Jugular valve function and petrosal sinuses pressure: a computational model applied to sudden sensorineural hearing loss

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Abstract

Reports of extra-cranial venous outflow disturbances have recently been linked to sudden sensorineural hearing loss (SSNHL). Aims of the present study are: i) to quantify, with mathematical model, the impact of jugular valve function on the pressure of the superior and inferior petrosal sinuses (SPS, IPS) and the main auricolar veins; ii) to verify the feasibility of the application of mathematical model in the clinical setting in terms of consistency respect to the usual measures of SSNHL outcome. Extra-cranial venous outflow and post analysis were respectively blindly assessed by echo colour-Doppler (ECD) and a validated mathematical model for the human circulation. The pilot study was conducted on 1 healthy control and in a group of 4 patients with different outcome of SSNHL. The main finding was the significant increased pressure calculated in the SPS and IPS of patients with ipsilateral jugular obstruction due to not mobile valve leaflets (6.55 mmHg), respect to the other subjects without extracranial complete obstruction (6.01 mmHg), P=0.0006. Moreover, we demonstrated an inverted correlation between the extrapolated pressure values in the SPS/IPS and the mean flow measured in the correspondent internal jugular vein (r= –0.87773; r-squared= 0.7697; P=0.0009). The proposed mathematical model can be applied to venous extra-cranial ECD investigation in order to derive novel clinical information on the
drainage of the inner ear. Such clinical information seems to provide coherent parameters potentially capable to drive the prognosis. This innovative approach was proven to be feasible by the present pilot investigation and warrants further studies with an increased sample of patients.

Introduction

Chronic cerebrospinal venous insufficiency (CCSVI) is a condition characterized by outflow obstruction in the extracranial venous system mainly caused by intraluminal obstacles, defective valves, hypoplasia, and/or compression of the internal jugular veins (IJV) and/or Azygos vein.[1-4] This condition was initially brought forth as a possible contributing factor to the pathogenesis and clinical manifestations of multiple sclerosis[2-4] and, quite recently, of other neurodegenerative diseases, including Alzheimer,[5] Parkinson,[6] Ménière disease,[7-10] and quite anedoctically, to sudden sensorineural hearing loss (SSNHL).[11,12]

SSNHL can be defined as a sensorineural hearing loss of 30 dB or greater over at least three contiguous audiometric frequencies occurring within a 72-h period.[13,14] It is an acute inner ear disorder, mostly unilateral. It has been reported that SSNHL has a reported overall incidence of 5-20/100,000 and that is more frequent in western countries.[11] Despite individuals of all ages can be affected, the peak incidence is reported between the fifth and sixth decade of life and occurs with same incidence in men and women.[13,14]

The pathogenesis of SSNHL is still unknown; viral infections and vascular occlusions are the more common mechanisms advocated. Other reported causes of SSNHL include infectious, autoimmune, traumatic, vascular, neoplastic, metabolic and neurologic diseases.[13-16] The vascular hypothesis of SSNHL pathogenesis seems the more promising, albeit clinical information about consequences of extracranial venous outflow disturbances in the main intracranial route of drainage of the inner ear is currently unavailable.[17,18] Alternatively, computation offers nowadays the possibility of quantifying brain haemodynamics.[19-22]

Aims of the present study are: i) to quantify, by means of an existing mathematical model,[19] the impact of extracranial cerebral venous outflow on bilateral pressure of the superior and inferior petrosal sinuses (SPS, IPS), posterior auricular, deep facial, mastoid emissary, IJV; ii) to verify the feasibility of the application of the

mathematical model in the clinical setting in terms of consistency respect to the usual measures of SSNHL outcome.

Materials and Methods

The pilot study was blindly conducted on 1 healthy control (HC) (male 60 y.o.) and in a group of 4 patients with different outcome of SSNHL (mean age 69 y.o. and ratio male:female 1:1).

The study was approved by the Ethical Committee of the Azienda Ospedaliero-Universitaria of Ferrara (Italy), with the registry number #101298 All patients and HC signed an informed consent.

Ultrasonographic study of cerebral venous return

The five subjects were blindly investigated in the vertebral veins (VVs) and in the IJVs, through an echo color Doppler (ECD) protocol recommended by an international consensus for assessing flow disturbances of cerebral venous return (Esaote MyLab 70, Probe 7.5 10mHz, Genoa, Italy).[20,21] This protocol includes also a M-mode study of the jugular valve motility.[23]

In this study we focused the attention on the junctional area where a valve is present in about 60% normal subjects.[23] If an abnormal valve was detected according to the criteria of adopted protocol the flow characteristic were deeply investigated measuring not only flow direction but also peak veloc-

Table 1. Clinical and demographic characteristic of the patients affected by SSNHL.

Subject	Age	Gender	SSNHL side	Responder to treatment	Clinical consistency (side and SPS/IPS pressure)	Clinical consistency (recovery and SPS/IPS pressure)
SSNHL #1	73 y.o.	F	Right	No recovery	Negative	Negative
SSNHL #2	54 y.o.	F	Right	No recovery	Positive	Positive
SSNHL #3	71 y.o.	M	Right	No recovery	Positive	Positive
SSNHL #4	79 y.o.	M	Left	Recovery	Negative	Positive

ity, time average velocity, flow and cross sectional area.[24-26]

Subsequently, we assigned, on the bases of the ECD investigation, a non-dimensional score of the valve status. This function varies between 0 and 1, and represents the rate of opening and closing of the valve; the 0 score represents a normal valve function and whose assigned when the flow was monodirectional with the values of the above haemodynamic parameters within range of normality.[26-29] We assigned a score of 0.25 when the flow was bi-directional, although prevalently directed outward the chest, in consequence of a not mobile single leaflet. Moreover, we assigned a score of 0.50 when the flow was completely bi-directional and/or when the defective valve increases the flow velocity >120 cm/sec; the score was 0.75 if the flow was bi-directional but prevalently directed inward the brain and/or if the flow velocity was greater than 150 cm/sec. Finally, in case of complete collapse of the lumen and/or absence of detectable flow, and/or not mobile valve with the flow unable to cross the intraluminal obstacle, we assigned a score of 1.

Application of the computational model

The non-dimensional number expressing the valve state, above reported, depends on a time-dependent function $\xi(t)$ which is given by the solution of variable-coefficient ordinary differential equations:

$$\frac{d}{dt}\xi(t) = \begin{cases} K_o [\Delta p(t) - \Delta p_o](1 - \xi(t)) & \text{if } \Delta p(t) > \Delta p_o \text{ (opening)}, \\ K_c [\Delta p(t) - \Delta p_c]\xi(t) & \text{if } \Delta p(t) < \Delta p_c \text{ (closing)}. \end{cases} \quad (1)$$

The non-dimensional valve state, with $0 \le \xi(t) \le 1$, represents the rate respectively of opening and closing of the IJV valve. K_o is the coefficient for opening the valce with Δp_o who representing the threshold pressure to open the leaflets of the valve. K_c is a coefficient to close the valve with Dp_c who acting for the threshold pressure for closing the leaflets. $Dp(t)$ is the pressure variation of time-dependent function.

Computational analysis was blindly performed respect to the clinical outcome on the basis of the ECD assessment and score of the IJV valve function, as described above. Extrapolation of the intracranial haemodynamics was achieved by applying a global mathematical model for the human circulation, previously validated against in vivo MRI data.[19] We performed five sets of simulations for each subject in supine position.

Clinical outcome evaluation

The clinical side of SSNHL at onset, as well as the prognosis and response to treatment (oral steroid therapy accordingly to the AAO-HNS indications),[29] were blindly assessed by the treating physician. The consistency of the computational parameters extrapolated at the level of the draining veins of the hearing apparatus with side and clinical outcome were subsequently analyzed.

Statistical analysis

The extrapolated pressure values in the SPS/IPS of subjects with complete obstruction of an extracranial venous segment were tested for significance vs the pressure values of people with score flow between 0 and 0.75 by the means of two-tailed Mann-Whitney test.

The value of flow in the IJVs were correlated with SPS/IPS pressure by the means of linear regression analysis. Value <0.05 were considered significant.

Table 2. Score assigned for intracranial computational analysis after high resolution Doppler sonography study of the valvular region of the IJVs.

Subjects	RIJV	LIJV	RVV	LVV
HC	0	0	0	0
SSNHL #1	0.25	0.75	1.0	1.0
SSNHL #2	1.0	0	0	0
SSNHL #3	1.0	0	0	1.0
SSNHL #4	0.25	0.25	0	0

Results

In Table 1 patients' demographic and clinical characteristics are given, including the side and the clinical outcome of SSNHL. Our cases reflect the male:female ratio of the disease (1:1). Moreover patients #1, #2, #3 were affected by SSNHL on the right side, and just patient #4 on the left one.

It is worth of note that in patients #2, #3, the abnormal right valve of the IJV determined absence of flow through the junction with consequent assignment of non-dimensional score 1. The worse score was also given to patient #1 for absence of Doppler detectable flow in both vertebral veins. Finally, in patient #4 few and not significant abnormalities were detected along the major brain outflow routes. The non-dimensional score assigned in accordance with ECD findings are summarized for all subjects in Table 2.

In Table 3 we give the complete detail of flow, velocity, pressure and cross sectional area extrapolated by computational analysis in the major anatomic draining pathways of the inner ear region. Particularly, in the SPS and IPS, which both represent the major intracranial draining route, the calculated value of pressure were significantly more elevated on the right side, in patients #2, #3, as compared to both the rest of the patients and the control. In Figure 1 the calculated pressure is very well apparent because the curves of patients #2, #3 are overlapped, showing a higher course respect the curves of the other subjects. For

patient #1 the computational model, despite the score 1 assigned to both VVs, did not calculate any significant pressure increment in SPS/IPS. This because the global model utilized takes into account the anatomical and physiological connections among the different vessels.

Despite the small sample, the pressure in the SPS/IPS of subjects with score 1 in one or more of the investigated outflow route, is significantly higher (6.55 mmHg) respect to the other subjects without extracranial complete obstruction (6.01 mmHg), P=0.0006 (Table 3). Moreover, in Figure 2 we show the inverted correlation between the extrapolated pressure values in the SPS/IPS of the 5 subjects respect to the mean flow measured in the correspondent IJVs (r= −0.87773; r squared= 0.7697; P=0.0009). The strong correlation found clearly indicates how the pressure increase in the SPS/IPS is dependent from the hampered IJV flow at the extracranial level.

Discussion and Conclusions

The pathogenesis of SSNHL is still unknown; viral infections and vascular disease are the more common mechanisms advocated, even if evidence in favour of a specific mechanism is still insufficient.[30] Of the possible causes of SSNHL, vascular involvement has captured much attention, and some studies in the literature have investigated the association between

SSNHL and vascular disease to date. A better understanding of the relationship between cochlear blood flow and hearing function is fundamental for improving the treatment and diagnosis of deafness that

potentially arises from circulatory abnormalities. Achieving such understanding has been challenging because of the experimental difficulties involved in monitoring cochlear blood flow.[30] However, computa-
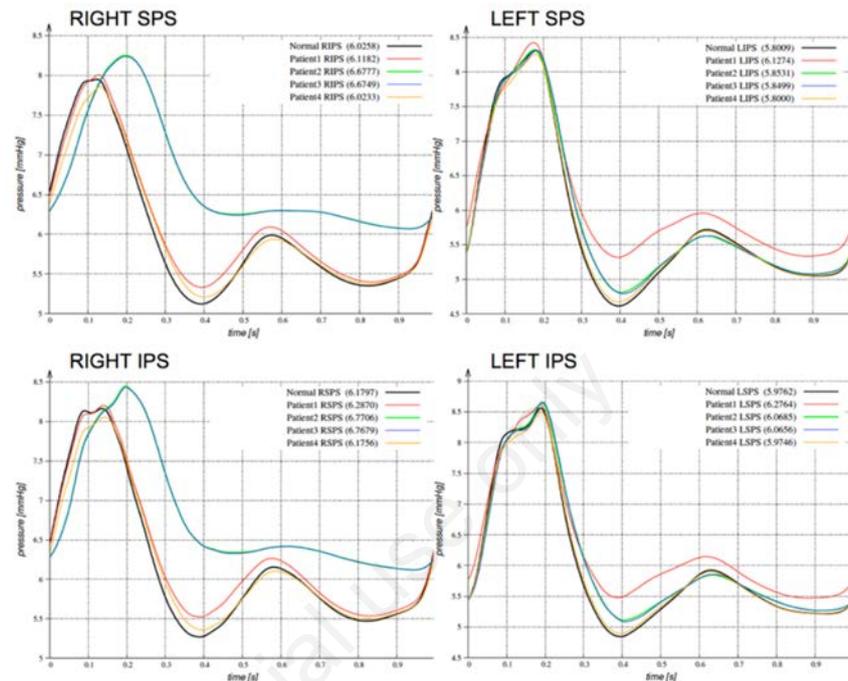

Figure 1. Right graphs: The increased pressure calculated on the right superior and inferior Petrosus sinus in patients with blocked flow at the level of the right IJV valve (#2, #3) is well apparent as compared the rest of the cohort. Left graphs: substantial overlapping of the pressure curves calculated on the left SPS/IPS in all subjects.

Table 3. Computational extra-intracranial venous haemodynamics calculated in patients and control.

Subject		R posterior auricular V	L posterior auricular V	R deep facial V	L deep facial V	R mastoid emissary V	L mastoid emissary V	R superior petrosal sinus	L superior petrosal sinus	R inferior petrosal sinus	L inferior petrosal sinus	R internal jugular V	L internal jugular V
HC	Flow	0.2315	0.2315	−0.1118	−0.1336	0.3160	0.2669	−0.1259	−0.0258	−0.0089	0.0894	3.6780	9.9242
	Pressure	6.8514	6.7820	5.9788	5.9210	6.1262	5.8838	6.1797	5.9762	6.0258	5.8009	5.5954	5.6758
	Velocity	0.1126	0.1128	−0.0056	−0.0067	0.0321	0.0274	−0.0192	−0.0039	−0.0015	0.0155	0.0735	0.0817
	CSA	2.0575	2.0557	20.1318	20.0886	9.8500	9.7938	6.5736	6.5667	5.7988	5.7921	51.0108	124.1327
SSNHL #1	Flow	0.2306	0.2304	−0.1114	−0.1713	0.3351	0.2630	−0.1167	−0.0644	0.0373	0.0350	4.2219	8.3219
	Pressure	6.8690	6.9898	6.0118	6.1847	6.2204	6.2099	6.2870	6.2764	6.1182	6.1274	5.5636	5.6530
	Velocity	0.1122	0.1120	−0.0056	−0.0086	0.0340	0.0267	−0.0178	−0.0098	0.0065	0.0060	0.0845	0.0687
	CSA	2.0579	2.0606	20.1484	20.2253	9.8693	9.8640	6.5687	6.5684	5.7941	5.7944	50.9385	123.9612
SSNHL #2	Flow	0.2302	0.2311	−0.2066	−0.1274	0.2684	0.2874	−0.1768	0.0376	−0.1404	0.2141	0.1946	11.5439
	Pressure	7.4177	6.8106	6.6517	5.9589	6.7689	5.9331	6.7706	6.0685	6.6777	5.8531	5.5792	5.6440
	Velocity	0.1112	0.1125	−0.0101	−0.0064	0.0269	0.0295	−0.0269	0.0058	−0.0242	0.0371	0.0039	0.0951
	CSA	2.0708	2.0564	20.4590	20.1092	9.9735	9.8051	6.5919	6.5680	5.8168	5.7920	50.9774	123.9877
SSNHL #3	Flow	0.2301	0.2310	−0.2063	−0.1272	0.2684	0.2866	−0.1768	0.0373	−0.1404	0.2142	0.1953	11.5997
	Pressure	7.4146	6.8062	6.6491	5.9548	6.7661	5.9303	6.7679	6.0656	6.6749	5.8499	5.5719	5.6394
	Velocity	0.1112	0.1125	−0.0101	−0.0064	0.0269	0.0294	−0.0269	0.0057	−0.0242	0.0371	0.0040	0.0956
	CSA	2.0708	2.0563	20.4579	20.1076	9.9730	9.8043	6.5914	6.5675	5.8163	5.7916	50.9660	123.9529
SSNHL #4	Flow	0.2309	0.2308	−0.1123	−0.1352	0.3144	0.2665	−0.1286	−0.0269	−0.0092	0.0883	3.7311	9.8364
	Pressure	6.8294	6.7710	5.9624	5.9157	6.1242	5.8828	6.1756	5.9746	6.0233	5.8000	5.5671	5.6510
	Velocity	0.1123	0.1124	−0.0056	−0.0068	0.0319	0.0273	−0.0196	−0.0041	−0.0016	0.0153	0.0746	0.0811
	CSA	2.0571	2.0555	20.1278	20.0884	9.8510	9.7948	6.5743	6.5675	5.7995	5.7928	50.9560	123.9738

tion analisys could offer nowadays the possibility of quantifying brain haemodynamics. In particular, we have applied a validated protocol of ECD evaluation of the extracranial veins to a confirmed computational model in order to assess haemodynamic parameters in the vein of the inner ear, and particularly in the major dural sinuses draining it. The main finding of our study is the increased pressure calculated by the clinical application of the model at the level of the right petrosus sinuses in patients presenting ECD with significantly compromised valve function at the level of the IJV junction. The curves comparing SPS/IPS pressure in patients and control (Figure 1) clearly show the raise in venous pressure, at the intracranial level, of patients exhibiting absence of Doppler detectable flow through the defective valve.[2,3,23,24,31,32]

The four patients presented some abnormalities in cerebral venous return, mainly focused on IJV valve function. The valve leaflets motility were M-mode investigated together with spectral-flow characteristics,[23] demonstrating how the presence of a defective valve opening determines also abnormal haemodynamics. This finding is particularly relevant as it is consistent with both the side of the SSNHL and the clinical outcome. When we calculated a significant increase of the SPS/IPS pressure this corresponded to the side of hearing loss; even more intriguing is the observation that the increased pressure in the dural sinuses is also corresponding to absence of recovery with the current treatment in the same cases (Table 1). Conversely, when we compared the clinical outcome of the patient with no increased pressure in the petrosus sinuses (patient #4) we found him responder to the treatment. This seems to indicate the potential use of this approach as a clinical prognostic factor. Also we analyzed the consistency of our ECD/computational model results with both the side of SSNHL and clinical outcome (Table 1). As far as the side of onset of the disease is concerned the increased SPS/IPS pressure side corresponds to the side of SSNHL in patients #2 and #3. Regarding the clinical outcome, again hyper-pressure in the SPS/IPS seems an important prognostic factor because recovery was achieved in patient #4 with level of pressure comparable to control, but not in patients #2 and #3.

The application of the computational model to the study of the drainage of the inner ear apparently may add a novel potential prognostic factor, particularly interesting in clinical practice. If little is known on the pathogenetic mechanisms that cause SSNHL, even less information is available on the biological mechanism of threshold

recovery. It has been reported that the SSNHL threshold-recovery can be in relation to many factors, such as: i) the hearing loss length prior to therapy; ii) the associated hearing loss symptoms; and iii) the audiogram features. It has also been reported that patients with higher hearing loss, at the SSNHL onset, show a lower recovery rate in comparison to patients with initial mild losses.[33,34] Among the audiogram shape, data from the literature show that patients with low-frequency or mid-frequency hearing losses present higher rates of recovery in comparison to patients with flat or sloping-down audiometric profiles.[33-35] Computational increased SPS/IPS pressure might be an additional factor because in this pilot study individuated patients with worse prognosis. The raising pressure of the dural sinuses seems to be a pivotal parameter with changes in case of abnormal jugular valve function. The latter can be non-invasively derived by means of ECD.

Quite recently another model of the intra and extracranial circulation applied to clinical cases demonstrated the correlation between increased dural sinuses pressure and clinical outcome in multiple sclerosis

patients presenting also extracranial venous obstacles.[20]

Possible shortcomings of our study are linked with the variability of ECD applied to the study cerebral venous return. Several meta-analysis show big variations depending from training and operator dependency of ultrasound.[1]

Surely there is an incidence of CCSVI in patients with SSNHL, but some authors show only 21.6% of the evaluated cases.[12] This difference compared to our study, where we have 4 SSNHL patients positive to the diagnoses of CCSVI, it is explicable on the grounds that our population has been identified for the application of the mathematical model with different areas of stenosis and valvular abnormalities. The small sample size does not give us the opportunity to give an incidence of CCSVI.

An impaired cochlear perfusion is widely reported to be a possible cause of SSNHL. Several data support this hypothesis. Firstly, the cochlea has a terminal capillary bed and is more susceptible to impaired drainage and increased pressure respect to regions with available collateral vessels. Secondly, since cochlear hair cells have a
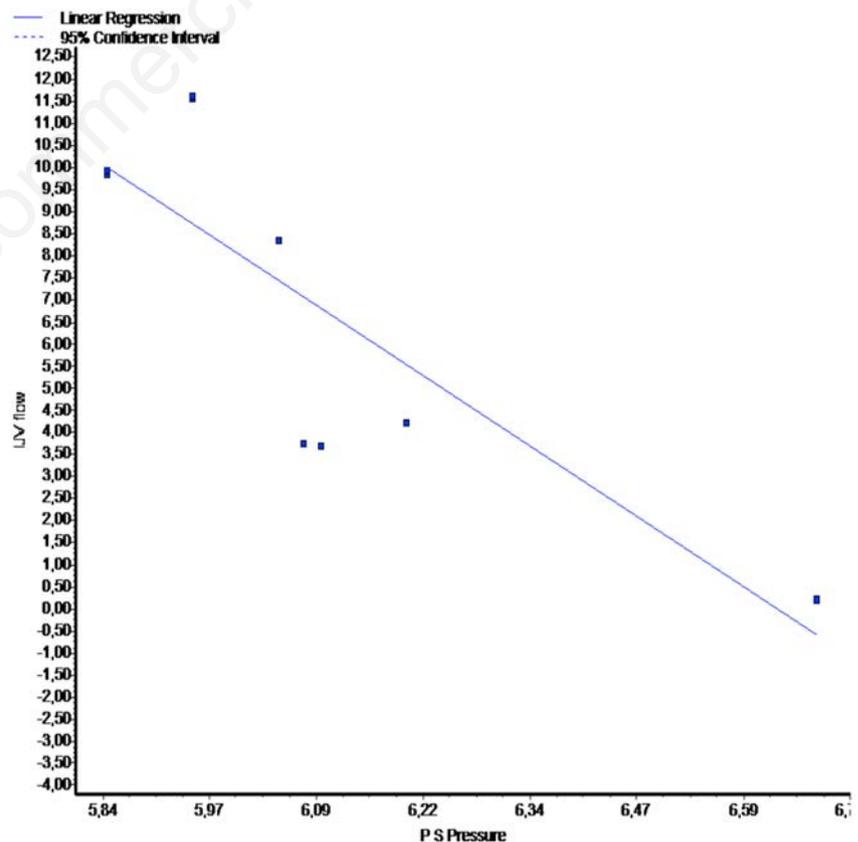

Figure 2. Inverted relationship between IJV flow rate and pressure at the level of the SPS/IPS Petrosus sinuses (r=-0.87773; r squared= 0.7697; p=0.0009).

high metabolic activity, they are particularly vulnerable to reduced perfusion.[33,36] Thirdly, several studies have found that risk factors for the endothelial cells, such as cigarette smoking, hypertension, and hyperlipidemia, are also risk factors for the development of SSNHL.[35-37] Defective IJV valves, similar to those detected by means ECD in this study, have significantly been reported to concur to the injury of the endothelial cells, suggesting a possible correlation with the above environmental risk factors.[38]

Since the present results are encouraging, the next step will consist in applying the combination of ECD extracranial venous outflow assessment coupled with computational analysis in a large sample of patients affected by SSNHL in order to verify the prognostic value of our innovative approach on a large case series.

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