Potential Contribution of Hypertension to Evolution of Chronic Migraine and Related Mechanisms

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Aims: To investigate the potential contributions of diastolic and systolic blood pressure (BP) and the circadian rhythm of BP to chronic migraine evolution. **Methods:** This cross-sectional study included four groups of patients selected based on migraine frequency (high frequency ≥ 10 days per month and low frequency < 10) and on the presence of hypertension. Among-group and pairwise comparisons were carried out to investigate potential neurophysiologic differences in the cerebral vessel reactivity to a nitroglycerin test, in autonomic balance (tilting test), and BP circadian rhythm. **Results:** A more marked decrease in cerebral blood flow velocity was observed in hypertensive high-frequency migraineurs compared to all other groups (P = .037). Moreover, a smaller decrease in vagal tone was recorded in the orthostatic position in hypertensive subjects, whether they were high- (P = .032) or low-frequency migraineurs (P = .014), with a consistently higher vagal to sympathetic tone ratio (P = .033). Finally, in nonhypertensive subjects, a higher but not significant prevalence of systolic nondippers was detected in high-frequency migraineurs (67%) compared to low-frequency subjects (25%; P = .099). **Conclusion:** These findings suggest that hypertension may contribute to the chronic evolution of headache with mechanisms shared with migraine; ie, vascular tone alteration and autonomic dysregulation. *J Oral Facial Pain Headache 2022;36:221–228. doi: 10.11607/ofph.3174*

Keywords: *autonomic dysregulation, glyceryl trinitrate, hypertension, migraine*

Migraine is currently conceived as a clinical continuum from episodic to chronic forms, which are likely to share common pathophysiologic mechanisms.[1] The rate of progression to the chronic form is approximately 3% per year, and different modifiable and nonmodifiable factors influence the risk of headache worsening.[2] In particular, young age, female gender, obesity, and low socioeconomic status, as well as stressful life events, head injuries, medication overuse, and the presence of somatic comorbidities, are associated with a higher chronification rate and a poorer prognosis.[3,4] A recent meta-analysis further identified high-frequency episodic migraine and depression as main predictors of transformation from episodic to chronic migraine.[5]

Clinical practice would also suggest the presence of a correlation between chronic migraine and arterial hypertension, especially diastolic. However, the evidence in this regard is incomplete and contradictory, as many studies have found a positive association while others have found nonsignificant results.[6–8] In recent years, longitudinal and population-based studies pointed out that migraine is associated with the occurrence of cardiovascular disease and, more generally, with the presence of vascular risk factors.[9–11] Moreover, sporadic studies suggest that hypertension may represent an important factor in the chronification of migraine.[12,13] Indeed, one SD increase in diastolic blood pressure (BP) levels was found to increase migraine probability by 30% in women and 14% in men, while a similar increase in systolic BP seems to play a protective role.[14] Such evidence agrees with some reports of the efficacy of antihypertensive agents (such as beta blockers, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin II receptor blockers) as preventive drugs in migraine.[15,16] However, conclusive results are still missing, likely due to the different effects of diastolic and

systolic BP and of changes in BP circadian rhythm, which are seldom considered, on the process of chronification of migraine.

A number of observations support the participation of multiple neurophysiologic abnormalities in the process of migraine progression to the chronic form. Vasodilation appears to be favored by the presence of endothelium dysfunction and hypersensitivity of the intracranial arteries to nitric oxide (NO), an important gaseous transmitter involved in the regulation of cerebral blood flow.[17] Moreover, the presence of vagal hyperactivity in migraineurs during attack-free periods contributes to perpetuating flow changes and to producing alterations of the vascular wall.[18]

An integrated view of all these pathophysiologic features and their link to arterial hypertension is still missing. The aim of this study was therefore to investigate the potential contributions of diastolic and systolic BP and the circadian rhythm of BP to chronic migraine evolution.

Materials and Methods

Subject recruitment started in January 2018 and was completed in December 2019. The study was designed, led, and coordinated by the IRCCS Mondino Foundation, with the collaboration of the University of Pavia, Italy. This study adhered to the Declaration of Helsinki and was approved by the local Ethical Committee (no. 29170039937). Participants or their legal representatives provided written informed consent for participation in the study. No participants received financial compensation.

Participants

A total of 48 subjects were enrolled among patients seen at the Headache Center of the IRCCS Mondino Foundation who required a medical consultation for headache. Inclusion criteria were: diagnosis of migraine with or without aura (made according to the International Classification of Headache Disorders, third edition beta[19] by a neurologist [M.C.R., G.P., or A.C.] with substantial experience in headache diagnosis and care), aged between 45 and 75 years, and ability to give written informed consent. This age range was chosen to make hypertensive migraineurs more comparable to nonhypertensive migraineurs, as hypertension is in fact more frequent in adults and elderly individuals than in young people. Exclusion criteria were: secondary headaches or other chronic pain conditions, including headache attributed to arterial hypertension,[19] cerebral vascular malformations, relevant metabolic disorders (renal failure, adrenal cortical syndrome, liver disease), and consumption of drugs known to alter BP (ie, steroids, drugs with adrenergic effect, nitrates, etc). Some patients with hypertension were treated with antihypertensive drugs, and it was not considered ethical to interrupt them. Therefore, low doses of ACE inhibitors and sartans were allowed.

All enrolled patients underwent a complete clinical and neurologic assessment including anthropometric measures (height, weight, and body mass index [BMI]) and the anamnestic collection of both vascular risk factors (such as hypertension, smoking, obstructive sleep apnea syndrome [OSAS] diagnosed with polysomnography, and respiratory and heart diseases) and migraine characteristics (headache days per month, attack intensity, attack duration, attack side, and drug consumption). The presence of autonomic dysregulation or altered vascular response was investigated by means of ambulatory 24-hour BP monitoring, an autonomic balance (ie, tilting) test, and a nitroglycerin test. The tilting and nitroglycerin tests were performed in the morning, around 11:00 am.

Study Design and Outcomes

Patients with migraine with or without aura were enrolled consecutively and assigned to one of two groups based on headache frequency: high-frequency migraineurs (HF; $\geq$ 10 headache days per month) and low-frequency migraineurs (LF; < 10 headache days per month). The threshold of 10 headache attacks per month was chosen in order to identify a high-frequency group including not only chronic forms ($\geq$ 15 days) but also subjects waiting for chronic evolution, as it is the authors' opinion that such a group allows for better study of the pathophysiologic modifications underlying the increase in headache frequency that probably takes place long before the chronic migraine is diagnosed. Within each group, hypertensive (H) and nonhypertensive (N) patients were selected in agreement with the criteria of the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines.[20] Four groups were therefore defined: LN and LH, including nonhypertensive and hypertensive subjects, respectively, with low-frequency migraine; and HN and HH, including nonhypertensive or hypertensive patients, respectively, with high-frequency migraine. The primary outcome was to investigate the differences among groups with regard to cerebral vessel reactivity (nitroglycerin test), autonomic balance (tilting test), and the circadian rhythm of BP. Before instrumental assessments, medications known to interfere with vascular tone and migraine preventives with a similar effect were interrupted for at least 24 hours. All assessments were performed in the interictal phase of migraine.

Nitroglycerin Test and Cerebral Blood Velocity Monitoring

Cerebral vascular reactivity was studied by monitoring the blood flow velocity in the medial cerebral artery (MCA) of both sides using two pulsed-wave Doppler probes (2 MHz) positioned at the temporal acoustic windows, as previously described.[17] The acquisition was carried out in a dimly lighted room with the patient in the supine position. After 10 minutes of basal recording, nitroglycerin (glyceryl trinitrate [GTN] 0.9 mg) was administered sublingually, and monitoring was carried out for a further 30 minutes. Afterwards, in offline mode, samplings of about 20 cycles every 2 minutes were considered in order to determine the mean velocity at baseline, while samplings of about 40 cycles were carried out at 10, 20, and 30 minutes after drug administration. Possible artifacts were excluded from the samplings. At each time point, the following indices were obtained: mean velocity (Vm), calculated by the ultrasound machine; pulsatility index (PI = peak systolic velocity – minimal diastolic velocity/V_m), and resistivity index (RI = systolic velocity – diastolic velocity/systolic velocity), with the latter two being indices of resistance of the microvascular bed. Mean BP (mBP) and heart rate (HR) were continuously recorded during the test using a pulse plethismographic device.

Tilting Test and 24-hour BP Monitoring

The tilting test was carried out with a tilting bed that allowed for continuous measurement of BP and HR at different degrees of inclination. In the authors' laboratory, the patients were evaluated first in the supine position for 10 minutes and then at an inclination of 60 degrees for a further 10 minutes. The aim of this test was to assess modulation of the sympathetic (low-frequency RR/diastolic blood pressure) and parasympathetic (high-frequency RR/RR interval) nervous systems, expressed as a percentage and as sympathetic-vagal balance, respectively.

Twenty-four hour BP monitoring was carried out with an automatic recorder equipped with an armlet applied to the nondominant arm, obtaining measurements every 15 minutes during the day and every 30 minutes during the night. This allowed for assessment of the circadian rhythm of BP and, in particular, any physiologic decrease in values during sleep (ie, dipping). Subjects were thus distinguished as "dippers" (showing a 10% to 20% nocturnal BP decline compared to the average daytime values), "nondippers" (showing a nocturnal decrease of less than 10%), and "reverse dippers" (showing an increase in nocturnal BP compared to daytime BP).

Statistical Analyses

Sample size calculation resulted in 11 subjects per group, considering a statistical power of 0.8 and $\alpha = .05$. Shapiro-Wilk test was used to investigate the normal distribution of the different variables. Demographic and clinical characteristics among groups were compared using analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables, and chi-square test for categorical variables. Bonferroni correction was used to control for multiple comparisons in post hoc analyses.

Differences in cerebral vascular reactivity and sympathetic-vagal balance among groups were measured using Kruskal-Wallis test, whereas differences in mBP among and within groups were assessed with analysis of covariance (ANCOVA). Nocturnal dipping, expressed as the percentage of BP decline compared to the daytime average, was first assessed using Kruskal-Wallis test; afterwards, patients were classified dichotomously as dippers or nondippers (with the latter group including reverse dippers) and compared using chi-square test for categorical variables. Statistical computations were performed using SPSS version 26.0 (IBM) with two-tailed *P* values < .05 considered to indicate significance.

Results

Patient Characteristics

Table 1 reports the sociodemographic and clinical features of the four groups included in the study. In all groups, there was a higher number of women, which is in accordance with the prevalence of migraine in the general population. No significant difference was found among groups with regard to age, height, or BMI. Cardiovascular and respiratory comorbidities, as well as smoking and regular physical activity, were also comparable in all groups.

High-frequency migraineurs were characterized by a larger intake of symptomatic drugs, without significant differences between HN and HH patients. When compared to low-frequency migraineurs, the HN group showed both a larger intake of drug doses ($P < .01$) and a higher number of days of drug intake ($P < .01$); on the other hand, the HH group showed a higher number of days of drug intake than the LH ($P < .05$) group, but with no significant difference regarding intake of drug doses.

Duration of migraine disease, attack duration, and attack side were all comparable among the four groups.

Cerebral Vascular Reactivity

Cerebral blood velocity (CBV) in MCA showed significant changes during GTN administration; in particular, a clear decrease was already evident after the

Table 1 Sociodemographic Data and Headache Features in the Four Groups

Variables	LN (n = 12)	LH (n = 12)	HN (n = 12)	HH (n = 12)	*P*
Female sex, n (%)	10 (83)	8 (67)	10 (83)	7 (58)	.42
Age, y	55.8 ± 9.6	58.0 ± 6.4	53.9 ± 11.9	55.5 ± 10.5	.79
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	1.7 ± 0.1	.44
Weight, kg	68.3 ± 11.6	71.3 ± 13.6	64.4 ± 13.2	74.8 ± 17.1	.32
BMI, kg/m^2	24.2 ± 4.4	25.3 ± 4.5	24.0 ± 5.2	26.7 ± 4.8	.49
Hypertension duration, y	0.0	0.9 (0–5)	0.0	1.5 (0–7)	.02 [a]
Smoking, n (%)	1 (8)	2 (17)	2 (17)	4 (33)	.46
Regular physical activity, n (%)	2 (17)	6 (50)	3 (25)	3 (25)	.30
Comorbidities, n (%)					
Cardiovascular disease	3 (25)	6 (50)	2 (17)	2 (17)	.21
OSAS	4 (33)	4 (33)	6 (50)	8 (67)	.30
Respiratory disease	1 (8)	4 (33)	0 (0)	2 (17)	.12
Migraine characteristics					
Migraine frequency, d/mo	3.0 (2–8)	3.5 (2–7)	17.5 (11–20)	17.5 (13–20)	< .001 [b]
Attack severity, 0–10 NRS	7.0 (6–8)	6.5 (6–9)	8.5 (7–10)	9.0 (8–10)	.04 [c]
Attack duration, h	24.0 (2–33)	5.5 (4–22)	24.0 (19–48)	8 .0 (2–46)	.83
Attack side, n (%)					
Bilateral	7 (58)	6 (50)	6 (50)	6 (50)	.97
Unilateral	5 (42)	6 (50)	6 (50)	6 (50)	
If unilateral					
No side prevalence	1 (8)	2 (17)	1 (8)	2 (17)	
Right prevalence	2 (17)	2 (17)	3 (25)	2 (17)	.99
Left prevalence	2 (17)	2 (17)	2 (17)	2 (17)	
Migraine duration, y	34.0 (19–49)	32.5 (19–41)	25.0 (15–39)	25.5 (16–48)	.80
Time with high frequency migraine, y	0.0	0.0	3.0 (1–19)	4.0 (1–23)	< .001 [d]
Days of symptomatic drug intake, d/mo	3.0 (1–6)	3.0 (2–7)	13.5 (9–20)	17.5 (3–24)	< .001 [e]
No. of doses of symptomatic drug intake, doses/mo	2.5 (2–6)	3.5 (2–8)	20.0 (9–29)	20.0 (2–25)	< .001 [f]

Age, height, BMI, and migraine history were normally distributed and were therefore expressed as mean ± SD; comparisons were carried out by one-way ANOVA. Nonnormally distributed variables were expressed as median (interquartile range; 25th to 75th quartile) and compared using Kruskal-Wallis test. *P* values < .05 are considered to indicate significance.

OSAS = obstructive sleep apnea syndrome, NRS = numerical rating scale.

Post hoc pairwise comparisons with Bonferroni correction for diagnostic groups:

[a] Hypertension duration: LH > LN and HN (P < .001); HH > LN and HN (*P* < .01).

[b] Monthly migraine frequency: HN > LN and LH (*P* < .001); HH > LN and LH (*P* < .001).

[c] Attack severity: HH > LH (*P* < .05).

[d] Time with high-frequency migraine: HN > LN and LH (*P* < .001); HH > LN and LH (*P* < .001).

[e] Days of symptomatic drug intake, d/mo: HN > LN and LH (*P* < .01); HH > LH (*P* < .05).

[f] Doses of symptomatic drug intake, doses/mo: HN > LN and LH (*P* < .01).

first 10 minutes of transcranial doppler ultrasound recording within each group (*P* = .049; Fig 1). A plateau effect was then observed in the last 10 minutes (from 20 to 30 minutes). No significant differences between sides were observed either at baseline or after GTN administration among all groups. When comparing the four groups, a more pronounced decline in CBV was found in HH on both sides and at every time point, with significance reached 20 minutes after GTN administration (*P* = .037). PI and RI did not show any significant differences among the groups at any time of recording.

Comparisons among and within groups were also conducted with regard to systemic BP levels. As expected, mean BP showed significantly higher values in hypertensive individuals at all time points (*P* = .01, *P* < .01, *P* = .044, and *P* = .039 at baseline, 10, 20, and 30 minutes after GTN administration, respectively). A similar trend was also confirmed for both systolic and diastolic values. Within each group, and particularly in the HH group, systolic and diastolic BP displayed stable values throughout the entire recording time.

Neurovegetative Balance and Nocturnal BP Pattern

Spectral analysis of the modulation of the autonomic nervous system showed a physiologic increase in sympathetic tone in the transition from the supine to the orthostatic position in all subjects, with no significant difference among groups. Conversely, a smaller decrease in vagal tone was observed in both LH (*P* = .032) and HH (*P* = .014) subjects as compared to LN and HN, respectively (Fig 2). Consistently, the vagal to sympathetic tone ratio in the orthostatic position was found to be significantly higher in hypertensive subjects (*P* = .033).

Systolic nocturnal BP profile showed a decline in all groups, but with a decreasing trend from low- to high-frequency migraine groups, and from the nonhypertensive subjects to the hypertensive ones. A similar trend, although less pronounced, was also observed for the diastolic dipping group (Fig 3). No significant difference was found among the four groups. However, when nonhypertensive subjects were classified dichotomously into dippers and nondippers, a higher number of systolic nondippers was observed in HN (67%) than in LN (25%), with a trend close to significance (P = .099). On the other side, the number of nondippers in hypertensive subjects was comparable (LH 42% vs HH 50%) (Fig 4a). With regard to the diastolic dipping pattern, the percentage of nondippers was similar across all four groups (25%) (Fig 4b).

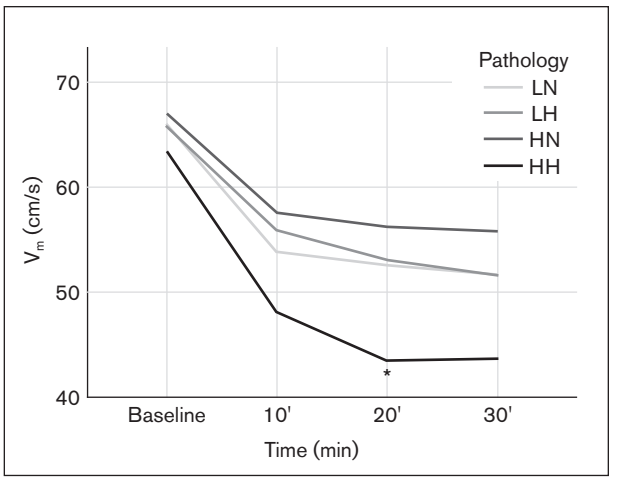

Fig 1 V_m of MCA during nitroglycerin test at different time points. *Significant difference (P < .05) at 20 minutes using Kruskal-Wallis test.

Discussion

To date, the role of arterial BP in chronic evolution of migraine is still uncertain, as the available evidence is inconclusive and sometimes contradictory.[6–8] The present study aimed to investigate whether and how changes in the circadian rhythm of BP may contribute to an increase in migraine frequency. Subjects with high-frequency migraine and hypertension showed a greater cerebrovascular reactivity in the nitroglycerin test, while hypertensive subjects showed a smaller decrease in vagal tone in the transition to an orthostatic position during the tilting test. Moreover, a high prevalence of altered systolic nocturnal dipping was observed in the groups of hypertensive subjects and in nonhypertensive subjects with high-frequency migraine.

The greater cerebrovascular response to GTN observed in HH migraineurs suggests an altered wall reactivity of the brain cerebral conductance vessels of medium to small caliber in this group. Separate analyses among groups considered a potential effect of GTN on the systemic BP and on the resistance indices of the microvascular bed (PI and RI) in order to rule out any confounding factors. Moreover, as already known in the literature, GTN has a prominent pharmacologic effect on arteries and arterioles, but a lesser effect on capillaries.[17] Several studies agree that migraine recognizes a chronic sterile (neurogenic) inflammation as the underlying pathophysiologic mechanism, based on a sustained response to different molecules released by perivascular nerves (such as NO, pituitary adenylate cyclase-activating peptide [PACAP], calcitonin gene-related peptide [CGRP], and vasoactive intestinal peptide [VIP]).[21] In the long term, this chronic activation can lead to an abnormal vascular response to NO donors, as observed in this

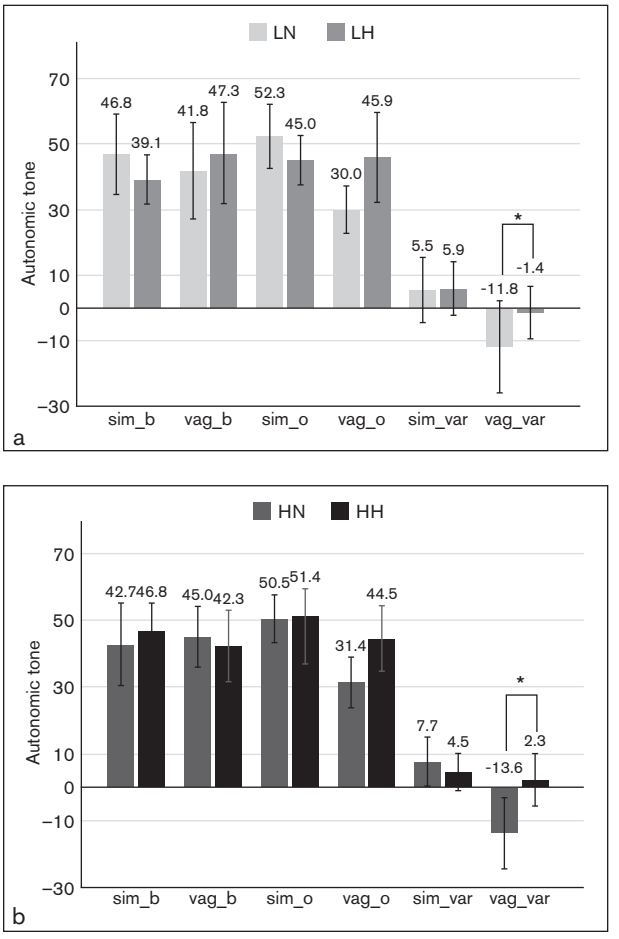

Fig 2 Sympathetic and vagal tone response during tilting test. Autonomic tone was expressed as mean ± CI (confidence interval set at 95%). *(a)* Patients with low-frequency migraine. *(b)* Patients with high-frequency migraine. Sim = sympathetic tone (low-frequency RR/diastolic blood pressure); vag = vagal tone (high-frequency RR/RR interval); b = baseline state; o = orthostatic position; var = variation from baseline to orthostatic position. *Significant (P < .05) pairwise comparison of vagal tone variation using Mann-Whitney U test.

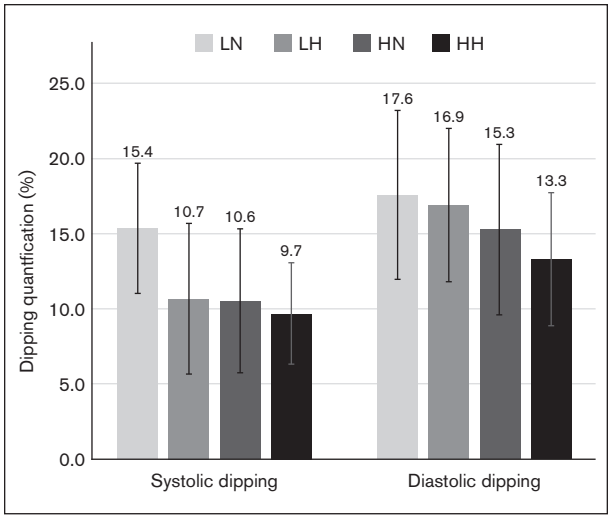

Fig 3 Percent quantification of systolic and diastolic nocturnal dipping.

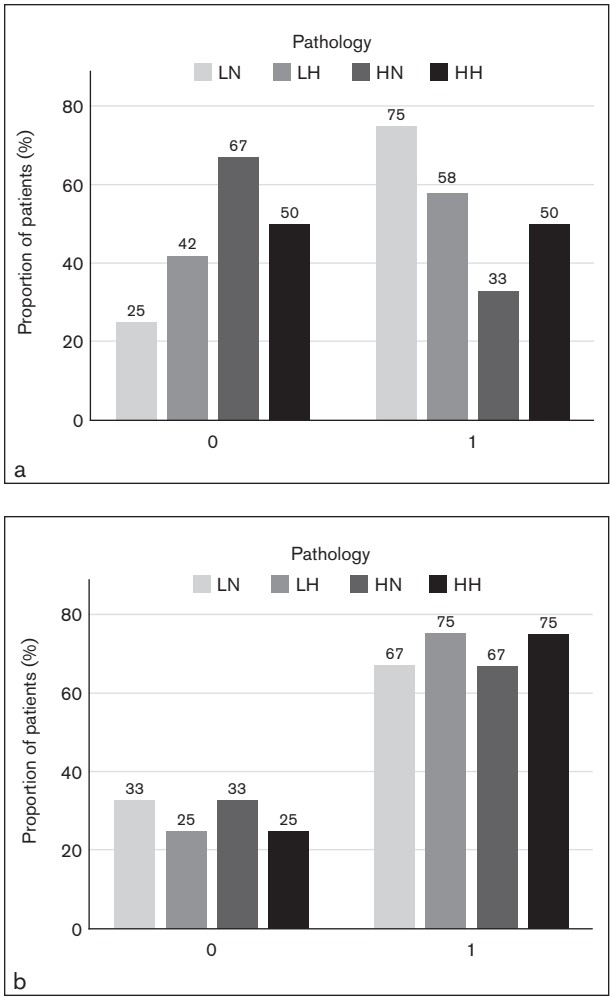

Fig 4 Proportion of patients presenting with *(a)* systolic and *(b)* diastolic nocturnal dipping. *0* = nondippers and reverse dippers; 1 = dippers.

study and others.[17,22,23] On the other hand, an increased vascular response to NO was also observed in hypertensive subjects regardless of migraine,[24] suggesting that the vessel wall may be a common target on which two separate processes converge: the sterile inflammation of migraine and the tangential stress of hypertension.[25] The present findings indicate that only the subjects with both migraine and hypertension displayed statistically greater vascular reactivity, suggesting that the effect of these two conditions could not be simply cumulative but also reinforce one another.

Vagal tone is known to play a crucial role in migraine pathophysiology and in generating the accompanying symptoms of headache during the attack (eg, nausea, vomiting, yawning). Vagal nerve is indeed the main regulator of the visceral and vascular functions within the cranial district. Autonomic dysregulation with a prevalence of vagal tone in subjects with migraine has already been often described in the literature.[18] A cross-sectional randomized study reported increased parasympathetic activity in the interictal phase of migraine and a greater sympathetic activity during the attack.[26] The present results revealed a lower reduction of the vagal tone with assumption of the standing position in hypertensive subjects, supporting the hypothesis that hypertension may contribute to alteration of sympathovagal modulation, which has been shown previously to be altered in nonhypertensive migraineurs.[18]

In the present study, systolic nocturnal BP profile showed a decline in all groups, with a decreasing trend from low- to high-frequency migraine groups, and from the nonhypertensive subjects to the hypertensive ones. A similar trend, although less pronounced, was observed for diastolic dipping. Both hypertension and migraine therefore seem to contribute to an altered nocturnal dipping, which in the present study was initially systolic. Alterations in the physiologic mechanisms of regulation of BP and vascular tone are in fact known to lead to initial changes in the BP profile at night earlier than during the day.[27] Moreover, the occurrence of migraine attacks has been previously associated with increased sympathetic activation with release of circulating noradrenaline,[26,28,29] and the occurrence of attacks with high frequency may therefore lead to a novel sympathovagal balance and to an altered vascular tone characterized by an increased sensitivity to catecholamines.[30]

The main limitations of this study are represented by the age range of the enrolled patients and by the presence of ongoing pharmacologic treatments, including antihypertensive drugs. In order to exclude relevant comorbidities that could have acted as confounding factors within the study, more people with an age close to the lower limit of the inclusion range

(55.8 ± 9.6 years)—and therefore with a shorter history of hypertension—were enrolled. This may have reduced the effect of hypertension on both autonomic dysfunction and vascular tone dysregulation more than expected. Moreover, due to the vascular risk associated with hypertension, it was ethically impossible to discontinue any ongoing antihypertensive therapy. Although no significant differences were found between the two groups (L and H migraine) of hypertensive patients with regard to the type and dosage of antihypertensive drugs taken, the pharmacologic control of hypertension may have mitigated the pathophysiologic changes described in this study. Future studies on subjects with a longer hypertension duration and matched for pharmacologic treatment are therefore needed to confirm and reinforce this evidence.

Conclusions

The present results suggest that arterial hypertension may contribute to an increase in attack frequency with pathophysiologic mechanisms common to those already described in migraine; ie, altered vascular wall reactivity and autonomic dysregulation. A combined pharmacologic approach aimed at reducing changes induced by both migraine and hypertension may constitute an interesting perspective in order to identify more effective therapeutic strategies in the prophylaxis of migraine patients with hypertension.

Key Findings

- Hypertension shares some pathophysiologic mechanisms with migraine.
- Altered vascular reactivity and autonomic dysregulation may contribute to an increase in the frequency of migraine.

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The authors declare that the research was conducted in the absence of any commercial, financial, or nonfinancial relationships that could be construed as a potential conflict of interest. This study was supported by a Research Grant of Ricerca Corrente from the Italian Ministry of Health to IRCCS C. Mondino Foundation.

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