

## Invited commentaries

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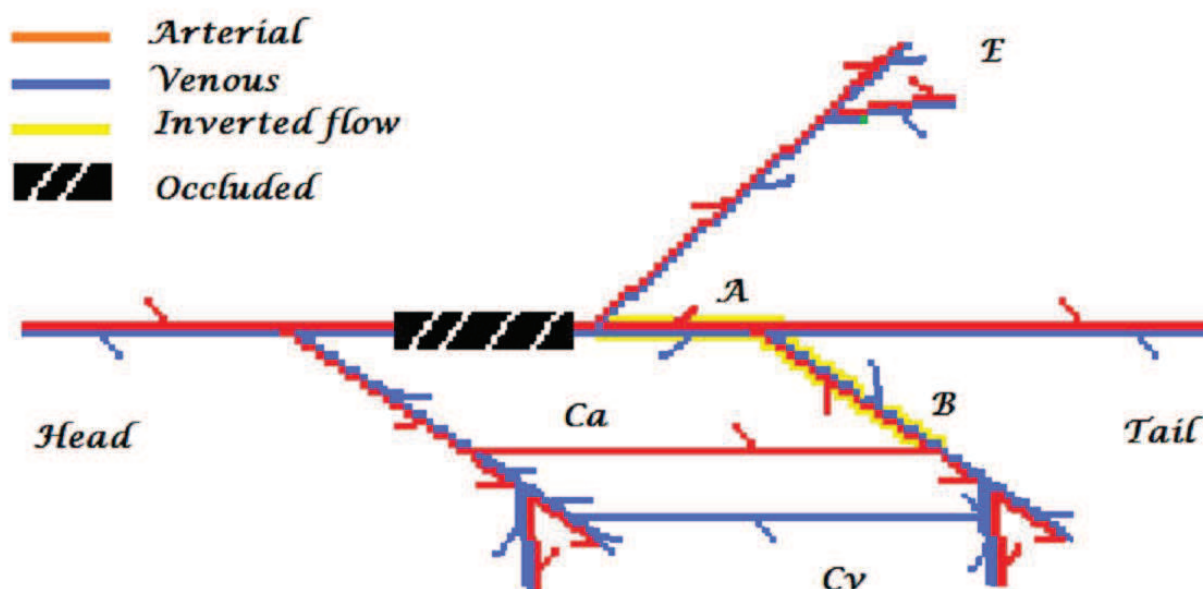


Figure 1 - Collateral circulation by-passing an obstruction in an arterial and venous schematic example. Half arrows point to the direction of flow, red for arteries, blue for veins. Yellow for inverted flow. Black for occlusion. A, inverted main trunk. B, inverted collateral path. E, excluded region. Ca, arterial anastomosis. Cv, venous anastomosis (from Passariello F. JTAVR 2017;2(1):33-35).

### Invited commentary on 'The hypothesis of the toxic effects of the venous collateral circulation' by F Passariello. The venous collateral circulation.

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The author formulated quite challenging hypothesis of the 'toxic' effects of the venous collateral circulation (TEVCC) based on the fact that the venous collateral circulation is generally spread in more peripheral vessels than in arteries, i.e. in veins, the collateral circulation can be intraparenchymal. Hence, a low concentration oxygen and high concentration carbon dioxide will exert a detrimental effect on downstream tissues around the collateral vessel<sup>1</sup>.

Indeed, 'abundant intraparenchymal collateral circulation' reminds me of well-known collateral condition among three hepatic veins which seems to be quite vulnerable to its *chronic* outlet obstruction/stenosis with limited/insufficient compensation despite excellent response to allow a partial -mostly for the living- liver transplantation with minimum morbidity.

Besides, the author drew further bold (?) conclusion for the TEVCC, claiming "the greater the volume of compensation, the greater the toxic damage" based on two different scenarios, one with the post-thrombotic syndrome (PTS) and another with the chronic cerebrovascular insufficiency (CCSVI)<sup>1</sup>.

Interestingly, for the CCSVI, the author cautioned that a venous surcharge inside the brain and the spinal cord system caused by the stenosis/occlusion in the venous cerebrospinal system could have an effect only when a *valid* collateral circulation giving same clinical impact to the tissue/ brain like PTS.

However, even if CVI/PTS would block normal/ efficient venous drainage to worsen the venous stagnation at the tissue level, it is hard to explain 'well developed' venous collaterals would cause/precipitate the venous stagnation to spread such 'toxic' effect to the tissue, which is odd with the definition/mission of the collaterals. After all, the collaterals are one of fool-proof life lines the nature created to compensate unseen jeopardy.

Although various components of the waste product/ metabolites would exert negative impact to tissue/cellular level to deter normal cellular metabolism when it failed to be evacuated properly (e.g. indolent venous stasis ulcer by CVI/PTS), 'deoxygenated' blood per se can hardly cause/ precipitate 'hypoxic' damage to the tissue. After all, 'low concentration oxygen and high concentration carbon dioxide' in the *venous* blood is not equivalent to the 'hypoxic' *arterial* blood.

Indeed, if TEVCC should be based on its/retrograde dissipation at the capillary level, its mechanism should be able to verify based on current Starling's law, and explain this phenomenon of 'retrograde seeping' of the deoxygenated blood from venous capillary into the tissue to cause such direct damage to the tissue/cellular level.

I also wonder how much pressure (gradient) will be needed to overcome the competent (vein) valves along the segment of A & B to allow retrograde flow to serve as a collateral(?) for segment E! We know substantial number of 'smaller' vein tributaries can remain resisting to the arterialized flow with a good valve competency when we do 'in situ' distal bypass for the critical limb ischemia. Another word, we stop doing the ligation of small twigs/branches routinely when we establish arterial flow following the valve resection along the GSV for the 'in situ' bypass

because only a few branches remain as AV shunting route but the majority does not by such unexpectedly strong valve competency against back flow.

Nevertheless, the natural collaterals to warrant sufficient venous drainage are essential not only for surviving through critical period of embryogenesis to complete complicated process of vasculogenesis/ angiogenesis, but also after the birth especially when the defective development should occur to interfere normal venous drainage (e.g. iliac vein aplasia; femoral vein hypoplasia)<sup>2</sup>.

When this natural compensatory mechanism through the collaterals (e.g. marginal/lateral embryonic vein) should fail, deranged venous drainage will cause back fire throughout its target organ/tissues; suprahepatic inferior vena cava (IVC) occlusive disease, also known as primary Budd-Chiari Syndrome (BCS), is the best example of inadequate compensation by natural collaterals to relieve hepatic vein outlet obstruction as the outcome of defective development to resulting in portal hypertension and chronic venous insufficiency<sup>3</sup>.

CCSVI is also well accepted condition of same nature/pathogenesis as a mirror image of primary BCS, caused by defective development along the extracranial venous drainage system: jugular-vertebral-superior vena cava (SVC)-azygos system. But actual impact/clinical outcome in its target/tissue level will be certainly different depending upon the degree and extent of the collaterals to compensate<sup>4</sup>.

Hence, 'maintaining enough collateral/compensatory circulation' route is crucial for the brain circulation system in particular so that it will go through rigorous fool-proof embryological development process till it is fully matured. But, when a defective development should occur during a long delicate evolution/involutional process and a valid collateral circulation is not sufficient to compensate, such unique condition of CCSVI will develop.

Indeed, by the beginning of the fourth week, primitive blood vessels develop from some clusters of angiogenetic cells -Pander's Island- and an extensive network of blood vessels starts as a complex capillary/reticular form of vascular plexuses first before proceeding to the next stage of the axial/truncal venous system development based on four pairs of embryonic cardinal veins<sup>5</sup>.

A pair of anterior cardinal/pre-cardinal veins leads the formation of matured extracranial venous system and complete 'jugular-vertebral-superior vena cava (SVC)' system as well as azygos/hemiazygos vein system together with two other pairs of posterior/post-cardinal and supracardinal veins. And three pairs of posterior cardinal, supracardinal, and subcardinal veins will also have to go

through much more complicated process to form IVC and further distal limb venous system<sup>5</sup>.

Naturally, the risk of defective development through such long-complicated evolution-involution process among four different pairs of cardinal veins to form one single matured vein system of SVC and IVC is quite high to resulting in unique condition of stenosis/obstruction to hamper the venous drainage from the target organ/tissue.

But in reality, the nature remains more generous(?) to allow a good portion of the embryonic/ cardinal veins

to become a natural escape route to relieve the obstruction as potential collaterals even though they already involuted after normal vena cava formation.

And such collaterals are able to provide reasonable compensation to abort clinical condition in majority (e.g. marginal vein to compensate iliac-femoral vein aplasia/hypoplasia)<sup>6</sup>. But if it should fail, we do see such clinical condition of CCSVI or primary BCS.

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## Invited commentary on 'The hypothesis of the toxic effects of the venous collateral circulation' by F Passariello. PTS, CCSVI-MS: Do intraparenchymal venous detours turn the blood toxic?

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Conflict of interest: None

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**Keywords** Venous obstruction, compensatory collateral venous outflow, postthrombotic syndrome,

chronic cerebrospinal venous insufficiency, multiple sclerosis

Sir,

The literature confronts us with ever new attempts made at explaining the clinical manifestations of puzzling hemodynamic affections by immunological, genetic or other biochemically determined processes.

The idea the intraparenchymal diversion of major compensatory venous outflow volumes might become pathogenic in overtaxing the transport capacity of the blood opens up a new perspective.

The postthrombotic syndromes of the lower limbs and the instances of multiple sclerosis relating to obstructions of major venous drainages of brain and spine show no doubt an intensified collateral venous drainage.

The lesions of neither can yet be said to emerge typically along and via the most overburdened collateral venous pathways of the affected limbs, spinal cords, and brains.

Already in legs affected by postthrombotic syndromes, the ever new forms of interaction of recurrent abrupt with protracted or even continuous flow inversions that present in as variable locations can hardly be explained by certain biochemical circumstances.

As little as the latter can be said to shed light on the ways in which the hemodynamic deviations clinically manifest.

In multiple sclerosis (MS) and chronic cerebrospinal venous insufficiency (CCSVI), the compensatory collateral venous flow patterns can no more be said to reflect either the ways in which MS lesions spread or to relate to the ways in which CCSVI is diagnosed.

The central vein sign, recently proposed for facilitating earlier and more reliable MS diagnoses, might possibly be adduced for buttressing your hypothesis.

If it is looked at more carefully, the pertinent postmortem evidence can yet again hardly be said to

indicate a compensatory collateral venous flow determined lesion spread.

Rather than focusing on MR spectroscopic evaluations of the blood of the lesion veins, focusing on the behavior of the MS lesions relative to their veins might hold the promise of coming closer to the biomechanical and hemodynamic factors which are here brought into play.

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Thus formulated criticism could be sound for instance for one of those points and not for the others.

If the venous compensating circulation is more peripheral than the arterial one, it could be just an interesting hypothesis, however not essential to TEVCC. Looking at the similar arterial/venous obstruction in Fig 1, it is easily seen that the arterial collateral circulation is always cephalad compared to the caudal venous one. Even if the previous remark could have no practical meaning, the arterial CC has generally a greater pressure than the venous CC and the higher pressure could select more direct arterial paths to destination than the lower venous pressure which could fill a wider and more peripheral venous bed.

## Answers to the commentary of Prof. BB Lee

Prof. BB Lee provided a lot of very interesting remarks which are worth answering in details.

*It is hard to explain 'well developed' venous collaterals would cause/precipitate the venous stagnation to spread such 'toxic' effect to the tissue.*

The TEVCC hypothesis could be better understood following the following analogy: drugs generally have several beneficial effects as well as they provide too several secondary adverse effects. In the same way, well-developed venous collaterals (see Cv in Fig. 1) would ease the drainage from territories excluded by the obstruction/stenosis, with an undoubted beneficial effect (E in Fig. 1). In the same time they could overcharge the territory they traverse (B and Cv in Fig. 1), increasing carbon dioxide concentration and catabolite content. As it can be easily seen, the two effects occur in different and separate parts of the venous bed: beneficial in E, overcharging in B and Cv.

*'low concentration oxygen and high concentration carbon dioxide' in the venous blood is not equivalent to the 'hypoxic' arterial blood.*

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## Answers to the invited commentaries on 'The hypothesis of the toxic effects of the venous collateral circulation' by F Passariello.

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submitted: Mar 27, 2018, accepted: Mar 27, 2018, Epub

Ahead of Print: Apr 01, 2018, published: Jun 30, 2018

Conflict of interest: None

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I have to thank the Authors for their commentaries to the paper on the toxic effect of the venous collateral circulation (TEVCC)<sup>1-3</sup>, as they were able to discover several points which deserve a thorough discussion.

### A common premise

The TEVCC hypothesis subdivided into 3 parts, almost totally independent on each other: 1) the TEVCC itself; 2) the more peripheral positioning of venous collateral circulation (CC) compared to the arterial one; 3) its intra-parenchymal placement.



I agree that a decreased O<sub>2</sub> and an increased CO<sub>2</sub> are somewhat physiological in the venous system, but of course it depends on the range of gas pressures and on the threshold values over which effective gas exchanges are insured from and towards tissues.

*'retrograde seeping' of the deoxygenated blood from venous capillary into the tissue to cause such direct damage to the tissue/ cellular level.*

This is a very interesting criticism about the mechanism by which TEVCC could exert its effect according to the well-known Starling principle<sup>4</sup>. Even if we accept this old pathophysiologic mechanism, the increased venular (and by consequence arteriolar) pressure causes the loss of the reabsorption phase along all the capillary.

Filtration and absorption are generally referred to the balance between capillaries and tissue, separated by a thin semipermeable capillary wall, under the mechanism described by the Starling principle. Starling stated the hypothesis that two gradients oppose across the semipermeable capillary membrane: the hydraulic pressure gradient and the osmotic pressure gradient.

The semipermeable membrane allows the transport of water and small molecules in both directions, while big molecules (like proteins) cannot traverse it. The difference in proteins concentration in the tissue and in the capillary generates a gradient of osmotic pressure, directed towards the capillary, while the pressure gradient is directed towards the tissue.

As the intra-capillary pressure falls down going from the arteriolar to the venular capillary terminal, while the osmotic pressure gradient and the tissue pressure are constant, the resulting net flow provokes the filtration and absorption of water and cristalloids, respectively at the arteriolar and the venular terminals.

This well-known hypothesis was later better defined<sup>5,6</sup> and then taken for an undoubted fact by many following researchers. The hypothesis justifies filtration and absorption of water and electrolytes in the extreme tissue territories and is generally presented in this way in almost all medical schools.

However, I would like to remind the interesting discussion we had on Vasculab in 2016 about the revised Starling principle<sup>7-9</sup>. The essential conclusion was that the old Starling's capillary exchange is nowadays obsolete and should be substituted by a three compartments mechanism, where the capillary is in a filtration phase along almost its length and fluid is almost completely absorbed by lymphatics, i.e. the old mechanism of capillary reabsorption at the capillary venous end should be considered just a myth and not true.

The main driving variable is then the venular pressure, which causes the entity of filtration. According to this interpretation context, the system is highly conditioned by the venular pressure. Consequently, the increased venous pressure in the non-draining territories reflects itself on the venous extremity of the capillary, conditioning the direction (towards the tissue) and the intensity of filtration.

*How much pressure gradient will be needed to overcome the competent (vein valves) along the segments A & B*

High pressure is able to force venous valves to cause inverted flow segments (A & B in Fig. 1), where however the obstruction does not involve the same segments, at least completely, as they must be completely or partially

patent to insure the collateral flow. Thus valves can be forced directly by pressure or by venous dilatation. As regards the inversion of several venous tributaries in the "in-situ bypass", it's worth noting that once the first A-V anastomoses are realized, a competitive flow occurs so that additional branches could also not be recruited. An additional remark deals with the level of pressure needed to force or disrupt the valve at the onset of the incompetence, while once the retrograde flow is established the exerted pressure can be much lower. Furthermore, an "in-situ bypass" is generally performed on an almost healthy greater saphenous vein (GSV), where valves can have a strong resistance to high pressure, while after a deep venous thrombosis (DVT) wall changes can extend also to nearby veins, which could exhibit altered elastic properties.

An increased pressure regimen is commonly detected in post-thrombotic syndrome (PTS) or in acute thrombotic events in lower limbs. Venous pressure can be easily measured non-invasively using the Bartolo's method<sup>10-12</sup>, using a pressure cuff and detecting the level of venous pressure when a wind-like noise appears. According to Franceschi<sup>13</sup> venous pressure must be measured in the supine position. Analogous experimental results were reported in the past following invasive phlebodynamometry<sup>14</sup>

*Venous collaterals in embryogenesis and defective development...the nature remains more generous...reasonable compensation to abort clinical condition in majority...*

Venous collaterals have of course a beneficial effect in several phases of vascular development as well as in chronic cerebro-spinal venous insufficiency (CCSVI) compensation. However, compensating veins can be classified at least into 2 groups:

- 1) Deep veins, generally with almost the same caliber of the occluded or non-well-developed vein. They generally pre-exist and convey almost the same amount of blood (cardinal veins, IVC, Open vicarious Path, Flat 1, all inside the N1 network)<sup>15-18</sup>,
- 2) Diversion to veins of the superficial network, i.e. saphenous or extra-saphenian segments in the lower limb, where generally the caliber as well as the amount of blood can be much lower (GSV, SSV, marginal vein). (Open vicarious Path, Type I or III according to the Graph Classification<sup>18</sup>.

These 2 types can have a completely different hemodynamic effect. In the 1<sup>st</sup> case the compensatory vascular bed is generally adequate and it extends almost totally inside big conducting veins but out of tissues. In the latter instead, the vascular bed extends towards non-conducting superficial veins, which are generally of inadequate caliber. These venous diversions could

influence in a greater extent the capillary circulation. Occasionally, these veins can convey on the contrary a great flow.

## Answers to the commentary of Dr. F Schelling

Dr. F Schelling commentary essentially is focused on the claimed venous CC positioning more in periphery and its devised consequences.

*...recurrent abrupt with protracted or even continuous flow inversions...*

This Multiple Sclerosis (MS) observation matches the common idea that in PTS more relevant clinical pictures are seen when mixed remnants of obstruction coexist with incompetent segments (valve destruction) of deep veins. In addition, it is clear that any acute or chronic obstruction always shows one or more inverted flow segments (A & B in Fig. 1), which are essential to the development of the compensation.

*...the compensatory collateral venous flow patterns can no more be said to reflect...MS lesions spread...central vein sign...focusing on the behavior of the MS lesions relative to their veins...*

I have not Dr Schelling's long-lasting wide experience in MRI and post-mortem investigations in MS nor his clinical insight in this disease to catch with competence the association between MS lesions and the patterns of venous compensation.

I agree with his proposal of a deeper study about the spatial relationship between MS lesions and their nearby veins.

I would like just to underline that the hemodynamical effects of a hampered drainage impinge also at distance from the excluded territory and in tissues around but also far from the compensating flow.

They are due indeed to the greater venular-arteriolar pressure, which cause the prevalence of the filtration over the reabsorption at the capillary level. Thus in search for a hemodynamic effect, upstream for excluded territories and just around the compensatory veins for the traversed territories, a much greater range should be considered.

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