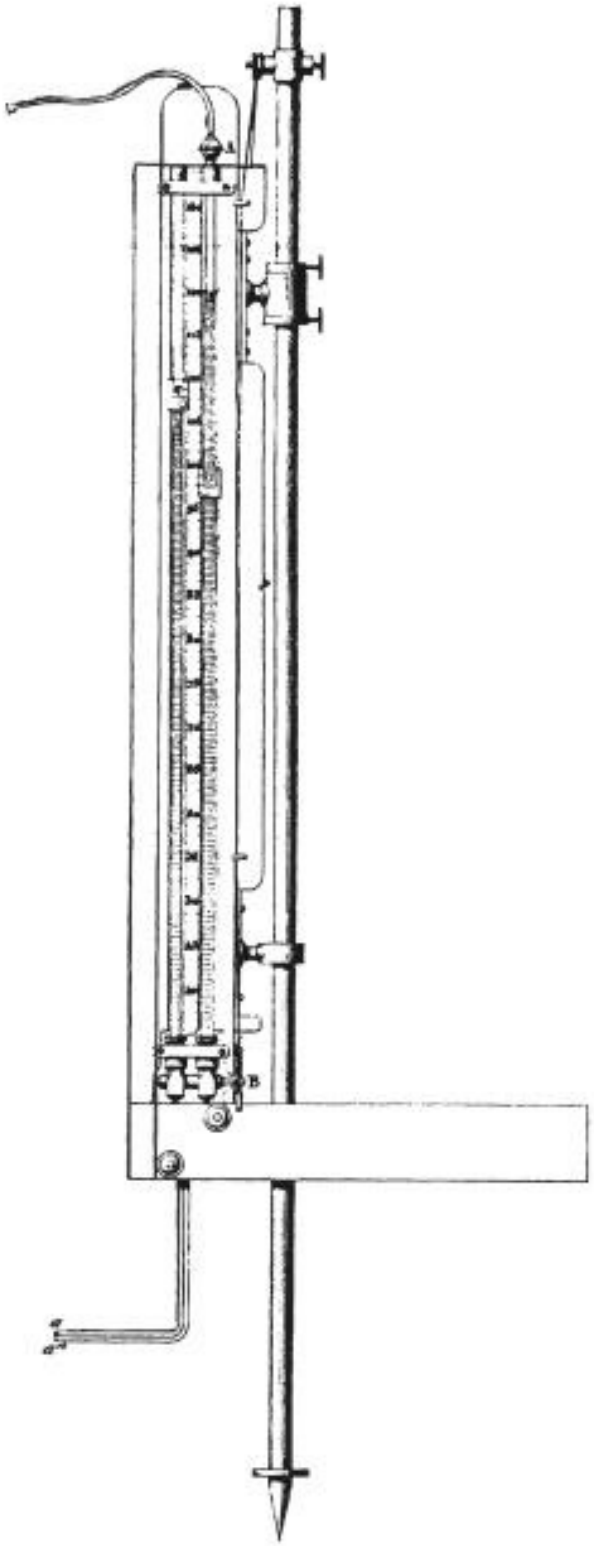


Figure 3 - The Darcy's Pitot tube (1858)

At the ultrasound examination porosity has the appearance of grains of irregular size, placed in layers which are roughly parallel to the skin surface, just about a floor of pebbles. The interstitial fluid worms itself between the layers and sometimes moves them, modelling a stratum of anechoic fluid (**lymphatic lake** or **lymphatic stratum**). The grains are the impenetrable or at least partially permeable part and the spaces between the medium grains are the pores. Inside a cross section the area really available to flow is smaller and linearly related to the overall value by the coefficient of porosity.

Active forces in the matrix

A spherical object, moving in the ECM (as in any other medium), undergoes mainly two different types of forces: the inertial forces, which are needed to accelerate the object, and the viscous forces, which oppose to the movement and slow down it.

Viscous forces F_V act impeding the sliding of fluid between its contiguous parts and on the obstacles in contact with it.

Viscous forces can be quantified by the **Stokes formula**

$$F_v = 6\pi\eta r v.$$

and depend on the fluid viscosity η, the spherical radius **r** and velocity **v**.

Inertial forces F_i can be quantified observing that during its movement the sphere moves the fluid, accelerating it until it reaches its equilibrium velocity. The volume of the moved fluid in 1s is included in a cylinder with base area equal to the area of the maximum circle of the sphere and height equal to its velocity, i.e. a volume equal to $\pi r^2 v$.

Fluid density is ρ and the kinetic energy, which is transferred in 1s to the moved fluid is

$$\frac{1}{2} m v^2 = \frac{1}{2}\pi r^2 v \rho v^2 = \frac{1}{2}\rho\pi r^2 v^3$$

This energy is equal to the impulse of the inertial forces, i.e. $F_i v$.

Matching the kinetic energy in 1s to the impulse, we have:

$$F_i = \frac{1}{2}\rho\pi r^2 v^2$$

The Reynolds number Re is defined as the ratio between the inertial and the viscous forces (Fig. 4)

$$Re = F_i/F_V = (1/2\ \rho\pi r^2 v^2)/(6\pi\eta r v) = 1/12\ (\rho r v/\eta)$$

and omitting constants

$$Re = \rho r v/\eta$$

Figure 4 - Searching for the right positioning in viscous phenomena. Reynolds Street in Key West, Florida (USA).

When Re is low (<< 1) viscous forces prevail, as it occurs generally in tissues and in details in the ECM.

The Darcy law is an experimental constitutive equation, which describes the flow in a liquid through a porous medium and holds in a regimen of viscous flow. The preponderance of the viscous forces makes apparent a connection, generally false, between the forces which cause the movement and its velocity. It is generally true that forces are proportional to the acceleration, while in unusual viscous regimens it can resemble that they are proportional to velocity.

These same conditions are present in the electrical conduction, ruled by the Ohm law RI = V or as an alternative I = kV, where **V** is the voltage, **I** the current intensity, **R** is the resistance, **k** the conductivity and the following relationship holds

$$R = \frac{1}{k}$$

The movement of electrons occurs in a viscous regimen, where a null voltage difference matches a null current intensity.

In an ideal fluid instead, according to the inertia law, movement should occur also in absence of forces or pressure gradients, but when viscous forces prevail, as occurs in the laminar flow, the **Poiseuille law** holds, which is a modified Ohm law with a complete specification of the resistance.

The Darcy law

The **Darcy law** is applied to a flow through an irregular porous medium, which experiments an additional obstacle to movement. It is an analogous of the Ohm and Poiseuille laws and of other laws which describe a fluid movement as well as the heat propagation according to JB Fourier. The Starling law in physiology can be also derived by the Darcy law.

Referring to a specific experimental set which uses a column container and a filter (Figure Column), the Darcy law is formulated as follows

$$Q = kA (h_1 - h_2)/L$$

where **Q** is the flow, **k** is the conductivity, **A** the upstream cross section, $\mathbf{h_1}$ the above and $\mathbf{h_2}$ the below piezo-metric level and **L** the length of the porous filter.

Dividing by A and setting $q = Q/A$ and $\nabla h = (h_1 - h_2)/L$, a generalized Ohm law is inferred.

$$q = -k \nabla h$$

where q is the flow through a unit area and ∇h (pronounced 'nabla h') is the hydrostatic pressure gradient.

It is worth noting that:

- the pressure difference is an analogous of the electrical difference of potential, thus the equivalence to the Ohm law;

- the minus sign is introduced because a mean gradient is defined as the downstream value (h2) minus the upstream value (h1), divided by the distance between the two points, i.e. just the opposite value of the terms in the first equation.

Another equivalent formulation of the Darcy law is the following

$$Q = kA \frac{h + L}{L}$$

where h = h1 - h2 and the formula holds for vertical conduits, when the fluid gathers itself on a porous material of height L until a level h, so that a global height h+L weights on the inferior limit of the material.

The above reported formulas describe the Darcy law in static conditions, while in dynamic conditions the Darcy-Weisbach formula holds, as follows

$$h_l = f \frac{L}{D} \frac{v^2}{2g}$$

which in pressure terms can be re-written

$$\Delta p = f \frac{L}{D} \rho \frac{v^2}{2}$$

where Δp and $\mathbf{h_l}$ are the pressure loss, **f** the Darcy friction factor, **L** the pipe length, **D** the hydraulic diameter, **v** the velocity, **g** the gravitational acceleration and ρ the fluid density.

Intuitively, the last kinetic term is reduced by a fraction equal to the friction coefficient, as many times as the length of the conduit measured in diameters.

Final considerations

As it can be easily seen, I treated essentially biophysical laws which can be applied to the ECM in lymph disease, thus defining all this as mathematics is quite inappropriate. However, I chose to maintain the original title I gave to a presentation to a Lymphedema Meeting several years ago[8], in order to underline the theoretical frame, often neglected, which is at the origin of this research.

Involving the study of porous media in lymphology is not completely new in bioengineering world[9,10], as the similarity was often used in the development of research models. I'm trying instead to put this research field in contact with the ultrasound clinical findings.

Circulation is commonly matched to the study of rivers in hydrography. Veins resemble the river sources which merge together into a great river, while arteries branch repeatedly, as it occurs in a river delta.

The idea of tracing back instead lymph circulation to the Darcy law makes lymphology much closer to the world of agriculture and geology, where groundwater gathers and flows following quite modified laws, in comparison with fluid dynamics or hemodynamics of big vessels.

The above similarity is not just a fascinating image, as it also offers the opportunity of using in lymphology several tools which are commonly used in geology.

Conclusions

The extracellular matrix is an important compensating pathway in lymph diseases, when lymph vessels are partially or totally incapable to drain tissues. The ultrasound examination show several frequent modifications, constituted by tissue granularity and wide interposed spaces. Flow is mainly viscous and obeys to the Darcy law, commonly used to model flow in porous media. This theoretical frame interprets lymphology as a discipline which is close to agriculture and geology. An interesting suggestion is then to adopt in lymphology several tools in use in geological studies.

Acknowledgements

I thank Mrs. Iolanda Palma for her invaluable help in typesetting the manuscript.

Endnotes

[1] Henry Darcy is also well know for having perfectioned the previous and only theoretical Pitot tube, producing a sophisticated tool for the daily use of engineers and professionals in hydrogeology. He would never imagine that his invention would have an additional wide use in a future discipline like aeronautics, being then part of the essential instruments in every aircraft (in another fluid, air and not water). He could also be considered a model of clear scientific behaviour and ethics, as he chose to neglect any patent for his invention, giving it instead to the scientific community. He had no opportunity however to see the great developments of his research, as he died while he was still perfectioning the instrument. I report a few lines from the obituary notes written by Charié-Marsaines (1858), as translated from French by Brown (2003):

"*Perfections brought by Darcy to this instrument are considerable and he would have been able to take a patent to profit from its exclusive manufacture during a certain number of years. However, as a believer in the customs of disinterestedness, he decided to abandon his invention to the public. The administration has already made a number of these instruments some of which are placed in the precision instrument deposit at l'École des Ponts et Chaussées, and others sent to state engineers to be used in operations that demand exact measurements of the water velocity*."

References

1) Albergati FG, Bacci PA, Mancini S. La matrice extracellulare. Minelli Ed, Arezzo 2004. ISBN: 88-9011405-0-X.

2) Passariello F, Carbone, R, Mancini, A. Semeiotica ultrasuonografica delle alterazioni linfatiche nell'arto inferiore. Min. Angiol. 1991 ; 16:suppl. 1 al n. 2, 453-7. Translation and reprint. [Ultrasound Semeiotics of the Lymphatic Modifications of the Lower Limbs]. JTAVR. 2016 Nov;1(2):131-135. DOI: 10.24019/jtavr.17.

3) Wikipedia. [Internet]. Henry Darcy. Available on line a the address https://en.wikipedia.org/wiki/Henry_Darcy at the date Mar 8, 2017.

4) Darcy H. The public fountains of the city of Dijon. Paris. Victor Dalmont, 1856.

5) Brown GO. 2003. Henry Darcy's perfection of the Pitot tube, in Henry P. G. Darcy and Other Pioneers in Hydraulics: Contributions in Celebration of the 200th Birthday of Henry Philibert Gaspard Darcy, Brown GO, Garbrecht JD, and Hager WH (eds), ASCE, Reston, VA. pg. 14-23.

6) Charié-Marsaines PG. (1858). [French] "Notice necrologique sur M. Darcy, Inspecteur Général des Ponts et Chaussées", Annales des Ponts et Chaussées. 1858; Series 3; 15, 90-109. Available online at the address http://gallica.bnf.fr/ark:/12148/bpt6k408489d.image.f93 at the date of Mar 8, 2017.

7) Darcy H. [French] Note relative à quelques modifications à introduire dans le tube de Pitot. Annales des Ponts et Chaussées. 1858; Series 3; 15, 351-9. Available online at the address http://gallica.bnf.fr/ark:/12148/bpt6k408489d.image.f354 at the date of Mar 8, 2017.

8) Passariello F. La Matematica del Linfedema. [Mathematics of Lymphedema]. VIII theoretical and practical workshop. Diagnosis and treatment of (phlebo)lymphedema. Apr 23rd, 2006, Bologna, Italy.

9) Swartz MA, Kaipainen A, Netti PA, Brekken C, Boucher Y, Grodzinsky AJ, Jain RK. Mechanics of interstitial-lymphatic fluid transport: theoretical foundation and experimental validation. Journal of Biomechanics 1999 May; 32:1297-307.

10) Swartz MA. The physiology of the lymphatic system. Advanced Drug Delivery Review. 2001;50:3-20.

LYMPHEDEMA TRANSLATION AND REPRINT

Ultrasound Semeiotics of Lymphatic Modifications in the Lower Limbs.

F Passariello[1], R Carbone[1], A Mancini[1]

[1]Società Italiana Operatori C.H.I.V.A. - Sede Napoli 02, Centro Diagnostico AQUARIUS, via Francesco Cilea, 280 - 80127 Napoli tel./fax 0039-081714110

presented to: Giornate Nazionali di Angiologia 1991. Milano, 23-29 giugno, 1991
submitted: Apr 9, 2017, accepted: Apr 9, 2017, EPub Ahead of Print: Apr 28, 2017, published: May 1, 2017
Conflict of interest: None

DOI: 10.24019/jtavr.17 - Corresponding author: Dr. Fausto Passariello, afunzionale@tiscalinet.it,

Abstract Reprint of a conference paper on ultrasound investigation in lymphedema.

Keywords Lymphopathies, Subcutaneous tissue, Ultrasound, Lympatic lakes, Phlebo-lymphedema

Foreword

Ultrasound investigation of the venous system of the lower limbs allows the coincidental observation of modifications that may be of a lymphatic origin.

In single patients a complete overlap of lymphatic and venous pathologies is never found in all areas. One zone may be affected by the lymph pathology, while another may be intact.
In the same way, venous insufficiency does not involve all the large veins of the various districts to the same extent.
Indeed, venous and lymphatic components appear with different intensities and in different areas of the lower limb.

When the two pathologies overlap, their characteristic signs may manifest several variations. Or, on the contrary, these signs may be present independently: for example, in patients without phlebopathy and with evident cutaneous and sub-cutaneous modifications.
The detection of the same ultrasound signs in the phlebopathic patient leads us to diagnose a connection with a lymphatic pathology.

In our sample there is a clear preponderance of venous or mixed lymphatic-venous pathology. The division of the symptoms by area and into the small number of pure lymphatic pathologies allowed us make a theoretical formulation of the **Semeiotics of Lymphatic Modifications**.

Normal and pathologic ultrasound anatomy

Normal appearance is considerably influenced by the device resolution and the probe emission frequency.

Skin, Subcutaneous layer and adipose tissue

Generally, it is possible to visualize the superficial hyper-echogenic layer, constituted by the epidermis and by the underlying derma (slightly less echogenic), which can be differentiated from the subcutaneous layer, which is comparatively less echogenic.
The subcutaneous layer is homogenous and transmits the US freely, with negligible reflection, allowing visualization of the underlying structures.

In some patients, instead, it is dense and inhomogeneous, with internal hyper-reflecting zones, separated by thin trabeculae, with mesh arrangement and an appearance comparable to the **clumps of dry desert ground, of cracked stones**, with countless fissures, almost like a **clay desert**.

This subcutaneous and suprafascial image produces poor quality visualization of deep structures and is present together with wider areas which appear as fissures or surfaces which are approximately parallel to the underlying fascia, even when cross-sectioned in any given direction.

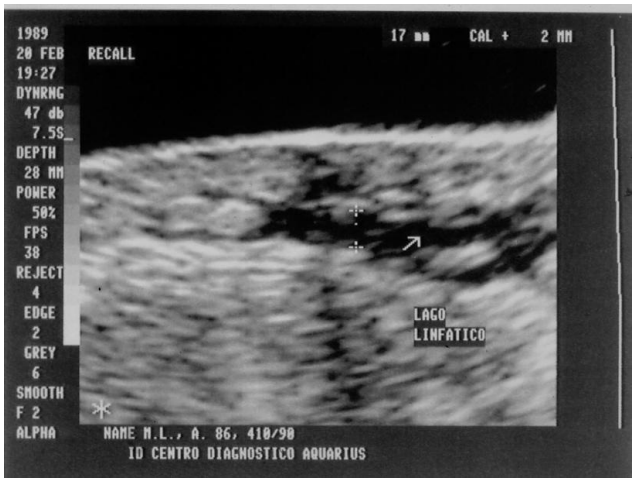


Figure 1 - A lymphatic lake.

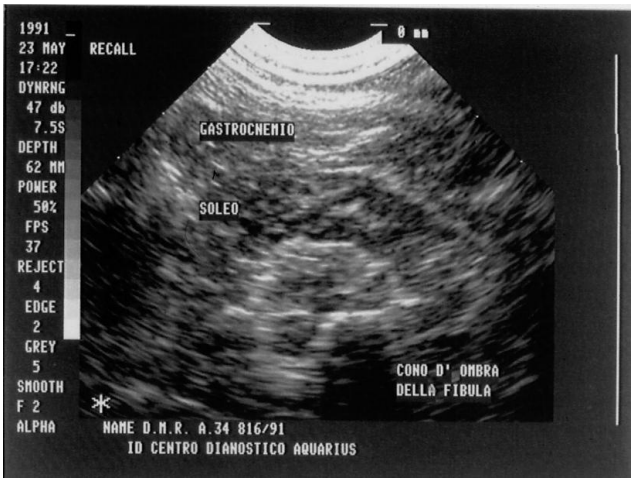


Figure 2 - Cross section of the normal calf. Subcutaneous tissue, muscles, fascia, bones.

They appear in a suprafascial position, with a low thickness completely anechogenic area, i.e. like a thick tissue only in several points, like an optical lens which is thin at the margins: layer or lymphatic lake. (Fig. 1)

A third element is the **hyper-reflectiveity of the epidermis**, which projects shadows into the shape made up of fine rectilinear lines, with a reduction in the quality of the image.
In very old patients this may be an expression of dryness and dehydration of the skin, as also in lymphopathologies, where a higher protein concentration is accompanied by a percent reduction of the hydric content.

Fascia, tendons and muscles

In deep layers, one encounters the hyper-echogenic fascia, that wraps the muscle mass and separates it individually through its septa, that form the deep muscular lodgings.

The anatomy of the single muscles of the limb is not of interest here, but rather their visibility, especially for those near the surface, because we may evaluate subcutaneous sclerosis based on the good visibility of the deep structures.

The tendons are quite dense fibrous connecting tissue and, therefore, are barely subject to variations in hydric content. An interest in their observation lies mainly in their greater stability, permitting identification of a reference point for investigations over time

Lymphnodes

The lymphatic vessels are not visible, but only the lymphnodes, even those of normal volume and structure.

On ultrasound examination one may easily identify them through their quite typical structure: a hyper-echogenic capsule, an hypo-anechogenic ring and a central zone of intermediate echogenicity. The volume is quite variable instead.

The inguinal stations are found near the confluences of the saphenous arch and distributed in groups. The nodes positioned cranially to the inguinal nodes (intra-abdominal for example) are more difficult to observe because they are masked by intestinal gas. Besides, routine examination does not entail their identification. They are generally observable in deep intra-abdominal, para-aortic and para-vertebral sites.

There is no typical alteration for lymphnodes in lymphopathologies of the lower limb. The only easily identifiable aspect is the increase in volume, up to palpability, that also includes an increase in the number of visible lymphnodes at examination.

In many subjects these are generally situated in the groin, with a frequency hardly altered by anti-infective therapy, that is, in a zone quite distant from the typical lymphatic cutaneous lesions, that reach down to below the knee.
In general a lymphatic edema is rhizomelic. This would be an unfavourable point for our observations, that should be limited just to alterations of a non-venous origin. In our experience lymphatic edema appears proximally isolated, while cutaneous lesions are distal and associated to the edema.

Regarding volumetric increase, it must be given importance to interdigital lesions of various origins, especially mycotic ones.

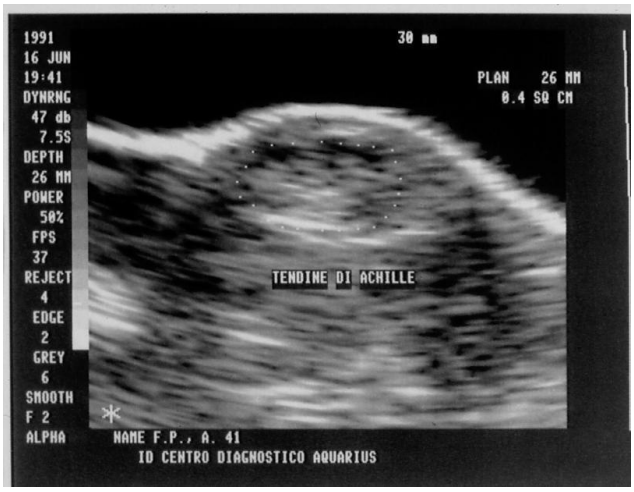


Figure 3 - Reflectivity of fibrous structures (Achille's tendon) as a reference for echogenicity.

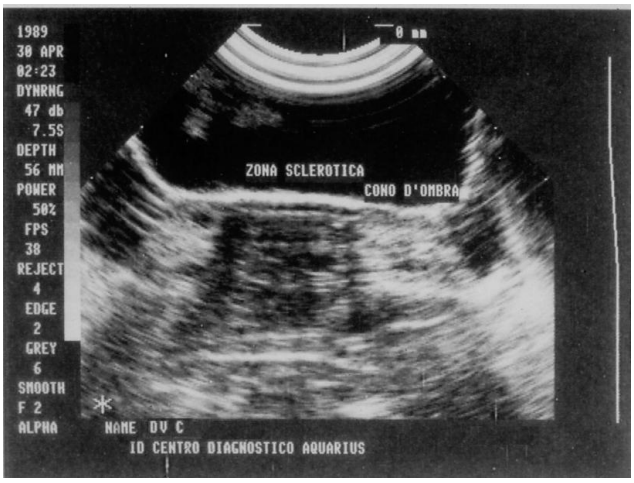


Figure 4 - Sclerotic layers (as in an ulcer) increase reflectivity, thus reducing visibility of deep structures.

Lymphatic-venous intersection

The presence of venous alterations in a district is clearly identifiable, when an insufficient venous vessel transits the zone, even more so if there are also insufficient large perforating or re-entry vessels.
The coexistence of lymphopathy in the zone may create mixed images of phlebo-lymphopathy.

The above observations characterize the stages of initial pathology, that later lead to the same final appearance.
As with a river that receives many tributaries, it is not possible to identify the origins of the single masses of water, so, even when a cutaneous or subcutaneous alteration is already established it is not possible to distinguish its origin.

An exception can be made for the echographic observation of a perforating vessel that leads to a lymphatic lake, because it shows a clear connection between the two pathologies. It is the index of a mixed form, that cannot exist in just pure forms. It is the sign of a net intersection of the symptoms, that are not only co-present in the same district but that have also influenced each other.

However, it is yet to be demonstrated that there has been a flow of material. The aspect is that of a closed cavity connected with a venous vessel, completely analogous to false arterial aneurism. In the venous symptomology, however, there is no pulsation, because the venous pressure is minimal and barely pulsating.
If the lymphatic lake increases in dimensions it does so over very long period of months or years.

The confluence of the lymphatic and venous spaces places a real doubt on the natural history of the echographic images of the illness. This history cannot be rebuilt through echography because the observations are not numerous enough.

One may only formulate informed hypotheses:

- 1. The perforating vessel provokes expansion of the tissues with the creation of the lymphatic lake. Normally the perforating vessels do not end in the subcutaneous layer, but in a surface vessel. The dislocation of the subcute with the appearance of fissures and breaks, and not simple movement of tissue, could be determined by the ebb and flow of the blood in the perforating vessel. The breakage of tissue could also generate the laceration of a vessel and, therefore, the lympho-venous connection.
- 2. The lymphatic lake is so highly stressed that it finds release in a venous vessel, determining a lympho-venous compensatory anastomosis.
- 3. The two aspects are the consequence of an unknown common cause.

Conclusions

The sum of the observations of echographic semeiotics shown here is the fruit of work experience maturing at the **Centro Diagnostico Aquarius** in the course of venous diagnostic examinations carried out for the **CHIVA** treatment of venous insufficiency in the lower limbs.

No criterion other than the clinical criterion was used for the qualification of lymphatic edema. Obviously, more accurate observations could derive from a comparison between ultrasound and another well-established method for the study of lymphopathologies.

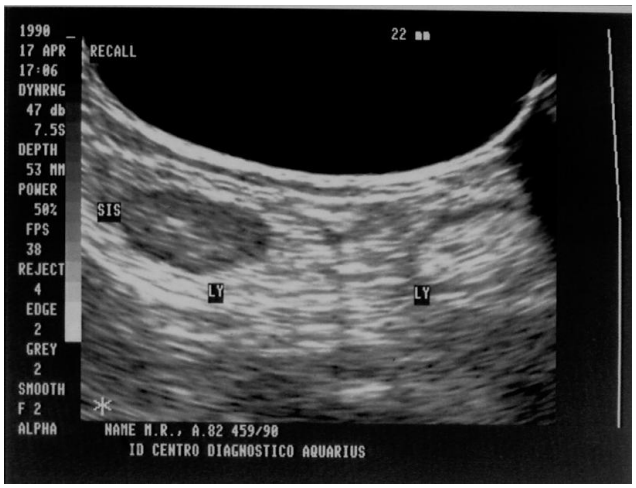


Figure 5 - Superficial lymphnodes (groin) are a common anatomical finding.

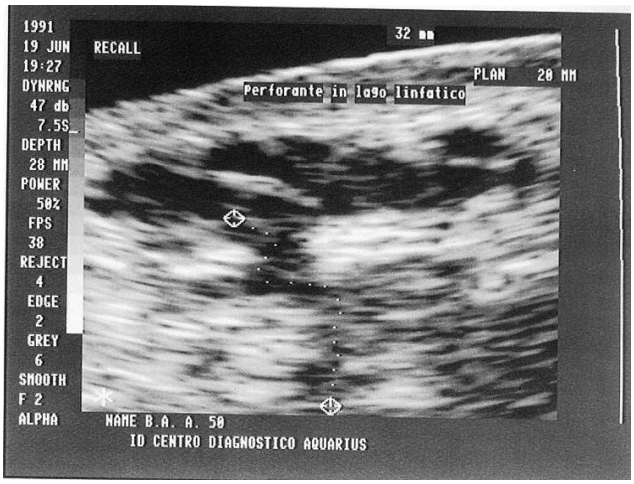


Figure 6 - The uncommon connection between a perforating vein and a lymphatic lake.

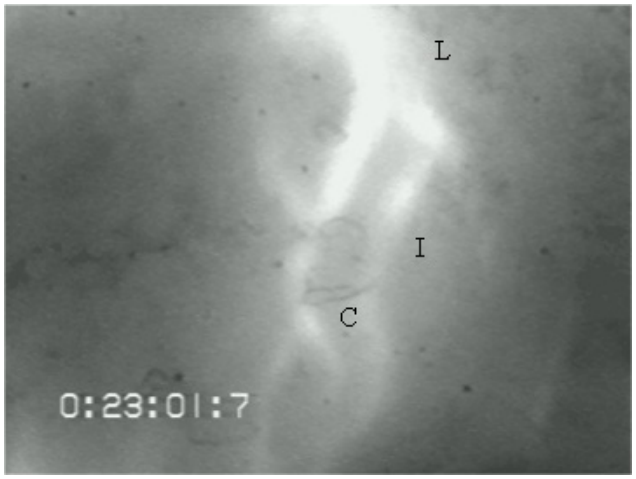


Figure 7 - Fluorescent Microlimphography. Microcirculatory Unit. L - lymphatic microvessel. I - interstitial tissue. C - blood capillary. Unpublished image, courtesy of C Allegra.

Some observations are necessary:

- Echographic examination is not able to directly evaluate the lymphatic circulation, but only the final, anatomical and functional, consequences of alterations that have already been present for some time.
- This does not mean that it cannot identify alterations that only involve some districts in the initial phase.
- Echographic examination allows non-invasive long-term monitoring of pharmacological or surgical treatment of lymphopathologies.

In order to allow a comparison of echographic images obtained from the same patient at a considerable distance of time, the **Centro Diagnostico Aquarius** is carrying out research on the automatic quantification of echographic images. This argument shall be fully treated in another work.

Notes to the reprint

This is the translation from Italian into English of an originary conference paper to the "Giornate Nazionali di Angiologia 1991. Milano, 23-29 giugno, 1991"[1].

It is the 1st detailed paper presented in Italy about ultrasound of soft tissues in lymph diseases.

It is not an absolute innovation because several signs were already reported in a 1986 book of C Franceschi *et al.*[2] and here reported methods were already practiced in 1987 at the *Centre d'explorations medicales, Av. de Wagram, Paris* of C Franceschi.

Later, this knowledge was quickly spread, nevertheless without citing the source nor acknowledging the priority of the *French School*.

The current reprint tries in some way to fill this gap.

The previous paper included only one picture and no references, while bibliography is added here instead, together with several images of the original presentation (Figures 2 - 6).

During the presentation in Milan, there was in the audience also *Prof. Marceau Servelle*(† 2002), who communicated to the Authors his favourable comments, hoping for an additional in-depth analysis of several treated topics.

The original paper was the start of a succession of research works in the following years at the *Centro*

Diagnostico Aquarius, Napoli (Italia), representing the basic precondition of them.

A last remark deals with the hypothesis of the connection between the venous system and a lymphatic lake through a perforating vein.

It is an anecdotal remark, of whom nowadays only a few ultrasound images can be provided (Fig 6). Thus, the phenomenon is uncommon and not much studied and it matches the concept of *phlebolymphedema*, resumed later by Cavezzi and Michelini[3,4], but already stated (not with the same term) in several, experimental but not ultrasound based, previous studies[5-13] (Fig 7).

Acknowledgements

A spontaneous Vasculab discussion in 2011 afforded the theme of phlebolymphedema[14]. We thank all the participants for their contribution and especially for their active role: C Allegra, M Andrade, PL Antignani, J Armer, A Bollinger, A Caggiati, C Campisi, L Corcos, A Džupina, D Eckert, J Ferreira, E Foeldi, I Forner-Cordero, C Franceschi, M Hirai, BB Lee, N Morrison, WL Olszewski, J Opie, H Partsch, E Pasqual, F Passariello, A Pieri, AA Ramelet, H Rieger, M Simka, E Stephen, N Theivacumar, AM Vaillant-Newman, RA Weiss, J Wigg.

References

1) Passariello F, Carbone R , Mancini A. Semeiotica Ultrasuonografica delle alterazioni linfatiche nell'arto inferiore [Ultrasound Semeiotics of Lymphatic Modifications in the Lower Limbs]. Proceedings of "Giornate Nazionali di Angiologia 1991. Milano, 23-29 giugno". Minerva Angiologica. Aprile Giugno 1991; 16(Suppl. 1 al N. 2):453-7.

2) Franceschi C, Franco G, Luizy F, Tanitte M. Précis d'échotomographie vasculaire. [A Primer of Vascular Echotomography] Paris, Éditions Vigot, 1986, p. 256-7.

3) Cavezzi A., Michelini S. Il Flebolinfedema, dalla diagnosi alla terapia. [Phlebo-lymphoedema: from diagnosis to therapy] Ed. Auxilia, Bologna 1997.

4) Cavezzi A, Michelini S. Phlebolymphoedema, from diagnosis to therapy. Ed. PR Communications, Bologna 1998, ISBN 88-900300-1-1.

5) Van der Molen HR. Über die chronische venöse Insuffizienz. Verhandlungen der Deutschen Gesellschaft für Venenerkrankungen. Schattauer, Stuttgart 1957, p. 41-59.

6) Haid H, Lofferer O, Mostbeck A, Partsch H. [Lymph kinetics in the postthrombotic syndrome under compression bandages. Med Klin. 1968. May 10;63(19): 754-7]

7) Proceeding of the 3rd International Congress of Phlebology in Amsterdam 1968 (Ed HR van der Molen, J. van Limborgh, W. Boersma, Édition Stenvert Zoon, Apeldoorn, NL)

8) Battezzati M, Donini I. Il Sistema Linfatico nella pratica clinica. [The lymphatic system in clinical practice] 1967. Piccin Ed., Padova, Italia.

9) Bollinger A, Isenring G, Franzeck UK. Lymphatic microangiopathy: a complication of severe chronic venous incompetence (CVI). Lymphology 1982 Jun;15(2):60-5.

10) Bollinger A, Partsch H, Wolfe JHN (eds.). The initial lymphatics, new methods and findings. Thieme-Stratton Inc., Stuttgart New York, 1985.

11) Haid H. Venenerkrankungen, 5th edition , G. Thieme 1985, p 250 .

12) Franzeck UK, Haselbach P, Speiser D, Bollinger A. Microangiopathy of cutaneous blood and lymphatic capillaries in chronic venous insufficiency (CVI). Yale J Biol Med. 1993 Jan-Feb; 66(1):37-46.

13) Allegra C, Carlizza A, Bartolo M jr. Lymphedema. Fluorescent Microlimphography. In Lee BB, Bergan J, Rockson SG (Editors). Lymphedema. 2011, Springer Ed. p. 191-8. ISBN 978-0-85729-566-8.

14) PhleboLymphedema. Vasculab Message Archive. DOI: 10.24019/2011.PhleboLymphedema - Msgs 4144-4221, Feb 6-20, 2011. https://it.groups.yahoo.com/neo/groups/vasculab/conversations/messages/4144 to 4221, Feb 6-20, 2011. Accessed on line on Mar 23, 2017. A (free) subscription is required.

Index of Authors 2016

Index of Reviewers 2016

We thanks the Reviewers for their volunteer support to the Journal:

History and philosophy of Biology

Mariano Bizzarri,Silvia Caianiello, Evelina Miteva, Andras Paldi, Eleonora Severini.

Biology and Medicine

Francesco Albergati, Francesco Boccardo, Francesco Ferrara, Andrea Fontanella, Isabel Forner Cordero, Arkadiusz Jawien, James Laredo, Nick Morrison, Candida Nastrucci, Fausto Passariello, Massimo Vaghi.

Fondazione Vasculab *impresa sociale ONLUS*

www.vasculab.eu

DONA IL TUO 5 PER MILLE

Sostieni le iniziative della Fondazione Vasculab ONLUS

- **Ricerca scientifica e divulgazione in Medicina**
- **Metodi alternativi alla sperimentazione animale**
- **Missioni mediche umanitarie all'estero**

Inserisci il Codice Fiscale della Fondazione

95218510634

nella dichiarazione dei redditi (Unico o 730)

nella sezione del *5 per mille*

Fondazione Vasculab impresa sociale (ONLUS)
Email fondazione@vasculab.it
tel/fax: +39 081 7144110 cell +39 3356250756

The Vasculab Foundation
Fondazione Vasculab

Fondazione Vasculab

impresa sociale ONLUS. CF 95218510634. The Vasculab Foundation is a non-profit organization aimed to scientific research and to social solidarity.

Donations

You can donate using several methods: cash or bank check during a Vasculab associated event - by credit card - by bank transfer See at the page http://www.vasculab.it/common/donate.htm

Supporting membership

Even a minimal donation gives you the status of Supporting membership. Send by email your name and complete address and additional info about the type of help offered with your donation. By default, contributes are given generically to all the institutional activities of the Foundation.

But if you want, you can choose to give your contribute to support: - scientific research - a young researcher - a specific and already active scientific research of Vasculab (specify which one by email) - the organization of a specific educational/scientific event (specify which one by email) - alternate methods to animal experiments in scientific research - solidarity and health missions in low income countries

Ask for a receipt

Add other data in order to emit a correct receipt:

name of donating people or company, address, VAT number or any other info, according to your country fiscal laws.

VASCULAB, The Vascular List

Vasculab is a free-access non-profit vascular mailing list on Internet

VASCULAB was born in 1990.

Since August 2015 VASCULAB is the official mailing list of the "Fondazione Vasculab impresa sociale ONLUS".

TOPICS

Vascular Diseases Discussion List, Vascular Ultrasound Diagnosis, Vascular Biomechanics, Chiva Discussion List (Chirurgie Hemodynamique de l'Insuffisance Veineuse en Ambulatoire), Haemodynamic Venous Map (MEV), Minimal MEV, V N e t, the Model of the Venous Circulation, Micro-Circulatory Disorders, Lymphatic Diseases, Lasers in Vascular Diseases, Foam and Sclerotherapy, Vascular Malformations.

VASCULAB RULES

1) VASCULAB is a restricted Yahoo! Message List, open only to members

2) Active participation to this List is subjected to approvation of the Moderator.

3) Accepted members, mainly people of several professions involved in the management of vascular diseases, must respect generic "Netiquette" rules (Net Etiquette), as also the specific rules and the discussion topics listed in the first message they receive from the List.

4) Topics are many, but they all are scientific ones.

5) Direct consultation with patients is not allowed.

6) Drugs or medical devices promotion is forbidden inside the messages (as also hidden in messages, e.g. mail address of companies and their web sites).

7) Outside of the messages and clearly separated from them, commercial information can be given, though generally subjected to a fee.

If these rules do not comply with you, it's better to unsubscribe. Participating actively to the discussions automatically implies the Vasculab Policy agreement.

The Vasculab Foundation

Journal of Theoretical and Applied Vascular Research
The Official Journal of the Vasculab Foundation

Volume 1 Nov 2016 Issue 2

JTAVR
A Journal on Research in Vascular Diseases

Back to Volume 1