Recurring paroxysmal positional vertigo: evaluation of the vascular factor

La valutazione del fattore vascolare nella vertigine parossistica ricorrente

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SUMMARY
To evaluate the effective incidence of vascular factor in the recurrence of benign paroxysmal positional vertigo (BPPV), we studied 50 subjects, 32 affected by idiopathic recurrent BPPV (study group) and 18 healthy subjects (control group). All subjects underwent complete otoneurological balance and haemodynamic evaluation by extracranial colour-coded duplex sonography (ECCS) of vertebral arteries (VA) with indication of arterial flow in ml/min, and retinal fluorangiography (FAG). The ECCS of 19 patients (59.3%) within the study group presented a reduction in vertebral arterial flow, exceeding the limits established by normative values (< 100 ml/min). In all cases, the same side was affected by BPPV, emphasised by vertebral hypoperfusion. The remaining 13 patients (40.6%) showed an arterial vertebral flow entirely within the normative values. The FAG excluded qualitative alterations of the cerebral microcirculation. The ECCS demonstrated that 59.3% of the study group showed a significant reduction in vertebral arterial flow ipsilateral to the semicircular canal affected by BPPV. This increased to 68.75% when the flow difference (D) between both the vertebral arteries was considered and reached 71.8% when vascular risk factors were evaluated. We conclude that reduced perfusion of the vestibular structures makes an already critical situation even more difficult, which can eventually develop into labyrinth suffering. The absence of fluorangiographic signs suggests that the labyrinthine neuroepithelium is much more sensitive to hypoperfusion than the retina. We hypothesise that this ischaemic situation could degenerate utricular macula, otolith detachment, leading to the development of recurrent BPPV. This risk situation for the labyrinth can also be revealed by the evaluation of three parameters: presence of vascular risk factors, reduction of vertebral flow < 100 ml/min and the difference in flow between the 2 vertebral arteries > 29 ml/min.

KEY WORDS: BPPV, cerebral blood flow, EcoColorCodedSonography, ECCS, vertebral flow, vascular vertigo, retinal fluorangiography

RIASSUNTO
La vascolarizzazione dell’orecchio interno è termino-terminale, questo espose il labirinto a danni da ipossia o ipossia-rivascolarizzazione. Riduzioni ulteriori di flusso ematico potrebbero essere alla base non solo della insorgenza, ma anche della maggiore frequenza di recidive della vertigine parossistica. Allo scopo di valutare l’incidenza di questi fattori abbiamo studiato 50 pazienti, 32 con VPPB ricorrenti e 18 soggetti sani. Tutti i soggetti sono stati sottoposti a esame otoneurologico completo, a valutazione emodinamica com'è come ecco wouldn't Doppler (ECD) delle arterie vertebrali con indicazione del flusso in ml/min e a fluorangiografia retinica (FAG). Nel gruppo di studio 19 pazienti (59,3%) all’ECD hanno presentato una riduzione del flusso vertebrale rispetto ai valori di normatività (< 100 ml/min). In tutti i casi il lato con maggiore ipoafflusso era lo stesso affetto da VPPB. I restanti 13 pazienti (40,6%) avevano valori ECD nella norma. La FAG non ha evidenziato alterazioni vascolari del microcircolo. L’esame ultrasonografico ha dimostrato quindi che il 59% dei soggetti con VPPB ricorrenti ha una riduzione significativa del flusso vertebrale omolaterale al lato affetto e che questo valore aumenta al 68,75% se la differenza del flusso tra le due arterie vertebrali è maggiore del valore soglia riscontrato nei soggetti normali e al 71,8%, se viene considerata anche la presenza di fattori di rischio. In conclusione, lo
Introduction

Benign paroxysmal positional vertigo (BPPV) is the most frequent cause of vertigo. The number of relapses is variable, but it has been observed that 27% of patients suffer from at least one new episode and of these 14% have one episode, 10% two relapses and about 3% of patients have 3 episodes per year. In 50% of cases, relapses occur within the first 6 months from the onset of the disease. The strong social impact of BPPV has encouraged continuous clinical research that has revealed many aspects of this pathological condition. However, the reasons for the frequent recurrence of idiopathic BPPV, without apparent cause, are yet to be clarified.

A new vertigo episode after a pause almost two months must be interpreted as a new event, where an unknown “facilitating factor” has a relevant role.

At present, there are no diagnostic exams that allow us to observe this “facilitating factor”, but when the recurrence is verified, we are normally oriented towards a hypothetical vascular cause.

According to Baloh, vertigo is often caused by vertebrobasilar insufficiency, and is present in many diseases caused by vascular damage, such as cerebellar infarct, lateral medullary infarct, and labyrinth and pons-medullar tract infarct. In two cases, hearing loss was associated with vertigo and caused by either vessel occlusion or simple reduction of vascular flux.

The vascularisation of the inner ear depends on the internal auditory artery, a branch of the basilar artery or anterior inferior cerebellar artery, which is a terminal vessel and make the labyrinth sensitive to ischaemic phenomena.

The experimental study on blood flow distribution in the Circle of Willis showed that reductions in cerebral capillary arterial flow in the posterior circulation are directly proportional to reductions in the vertebral arteries flow. Extracranial colour-coded duplex sonography of vertebral arteries (ECCSVA) can be a useful and low-cost screening tool for the evaluation of posterior cerebral circulation. It has been demonstrated, furthermore, that the blood that comes from the two vertebral arteries, after having engaged in the basilar artery, flows separately and is divided from a central zone where the flux is absent, defined “dead point”. This indicates that the perfusion of the labyrinth is not only proportional to the vertebral blood flow, but can also depend on the side in which the flow is reduced.

Materials and methods

Fifty consecutive samples were recruited from January 2016 to December 2017 in our Audiovestibology Unit of the ENT Department in the University Hospital SS Annunziata in Chieti. Of these, 32 patients were affected by recurring idiopathic BPPV with a frequency of recurrence not less than 3 episodes/year, and the remaining 18 subjects were enlisted as the control group.

The exclusion criteria were a recurrence frequency of < 3 episodes/year; labyrinthine disease different from BPPV, age 70 years and over; a history of trauma or cervico-facial district contusion; and degenerative neurological pathologies.

All patients were informed about the study in detail, which adhered to the Declaration of Helsinki and ICH-GCP, GU 184/2003. Written informed consent was obtained from all patients.

All subjects underwent physical ENT examination, pure tone audiometry, vestibular spontaneous and positional testing using videonystagmoscopy and bithermal caloric evaluation according to Fitzgerald-Hallpike.

The haemodynamic quantitative analysis of vertebral artery flow, expressed in ml/min, was obtained by the same operator using ECCS Mmindray DC-70 through the acoustic windows from the transverse processes of the vertebrae in one segment (or more) of the V2 section. The Doppler waveforms and flux were obtained with an angle of insonation of 60° or less. On the basis of the literature, we considered...
that a vertebral artery flow of < 100 ml/min was valid indicator of vertebral artery hyperperfusion.
Evaluation of cerebral microcirculation was investigated using retinal fluorescein angiography (FAG).
Finally, we evaluated in each person of both groups the flow difference between the vertebral arteries (D) considering as normal the highest difference found in the control group (29 ml/min) (Tab. I). Statistical analysis was performed using independent-samples t-test for P ≤ 0.05 to determine if a difference exists between two means of two independent groups on continuous dependent variables.

Results
Fifty subjects, 36 females (72%) and 14 males (28%), were included in this study; 32 patients (study group) had recurring BPPV and 18 subjects (control group) had no vertigo or vascular pathologies. Audiometry results showed age-related disorders in all 50 subjects.
The study population was composed of 22 females (69%) and 10 males (31%) with age ranged between 24 and 70 years (average age 52 years). In this sample, 12 patients (37.5%) presented a documented pathological vascular risk (Tab. I) while in 20 cases (62.5%), BPPV was idiopathic. The most common vascular risk factors were hypertension (28%), diabetes (18.7%) and hyperlipidaemia (15.6%). Types of BPPV were found to be distributed as right posterior in 11 (34%), right lateral in 6 (18.7%), left posterior in 10 (31%) and left lateral canal in 5 (15%).
In the study group, on bithermal caloric testing 14 patients (43%) were found to have labyrinthine hypofunction of the affected side.

Ultrasonography in the control group showed normal vertebral flow in all subjects with values between 104 and 218 ml/min (average 149.6) in the right side, 109 and 195 ml/min (150.3) in the left side with a D between 2 and 29 ml/min. The ECCSVA in the study group presented in 19 patients (59.3%) a reduction in arterial vertebral flow, exceeding the normal range (< 100 ml/min) between 26 and 96 ml/min, 13 patients (40.6%) demonstrated hypoperfusion on only one side, and 6 patients (18.75%) presented a reduction on both sides. In all pathological cases (64%), BPPV was present on the side where the blood flow was most decreased. The remaining 13 patients (40.6%) had a normal VA flow (> 100 ml/min) (Tabs. II, III).

In the 12 patients (37.5%) with vascular risk, we detected hypoperfusion in 9 subjects (75%): unilateral in 4 subjects and bilateral in 5.
The hypoperfusion in the 20 patients (62.5%) with idiopathic BPPV was unilateral in 8 (25%) and bilateral in 2 subjects.
In the study group, the D between the two VAs observed in each patient was superior to the normality range in 21 cases (65.6%); 9 patients (28.1%) with vascular risk and 12 patients (37.5%) with idiopathic BPPV.
FAG exam in all patients excluded qualitative and dynamic alterations of the retinal situation that could explain the eventual damage at the microcirculatory level.
The results of the control group are shown in Table I.

Discussion
BPPV is a recurring pathological condition. While a clear clinical diagnosis is available in 86% of cases 19, the frequency of relapses depends on unknown causes. Since instrumental exams and imaging are often not capable of demonstrating evident alterations, it is possible that the frequency of relapses may have a facilitating factor that remains unknown.
When it is not possible to identify a definite cause of BPPV, a vascular cause is suspected. The main cause of vascular aetiology is vertebrobasilar ischaemia, generated by pa-
It has been hypothesised that otolith detachment in idiopathic BPPV could be secondary to microvascular problems, without necessarily being accompanied by the most important vascular pathologies (myocardial infarction, heart failure, ictus). The reduction in vertebral arterial flow, moreover, might not be significant for organs like the brain or cerebellum, which are endowed with a remarkable compensatory capacity, but can have a significant role in compromising the perfusion of organs supplied by a terminal-type circulation. For example, it might affect the utricular macula or semicircular canals, and this ischaemia of their neuroepithelium can facilitate its degeneration with consequent detachment of otoliths.

In this study, we tried to understand whether the use of tests that specifically explore the vascular district, namely retinal FAG for microcirculation and ECCS for the vertebral artery, may be useful for diagnosis in patients with recurring BPPV. A normal vertebral flow upper to 100 ml/min was considered. This is in agreement with Jang who reported a normal limit of vertebral hypoperfusion < 100 ml/min. The results showed that the retinal FAG is inadequate for indirect evaluation of vestibular microcirculation because patients, even those with verified reduction in vertebral arterial flow, did not present alterations in retinal microcirculation. In 6 cases, where both vertebral arteries had a reduced flow compared to the mean, the pathology of

Table II. Vertebral flow in ml/min in BPPV group with vascular risk.

| Patient | Age | Risk factors          | Right VA (ml/min) | Left VA (ml/min) | BPPV | Δ |
|---------|-----|-----------------------|-------------------|------------------|------|---|
| F.P.    | 50  | Hypertension          | 140               | 164              | R PSC| 24 |
| D.P.M.  | 68  | Diabetes              | 81                | 45               | L LSC| 36 |
| D.L.G.  | 64  | Hypertension dyslipidaemia | 63              | 198              | R PSC| 135|
| C.F.    | 65  | Hypertension dyslipidaemia | 86               | 24               | L PSC| 62 |
| C.S.    | 57  | Hypertension diabetes | 49                | 137              | R LSC| 88 |
| S.Z.    | 50  | Hypertension diabetes | 96                | 25               | L PSC| 70 |
| L.D.C.  | 63  | Hypertension dyslipidaemia | 59               | 182              | R PSC| 123|
| M.V.    | 58  | Hypertension dyslipidaemia | 76               | 44               | L LSC| 32 |
| F.C.    | 68  | Diabetes              | 52                | 140              | R LSC| 88 |
| G.S.    | 66  | Hypertension diabetes | 145               | 155              | R PSC| 10 |
| CP      | 62  | Diabetes              | 77                | 56               | L PSC| 21 |
| M.C.    | 51  | Hypertension dyslipidaemia | 130              | 160              | L PSC| 30 |

Table III. Vertebral flow in ml/min in BPPV group without vascular risk.

| Patient | Age | Right VA (ml/min) | Left VA (ml/min) | BPPV | Δ |
|---------|-----|-------------------|------------------|------|---|
| C.F.    | 56  | 64                | 119              | R PSC| -55 |
| D.L.    | 45  | 160               | 189              | R PSC| -29 |
| D.A.    | 45  | 89                | 154              | R LSC| -65 |
| D.A.R.  | 51  | 195               | 129              | L PSC| 66 |
| M.F.    | 70  | 128               | 66               | L PSC| 62 |
| T.M.    | 64  | 164               | 179              | L PSC| -15 |
| T.R.    | 52  | 128               | 129              | R LSC| -1 |
| T.A.    | 70  | 66                | 33               | L LSC| 33 |
| L.M.    | 58  | 140               | 149              | L LSC| -9 |
| V.L.    | 53  | 188               | 160              | R PSC| 28 |
| C.R.    | 57  | 72                | 128              | R PSC| -56 |
| F.G.    | 58  | 34                | 135              | R PSC| -101 |
| D.A.P.  | 49  | 170               | 113              | L PSC| 57 |
| M.M.    | 51  | 198               | 228              | R PSC| -30 |
| D.P.E.  | 35  | 133               | 143              | R PSC| -10 |
| C.S.    | 57  | 49                | 136              | R LSC| -87 |
| D.A.P.  | 36  | 93                | 82               | L PSC| 11 |
| C.P.    | 56  | 141               | 148              | L LSC| -7 |
| M.M.    | 47  | 75                | 110              | L PSC| -35 |
| C.C.    | 55  | 87                | 140              | L RSC| -53 |

R PSC: Right Posterior Semicircular Canal; R LSC: Right Lateral Semicircular Canal; L LSC: Left Lateral Semicircular Canal; L PSC: Left Posterior Semicircular Canal.
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The semicircular canal was ipsilateral to the side most hypo perfused (Tabs. II, III).

The predominance of the VA compared to the one on the contralateral side is physiologically normal. Hence, our study, using statistical analysis on the control group, highlighted that such a prevalence does not exceed the limits of normality (Tab. III).

Our study demonstrated that the reduction of the VA flow, unilateral to the injured side, was present in 59.3% of patients with recurring BPPV. In particular, it was observed in 10 patients with idiopathic recurring BPPV (31.2%) and 9 patients (28.1%) with recurring BPPV and documented vascular risk.

These results confirm the absolute dependence of the vestibular system of one side to the ipsilateral VA flow, as demonstrated by studies of circulatory physiology of the Circle of Willis by Mc Donald and Potter (1951) and Carney (1981) 13. These studies demonstrated that, inside the basilar artery (BA), the blood flow merger by the two vertebral arteries remains distinct and separated by a zone defined as the “dead point,” where the value of vertebral flow is zero. Consequently, the pressure of the flow in the vertebral vessels, measured by ECCS in ml/min (Fig. 1), was found to be directly proportional to the flow of the ipsilateral internal auditory artery.

Another parameter considered is D which represents the highest difference in flow values registered between the two vertebral arteries (Tabs. II, III). In the healthy subjects of our case series (Tab. I), this value is 29 ml/min. In the study group, this parameter was greater than 29 ml/min in 21 patients (65.6%), and most precisely 12 of them (37.5%) among those without vascular risk and 9 (28.1%) with reported vascular risk.

Notably, the results of the two parameters (D and flow in ml/min) are comparable and documented independently from each other, along with the validity of the methodology and their extreme correlation with the onset of recurring BPPV.

The study of blood flow distribution on experimental models of the Circle of Willis, constructed by David in 2002 10 showed that blood confluence from the vertebral arteries into the basilar artery is almost diverted into the larger artery like the posterior cerebral artery. It was also demonstrated that only a moderate quantity of blood is distributed in smaller vessels, like the posterior cerebellar artery, and above all, the internal auditory artery. In other words, the labyrinth is physiologically less supplied.

In this situation, further reduction in perfusion can precipitate an already critical condition that can translate into labyrinthine suffering.

However, ischaemia cannot be compensated by the flow of the opposite vertebral artery because, as previously mentioned, the flow of the two vertebral arteries remains separated inside the basilar artery. This can be translated into degeneration of the utricular macula with repeated detachment of otolith material and consequent BPPV 27. Therefore, we can legitimately hypothesise that the influence of general factors, like the vascular factors during persistent ischaemic states in the vertebrobasilar area lead to secondary distress of neuroepithelial structures of the macula, which can be followed by detachments of the otoconial membrane 28. This could also be the cause of the subclinical labyrinthine hypofunction revealed by the bithermal caloric tests in 40% of our sample.

Deterioration of the circulation in the vertebral artery, which is already hypofunctional, can result in the alteration of the endothelial wall, which might even be insignificant and not

Figure 1. ECCS of the vascular vertebral left (A) and right (B) arteries (flow value in ml/min is circled in red).
appreciable with any diagnostic technique. As demonstrated by Fischer in 2002, in carotid circulation the presence of stenosis, atherosclerosis, or flow obstruction can generate turbulence capable of further stenosis and worsened altered circulation 23. This could also explain why BPPV is related to future ischaemic strokes regardless of age 29.

Conclusions

A correct interpretation of vascular vertigo is of extreme prognostic importance because isolated and repeated episodes of vertigo can precede stroke in a relevant number of cases. In 25% of patients with basilar artery obstruction, recurring vertigo was revealed to be the symptom in 50% of patients during autopsy, while in 60-70% of subjects who subsequently developed a vascular deficit, vertigo is the principal symptom. A brief episode of vertigo frequently occurs during the three days immediately preceding the stroke, or during the last six weeks. These observations suggest that when diagnosing BPPV it is very useful to utilise other diagnostic, and not vestibological, tools, such as ECCS of the VA, which gives information directly on labyrinthic vascular flow. It is possible to consider the results of this exam as a new risk factor for recurrent BPPV and vascular risk.

In conclusion, from our results, we confirm that ultrasound examination of the vertebral arteries represents a method of choice in the diagnosis of recurring vascular vertigo, provided that the vertebral artery flow is specifically measured in ml/min and not in cm/sec as normally occurs in ultrasound laboratories. This value, in fact, does not indicate the flow rate of blood, but rather the speed relative to the caliber of the artery, an observation therefore only indirect and in our opinion not very significant. The absence of fluorangiographic signs suggests that the labyrinthine neuroepithelium is much more sensitive to hypoperfusion than the retina. For this reason, the labyrinth could be considered to be a more reliable sentinel than the retina to intercept microcirculatory vascular disorders even earlier. BPPV, especially if recurrent, should always be evaluated with ECCS to reveal possible signs of hypoperfusion. The vascular risk situation for the labyrinth can also be better revealed by evaluation of all three parameters: presence of vascular risk factors, reduction of vertebral flow < 100 ml/min and the difference in flow between the 2 vertebral arteries > 29 ml/min. Moreover, this data is confirmed empirically by the reduction in recurring vertigo subsequent to the use of drugs that activate the microcirculation like betahistine 27, mesoglycan, or sulodexide 30.

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