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Factors influencing the hemodynamic response to balloon angioplasty in the treatment of outflow anomalies of internal jugular veins

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ABSTRACT

Objective: Percutaneous transluminal angioplasty (PTA) of the internal jugular veins (IJVs) has been proposed in recent years to treat chronic cerebrovascular venous insufficiency, with discordant results. Moreover, very little is known about the efficacy of PTA in restoring a normal cerebral venous outflow. The aim of this study was to investigate the anatomic factors and patient characteristics that might influence the efficacy of PTA of the IJV.

Methods: There were 797 consecutive patients with venous outflow anomalies who underwent standardized, operator-independent catheter venography and PTA of the IJVs. Before and after PTA, morphologic and hemodynamic anomalies of the IJVs were documented. The primary end point of the study was to evaluate the morphologic factors influencing the efficacy of angioplasty in improving IJV outflow.

Results: PTA resulted in an increased outflow through the IJVs in most patients. However, younger individuals with transverse endoluminal defects and higher pre-PTA flows are more likely to respond well to PTA compared with those who exhibit hypoplasia, stenosis, or longitudinal endoluminal defects.

Conclusions: This study identified the factors that influence and could predict the efficacy of PTA in the treatment of IJV anomalies. (J Vasc Surg: Venous and Lym Dis 2017;5:777-88.)

In recent years, there has been considerable interest in the use of percutaneous transluminal angioplasty (PTA) of the internal jugular veins (IJVs) to treat chronic cerebrospinal venous insufficiency (CCSVI), a vascular condition reportedly associated with multiple sclerosis (MS).[1-6] Many thousands of PTA operations have been performed around the world, with the procedure generally considered to be safe.[7-10] Despite this, the use of PTA to alleviate CCSVI remains controversial,[11,12] with published evidence in support of the procedure being somewhat limited. Although a number of studies have demonstrated that PTA can improve quality of life indicators in MS patients[13-15] and normalize venous hypertension[16] and cerebrospinal fluid motion,[17] relatively little is known about its efficacy with respect to the normalization of cerebral venous outflow. A previous work has shown a high prevalence of anomalous delayed flow through IJVs in patients with MS.[18] That study also demonstrated that although PTA generally improves IJV blood flow in MS patients with moderate delayed flow, in those with severe delayed flow, the procedure is successful in only a minority of patients.[18] This suggests that variations in vascular disease may strongly influence the efficacy of the procedure, with some morphologic features more amenable to PTA than others. With this in mind, we undertook the study presented here to investigate the hemodynamic response to balloon angioplasty in the treatment of cerebral outflow abnormalities. In particular, we were interested in understanding the extent to which stenosis, hypoplasia, endoluminal defects, and muscle compression influence the efficacy of the PTA procedure.

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METHODS

Study design. This was a single-center clinical study designed to evaluate, using a standardized and operator-independent catheter venography protocol, the morphologic factors influencing the efficacy of balloon angioplasty in the treatment of outflow anomalies of IJVs. The study was unfunded, with the Italian National Health System covering all the costs of the procedures. The patients and investigators were not paid for their participation. The study was approved by the ethical committee of the University Hospital of Catania. All patients signed an informed consent form on which the potential risks and benefits of the study treatment were detailed.

From May 2011 to December 2014, a total of 996 consecutive patients with venous outflow anomalies underwent balloon angioplasty of the IJVs. All patients underwent color Doppler ultrasound of the IJVs in accordance with the recommendations of the international consensus conference on the use of color Doppler ultrasound in patients with CCSVI.[19,20] Patients were included in our study and underwent catheter venography of the IJVs with IJV stenosis >50%, associated with anomalous outflow, and with at least two of the following symptoms: headache or migraine, chronic fatigue, bladder dysfunction, and walking impairment. Asymptomatic patients or patients with IJV bilateral thrombosis, presence of pacemakers, documented severe intolerance to contrast medium, and no compliance with therapy were excluded.

IJV morphologic and hemodynamic anomalies were documented before and after PTA using a standardized, validated, operator-independent catheter venography protocol in all patients.[18,21] In brief, all procedures were performed under local anesthesia, and access to the venous system was achieved through a percutaneous anterograde approach of the right common femoral vein under ultrasound guidance to avoid pain and accidental arterial puncture. After placement of an 8F sheath introducer, an intravenous bolus of 5000 units of heparin was administered. The right IJV was first cannulated, and selective venography was performed by automatic injection of a low-viscosity contrast medium at 4 mL/s for 2 seconds (a total of 8 mL for each aquisition). The frame rates were as follows: 3 frames/s for the first 4 seconds and then 2 frames/s for 8 seconds, for a total of 28 frames in 12 seconds. The long acquisition time was used to detect a delay of contrast medium clearance through the IJVs. After receiver operating characteristic analysis,[18] IJVs with a clearance time of ≤4 seconds (frames 7-11) were considered normal.

As a consequence, IJVs with a clearance time between 12 and 15 frames (4.1-6 seconds) were considered to have a moderate delayed flow, whereas IJVs with a clearance time >16 frames (>6.1 seconds) were considered to have a severe delayed flow. The same procedure was used for the left IJV. In particular, for the right and left IJVs, we evaluated the following factors:

- Presence of an anomalous valve with longitudinal defect (angle <30 degrees), determining stenosis >50% with respect to the proximal adjacent vein segment and associated with a moderate to severe delay in flow through the IJV (Fig 1).
- Presence of an anomalous valve with transverse defect (angle >30 degrees), determining stenosis >50% with respect to the proximal adjacent vein segment and associated with a moderate to severe delay in flow through the IJV.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective study of prospectively collected data
- **Take Home Message:** Analysis of 797 patients undergoing balloon angioplasty of the internal jugular vein revealed that younger individuals with transverse endoluminal defects are more likely than those with hypoplasia and stenosis to respond well to balloon angioplasty.
- **Recommendation:** Anatomic characteristics and age should be considered in the selection of patients for balloon angioplasty of the internal jugular vein.

- Presence of anomalous extrinsic muscle compression, determining stenosis >80% and absence of flow in the IJV (Figs 2 and 3).
- Presence of IJV hypoplasia with presence of collateral pathways and a moderate to severe delay in flow through the IJV (Fig 4).

No patient presented with both transverse and longitudinal defects in the same IJV.

IJV angioplasty was performed only in the presence of moderate delayed flow or severe delayed flow at catheter venography. If endoluminal defects were observed in the presence of a normal clearance time, the vein was not dilated. Compliant balloons of variable diameters (10-18 mm) were chosen to be approximately 10% larger than the native vein diameter.[18] The balloon angioplasty was considered effective when it reduced the abnormal delayed flow. The patient's characteristics, morphologic and hemodynamic data, technical aspects of the balloon angioplasty procedures, and images were collected and saved in a database. Two expert physicians reviewed the images. The primary end point of the study was to evaluate the morphologic factors influencing the efficacy of angioplasty in improving IJV outflow. Data relating major adverse events, death, and the need for open repair related to the procedure were collected 30 days after intervention. Although 996 patients with venous outflow anomalies underwent balloon angioplasty of the IJVs, to exclude as many confounding variables as possible, we excluded all those patients whose profile was unusual (ie, thrombosis or previous stenting), in whom PTA was considered not indicated or not feasible, as these might obscure the underlying effects that we were trying to identify. Patients who had been treated on one side only were also excluded because we were unsure whether unilaterally treated patients would behave in a similar manner to bilaterally treated patients. As such, unilateral treatment might have represented a potential confounder. The final study data set included 797 patients treated with bilateral PTA of the IJVs.

Fig 1. Catheter venography of the right internal jugular vein (IJV) showing nearly total occlusion of the proximal area caused by anomalous valve apparatus with longitudinal endoluminal leaflets (*arrows*).

Statistical analysis. To perform statistical analysis, the frame counts for each subject were converted into clearance times in accordance with the rules outlined before. Statistical analysis of the data was then performed using in-house algorithms written in R (open source statistical software) and MATLAB (MathWorks, Natick, Mass). P.V. has full access to all the data used in the study and takes responsibility for its integrity and the data analysis.

Univariate analysis was performed on the left and right IJVs separately, with all 797 subjects grouped together and then with the subjects grouped according to clinical

Fig 2. Catheter venography of the right internal jugular vein (IJV) documented a severe extrinsic compression caused by omohyoid muscle entrapment (pencil tip sign, *arrows*).

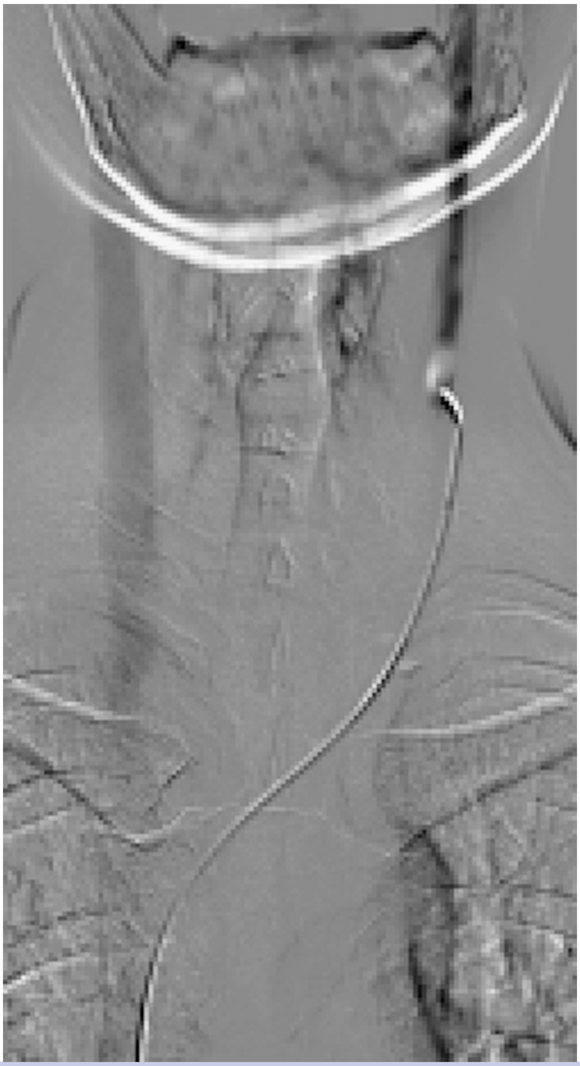

Fig 3. Catheter venography documented an occlusion of the medium portion of the left internal jugular vein (IJV) caused by omohyoid muscle compression, with retrograde anomalous outflow through the contralateral IJV.

Fig 4. Severe internal jugular vein (IJV) hypoplasia with flow through collateral pathways toward ipsilateral vertebral plexus and contralateral brachiocephalic trunk.

status (ie, the presence or absence of stenosis, hypoplasia, muscle compression, and endothelial defects [both transverse and longitudinal]). Differences in IJV clearance time before and after PTA were tested using a two-tailed Wilcoxon signed rank test; changes in the stenosis status were evaluated using a McNemar test. The effect sizes (r values) associated with the Wilcoxon signed rank tests were computed from the Z statistic using the methodology outlined by Pallant,[22] with $r \geq 0.1$ deemed to be a small effect, $r \geq 0.3$ a medium effect, and $r \geq 0.5$ a large effect.

To gain deeper insights into the impact of PTA on IJV blood flow, for the respective pre-PTA frame count clearance times, we computed the fraction of subjects whose blood flow improved after PTA. For each clinical subgroup, the difference in the fraction of the cohorts that improved and did not improve was evaluated using a χ^2 test. For all tests, P values $< .05$, adjusted for multiple comparisons using Bonferroni correction, were deemed to be significant.

Variables that were independently associated with the success or failure of PTA were identified using logistic regression analysis, which was performed using the clinical subgroup status variables plus the variables sex, age, and pre-PTA flow. Backward exclusion was used to eliminate variables from the respective logistic regression models, with $P > .1$ used as the exclusion criterion. To ensure that the statistical power of the logistic regression analysis was adequate, we used the methodology proposed by Peduzzi et al[23] to calculate the minimum

Table I. Demographic and clinical results for the right and left internal jugular veins (*IJVs*) before percutaneous transluminal angioplasty (*PTA*) for the whole study cohort (N = 797)

	Right IJV before PTA (n = 797)	Left IJV before PTA (n = 797)	Test statistic	*P* value
Age, years	45.04 (10.51)	45.04 (10.51)	NA	NA
Emptying time, seconds	6.54 (0.74)	6.70 (0.58)	Z = −5.04[a]	<.001[c]
Stenosis	679 (85.2)	673 (84.4)	$\chi^2 = 0.20$ ($df = 1$)[b]	.655
Hypoplasia	19 (2.4)	51 (6.4)	$\chi^2 = 15.06$ ($df = 1$)[b]	<.001[c]
Muscle compression	70 (8.8)	53 (6.6)	$\chi^2 = 3.85$ ($df = 1$)[b]	.050
No endoluminal defects	130 (16.3)	125 (15.7)	$\chi^2 = 0.15$ ($df = 1$)[b]	.702
Longitudinal endoluminal defects	608 (76.3)	629 (78.9)	$\chi^2 = 1.93$ ($df = 1$)[b]	.165
Transverse endoluminal defects	54 (6.8)	38 (4.8)	$\chi^2 = 3.28$ ($df = 1$)[b]	.070

df, Degrees of freedom; *NA,* not applicable.
Categorical variables are presented as number (%). Continuous variables are presented as mean (standard deviation).
[a]*P* value determined using the Wilcoxon signed rank test (two tailed).
[b]*P* value determined using the McNemar test.
[c]Significant after Bonferroni correction.

required sample size. This involved multiplying the number of dependent variables used in the initial model by 10 and then dividing this by the fraction of positive cases. This revealed that a minimum of 350 subjects were required, far less than the 797 cases that we actually included in our analysis.

RESULTS

Demographic results. Of the 797 subjects included in the study, 477 were female and 320 were male ($P <$ .001). The demographic and pre-PTA clinical results are presented in Table I. Other than hypoplasia, which was more prevalent on the left side, and muscle compression, which was slightly more prevalent on the right, there was no significant difference in clinical characteristics between the right and left IJVs. Stenosis was particularly prevalent (>84%) in the study cohort, with longitudinal endothelial defects much more prevalent (>76%) than transverse defects (<7%). None of the study patients died or were documented to have major adverse events or IJV complications needing open repair or adjunctive procedures.

Pre- and post-PTA data. The pre- and post-PTA results for all 797 subjects aggregated together are presented in the first row of Table II, which shows the pre- and post-PTA changes in the contrast medium clearance time. PTA intervention resulted in a statistically significant increase in blood flow rate for both the right and left IJVs, as confirmed by a reduction in the mean clearance time. PTA was also associated with a statistically significant reduction in the incidence of residual stenosis in both the left (pre-PTA, 673; post-PTA, 552; $P < .001$; McNemar $\chi^2 = 133.1$ [$df = 1$]) and right (pre-PTA, 673; post-PTA, 552; $P < .001$; McNemar $\chi^2 = 115.3$ [$df = 1$]) IJVs.

To gain deeper insights into the impact of PTA on IJV blood flow, we computed the number of subjects for the pre- and post-PTA clearance times equating to the respective frame counts. The results of this analysis are presented in Fig 5, which shows the percentage of subjects whose IJV blood flow improved for respective pre-PTA frame count clearance times for the right and left IJVs. From this, it can be seen that for both the left and right IJVs, the PTA intervention increased flow rates in a sizable proportion of patients. However, it is also noticeable that the intervention failed to improve the IJV flow rate in a substantial number of subjects. This phenomenon was observed for both the right and left IJVs (Fig 6).

Results for clinical subgroups. The analysis of the pre- and post-PTA IJV flow rates for the various clinical subgroups (Table III) demonstrated that with the exception of the patients with hypoplasia, significant decreases in clearance time in both IJVs were observed for all the clinical subgroups. The impact of the PTA was of medium effect ($r > 0.3$) for most subgroups, with the exception of those patients with a transverse endothelial defect, for whom the PTA had a large effect ($r > 0.5$; Fig 7).

Patients were also divided into two outcome groups: those whose IJV blood flow improved after PTA and those who did not improve (Table III). The results of this analysis suggest that younger patients, with fewer longitudinal endothelial defects and more transverse defects, and patients without hypoplasia are more likely to improve after PTA. No difference in this finding was observed between the left and right sides of the neck.

Whereas the results in Tables II and III quantify the impact of PTA on the various clinical subgroups, these results do not take into account any interactions that

Table II. Emptying times before and after percutaneous transluminal angioplasty (*PTA*) for patients classified according to clinical subgroup

Status	Age, years, mean (SD)	Emptying time, seconds, mean (SD)		*P* value (Z)
		RIJV before PTA	R IJV after PTA	
All subjects RIJV, N = 797 LIJV, N = 797	45.04 (10.51)	6.54 (0.74)	6.29 (0.90)	<.001[a] (14.74)[b]
Stenosis negative RIJV, n = 118 LIJV, n = 124	42.19 (10.35)	6.03 (0.99)	5.76 (1.08)	<.001[a] (6.29)[b]
Stenosis positive RIJV, n = 679 LIJV, n = 673	45.54 (10.47)	6.63 (0.65)	6.38 (0.83)	<.001[a] (13.33)[b]
Hypoplasia negative RIJV, n = 778 LIJV, n = 746	44.96 (10.53)	6.54 (0.74)	6.29 (0.74)	<.001[a] (14.67)[b]
Hypoplasia positive RIJV, n = 19 LIJV, n = 51	48.26 (9.63)	6.58 (0.87)	6.53 (0.94)	.500 (1.41)[b]
Muscle compression negative RIJV, n = 727 LIJV, n = 744	45.08 (10.51)	6.53 (0.74)	6.29 (0.90)	<.001[a] (14.07)[b]
Muscle compression positive RIJV, n = 70 LIJV, n = 53	44.64 (10.59)	6.58 (0.72)	6.28 (0.88)	<.001[a] (4.41)[b]
Endoluminal defect negative RIJV, n = 130 LIJV, n = 125	42.49 (10.57)	6.11 (1.00)	5.88 (1.08)	<.001[a] (5.93)[b]
Longitudinal defect positive RIJV, n = 608 LIJV, n = 629	45.66 (10.33)	6.63 (0.63)	6.45 (0.77)	<.001[a] (11.75)[b]
Transverse defect positive RIJV, n = 54 LIJV, n = 38	44.43 (11.55)	6.59 (0.73)	5.52 (1.06)	<.001[a] (6.20)[b]

LIJV, Left internal jugular vein; *RIJV*, right internal jugular vein; *SD*, standard deviation.
Effect size *r* value: small, $r \geq 0.1$; medium, $r \geq 0.3$; and large, $r \geq 0.5$.
[a]Significant after Bonferroni correction.
[b]*P* value determined using a Wilcoxon signed rank test (two tailed).

might be occurring between the various pathologic processes. Many of the patients in the study exhibited multiple pathologic changes of the IJV and so were included in more than one subgroup. Therefore, to identify which variables could be used to predict the success or failure of PTA, logistic regression analysis was performed using the clinical subgroup variables plus sex, age, and pre-PTA flow. The results of this analysis are presented in Table IV, which reveals that pre-PTA flow and transverse defects were the best indicators of PTA success for the right IJV, whereas age, stenosis, hypoplasia, and transverse defects were the best indicators for the left IJV. Noticeably, the sex of the subject appeared to have had no significant impact on IJV flow after PTA. Inspection of the models revealed the following (Fig 8):

- For both the right and left IJVs, the presence of transverse endoluminal defects is the single most important criterion for determining whether PTA will be successful.
- Whereas transverse endothelial defects have a positive coefficient, all the other variables in the models have negative coefficients, implying opposite effects.

Collectively, this suggests that younger individuals with transverse endoluminal defects and higher pre-PTA flows are more likely to respond well to PTA compared with those who exhibit hypoplasia, stenosis, or longitudinal endoluminal defects.

DISCUSSION

Previous studies involving the treatment of CCSVI using endovascular interventions (PTA or stenting) have reported positive results in terms of neurologic outcomes and effects on the quality of life.[24-30] Moreover, PTA has been shown to result in a significant improvement of hypercapnia and hypoxemia in the veins draining the brain and spinal cord in MS patients.[31] Nevertheless, PTA of IJVs

Table II. Continued.

Effect size *r* value (magnitude)	Age, years, mean (SD)	Emptying time, seconds, mean (SD)		*P* value (Z)	Effect size *r* value (magnitude)
		LIJV before PTA	LIJV after PTA		
0.369 (medium)	45.04 (10.51)	6.70 (0.58)	6.47 (0.76)	<.001[a] (13.57)[b]	0.340 (medium)
0.409 (medium)	42.52 (10.45)	6.46 (0.78)	6.18 (0.97)	<.001[a] (6.06)[b]	0.384 (medium)
0.362 (medium)	45.51 (10.46)	6.74 (0.53)	6.53 (0.71)	<.001[a] (12.15)[b]	0.331 (medium)
0.372 (medium)	44.98 (10.46)	6.69 (0.59)	6.45 (0.77)	<.001[a] (13.45)[b]	0.348 (medium)
0.229 (small)	46.00 (11.29)	6.91 (0.33)	6.85 (0.45)	.250 (1.73)[b]	0.171 (small)
0.369 (medium)	45.03 (10.48)	6.70 (0.57)	6.47 (0.76)	<.001[a] (13.23)[b]	0.343 (medium)
0.373 (medium)	45.15 (11.09)	6.76 (0.53)	6.53 (0.84)	.002[a] (3.03)[b]	0.294 (small)
0.368 (medium)	43.96 (11.35)	6.57 (0.74)	6.37 (0.92)	<.001[a] (5.09)[b]	0.322 (medium)
0.337 (medium)	45.39 (10.32)	6.73 (0.52)	6.56 (0.67)	<.001[a] (11.34)[b]	0.320 (medium)
0.596 (large)	43.74 (10.68)	6.59 (0.72)	5.56 (0.95)	<.001[a] (5.04)[b]	0.578 (large)

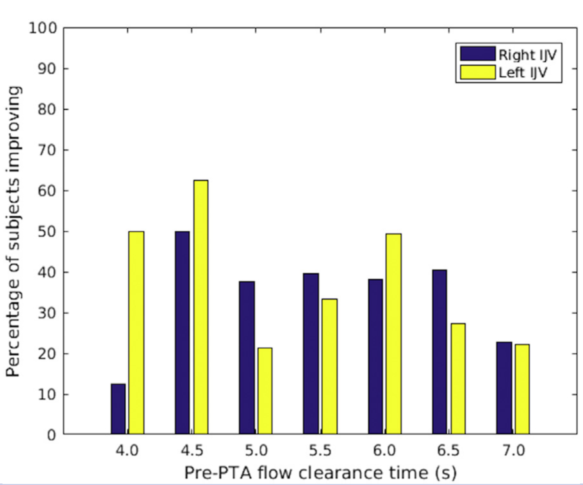

Fig 5. Proportion (%) of patients whose internal jugular vein (*IJV*; *left* and *right*) blood flow improved for various frame counts before percutaneous transluminal angioplasty (PTA).

is complicated by a high rate of early stenotic recurrence, with an incidence of restenosis between 30% and 50% of cases.[13-15,32] This high restenosis rate is probably related to an inadequate treatment of venous outflow anomalies rather than a true restenosis or recurrence. As a consequence, we tried to understand which of the different morphologic anomalies responded better to PTA. The results of this study present a clear and consistent picture, namely, that overall the intervention of PTA significantly increases the rate at which contrast agent is cleared from the IJVs. However, this effect was not homogeneous, with PTA being more successful in some clinical subgroups than in others. In particular, PTA appears to be more effective in younger individuals with transverse luminal defects and absence of hypoplasia, compression, or longitudinal luminal defects. The excessive length and consequent longitudinal placement relative to the wall of the valve leaflets appear to be decisive factors in predicting a possible failure of PTA in about 75% of cases.

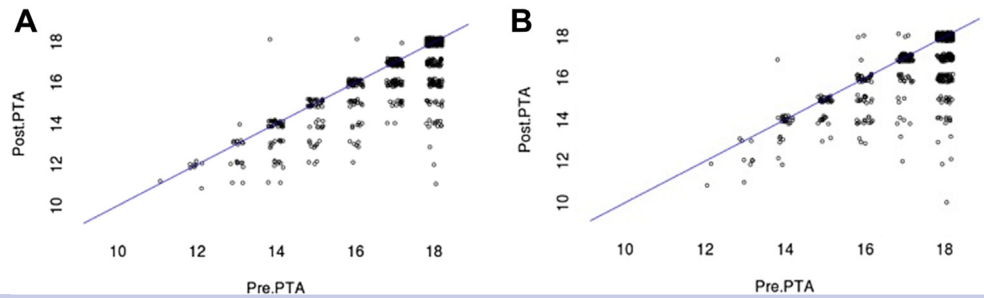

Fig 6. Correlation plot of pre-percutaneous transluminal angioplasty (*PTA*) flow frame count vs post-PTA flow frame count for **(A)** the right internal jugular vein (IJV) and **(B)** the left IJV. (Jitter perturbations have been added to enable visualization of the counts for each correlation.) The *blue line* represents no change in IJV blood flow.

With longitudinal luminal defects, it appears that although the leaflets are easily pushed against the wall by the inflated balloon, once the balloon is deflated, they readily return to their previous position. By contrast, PTA appears to be effective in treating rigid septa placed transversely with respect to the jugular wall. Furthermore, hypoplasia appears not to be a favorable presentation of CCSVI,[33,34] leading in our analysis to PTA failure in most cases. A plausible interpretation is that an immature venous trunk with development arrest cannot be dilated with the desired efficacy, even by using high-pressure balloons. It is known that CCSVI stenotic venous segments contain a high proportion of type III collagen less prone to be stretched with respect to type I.[35] Finally, our study confirmed PTA failure in case of extrinsic muscle compression.[36,37]

Collectively, the findings of our study suggest that it should be possible to preoperatively identify CCSVI anatomic presentations favorable to PTA treatment through careful assessment of the color Doppler ultrasound criterion 3.[38] Ultrasound permits the detection of nonmobile valve leaflets by means of M mode, whereas B mode yields complementary information on valve leaflet disposition with respect to the luminal wall.[39,40]

Table III. Percutaneous transluminal angioplasty (PTA) results (improvement vs no improvement) for the right and left internal jugular veins (*IJVs*) for all subjects (N = 797)

	Right IJV			Left IJV		
	No improvement (n = 566)	Improvement (n = 231)	*P* value (statistic)	No improvement (n = 592)	Improvement (n = 205)	*P* value (statistic)
Reduction in clearance time, seconds	0.87 (0.49)	−0.01 (0.10)	<.001[a] (27.6)[b]	0.90 (0.55)	−0.01 (0.09)	<.001[a] (27.5)[b]
Age, years	45.54 (10.32)	43.81 (10.89)	.039 (−2.1, *df* = 408)[c]	45.85 (10.32)	42.71 (10.75)	<.001[a] (−3.6, *df* = 343)[c]
No endoluminal defect	92 (16.3)	38 (16.5)	.946 (0.0, *df* = 1)[d]	99 (16.7)	26 (12.7)	.170 (1.9, *df* = 1)[d]
Longitudinal endoluminal defect	460 (81.3)	148 (64.1)	<.001[a] (26.8, *df* = 1)[d]	480 (81.1)	149 (72.7)	.011 (6.5, *df* = 1)[d]
Transverse endoluminal defect	10 (1.8)	44 (19.0)	<.001[a] (77.6, *df* = 1)[d]	10 (1.7)	28 (13.7)	<.001[a] (48.0, *df* = 1)[d]
Stenosis	488 (86.2)	191 (82.7)	.202 (1.6, *df* = 1)[d]	505 (85.3)	168 (82.0)	.254 (1.3, *df* = 1)[d]
Hypoplasia	17 (3.0)	2 (0.9)	.073 (3.2, *df* = 1)[d]	48 (8.1)	3 (1.5)	<.001[a] (11.2, *df* = 1)[d]
Muscle compression	48 (8.5)	22 (9.5)	.639 (0.2, *df* = 1)[d]	41 (6.9)	12 (5.9)	.596 (0.3, *df* = 1)[d]

df, Degrees of freedom.
Categorical variables are presented as number (%). Continuous variables are presented as mean (standard deviation). The values refer to the numbers of patients from each clinical subgroup in the respective improvement and no improvement groups. Statistical significance relates to the differences in the respective fractions for each clinical subgroup between those who improved and those who did not improve.
[a]Significant after Bonferroni correction.
[b]*P* value determined using a two-tailed Mann-Whitney *U* test.
[c]*P* value determined using a two-tailed *t*-test.
[d]*P* value determined using a χ^2 test.

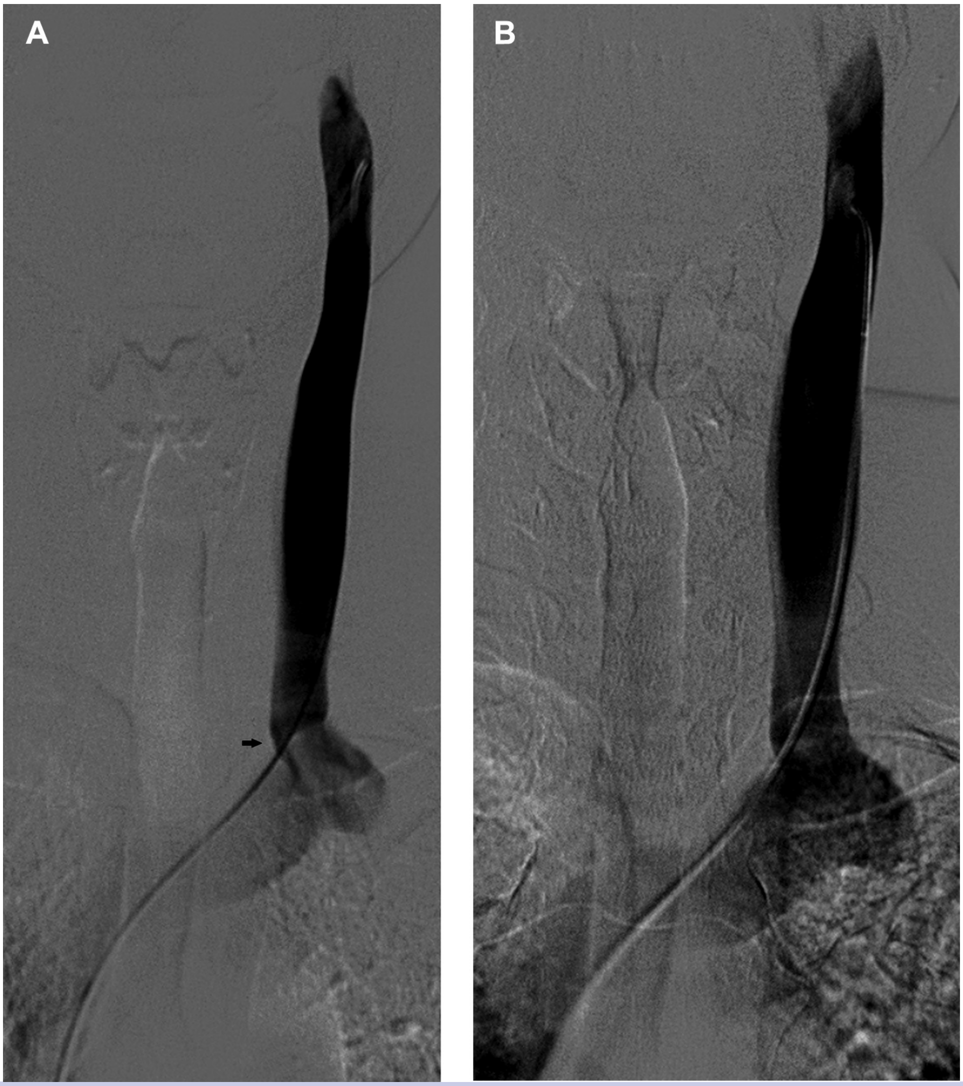

Fig 7. Catheter venography demonstrating **(A)** severe stenosis of left internal jugular vein (IJV) caused by transverse endoluminal septum (*arrow*), with **(B)** restoration of normal outflow after percutaneous transluminal angioplasty (PTA).

Moreover, muscle compression of the IJV more frequently by the omohyoid muscle can be detected preoperatively by means of the pencil tip sign. Finally, the third unfavorable presentation, hypoplasia, can be easily identified through assessment of the IJV cross section area at J1, J2, and J3 level.[20] However, color flow

Table IV. Results of logistic regression for the right and left internal jugular veins (*IJVs*; N = 797)

IJV side	Groups included	Independent variables	Coefficient (b)	*P* value	Odds ratio	95% CI
Right IJV	Improvers and nonimprovers	Intercept	1.6845	.0132	5.390	1.411-20.396
		Pre-PTA clearance time	−0.4281	<.0001	0.652	0.531-0.801
		Transverse endoluminal defects	2.6485	<.0001	14.132	7.210-30.425
Left IJV	Improvers and nonimprovers	Intercept	0.7281	.0768	2.071	0.926-4.659
		Age	−0.0262	.0018	0.974	0.958-0.990
		Stenosis	−0.7870	.0018	0.455	0.278-0.751
		Hypoplasia	−2.3614	.0002	0.094	0.022-0.286
		Transverse endoluminal defects	2.2596	<.0001	9.579	4.608-21.599

CI, Confidence interval; *PTA*, percutaneous transluminal angioplasty.

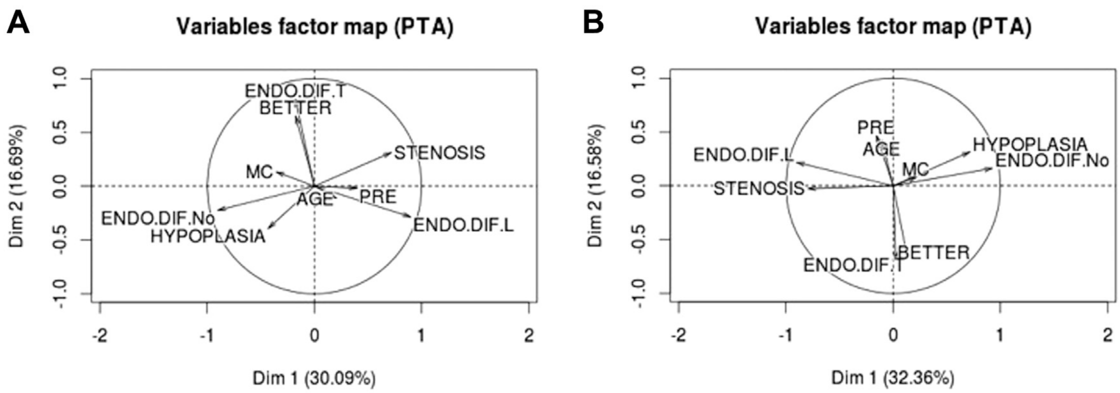

Fig 8. Results of percutaneous transluminal angioplasty (*PTA*) for the right **(A)** and left **(B)** internal jugular veins (IJVs), showing the relationships between the variables in the respective eigensystems. *Endo.DIF.*, Endoluminal defect; *Endo.DIF.L.*, endoluminal defect longitudinal; *Endo.DIF.T.*, endoluminal defect transversal; *MC*, muscle compression.

Doppler echocardiography has not been completely validated for the monitoring of patients undergoing PTA in long-term follow-up.[20]

As such, our study poses questions about the future treatment of cases that are not suitable for balloon angioplasty. Balloon angioplasty is safe but failed to improve the IJV flow rate in a substantial number of subjects, as demonstrated in this study, suggesting that an alternative approach may be more appropriate in these patients. In cases unsuited to PTA, stenting of IJVs may be one solution; stenting has reportedly been used in studies ranging from 10% to 44% of patients, with no increase of risk.[7,41,42] However, the safety profile of stenting techniques is less attractive because of a warning from the Food and Drug Administration against the use of off-label stents in the extracranial veins. The use of cutting balloons for the treatment of obstructive lesions in the IJVs has recently been reported with an immediate technical success of 94.3%.[43] The authors concluded that cutting balloon could be used in case of poor results of PTA, but the use is limited by the fact that only small diameters of the device are available.

Because of unsatisfactory early results of standard balloon angioplasty of IJVs, an open surgical treatment comprising removal of the septum followed by autologous patch angioplasty has been proposed. The surgical procedure was complemented by the section of the omohyoid muscle when appropriate, with an 18-month patency rate of 75%. This study also demonstrated that the procedure restored cerebral venous outflow, with overall cerebral perfusion also being improved.

This study did not correlate hemodynamic effect of PTA with clinical outcomes. There are many studies in the literature describing the use of PTA for the treatment of occlusive disease of the IJVs, with conflicting results. One of the main concerns for such discordant results is the lack of a valid method for quantifying the venous outflow before and after PTA. Therefore, clinical outcomes could not be accurately evaluated without a validated method for quantifying the hemodynamic efficacy of PTA. Our study addresses this important issue and for the first time attempts to identify the factors that could influence the immediate hemodynamic results obtained using PTA.

One of the major limitations of previous studies investigating the efficacy of IJV PTA is that they have tended to ignore the effect of differences in luminal defect on the ability of PTA to restore patency in occluded vessels. As such, the findings of these studies could be compromised because not all defects might respond to ballooning in a similar manner. Consequently, there was pressing need for a rigorous study to investigate the impact that different luminal defects have on the hemodynamic response to IJV PTA. Without a good understanding of the vascular pathophysiologic factors that influence the patency of ballooned IJVs, it is difficult to perform any meaningful work relating any neurologic condition that may or may not be associated with constricted cerebral venous outflow. If it is not recognized that different IJV luminal defects respond differently to PTA, it might be all too easy to come to erroneous conclusions about the treatment. Consequently, we undertook this study with the sole aim of better understanding the vascular factors that limit the effectiveness of IJV PTA with regard to restoring blood flow.

Moreover, there are no validated alternative methods to angiography (including color Doppler ultrasound) with which to evaluate the hemodynamic results of PTA in the long term, making any correlation with clinical outcomes extremely difficult. Performing venous angiography to evaluate hemodynamic performance in the long term may be unreliable, particularly in stable patients. Notwithstanding this, an ongoing study evaluating and validating color Doppler ultrasound as a useful tool for monitoring the hemodynamic effect of PTA is being undertaken, in which we hope to be able to correlate safely clinical outcomes with the effect of PTA in the long term.

Although IJV morphologic and hemodynamic anomalies were documented for all patients using a well-standardized and validated catheter venography protocol, data on intra-rater and inter-rater variability of the measurements taken were not available. As such, this represents a limitation of the study. Another limitation relates to our decision to exclude subjects who were treated on one side only or who had thrombosis or previous stenting. However, PTA has only limited indications in such patients, making them unrepresentative of the general population of patients.

CONCLUSIONS

Our study identifies the factors that influence the hemodynamic response to balloon angioplasty in the treatment of IJV anomalies. Younger patients with transverse endoluminal defects are more likely to experience a significant improvement in IJV outflow after PTA, whereas in older patients with IJV hypoplasia or longitudinal endoluminal defects, angioplasty is likely to have only a limited effect.

AUTHOR CONTRIBUTIONS

Conception and design: AG, PV
Analysis and interpretation: CB, MV, EDM, AS, CV, PV
Data collection: AG, CB, EDM, AS, CV, PV
Writing the article: AG, CB, MV, CV, PV
Critical revision of the article: CB, MV, EDM, AS, PV
Final approval of the article: AG, CB, MV, EDM, AS, CV, PV
Statistical analysis: CB, EDM
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Overall responsibility: PV

REFERENCES

1. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Tacconi G, Dall'Ara S, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2009;80:392-9.
2. Radak D, Kolar J, Tanaskovic S, Sagic D, Antonic Z, Mitrasinovic A, et al. Morphological and haemodynamic abnormalities in the jugular veins of patients with multiple sclerosis. Phlebology 2012;27:168-72.
3. Zaniewski M, Kostecki J, Kuczmik W, Ziaja D, Opala G, Świat M, et al. Neck duplex Doppler ultrasound evaluation for assessing chronic cerebrospinal venous insufficiency in multiple sclerosis patients. Phlebology 2013;28:24-31.
4. Simka M, Kostecki J, Zaniewski M, Majewski E, Hartel M. Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. Int Angiol 2010;29:109-14.
5. Zamboni P, Menegatti E, Conforti P, Shepherd S, Tessari M, Beggs C. Assessment of cerebral venous return by a novel plethysmography method. J Vasc Surg 2012;56:677-85.
6. Haacke EM, Feng W, Utriainen D, Trifan G, Wu Z, Latif Z, et al. Patients with multiple sclerosis with structural venous abnormalities on MR imaging exhibit an abnormal flow distribution of the internal jugular veins. J Vasc Interv Radiol 2012;23:60-8.
7. Petrov I, Grozdinski L, Kaninski G, Iliev N, Iloska M, Radev A. Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Endovasc Ther 2011;18:314-23.
8. Simka M. Commentary: safety of endovascular treatment for CCSVI and future perspectives. J Endovasc Ther 2011;18:326-7.
9. Lupattelli T, Bellagamba G, Righi E, Di Donna V, Flaishman I, Fazioli R, et al. Feasibility and safety of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Vasc Surg 2013;58:1609-18.
10. Simka M, Latacz P, Ludyga T, Kazibudzki M, Swierad M, Janas P, et al. Prevalence of extracranial venous abnormalities: results from a sample of 586 multiple sclerosis patients. Funct Neurol 2011;26:197-203.
11. Mayer CA, Pfeilschifter W, Lorenz MW, Nedelmann M, Bechmann I, Steinmetz H, et al. The perfect crime? CCSVI not leaving a trace in MS. J Neurol Neurosurg Psychiatry 2011;82:436-40.
12. Mayer CA, Ziemann U. CCSVI: is blinding the key? Eur J Vasc Endovasc Surg 2012;43:124-5.
13. Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Gianesini S, Bartolomei I, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg 2009;50:1348-58.e1-3.
14. Bavera PM. May symptoms of chronic cerebrospinal venous insufficiency be improved by venous angioplasty? An independent 4-year follow up on 366 cases. Veins Lymphatics 2015;4:5400.
15. Zamboni P, Galeotti R, Weinstock-Guttman B, Kennedy C, Salvi F, Zivadinov R. Venous angioplasty in patients with multiple sclerosis: results of a pilot study. Eur J Vasc Endovasc Surg 2012;43:116-22.
16. Radak D, Kolar J, Sagic D, Ilijevski N, Tanaskovic S, Aleksic N, et al. Percutaneous angioplasty of internal jugular and azygous veins in patients with chronic cerebrospinal venous insufficiency and multiple sclerosis: early and mid-term results. Phlebology 2014;29:367-75.
17. Zivadinov R, Magnano C, Galeotti R, Schirda C, Menegatti E, Weinstock-Guttman B, et al. Changes of cine cerebrospinal fluid dynamics in patients with multiple sclerosis treated with percutaneous transluminal angioplasty: a case-control study. J Vasc Interv Radiol 2013;24:829-38.
18. Veroux P, Giaquinta A, Perricone D, Lupo L, Gentile F, Virgilio C, et al. Internal jugular veins out flow in patients with multiple sclerosis: a catheter venography study. J Vasc Interv Radiol 2013;24:1790-7.
19. Zamboni P, Morovic S, Menegatti E, Viselner G, Nicolaides AN. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound—recommendations for a protocol. Int Angiol 2011;30:571-97.
20. Nicolaides AN, Morovic S, Menegatti E, Viselner G, Zamboni P. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound: recommendations for a protocol. Funct Neurol 2011;26:229-48.
21. Ferral H. Review of catheter venography protocols in the evaluation of chronic cerebrospinal venous insufficiency. Phlebol Rev 2014;22:11-7.
22. Pallant J. SPSS survival manual. 3rd ed. New York: Open University Press; 2007. p. 225.
23. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-9.

24. Zivadinov R, Bastianello S, Dake MD, Ferral H, Haacke EM, Haskal ZJ, et al. Recommendations for multimodal noninvasive and invasive screening for detection of extracranial venous abnormalities indicative of chronic cerebrospinal venous insufficiency: a position statement of the International Society for Neurovascular Disease. J Vasc Interv Radiol 2014;25:1785-94.
25. Salvi F, Bartolomei I, Buccellato E, Galeotti R, Zamboni P. Venous angioplasty in multiple sclerosis: neurological outcome at two years in a cohort of relapsing-remitting patients. Funct Neurol 2012;27:55-9.
26. Hubbard D, Ponec D, Gooding J, Saxon R, Sauder H, Haacke M. Clinical improvement after extracranial venoplasty in multiple sclerosis. J Vasc Interv Radiol 2012;23:1302-8.
27. Denislic M, Milosevic Z, Zorc M, Ravnik IZ, Mendiz O. Disability caused by multiple sclerosis is associated with the number of extra cranial venous stenoses: possible improvement by venous angioplasty. Results of a prospective study. Phlebology 2013;28:353-60.
28. Malagoni AM, Galeotti R, Menegatti E, Manfredini F, Basaglia N, Salvi F, et al. Is chronic fatigue the symptom of venous insufficiency associated with multiple sclerosis? A longitudinal pilot study. Int Angiol 2010;29:176-82.
29. Zivadinov R, Weinstock-Guttman B. Role of venoplasty for treatment of multiple sclerosis: value of open-label studies and surrogate treatment outcomes. J Vasc Interv Radiol 2012;23:1308-10.
30. Kostecki J, Zaniewski M, Ziaja K, Urbanek T, Kuczmik W, Krzystanek E, et al. An endovascular treatment of chronic cerebro-spinal venous insufficiency in multiple sclerosis patients—6 month follow-up results. Neuro Endocrinol Lett 2011;32:557-62.
31. Petrov I, Grozdinski L, Tsonev S, Iloska M, Tasheva I. Hypercapnia and hypoxaemia due to impaired venous blood draining and significant improvement after endovascular treatment in patients with chronic cerebrospinal venous insufficiency. Phlebol Rev 2016;24:20-4.
32. Siddiqui AH, Zivadinov R, Benedict RH, Karmon Y, Yu J, Hartney ML, et al. Prospective randomized trial of venous angioplasty in MS (PREMiSe). Neurology 2014;83:441-9.
33. Lee BB, Baumgartner I, Berlien HP, Bianchini G, Burrows P, Do YS, et al. Consensus Document of the International Union of Angiology (IUA)—2013. Current concept on the management of arterio-venous management. Int Angiol 2013;32:9-36.
34. Krsmanović Ž, Živković M, Lepić T, Stanković A, Raičević R, Dinčić E. Small internal jugular veins with restricted outflow are associated with severe multiple sclerosis: a sonographer-blinded, case-control ultrasound study. BMC Neurol 2013;13:90.
35. Coen M, Menegatti E, Salvi F, Mascoli F, Zamboni P, Gabbiani G, et al. Altered collagen expression in jugular veins in multiple sclerosis. Cardiovasc Pathol 2013;22:33-8.
36. Gianesini S, Menegatti E, Mascoli F, Salvi F, Bastianello S, Zamboni P. The omohyoid muscle entrapment of the internal jugular vein. A still unclear pathogenetic mechanism. Phlebology 2014;29:632-5.
37. Simka M, Majewski E, Fortuna M, Zaniewski M. Internal jugular vein entrapment in a multiple sclerosis patient. Case Rep Surg 2012;2012:293568.
38. Tromba L, Blasi S, Vestri A, Kiltzanidi D, Tartaglia F, Redler A. Prevalence of chronic cerebrospinal venous insufficiency in multiple sclerosis: a blinded sonographic evaluation. Phlebology 2015;30:52-60.
39. Toro EF, Muller LO, Cristini M, Menegatti E, Zamboni P. Impact of jugular vein valve function on cerebral venous haemodynamics. Curr Neurovasc Res 2015;12:384-97.
40. Menegatti E, Tessari M, Gianesini S, Vannini ME, Sisini F, Zamboni P. Human internal jugular valve M-mode ultrasound characterization. Curr Neurovasc Res 2014;11:149-55.
41. Ludyga T, Kazibudzki M, Simka M, Hartel M, Swierad M, Piegza J, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? Phlebology 2010;25:286-95.
42. Mandato KD, Hegener PF, Siskin GP, Haskal ZJ, Englander MJ, Garla S, et al. Safety of endovascular treatment of chronic cerebrospinal venous insufficiency: a report of 240 patients with multiple sclerosis. J Vasc Interv Radiol 2012;23:55-9.
43. Kazibudzki M, Latacz P, Ludyga T, Simka M. Efficacy and safety of cutting balloons for the treatment of obstructive lesions in the internal jugular veins. J Cardiovasc Surg (Torino) 2016;57:514-8.

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