A new hemodynamic model for the study of cerebral venous outflow

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Gadda G, Taibi A, Sisini F, Gambaccini M, Zamboni P, Ursino M. A new hemodynamic model for the study of cerebral venous outflow. Am J Physiol Heart Circ Physiol 308: H217–H231, 2015. First published November 14, 2014; doi:10.1152/ajpheart.00469.2014.—We developed a mathematical model of the cerebral venous outflow for the simulation of the average blood flows and pressures in the main drainage vessels of the brain. The main features of the model are that it includes a validated model for the simulation of the intracranial circulation and it accounts for the dependence of the hydraulic properties of the jugular veins with respect to the gravity field, which makes it an useful tool for the study of the correlations between extracranial blood redistributions and changes in the intracranial environment. The model is able to simulate the average pressures and flows in different points of the jugular ducts, taking into account the amount of blood coming from the anastomotic connections; simulate how the blood redistribution due to change of posture affects flows and pressures in specific points of the system; and simulate redistributions due to stenotic patterns. Sensitivity analysis to check the robustness of the model was performed. The model reproducibly average physiologic behavior of the jugular, vertebral, and cerebral ducts in terms of pressures and flows. In fact, jugular flow drops from ~11.7 to ~1.4 ml/s in the passage from supine to standing. At the same time, vertebral flow increases from 0.8 to 3.4 ml/s, while cerebral blood flow, venous sinuses pressure, and intracranial pressure are constant around the average value of 12.5 ml/s, 6 mmHg, and 10 mmHg, respectively. All these values are in agreement with literature data. mathematical modeling; cerebral outflow; posture dependence; jugular veins collapse; collateral routes

THE EXTRACRANIAL VENOUS SYSTEM represents an important determinant of the brain circulation, but its role in the pathology of the central nervous system is not fully understood yet (4, 26). It is recognized that, in supine position, the jugular veins represent the main outflow route for the cerebral circulation (2, 6, 25, 36, 38), being able to carry most of blood flow from the brain and from other extracerebral territories (~700–720 ml/min; Refs. 27, 33) with respect to a cerebral blood inflow of ~750 ml/min (45). However, the jugular venous system exhibits important flow limitation during upright posture changes, because the jugular veins tend to collapse as a consequence of the decrease of transmural pressure due to the gravitational field, causing a significant increase in resistance (3, 7, 12, 14, 26). In the absence of other routes for extracranial outflow, this flow limitation would have dramatic effects on the cerebral circulation, since, apart from brief transient time intervals, the average cranial arterial inflow is expected to be equal to the cranial venous outflow for the mass preservation.

As a consequence, large attention has been devoted to the venous circulation in the upright state, in an effort to understand which alternative routes can carry the brain venous outflow. It has long been postulated that the vertebral venous system may provide an important alternative route for venous outflow when standing or sitting; this was first demonstrated with the use of contrast media in rhesus monkeys (9) and subsequently measured in humans with the Doppler and magnetic resonance imaging technique (2, 6, 7, 25, 38). Valdueza et al. (33) observed that blood flow in the jugular veins decreases from 700 ml/min in supine position down to 70 ml/min at 90° elevation, while blood flow in the vertebral veins raises from 40 to 210 ml/min.

Accordingly, a classical model of the cerebral venous outflow assumes the existence of two main alternative routes: a route through the jugular veins, with smaller resistance in supine conditions, and a parallel vertebral route with higher resistance. In upright conditions, when the first route collapses, blood flow is diverted to the second one. Based on this idea, Gisolf et al. (14) developed a mathematical model of cerebral venous outflow: the model consists of two jugular veins (each composed of a chain of 10 units with resistances and capacitances) and a vertebral plexus (described with a single resistance). The elements in the jugular veins collapse according to the “tube law” (3, 12) during a posture change but can reopen during a Valsalva maneuver. With this model, the authors studied how venous blood flow changes from supine to upright position and confirmed that the cerebral venous distribution depends on posture. Despite the previous pivotal studies, many aspects of the cerebral venous outflow system are still problematic.

First, it is well known that cerebral autoregulation maintains blood flow to the brain quite constant, despite pressure changes (1, 21): this signifies that an amount of blood flow much greater than that measured in the vertebral system must be carried out in the upright state. This discrepancy was clearly recognized by Valdueza et al. (33) who observed that “a mean difference of about 450 ml/min remained.” These authors hypothesized that other routes, such as the epidural veins, significantly contribute to the orthostatic venous outflow.

Second, some authors, using the color Doppler technique, recently observed that blood flow along the jugular veins in upright conditions is not longitudinally constant but increases progressively when the measurement site is moved from the upright sections (close to the jugular foramen into the skull) to the downstream sections (close to the subclavian vein) (6, 28, 41, 44). This observation supports the idea that additional anastomotical routes carry part of the cranial blood flow to the jugular veins even in upright position, bypassing the upstream more collapsed sections. In fact, as a consequence of the different effect of gravity, only the higher portions of the
jugular veins are probably fully collapsed, whereas the downstream sections are opened. A comprehensive model of the cerebral venous outflow should also include these further collateral routes.

Due to the complexity of the relationships involved, and the large variability in the anatomical parameters, it is extremely difficult to understand the effect of alterations in the extracranial venous circulation in simple qualitative terms. The study of the cerebral venous outflow, and of its implications in healthy and diseased conditions, can largely benefit from the use of computational models.

So far, most models of the cerebral circulation focused on the intracranial circulation and on its control mechanisms, by providing just a very simplified description of extracranial venous return. A notable exception is the model by Gisolf et al. (14) mentioned above, which, however, includes only the vertebral plexus as an alternative drainage pathway.

The aim of the present study is to develop and validate a comprehensive original lumped parameter model of the cerebral venous outflow system, which overcomes some of the limitations noticed above. In particular, compared with the model by Gisolf et al. (14) the present model also includes:

1) An accurate model of the intracranial circulation developed in past years, which incorporates the autoregulation of cerebral blood flow (13, 30, 32). This model provides the correct values of cerebral blood flow to the venous return model. Moreover, it allows a quantitative analysis of the effect of alterations in the venous pathways on intracranial quantities, such as the effect on intracranial pressure, venous sinuses pressure, capillary pressure, and cerebrospinal fluid circulation.

2) A more sophisticated description of the collateral pathways, including not only the vertebral plexus but also other anastomoses leading blood to the downstream sections of the jugular veins (6, 28, 41, 44).

In the following, the model is described qualitatively, with emphasis on the new aspects, and parameters are given in accordance with the physiology. All equations are presented in the Appendix. The model is validated against results in the literature, concerning the effect of a posture change in healthy and diseased conditions, can largely benefit from the use of computational models.

The model may represent an useful tool for the study of the correlation among posture variations, vessel conductances (normal or abnormal), and the consequent pressure and flow changes. This may have a great impact toward a deeper understanding of pathological disorders involving abnormalities of the cerebral venous outflow. In perspective, it may be used to assess which alterations in the extracranial venous outflow may be in relation with central nervous system disorders and aging (6, 10, 24, 40, 42).

MATERIALS AND METHODS

Model Description

Our mathematical model for the simulation of the head and cerebral circulation and drainage system includes two submodels built using lumped parameter method. The model is represented in Fig. 1.

Mathematical models may represent an useful tool for improving comprehension of complex systems like this, describing the behavior of a real process using a system of equations (14, 20, 22). What we are developing is a lumped parameter model, i.e., a model in which the continuous variation in space of the state variables of the system is represented by a finite number of variables (35). In other words, a lumped parameter model allows the description of spatially distributed physical systems to be simplified using a network of discrete entities that approximate the real system. The use of a lumped parameter model presents a significant advantage since it exhibits a small number of parameters able to account for an entire physiological or clinical phenomenon in a concise way. This fact improves the clinical meaning of the results obtained: the behavior of the model can be studied more easily than the system that it represents.

Every segment x of Fig. 1 consists of a capacitor Cx that simulates the property of the segment to accommodate volume and of a conductance Gx that simulates the property of the segment to drain blood.

All the model equations are presented in the Appendix.

The mathematical model of the cerebral hemodynamics, enclosed in the “BRAIN” dashed rectangle of Fig. 1, has been fully developed and validated by Ursino and colleagues in previous works (13, 30, 32). This model simulates the hemodynamics of the arterial-arteriolar and venous cerebrovascular bed, the cerebral arterioles regulation mechanisms, the cerebrospinal fluid production and reabsorption processes, the Starling resistor mechanism for the cerebral veins, and the nonlinear pressure-volume relationship of the craniospinal compartment.

The structure of the cerebral venous outflow model (shown in Fig. 1 out of the “BRAIN” dashed rectangle) has been developed starting from a recent work of Zamboni et al. (44). The main part of the model is composed of four venous ducts: two internal jugular veins (IJVs; left and right) and two vertebral veins (VVVs; left and right). In the internal jugular veins are modeled by dividing them into three segments with different conductive and capacitive values, to better implement the different biomechanical properties of these vessels along their length and to better simulate the effect of hydrostatic pressure gradient in upright position.

Indeed, jugular veins are collapsible blood vessels characterized by marked changes in their cross-sectional configuration depending on transmural pressure P trans − P ext (26). The latter is affected by hydrostatic pressure gradient during a posture change (7). On the other side, the hydrostatic pressure gradient does not significantly affect the lumen of the vertebral veins.

Anatomically speaking, left and right lower jugular segments (J1) correspond to the segments close to the junction of the internal jugular veins with the subclavian vein, at the confluence with the brachiocephalic vein trunk. The middle segments (J2) correspond to the point where the veins are in an anatomical relationship with the more lateral contour of the thyroid gland. The upper segments (J3) correspond to the point before the passage through the jugular foramen into the skull (43).

To account for the growth of blood flow from J3 to J1 (6, 8, 10, 28, 33, 41, 44), we must consider that a quota of the head inflow is conveyed into the internal jugular veins more caudally with respect to the J3 position, through intra- and extracranial anastomosis. To account for this experimental evidence, the model is developed so that the two jugular veins are linked by a network of eight constant conductances and two constant capacitors that simulate the presence of collaterals and anastomotic connections. This collateral network also allows the drainage of the extracranial venous blood, i.e., of that part of blood coming from the two external arteries to serve the head organs and tissues out of the braincase (44).

In the model, the conductance of the external arteries (i.e., the conductance of the tract with blood flow Qext in Fig. 1) has been maintained constant. Conversely, as described in previous works (30) and explained through Eqs. 7–11 in the Appendix, the conductance of the intracerebral arterioles is subjected to autoregulatory mechanisms, which work to maintain quite a constant cerebral blood flow despite moderate changes in cerebral perfusion pressure. The choice of a constant extracranial conductance can be justified by the observation that autoregulation in extracranial vessels is generally weak and slow. Moreover, during hypotension a vasoconstriction of baroreflex origin.

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may counteract this weak vasodilatory autoregulation, thus resulting in negligible conductance changes.

We assume that, in the basal supine condition, the anastomotic upper connection c3 is latent: blood flows in it only when the posture is upright or when there is a lack of drainage in one vessel tract, or more than one.

Moreover, a basic submodel of six constant conductances and three constant capacitors is implemented in the main model to describe the lumbo-azygos system (AZY), which links jugular and vertebral pathways at the level of superior vena cava (36).

The model is made up of several differential equations. Every equation links together the elements representative of a specific point \( x \) (i.e., pressure \( P_x \), conductance \( G_x \), and capacity \( C_x \)) with the elements representative of the other segments of the system to account for mass preservation and to include effects due to posture changes.

We report here (Eqs. 1 and 2) examples of the two types of equations used to built the cerebral venous outflow model.

**Equation 1**, one of the state equations of the model listed in the **APPENDIX**, implements the mass preservation. We can see how the pressure at a given point \( jr3 \) in this example) is related to capacity, conductances, and drops of pressure.

\[
\frac{dP_{jr3}}{dt} = \frac{1}{C_{jr3}} \left[ (P_{vs} - P_{jr3}) G_{jr3} - (P_{jr3} - P_{c3}) G_{cj3} - (P_{jr3} - P_{jr2}) G_{jr2} \right]
\]

To include dynamics due to posture changes from supine to upright in the gravity field, conductances in the jugular veins are modeled using a nonlinear relation (Eq. 2) with switch-like properties so that for negative or low transmural pressure \( P_{x_{int}} - P_{x_{ext}} \) at a given point \( x \), the related vessel conductance \( G_x \) is low, while for high transmural pressure, vessel conductance approaches a maximum value (14).

\[
G_x = k \left[ 1 + \left( \frac{2}{\pi} \right) \arctan \left( \frac{P_{x_{int}} - P_{x_{ext}}}{A} \right) \right]^2
\]

The effect of hydrostatic pressure gradient is hidden in the internal pressure \( P_{x_{int}} \). The value of this pressure decreases by a factor \( gph \) during the transition from supine to standing position. Obviously, the collapse of the upper segment of the jugular veins (J3) is more pronounced with respect to the lower segments (J1), due to the presence of the height \( h \). We use the superior vena cava as the zero level for the hydrostatic pressure.
Assignment of Basal Parameters

We adjusted every parameter value in search of agreement between model simulations and measurements that can be obtained from literature results. Starting from the work on the intracranial circuit already developed by Ursino and Lodi (30), we moved around several literature data to choose the right inputs for the jugular-vertebral network, adopting reasonable criteria to determine parameters not available from literature.

Parameters were assigned on the basis of the following criteria:

1) All parameters concerning the intracranial circulation were given the same values as in the previous works (30, 32), where a thorough justification can be found. Briefly, intracranial vascular resistances and capacities were assigned on the basis of physiological and anatomical data on brain hemodynamics in a normal subject. The autoregulation gain and time constants were given to simulate the typical autoregulation response of an healthy individual who exhibits mild cerebral blood flow changes despite cerebral perfusion pressure changes (see Fig. 2). Parameters summarizing the cerebrospinal fluid circulation and intracranial compliance were set to establish a normal hydrodynamics, as derived from infusion or PVI tests in the neurological literature. All the intracranial basal parameters are summarized in Table 1.

2) The values of all conductances in the extracranial circulation were assigned starting from physiological values of pressures and flows (see Tables 2 and 3, respectively). In particular, as shown in Table 2, we assumed a progressive pressure reduction from the venous sinuses to the right atrium (i.e., the central venous pressure), assuming normal values as large as 6 and 5 mmHg, respectively. Typical average values reported in Table 2 are assigned as basal values to the pressure of the superior tract of collateral $P_{c3}$, of venous sinuses pressure $P_{v3}$ (30), and of central venous pressure $P_{cv}$ (14). Intermediate basal pressure values ($P_{v3}$, $P_{v2}$, etc...) are assigned to simulate a homogeneous pressure drop along the whole circuit from the exit of venous sinuses to the vena cava. External pressure $P_{ext}$ to the upper sections of the jugular veins J3 and J2 is set to zero, while at the lower segments J1 is set to the average thoracic pressure during a complete respiratory cycle (18). Looking at the basal flows shown in Table 3, cerebral blood flow $Q$ is the total blood volume entering the cranial cavity per unit time (45). At the exit from the skull, it is drained both by jugular and vertebral veins, with the two jugular veins that contribute to drain the main part of blood only in supine position. The flow through left and right external carotid arteries $Q_{can}$ is set according to the data of Yazici et al. (37) and taking into account the lower cerebral flow reported by these authors (i.e., we assumed the same ratio between the extracranial carotid blood flow and blood flow in the common carotid artery as in Ref. 37). It is also assumed that 40% of this flow is directed to every jugular via the anastomotic connections, while the remaining blood is drained down through the middle collateral. Finally, half of the vertebral flow enters in the azygos vein, while the other half is divided between lumbar vein duct (1/3 of the total) and renal vein duct (2/3 of the total).

3) The values of the capacities in the extracranial circulation (Table 4) have been determined using the following considerations:

i) Capacities in the jugular tracts and in the vertebral veins have been computed from the values of transmural pressures, lengths, and areas reported in the literature (33) and assuming a negligible unstressed volume (i.e., we consider an average capacity, quite independent of transmural pressure).

**Table 1. Basal values of quantities related to the intracranial circuit (supine condition)**

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{pan}$</td>
<td>0.205 ml/mmHg</td>
</tr>
<tr>
<td>$\Delta C_{ps1}$</td>
<td>2.87 ml/mmHg</td>
</tr>
<tr>
<td>$\Delta C_{ps2}$</td>
<td>0.164 ml/mmHg</td>
</tr>
<tr>
<td>$G_{aut}$</td>
<td>3</td>
</tr>
<tr>
<td>$k_E$</td>
<td>0.077 ml$^{-1}$</td>
</tr>
<tr>
<td>$k_R$</td>
<td>13.1 $\times$ 10$^3$ mmHg$^{-1}$ s $^{-1}$</td>
</tr>
<tr>
<td>$k_{ven}$</td>
<td>0.155 ml$^{-1}$</td>
</tr>
<tr>
<td>$P_a$</td>
<td>100 mmHg</td>
</tr>
<tr>
<td>$P_{cv}$</td>
<td>9.5 mmHg</td>
</tr>
<tr>
<td>$P_{ps}$</td>
<td>58.9 mmHg</td>
</tr>
<tr>
<td>$P_{pa}$</td>
<td>14.1 mmHg</td>
</tr>
<tr>
<td>$P_{v1}$</td>
<td>2.5 mmHg</td>
</tr>
<tr>
<td>$P_{v2}$</td>
<td>6 mmHg</td>
</tr>
<tr>
<td>$Q_a$</td>
<td>12.5 ml/s</td>
</tr>
<tr>
<td>$R_{0}$</td>
<td>526.3 mmHg s ml$^{-1}$</td>
</tr>
<tr>
<td>$R_{f}$</td>
<td>2.38 $\times$ 10$^3$ mmHg s ml$^{-1}$</td>
</tr>
<tr>
<td>$R_{ls}$</td>
<td>0.6 mmHg s ml$^{-1}$</td>
</tr>
<tr>
<td>$R_{pv}$</td>
<td>0.880 mmHg s ml$^{-1}$</td>
</tr>
<tr>
<td>$R_{ex}$</td>
<td>0.366 mmHg s ml$^{-1}$</td>
</tr>
<tr>
<td>$\tau_{aut}$</td>
<td>20 s</td>
</tr>
<tr>
<td>$x_{aut}$</td>
<td>2.16 $\times$ 10$^{-4}$</td>
</tr>
</tbody>
</table>
HEMODYNAMIC MODEL OF THE CEREBRAL VENOUS OUTFLOW

Table 2. Basal values of pressures related to the jugular-vertebral circuit (supine condition)

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Symbol</th>
<th>Value, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the collateral (superior tract)</td>
<td>( P_{c3} )</td>
<td>6.00</td>
</tr>
<tr>
<td>At the right jugular (superior tract)</td>
<td>( P_{jl3} )</td>
<td>5.85</td>
</tr>
<tr>
<td>At the left jugular (superior tract)</td>
<td>( P_{jl2} )</td>
<td>5.85</td>
</tr>
<tr>
<td>At the collateral (middle tract)</td>
<td>( P_{c2} )</td>
<td>5.85</td>
</tr>
<tr>
<td>At the vertebral vein</td>
<td>( P_{vv} )</td>
<td>5.80</td>
</tr>
<tr>
<td>At the right jugular (middle tract)</td>
<td>( P_{jl2} )</td>
<td>5.70</td>
</tr>
<tr>
<td>At the left jugular (middle tract)</td>
<td>( P_{jl2} )</td>
<td>5.70</td>
</tr>
<tr>
<td>At the azygos vein</td>
<td>( P_{azy} )</td>
<td>5.50</td>
</tr>
<tr>
<td>At the superior vena cava (superior tract)</td>
<td>( P_{svc1} )</td>
<td>5.40</td>
</tr>
<tr>
<td>At the superior vena cava (inferior tract)</td>
<td>( P_{svc} )</td>
<td>5.20</td>
</tr>
<tr>
<td>At the right atrium (central venous pressure)</td>
<td>( P_{x} )</td>
<td>5.00</td>
</tr>
<tr>
<td>External at J1 and J2</td>
<td>( P_{ext1} )</td>
<td>0</td>
</tr>
<tr>
<td>External at J1</td>
<td>( P_{ext} )</td>
<td>-6.50</td>
</tr>
</tbody>
</table>

Table 4. Capacities related to the jugular-vertebral circuit (supine condition)

<table>
<thead>
<tr>
<th>Capacity</th>
<th>Symbol</th>
<th>Value, ml/mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the venous sinuses</td>
<td>( C_{vs} )</td>
<td>0.5</td>
</tr>
<tr>
<td>At the right jugular (superior tract)</td>
<td>( C_{jl3} )</td>
<td>1.0</td>
</tr>
<tr>
<td>At the left jugular (superior tract)</td>
<td>( C_{jl2} )</td>
<td>1.0</td>
</tr>
<tr>
<td>At the right jugular (middle tract)</td>
<td>( C_{jl2} )</td>
<td>2.5</td>
</tr>
<tr>
<td>At the left jugular (middle tract)</td>
<td>( C_{jl2} )</td>
<td>2.5</td>
</tr>
<tr>
<td>At the central collateral (superior tract)</td>
<td>( C_{c3} )</td>
<td>0.7</td>
</tr>
<tr>
<td>At the central collateral (middle tract)</td>
<td>( C_{c2} )</td>
<td>1.4</td>
</tr>
<tr>
<td>At the superior vena cava (lower tract)</td>
<td>( C_{svc} )</td>
<td>20.0</td>
</tr>
<tr>
<td>At the azygos vein</td>
<td>( C_{azy} )</td>
<td>0.5</td>
</tr>
<tr>
<td>At the vertebral vein</td>
<td>( C_{vv} )</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Reasonable agreement with our knowledge on the biomechanics of compressible vessels. These curves, reported in Fig. 3, show that the collapse initiates at a transmural pressure approximately as high as 1–2 mmHg and is almost completed at moderate negative transmural pressure values in agreement with the literature information (5, 14, 16).

In the current model the value of the parameter \( A \) is 0.8, while we assigned to \( k_{jl3}, k_{jl2}, \) and \( k_{jl1} \) the value of 11.0, 13.0, and 6.9, respectively (the same values are assigned to the left coefficients \( k_{jl3}, k_{jl2}, \) and \( k_{jl1} \)). By choosing these parameters, Fig. 3 shows the relation between conductance of the jugular segments and the transmural pressure.

RESULTS AND DISCUSSION

Once we verified that the model, with basal parameter values, can simulate the main blood flow changes from supine to upright position, we performed a sensitivity analysis on some model parameters. We focused our attention on changes in conductances in the venous pathways. Indeed, analysis of the correlation between conductances and posture variation and the subsequent pressures and flows changes might give information about the parameters that have greater impact on intracranial hemodynamics (and then on related disorders). From our particular point of view, analysis of the results before and after the variation of a conductance is meaningful, since it provides information on how the closure of a particular drainage tract affects important physiological parameters, such as venous sinuses pressure \( P_{vs} \) (and so intracranial pressure \( P_{ic} \)) and cerebral circulation) or flows in the jugular and vertebral veins (\( Q_{svc1} \) and \( Q_{vv} \), respectively). For simplicity, we focused only on the right conductance variations, since analysis on left conductance variations will be symmetrical.

Each conductance under examination was varied from the baseline value, that is representative of physiological condition, to zero value that simulates total absence of drainage from a section of the network; simulations of posture variation were performed in both situations.

Once we performed the sensitivity analysis by setting one conductance to zero, we chose to simulate total and halved occlusions of more than one drainage tract at the same time, following the typical patterns reported in Zamboni et al. (39). This work is one of the recent studies concerning the relations among the main cerebral venous outflow routes, their disorders, and the occurrence of neurological diseases (10, 17, 19, 28, 29, 34).

Simulation results of particular interest are shown in the following.
Simulation with Basal Parameter Values

Figure 4 shows how the model simulates the total amount of jugular flow $Q_{j3}$ and vertebral flow $Q_{vv}$ at the equilibrium in both supine and upright conditions. Results are also compared with the experimental mean flows reported in Valdueza et al. (33). The very good agreement between simulated supine and upright flows and experimental results means that parameters of the model are well assigned.

In Fig. 5, we show the behavior of the simulated venous sinuses pressure $P_{vs}$ over time when passing from supine to upright condition. When basal parameters are used, our model predicts an increase of 2.68 mmHg (from 6.00 to 8.68 mmHg) with change of posture. It also predicts that $P_{vs}$ needs ~3 s to reach the upright equilibrium.

In Fig. 6, the behavior of the simulated right jugular flow $Q_{jr3}$ and right vertebral flow $Q_{vvr}$ over time is reported in the same conditions of Fig. 5. For simplicity, we focus the attention only on the right jugular and vertebral flows, since results on left vessels are symmetrical. Figure 6 shows that our model predicts a strong decrease of the right jugular flow $Q_{jr3}$ when changing from supine to upright (from 5.87 to 0.69 ml/s). Conversely, flow at the right vertebral vein $Q_{vvr}$ rises from 0.40 to 1.70 ml/s during the change from the supine to upright condition. Figure 6 also shows that upright $Q_{jr3}$ and $Q_{vvr}$ flows reach their equilibrium with different behaviors.

In these conditions the flow through jugular and vertebral veins is equally distributed between left and right side. The collateral tract $c3$ is latent in supine position, while in upright it drains the amount of blood that does not flow through jugular or vertebral veins (~7.7 ml/s).

Figure 7 summarizes amounts of simulated total inflow $Q_{tot}$, flow to face and neck $Q_{ex}$, cerebral blood flow $Q$, and total jugular, vertebral, and collateral flows at equilibrium ($Q_{j3}$, $Q_{j2}$, $Q_{j1}$, $Q_{vv}$, and $Q_{c3}$) in supine and upright conditions.

We see that $Q_{tot}$ is the sum of $Q_{ex}$ and $Q$. Moreover, the histogram shows the different type of drainage the cerebral blood flow $Q$ undergoes in supine and upright position. These different blood distributions are due to the changes in jugular conductances that occur when upright position is simulated (Eq. 2).

Results can be summarized as follow. Cerebral blood flow $Q$ remains substantially constant despite the posture change, as a consequence of the action of autoregulatory mechanisms. In fact, the moderate increase in venous sinuses pressure lies well inside the autoregulatory range (30). Blood flow $Q_{j3}$ in the upper portion of the jugular vein exhibits a dramatic fall in the upright state: most of the cerebral blood flow passes through the collateral route $c3$. Moreover, blood flow in the vertebral veins $Q_{vv}$ increases by about four times. These results agree with those reported in literature (33). Furthermore, blood flow in the jugular veins progressively increases from J3 to J1, since part of blood flow is drawn from the collateral route to the jugular tract via the anastomoses $cj3$ and $cj2$ (see Fig. 1). The reason is that the last portion of the jugular veins exhibits a less pronounced collapse in upright condition compared with the first tract, due to a
smaller gravitational pressure gradient and due to the effect of the negative intrathoracic pressure.

**Sensitivity Analysis**

To clarify the role of the main routes involved in cerebral venous outflow, and a possible effect of a pathological alteration, we performed a thorough sensitivity analysis. It consists of two steps:

1) We first interrupted blood flow in a single route by assigning a zero value to the corresponding conductance and checked the effect in steady-state conditions.

2) Then, we simulated four typical pathological alterations already reported in the clinical literature (39) and characterized by a conductance reduction in multiple venous paths.

**Effect of a single closure.** Results are summarized in Figs. 8, 9, and 10 with regards to the effect of a single closure on venous sinuses pressure $P_{vs}$, outflow from the confluence of the two jugular veins $Q_{svc1}$ and vertebral blood flow $Q_{vv}$, respectively. Results show that the cerebral venous outflow system is quite robust in response to a single vessel closure, both in supine and upright conditions. This signifies that interruption of a single path can be quite easily replaced by an alternative route. Pressure $P_{vs}$ at the venous sinuses, the link between intracranial and jugular-vertebral circuit, increases with change of posture from supine to upright in basal conditions ($+2.68 \, \text{mmHg}$) as shown in Fig. 8. In supine posture, total occlusion of right jugular vein ($G_{jr3} = 0$, $G_{jr2} = 0$, and $G_{jr1} = 0$) produces little increases of the value of $P_{vs}$. Also, changes due to occlusions of collateral network and vertebral veins are not appreciable. Conversely, looking at the simulation of upright condition, it is evident that $P_{vs}$ is more influenced by lack of drainage of the collateral network ($G_{c3} = 0$), while all the other kinds of occlusion only affect $P_{vs}$ with little or not appreciable increases.

Figure 9 shows that output flow from the confluence of jugular veins $Q_{svc1}$ decreases of about $-3.1 \, \text{ml/s}$ from the supine to upright condition. In supine condition, every kind of occlusion evokes little or negligible changes of this flow. The same situation also occurs in upright condition.

Output flow from the vertebral veins $Q_{vv}$ rises of $2.6 \, \text{ml/s}$ during change from supine to upright conditions as reported in Fig. 10. Little variations from the basal supine value occur when a jugular vein is occluded. Conversely, basal upright flow is quite increased by occlusion of the collateral network ($G_{c3} = 0$) and lowered by occlusion of right vertebral vein ($G_{vvr} = 0$).

The most influential closure is found in the collateral circulation: in upright conditions it provokes a further increase in venous sinuses pressure up to $-10 \, \text{mmHg}$ and also a redistribution of blood flow toward the vertebral-azygos complex. Obstruction of a jugular vein is relevant especially when it occurs close to its terminal part, causing a reduction of jugular outflow down to $11.4 \, \text{ml/s}$. Naturally, an obstruction in a vertebral vein causes a significant decline in vertebral blood flow, with a redistribution toward the jugular and collateral circulations.
Finally, we tested the behavior of the external flow $Q_{\text{ext}}$ for all the conditions described above. In the present model $Q_{\text{ext}}$ diminishes by 0.05 ml/s when venous sinuses pressure increases (for example, when moving from supine to upright condition both in a healthy and a pathological subject). This external flow is not significantly affected by any kind of occlusion we tested, apart for a little decrease during the occlusion of the lower jugular segment and a little increase during the occlusion of the collateral pathway $c3$ (~0.03 and +0.02 ml/s, respectively). We also performed the whole sensitivity analysis in the conditions of weak autoregulation reported in Fig. 2. Results show that for reduced cerebral autoregulation (i.e., by changing the value of $G_{\text{aut}}$ till 1/10 of its initial value) every value of pressure and flow reported in the sensitivity analysis does not change significantly. The reason is that, in our simulations, venous sinuses pressure always exhibits a mild change (+1 or +2 mmHg), which is a minimal fraction of cerebral perfusion pressure. Since cerebral blood flow is subjected to regulation mechanisms, the final change in cerebral blood flow is always <1% of basal (even when using a moderate autoregulation gain), which has negligible effects on the final results.

Multiple occlusions. The effect of multiple occlusions may be much more dramatic. In the following, we will especially analyze the changes in venous sinuses pressure, since this quantity represents a link between the cerebral circulation and the extracranial venous outflow system. We report in Fig. 11 a histogram to show how the basal venous sinuses pressure $P_{\text{vs}}$ varies when stenotic patterns occur. Together with the simulations of null conductance, we reported also the simulations of the same patterns but with halved conductances.

A more complete description can be found in Tables 5 and 6, which report results concerning blood flows and pressures redistribution due to the different stenotic patterns described in Ref. 39, compared with the simulation of a healthy distribution.

Pattern A refers to simulation of obstruction of the proximal aygous $azy2$, associated with a closed stenosis of the left internal jugular vein. Pattern B refers to simulation of obstructions of both the internal jugular veins and the proximal aygous. Pattern C refers to simulation of obstructions of both the internal jugulars but without stenoses in the aygous system. Finally, pattern D refers to simulation of obstructions in different tracts of the aygous vein ($azy1$ and $azy2$) associated with occlusion of the lumbar vein.

Results show that two particular pathological patterns (i.e., patterns B and C) may have a strong effect on venous sinuses pressure, which reaches values as high as 13–16 mmHg both in supine and upright positions. Such value may have consequences on intracranial pressure, cerebrospinal fluid circulation, and cerebral tissue. However, this pressure increase occurs only if the stenotic lesions are very severe (conductances close to zero). Moderate levels of conductance changes, although multiple, cause more acceptable pressure rises.

For what concerns model validation, we cannot use animal data taken from the literature, as usually done, since the extracranial venous drainage pathways are significantly different in animals compared with humans. In particular, the extracranial venous circulation in humans is specifically adapted...
to the maintenance of an upright posture, which is the peculiar subject of the present work. For this reason, we are designing some ad hoc measurements on volunteers, using the Doppler technique, to assess blood flow changes and cross-sectional areas in the different portions of the jugular veins and to provide a complete quantitative set for model validation (or for discovering aspects requiring improvement). This will be the subject of a future work. When imaging with the current diagnostic methods multiple stenotic patterns or flow abnormalities in the major extracranial and extraspinal veins, which are typical of chronic cerebrospinal venous insufficiency (CCSVI), it is difficult to confidently assign their hemodynamic significance for the intracranial circulation. It has been recently emphasized that the main issue to be investigated in this field is the definition of the hemodynamic impact in the intracranial venous system of obstruction/narrowing of the extracranial veins (46). Since, at this time, there is no established invasive or noninvasive diagnostic imaging modality capable to assess intracranial and/or parenchymal circulatory parameters in relation to extracranial brain outflow (47), the clinical application of the present model seems highly desirable. For instance, in the present study we tested our model on four clinical patterns of extracranial venous obstruction, clinically detected in patients by means of catheter venography (39). In Fig. 11, we report the estimated pressure values in the cerebral dural sinuses in relation to the different CCSVI patterns. The application of the model demonstrates a significant increase of venous sinuses pressure especially for type B and C but not in patterns A and D. Such a result appears to be coherent with the clinical severity and/or the topography of multiple sclerosis, the neurological disease associated with the observed patterns of venous obstruction in this cohort of patients. As far as the severity is concerned, patients with type A pattern (characterized by reduced sinusal pressure) demonstrated, with respect to B and C patterns, a significantly reduced probability to worsen to the secondary progressive clinical stage (39). Regarding the topography of the lesions in the central nervous system, type D pattern exhibits few cerebral lesions and prevalent MRI plaque dissemination in the spinal cord (39). Speculatively, this result suggests that increased pressure in the cerebral sinuses may clinically influence either the disease progression or the topography of multiple sclerosis plaques and warrants further studies in this direction.

Conclusions

We developed a lumped mathematical model for the study of cerebral venous outflow, able to simulate the average blood flows in the main drainage vessels of the brain. The two main features of the model are that it accounts for the dependence of the hydraulic properties of the jugular veins with respect to the gravity field and that it includes a validated model for the simulation of the intracranial circulation. That makes it an useful tool for the study of the correlations between extracra-
nial blood redistributions and changes in the intracranial environment.

We performed simulations of the effect of posture change from supine to upright on pressures and blood flows, first with basal drainage and then assuming a lack of conductance of some particular vessel tract.

Results show that the model is able to reproduce the average physiologic behavior of the jugular, vertebral, and cerebral ducts, with values in good agreement with literature data. In addition to that, the model is able to give information about the average flows in different points of the jugular ducts, so taking into account the amount of blood coming from the anastomotic connections.

Moreover, we can easily use it to verify how the blood redistribution due to change of posture affects the pressures in specific points of the system.

We are aware only of a previous model that investigates cerebral venous return in accurate quantitative terms (14). The present model shows some similarities with that model, but it also exhibits many important new aspects.

First, the description of the cerebral venous return now includes a larger number of drainage pathways encompassing not only the vertebral one but also additional collateral and anastomoses to the downstream jugular sections. Inclusion of such a more complex network of collaterals is important to simulate several experimental observations. Basically, blood flow measurements show that the sum of the jugular and vertebral blood flows decrease from supine to upright position (33). This result is in contradiction with the existence of strong autoregulation mechanisms in the brain, which maintain quite a constant cerebral blood flow despite moderate pressure changes, and reveals the existence of further collateral routes beside the vertebral veins, able to drain cerebral blood flow in the erect position. Furthermore, measurements with the Doppler technique show that the amount of blood flow in the jugular veins increases from the upstream to the downstream sections (6, 8, 10, 28, 33, 41, 44), a result that requires the presence of anastomoses, which allow a progressive reentry of blood flow.

The second new aspect of the model consists in the strict link between the cerebral circulation (with its regulatory mechanisms), the cerebrospinal fluid circulation, and the cerebral venous return system.

Indeed, previous models were just devoted to study the cerebral venous return without paying attention to the cerebral circulation [Gisolf et al. (14)]. Other models were especially devoted to brain circulation and cerebral blood flow control with just an approximate description of the venous return, as for example in Ursino and Lodi (30). We claim that a model that incorporates both aspects is necessary, since the interconnections between the cerebral circulation and venous return systems may have important hemodynamics effects, especially in pathological conditions. In particular, the presence of regulatory mechanisms able to maintain a constant cerebral blood flow even when cerebral perfusion pressure falls down to...

![Fig. 11. Venous sinuses pressure Pvs in healthy and stenotic patterns simulation. The black columns represent the simulation of stenotic patterns with halved conductances with respect to the basal values.](image_url)

| Table 5. Venous sinuses pressure and intracranial pressure at equilibrium in simulation of basal conditions and typical stenotic patterns |
|---|---|---|---|---|---|
| Pressure, mmHg | Basal | Pattern A | Pattern B | Pattern C | Pattern D |
| Supine | | | | | |
| \(P_{vs}\) | 5.98 | 6.51 | 16.60 | 13.22 | 6.01 |
| \(P_{vc}\) | 9.44 | 9.51 | 11.09 | 9.95 | 9.44 |
| Upright | | | | | |
| \(P_{vs}\) | 8.68 | 9.57 | 16.55 | 13.23 | 9.14 |
| \(P_{vc}\) | 9.81 | 9.93 | 11.12 | 9.95 | 9.87 |

| Table 6. Flows at equilibrium in simulation of basal conditions and typical stenotic patterns |
|---|---|---|---|---|---|
| Flow, ml/s | Basal | Pattern A | Pattern B | Pattern C | Pattern D |
| Supine | | | | | |
| \(Q_{vv}\) | 0.79 | 0.51 | 3.86 | 7.86 | 0.33 |
| \(Q_{ve}\) | 5.87 | 11.14 | 3.04 | 2.13 | 6.08 |
| \(Q_{ve2}\) | 5.87 | 0.81 | 3.04 | 2.13 | 6.08 |
| \(Q_{ve2}\) | 6.87 | 12.90 | 2.98 | 1.86 | 7.08 |
| \(Q_{ve2}\) | 6.87 | 0.88 | 2.98 | 1.86 | 7.08 |
| \(Q_{ve1}\) | 7.86 | 15.39 | 0.00 | 0.00 | 8.08 |
| \(Q_{ve1}\) | 7.86 | 0.00 | 0.00 | 0.00 | 8.08 |
| \(Q_{svc1}\) | 15.72 | 15.39 | 0.00 | 0.00 | 16.16 |
| \(Q_{vc1}\) | 1.00 | 1.57 | 12.98 | 9.24 | 1.01 |
| \(Q_{vc1}\) | 17.50 | 17.47 | 16.91 | 17.10 | 17.50 |
| Upright | | | | | |
| \(Q_{vv}\) | 3.39 | 1.54 | 3.64 | 7.87 | 1.37 |
| \(Q_{ve}\) | 0.69 | 1.62 | 1.14 | 2.10 | 1.10 |
| \(Q_{ve2}\) | 0.69 | 1.32 | 1.14 | 2.10 | 1.10 |
| \(Q_{ve2}\) | 1.92 | 4.99 | 2.95 | 1.84 | 2.48 |
| \(Q_{ve2}\) | 1.92 | 1.62 | 2.95 | 1.84 | 2.48 |
| \(Q_{ve2}\) | 6.30 | 13.38 | 0.00 | 0.00 | 7.24 |
| \(Q_{ve2}\) | 6.30 | 0.00 | 0.00 | 0.00 | 7.24 |
| \(Q_{ve2}\) | 12.59 | 13.38 | 0.00 | 0.00 | 14.48 |
| \(Q_{ve1}\) | 1.46 | 2.48 | 12.97 | 9.23 | 1.59 |
| \(Q_{ve1}\) | 17.45 | 17.40 | 16.91 | 17.10 | 17.44 |

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HEMODYNAMIC MODEL OF THE CEREBRAL VENOUS OUTFLOW

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50–60 mmHg might produce large increases in venous sinuses pressure, if the venous return system becomes unable to drain all the required amount of blood.

The present simulations suggest two important considerations. The cerebral venous return system is quite robust: a single occlusion, or even multiple occlusions of moderate entity, can induce only mild changes in venous sinuses pressure and in total blood flow. Indeed, this is the fundamental role of the strong anatomotical connections incorporated in the model. However, we have also shown that pathological states, characterized by multiple severe obstructions, can lead to significant pressure changes in the venous sinuses, hence, in possible alteration in cerebrospinal fluid circulation and brain tissue pressure. Which adjustments may be produced in these cases (either the opening of new collaterals, a reset of the autoregulation set point, or a permanent pressure increase) remains to be investigated.

A final important aspect of the model consists in the possibility to simulate the progressive increase in jugular blood flow when moving from the upstream sections close to the skull to the downstream sections in the thoracic portion. These changes are amplified by a posture change, when the different sections of the jugular veins experience a different amount of collapse and are significantly affected by any individual or pathological alteration in the collateral pathways.

Hence, a study of these blood flow variations, for instance via quantitative Doppler measurements, may represent a strong test to validate the model and to adapt its parameters to individual characteristics.

APPENDIX

Intracranial Circuit

Mathematical equations for intracranial blood dynamics and cerebrospinal fluid circulation have been written by imposing the mass preservation principle at all the circuit nodes.

In the following, we refer to resistance of a given tract $R_i$, as the inverse of the conductance $G_i$ of the same tract. Table A1 provides a glossary of terms.

Mass preservation at the node of cerebral veins $vi$ implies the following equation:

$$\frac{d(P_v - P_{vc})}{dt} = \frac{1}{C_{vi}} \left[ P_c - P_{vc} - \frac{dC_{pa}}{dt} (P_{pa} - P_{ic}) \right]$$

(3)

Capillary pressure $P_{c}$ is given by:

$$P_c = \frac{P_v}{R_{pv}} + \frac{P_{pa}}{R_{pa}/2} + \frac{P_{ic}}{R_{ic}/2} \left( \frac{1}{R_{pv}} + \frac{1}{R_{pa}/2} + \frac{1}{R_{ic}/2} \right)$$

(4)

The left term of Eq. 3 is the variation of transmural pressure in time at the node of pial arterioles. It depends on the blood flow entering and leaving the node (the first 2 terms at the brackets at the right side) and on the active changes in arterial capacity $C_{pa}$ over time (the last term in brackets). The value of $C_{pa}$ at the denominator accounts for the ability of the duct to store blood without variations of transmural pressure: the higher the value of $C_{pa}$ the lower the change in pressure over time. All other mass preservation equations have a similar meaning.

Mass preservation at the node of cerebral veins $vi$ implies the following equation:

$$\frac{d(P_v - P_{vc})}{dt} = \frac{1}{C_{vi}} \left[ P_c - P_{vc} \frac{P_v - P_{vc}}{R_{pv}} - \frac{dC_{pa}}{dt} (P_{pa} - P_{ic}) \right]$$

(5)

The relationship between $C_{vi}$ and pressure is given by the following equation:

$$C_{vi} = \frac{1}{k_{vc} (P_v - P_{vc} - P_{vi})}$$

(6)

Control mechanisms work at the level of the arteriolar cerebrovascular bed by modifying $R_{pa}$ and $C_{pa}$. Autoregulation activated by relative changes in cerebral blood flow $Q$ is given by the following equation:

$$\frac{dx_{aut}}{dt} = \frac{1}{\tau_{aut}} \left[ -x_{aut} + G_{aut} \left( \frac{Q - Q_n}{Q_n} \right) \right]$$

(7)

where the minus sign of $x_{aut}$ simulates the fact that a fall in blood flow causes a rapid dilatation of resistance vessels, whereas a rise in blood pressure causes vasoconstriction.

The existence of maximal limits for the vascular response (total vasodilatation and maximal vasoconstriction) is simulated by a sigmoidal relationship with upper and lower saturation levels acting on pial arteries capacity $C_{pa}$, so that:

$$C_{pa} = \frac{\left( C_{pa} - \frac{\Delta C_{pa}}{2} \right) + \left( C_{pa} + \frac{\Delta C_{pa}}{2} \right) \exp \left( \frac{-x_{aut}}{kC_{pa}} \right)}{1 + \exp \left( \frac{-x_{aut}}{kC_{pa}} \right)}$$

(8)

The sigmoidal curve cannot be symmetrical because the increase in blood volume induced by vasodilation is higher than the blood volume decrease induced by vasoconstriction. Hence, two different values must be chosen for the parameter $\Delta C_{pa}$, depending on whether vasodilation or vasoconstriction is considered. We have

if $x_{aut} < 0$ then $\Delta C_{pa} = \Delta C_{pa1}$ and $kC_{pa} = \Delta C_{pa1}/4$ (9) for the vasodilation simulation, and

if $x_{aut} > 0$ then $\Delta C_{pa} = \Delta C_{pa2}$ and $kC_{pa} = \Delta C_{pa2}/4$ (10) for the vasoconstriction simulation.

The value of pial arterial resistance is given by the formula:

$$R_{pa} = \frac{k_{fr} C_{pa}}{(P_{pa} - P_{ic}) C_{pa}^2}$$

(11)

The following equations account for cerebrospinal fluid formation rate $Q_f$ and outflow rate $Q_0$:

$$Q_f = \frac{P_{ic} - P_{ic}}{R_f} \text{ if } P_{ic} < P_{ic} \text{, else } Q_f = 0$$

(12)

$$Q_0 = \frac{P_{ic} - P_{vs}}{R_0} \text{ if } P_{ic} > P_{vs} \text{, else } Q_0 = 0$$

(13)

An expression for the resistance of the terminal intracranial veins $R_{vs}$ is computed as follows:

$$R_{vs} = \frac{P_{vs}}{P_v - P_{ic}} \text{ if } P_{ic} > P_{vs} \text{, else } R_{vs} = R_{vs1}$$

(14)

Application of mass preservation at the intracranial volume leads to the following equations:

$$\frac{dP_{ic}}{dt} = \frac{d(P_{pa} - P_{ic})}{dt} C_{pa} + \frac{d(P_v - P_{ic})}{dt} C_{vi} + \frac{dC_{pa}}{dt} (P_{pa} - P_{ic})$$

(15)
Table A1. Glossary of terms

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Quantity</th>
<th>Symbol</th>
<th>Quantity</th>
<th>Symbol</th>
<th>Quantity</th>
<th>Symbol</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>Parameter related to the resistance of the jugular segments to collapse</td>
<td>$C_{\text{azy}}$</td>
<td>Capacity of the azygos system</td>
<td>$C_{\text{pa}}$</td>
<td>Capacity of the pial arterioles</td>
<td>$\Delta C_{\text{pa}}$</td>
<td>Amplitude of the curve of the pial arterioles capacity</td>
</tr>
<tr>
<td>AZY</td>
<td>Lumbo-azygos system</td>
<td>$C_{2}$</td>
<td>Capacity of the middle segment of the collateral network</td>
<td>$C_{\text{pms}}$</td>
<td>Basal capacity of the pial arterioles</td>
<td>$\Delta C_{\text{pa1}}$</td>
<td>Value of the capacity of the pial arterioles during vasodilation simulation</td>
</tr>
<tr>
<td>azy1</td>
<td>Distal azygos</td>
<td>$C_{c3}$</td>
<td>Capacity of the upper segment of the collateral network</td>
<td>$\text{CSF}$</td>
<td>Cerebrospinal fluid</td>
<td>$\Delta C_{\text{pa2}}$</td>
<td>Value of the capacity of the pial arterioles during vasoconstriction simulation</td>
</tr>
<tr>
<td>azy2</td>
<td>Proximal azygos</td>
<td>$C_{c1}$</td>
<td>Intracranial capacity</td>
<td>$C_{\text{vcc}}$</td>
<td>Capacity of the superior vena cava</td>
<td>$g$</td>
<td>Gravity acceleration</td>
</tr>
<tr>
<td>c3</td>
<td>Upper segment of the collateral network</td>
<td>$C_{c3}$</td>
<td>Capacity of the middle segment of the collateral network</td>
<td>$C_{\text{cis}}$</td>
<td>Capacity of the intracranial veins</td>
<td>$G_0$</td>
<td>Conductance of the cerebrospinal fluid outflow tract</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
<td>$C_{c3}$</td>
<td>Capacity of the upper segment of the collateral network</td>
<td>$C_{\text{vis}}$</td>
<td>Capacity of the terminal intracranial veins</td>
<td>$G_{\text{aut}}$</td>
<td>Gain of the autoregulation mechanism related to CBF variations</td>
</tr>
<tr>
<td>cj2</td>
<td>Lower anastomoses</td>
<td>$C_{c3}$</td>
<td>Capacity of the middle segment of the right jugular vein</td>
<td>$C_{\text{vv}}$</td>
<td>Capacity of the vertebral veins</td>
<td>$G_{\text{asy1}}$</td>
<td>Conductance of the distal azygos</td>
</tr>
<tr>
<td>cj3</td>
<td>Upper anastomoses</td>
<td>$C_{c3}$</td>
<td>Capacity of the upper segment of the right jugular vein</td>
<td>$C_{s}$</td>
<td>Capacity of the generic segment of the circulatory system</td>
<td>$G_{\text{asy2}}$</td>
<td>Conductance of the proximal azygos</td>
</tr>
<tr>
<td>$G_{c1}$</td>
<td>Conductance of the lower segment of the collateral network</td>
<td>$G_{c1}$</td>
<td>Conductance of the external carotid arteries</td>
<td>$G_{j1}$</td>
<td>Conductance of the lumbar vein</td>
<td>$G_{s}$</td>
<td>Conductance of the generic segment of the circulatory system</td>
</tr>
<tr>
<td>$G_{c2}$</td>
<td>Conductance of the middle segment of the collateral network</td>
<td>$G_{c2}$</td>
<td>Conductance of the lower segment of the left jugular vein</td>
<td>$G_{\text{vca}}$</td>
<td>Conductance of the upper segment of the superior vena cava (jugular confluence)</td>
<td>$h$</td>
<td>Length of a jugular segment</td>
</tr>
<tr>
<td>$G_{c3}$</td>
<td>Conductance of the upper segment of the collateral network</td>
<td>$G_{c3}$</td>
<td>Conductance of the middle segment of the left jugular vein</td>
<td>$G_{\text{vca}}$</td>
<td>Conductance of the lower segment of the superior vena cava</td>
<td>$h_{bf}$</td>
<td>Mock cerebrospinal fluid possibly injected into or subtracted from the cranial cavity</td>
</tr>
<tr>
<td>$G_{c3/2}$</td>
<td>Conductance of the lower anastomotic connection (left side)</td>
<td>$G_{c3/2}$</td>
<td>Conductance of the upper segment of the left jugular vein</td>
<td>$G_{\text{vas}}$</td>
<td>Conductance of the terminal intracranial veins</td>
<td>$\text{JIV}$</td>
<td>Internal jugular vein</td>
</tr>
<tr>
<td>$G_{c3/3}$</td>
<td>Conductance of the upper anastomotic connection (left side)</td>
<td>$G_{c3/3}$</td>
<td>Conductance of the lower segment of the right jugular vein</td>
<td>$G_{\text{vsa}}$</td>
<td>Conductance of the lower part of the vertebral vein</td>
<td>$\text{J1}$</td>
<td>Lower segment of the internal jugular veins</td>
</tr>
<tr>
<td>$G_{c3/2}$</td>
<td>Conductance of the lower anastomotic connection (right side)</td>
<td>$G_{c3/2}$</td>
<td>Conductance of the middle segment of the right jugular vein</td>
<td>$G_{\text{vsa}}$</td>
<td>Conductance of the left vertebral vein</td>
<td>$\text{J2}$</td>
<td>Middle segment of the internal jugular veins</td>
</tr>
<tr>
<td>$G_{c3/3}$</td>
<td>Conductance of the upper anastomotic connection (right side)</td>
<td>$G_{c3/3}$</td>
<td>Conductance of the upper segment of the right jugular vein</td>
<td>$G_{\text{vsv}}$</td>
<td>Conductance of the right vertebral vein</td>
<td>$\text{J3}$</td>
<td>Upper segment of the internal jugular veins</td>
</tr>
<tr>
<td>$ji3$</td>
<td>Upper segment of the right jugular vein</td>
<td>$k_{i3}$</td>
<td>Parameter for the basal conductance of the middle segment of the right jugular vein</td>
<td>$P_{\text{ary}}$</td>
<td>Pressure in the azygos system</td>
<td>$P_{j1\text{ext}}$</td>
<td>Pressure outside the lower segment of the jugular veins</td>
</tr>
<tr>
<td>$k_{\text{ca}}$</td>
<td>Parameter for the capacity of the pial arterioles</td>
<td>$k_{i3}$</td>
<td>Parameter for the basal conductance of the upper segment of the right jugular vein</td>
<td>$P_{x}$</td>
<td>Pressure in the intracranial capillaries</td>
<td>$P_{j2\text{ext}}$</td>
<td>Pressure outside the middle segment of the jugular veins</td>
</tr>
<tr>
<td>$k_{E}$</td>
<td>Intracranial elastance coefficient</td>
<td>$k_{i3}$</td>
<td>Parameter for the resistance of pial arterioles</td>
<td>$P_{c2}$</td>
<td>Pressure in the middle segment of the collateral network</td>
<td>$P_{j3\text{ext}}$</td>
<td>Pressure outside the upper segment of the jugular veins</td>
</tr>
<tr>
<td>$k_{j1}$</td>
<td>Parameter for the basal conductance of the lower segment of the left jugular vein</td>
<td>$k_{i3}$</td>
<td>Parameter for the intracranial venous capacity</td>
<td>$P_{c3}$</td>
<td>Pressure in the upper segment of the collateral network</td>
<td>$P_{j3}$</td>
<td>Pressure in the upper segment of the left jugular vein</td>
</tr>
<tr>
<td>$k_{j2}$</td>
<td>Parameter for the basal conductance of the middle segment of the left jugular vein</td>
<td>$k_{i3}$</td>
<td>Parameter for the basal conductance of jugular and vertebral veins</td>
<td>$P_{c}$</td>
<td>Pressure in the vena cava</td>
<td>$P_{j3}$</td>
<td>Pressure in the upper segment of the right jugular vein</td>
</tr>
<tr>
<td>$k_{j3}$</td>
<td>Parameter for the basal conductance of the upper segment of the left jugular vein</td>
<td>$k_{i3}$</td>
<td>Pial arterioles</td>
<td>$P_{ac}$</td>
<td>Intracranial pressure</td>
<td>$P_{j2}$</td>
<td>Pressure in the middle segment of the right jugular vein</td>
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</tbody>
</table>

Continued
Cerebrospinal fluid inflow or outflow. Intracranial capacity refers to change on pial artery capacity, while the other terms refer to pressure at the level of arterioles and cerebral veins, the third term in brackets at the right side of Eq. 15 refers to change on pial artery capacity, while the other terms refer to cerebrospinal fluid inflow or outflow. Intracranial capacity $C_{ic}$ at the denominator accounts for the ability of the skull to store volume.

**Jugular-Vertebral Circuit**

Mathematical equations for cerebral venous outflow simulation have been written by imposing the mass preservation principle at all the circuit nodes.

The state equations used to build the jugular-vertebral circuit are the following:

$$C_{ic} = \frac{1}{k_{E}P_{ic}}$$

This formula states that the variation in time of the intracranial pressure is the result of several factors. The first and the second term in brackets at the right side of Eq. 15 refer to changes in transmural pressure at the level of arterioles and cerebral veins, the third term refers to change on pial artery capacity, while the other terms refer to cerebrospinal fluid inflow or outflow. Intracranial capacity $C_{ic}$ at the denominator accounts for the ability of the skull to store volume.

Mathematical equations for cerebral venous outflow simulation have been written by imposing the mass preservation principle at all the circuit nodes.

The state equations used to build the jugular-vertebral circuit are the following:

$$\frac{dP_{vs}}{dt} = \frac{1}{C_{vs}}\left[\left(P_{vs} - P_{vs}\right)G_{vs} - \left(P_{vs} - P_{vc}\right)G_{vc} - \left(P_{vs} - P_j\right)G_{j3} - (P_{vs} - P_{vr})G_{vr}\right]$$

$$\frac{dP_{jr3}}{dt} = \frac{1}{C_{jr3}}\left[\left(P_{jr3} - P_{jr2}\right)G_{jr2} - \left(P_{jr2} - P_{c}\right)G_{cjr3} - \left(P_{jr3} - P_{jr2}\right)G_{jr2}\right]$$

$$\frac{dP_{jr2}}{dt} = \frac{1}{C_{jr2}}\left[\left(P_{jr2} - P_{jr1}\right)G_{jr1} - \left(P_{jr1} - P_{c}\right)G_{cjr2} - \left(P_{jr2} - P_{svc}\right)G_{jr2}\right]$$

$$\frac{dP_{jr1}}{dt} = \frac{1}{C_{jr1}}\left[\left(P_{jr1} - P_{jr0}\right)G_{jr0} - \left(P_{jr0} - P_{c}\right)G_{cjr1} - \left(P_{jr1} - P_{jr0}\right)G_{jr0}\right]$$

$\frac{dQ_{j1}}{dt} = \frac{1}{C_{j1}}\left[R_{j1} - R_{j2} - R_{j3}\right]$

$\frac{dQ_{j2}}{dt} = \frac{1}{C_{j2}}\left[R_{j2} - R_{j3}\right]$

$\frac{dQ_{j3}}{dt} = \frac{1}{C_{j3}}\left[R_{j3}\right]$
The equations used to include dynamics due to posture changes from supine to upright in the gravity field are the following:

\[
\frac{dP_{j2}}{dt} = \frac{1}{C_{j2}} \left[ (P_{j3} - P_{j2})G_{j2} - (P_{j2} - P_{c2})G_{c2} - (P_{j2} - P_{svc})G_{j1} \right]
\]

(21)

\[
\frac{dP_{c3}}{dt} = \frac{1}{C_{c3}} \left[ (P_{vc} - P_{c3})G_{c3} + (P_{vc} - P_{c3})G_{j3} + (P_{j3} - P_{c3})G_{c3} \right]
\]

+ \left[ (P_{c3} - P_{svc})G_{svc} - (P_{c3} - P_{svc})G_{ex} - (P_{c3} - P_{svc})G_{c2} \right] \]

(22)

\[
\frac{dP_{c2}}{dt} = \frac{1}{C_{c2}} \left[ (P_{c3} - P_{c2})G_{c2} + (P_{j2} - P_{c2})G_{j2} + (P_{j2} - P_{c2})G_{c2} \right]
\]

- \left[ (P_{c2} - P_{cv})G_{c3} \right] \]

(23)

\[
\frac{dP_{svc}}{dt} = \frac{1}{C_{svc}} \left[ (P_{svc} - P_{svc})G_{svc} + (P_{axy} - P_{svc})G_{axy2} \right]
\]

- \left[ (P_{svc} - P_{cv})G_{svc2} \right] \]

(24)

\[
\frac{dP_{vv}}{dt} = \frac{1}{C_{vv}} \left[ (P_{vv} - P_{vv})G_{vv} + (P_{vv} - P_{vv})G_{vv} - (P_{vv} - P_{vv})G_{vv} \right]
\]

- \left[ (P_{vv} - P_{lv})G_{vv2} \right] \]

(25)

\[
\frac{dP_{axy}}{dt} = \frac{1}{C_{axy}} \left[ (P_{vv} - P_{axy})G_{axy1} + (P_{lv} - P_{axy})G_{lv} \right]
\]

- \left[ (P_{axy} - P_{vv})G_{axy2} \right] \]

(26)

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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\[
G_{j3} = k_{j3} \left[ 1 + \left( \frac{2}{\pi} \right) \arctan \left( \frac{P_{vs} - P_{vtext}}{A} \right) \right]^2 \]

(27)

\[
G_{j3} = k_{j3} \left[ 1 + \left( \frac{2}{\pi} \right) \arctan \left( \frac{P_{vs} - P_{vtext}}{A} \right) \right] \]

(28)

\[
G_{j2} = k_{j2} \left[ 1 + \left( \frac{2}{\pi} \right) \arctan \left( \frac{P_{j2} - P_{text}}{A} \right) \right]^2 \]

(29)

\[
G_{j2} = k_{j2} \left[ 1 + \left( \frac{2}{\pi} \right) \arctan \left( \frac{P_{j2} - P_{text}}{A} \right) \right] \]

(30)

\[
G_{j1} = k_{j1} \left[ 1 + \left( \frac{2}{\pi} \right) \arctan \left( \frac{P_{j1} - P_{text}}{A} \right) \right]^2 \]

(31)

\[
G_{j1} = k_{j1} \left[ 1 + \left( \frac{2}{\pi} \right) \arctan \left( \frac{P_{j1} - P_{text}}{A} \right) \right] \]

(32)


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