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BRIEF ARTICLE

Migraine attack restores the response of vascular smooth muscle cells to nitric oxide but not to norepinephrine

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Author contributions: Napoli R had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Napoli R, Carrieri PB and Saccà L studied concept and design; Napoli R, Guardasole V, Zarra E, De Sena A, Saccà F, Ruvolo A, Grassi S, Giugliano S, De Michele G and Cittadini A did the experiments and acquisition of data; Napoli R, Carrieri PB and Saccà L did the analysis and interpretation of data; Napoli R and Saccà L did the drafting of the manuscript; Guardasole V, Zarra E, De Sena A, Saccà F, Ruvolo A, Grassi S, Giugliano S, De Michele G, Cittadini A and Carrieri PB made critical revision of the manuscript for important intellectual content; Napoli R and Saccà L performed statistical analysis; Napoli R and Saccà L did study supervision; all authors have read and approved the final version of the article.
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Abstract

AIM: To clarify whether the vasoconstrictory response is impaired and to study vascular function in patients with migraine during the headache attack.

METHODS: We studied vascular reactivity in the resistance arteries by using the forearm perfusion technique associated with plethysmography. We measured forearm blood flow by strain-gauge plethysmography during intra-brachial infusion of acetylcholine, sodium nitroprusside or norepinephrine in 11 controls and 13 patients with migraine, 11 of them (M) in the interval between the migraine attacks and 4 during a headache attack (MH). Written informed consent was obtained from patients and healthy controls, and the study was approved by the Ethics Committee of the University Federico Ⅱ.

RESULTS: Compared to healthy control subjects, in patients with migraine studied during the interictal period, the vasodilating effect of acetylcholine, that acts through the stimulation of endothelial cells and the release of nitric oxide, was markedly reduced, but became normal during the headache attack ($P < 0.05$ by analysis of variance). The response to nitroprusside, which directly relaxes vascular smooth muscle cells (VSMCs), was depressed in patients with migraine studied during the interictal period, but normal during the headache attack ($P < 0.005$). During norepinephrine infusion, forearm blood flow decreased in control subjects (-40% ± 5%, $P < 0.001$). In contrast, in patients with migraine, either when studied during or free of the headache attack forearm blood flow did not change compared to the baseline value (-3% ± 13% and -10.4% ± 15%, $P > 0.05$).

CONCLUSION: In migrainers, the impaired relaxation of VSMCs is restored during the headache attack. The vasoconstrictory response is impaired and remains unchanged during the migraine attack.

Key words: Migraine; Nitric oxide; Endothelium; Vascular smooth muscle cells

Core tip: Patients with migraine without aura studied in the interictal period are characterized by impaired abil-

ity of vascular smooth muscle cells (VSMCs) to relax in response to nitric oxide and to contract in response to norepinephrine. We hypothesize that the two defects compensate for each other and this provides for the maintenance of normal vascular resistance and blood pressure homeostasis. In contrast, during the headache attack, the VSMCs regain their ability to respond to nitric oxide, but remain unresponsive to norepinephrine. Such differential effect of the migraine attack is not surprising, given that nitric oxide and norepinephrine activate different intracellular signaling pathways in VSMCs.

Napoli R, Guardasole V, Zarra E, De Sena A, Saccà F, Ruvolo A, Grassi S, Giugliano S, De Michele G, Cittadini A, Carrieri PB, Saccà L. Migraine attack restores the response of vascular smooth muscle cells to nitric oxide but not to norepinephrine. *World J Cardiol* 2013; 5(10): 375-381 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i10/375.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i10.375

INTRODUCTION

Migraine is a widely common disease. Two thirds of migraineurs suffer from migraine without aura, whereas a third of patients present with migraine preceded by aura. Migraine has been associated with an increased risk of cardiovascular events, including myocardial infarction and ischemic stroke[1-3]. However, we have recently demonstrated that patients with migraine without aura, studied during the interictal period, do not present peripheral endothelial dysfunction, which is classically associated with a worse cardiovascular risk profile, but rather an abnormal relaxation of the vascular smooth muscle cells (VSMCs), that results in impaired vasodilation[4,5]. However, it is unclear whether the inability of VSMCs to respond to vasodilators is an isolated abnormality or, rather, reflects a more complex hemodynamic alteration, also involving the vasoconstrictory component. Furthermore, the peripheral vascular function in patients with migraine has been studied mainly during the interictal period. Therefore, whether the abnormalities in vascular function observed in patients with migraine are also present during the headache attack is unknown. Elucidation of the vascular response in patients with migraine both free of and during the headache episode would be of great importance to our understanding of the mechanisms involved in the pathogenesis of the disease and to better design appropriate therapeutic approaches.

MATERIALS AND METHODS

Patients

We studied 13 patients affected by migraine without aura and eleven healthy subjects in whom migraine was excluded, who served as controls (Table 1). The control subjects (C group) were recruited from hospital and laboratory personnel and were matched to the patients with regard to age, body mass index and sex. The diagnosis of migraine was made according to the criteria of the International Headache Society[6,7]. Subjects with hypertension, diabetes, high cholesterol, history of cardiovascular events and cigarette smoking were excluded from the study. None of the patients was taking any medication except those to treat the migraine attack. On the day of study, patients were either headache free for at least five days (11 subjects, M group) or were experiencing a headache attack that had started a few hours earlier (4 patients, MH group). These patients abstained from taking any medication until the end of the study period. Two patients underwent both studies (free of or during the headache attack). Written informed consent was obtained from patients and healthy controls, and the study was approved by the Ethics Committee of the University Federico Ⅱ. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Table 1 Baseline clinical characteristics of the subjects studied (mean ± SE)

	Sex (male/female)	Age (yr)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	HR (beats/min)
Controls (n = 11)	5/6	33 ± 3.4	24 ± 0.8	127 ± 2.1	60 ± 1.8	65 ± 2
M (n = 11)	4/7	34 ± 1.9	24 ± 1.1	125 ± 3.3	65 ± 2.6	68 ± 3
MH (n = 4)	0/4	28 ± 3.9	24 ± 0.9	115 ± 4.2	60 ± 1.8	68 ± 2

The patients with migraine were studied during the interictal period (group M) or the headache attack (group MH). BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

Vascular reactivity

We studied vascular reactivity in the resistance arteries by using the forearm perfusion technique associated with plethysmography, as previously described[4,8-11]. Briefly, a plastic cannula (20 G) was inserted into the brachial artery of the nondominant arm under local anesthesia and used for the infusion of the test substances and the monitoring of arterial blood pressure and heart rate. Forearm blood flow (FBF) was measured in both forearms by strain gauge plethysmography, with a calibrated mercury-in-silastic strain gauge applied around the forearm and connected to a plethysmography (Hokanson 045 EC4, PMS. Instruments, Berks, United kingdom) associated with a McLab computer. Each subject underwent the following step-wise infusions into the brachial artery: (1) acetylcholine (Ach) to assess endothelial-mediated vasodilation; and (2) sodium nitroprusside (NP), a nitric oxide (NO) donor that directly stimulates VSMCs, to assess non-endothelial-mediated vasodilation. At least half an hour after the NP infusion and when baseline FBF was restored, each subject received the infusion into the brachial artery of norepinephrine (NE) at the rate of 280 μg/L per minute for 5.5 min to assess the vascular response to sympathetic stimulation. This dose of NE was chosen on the basis of our previous experiments that

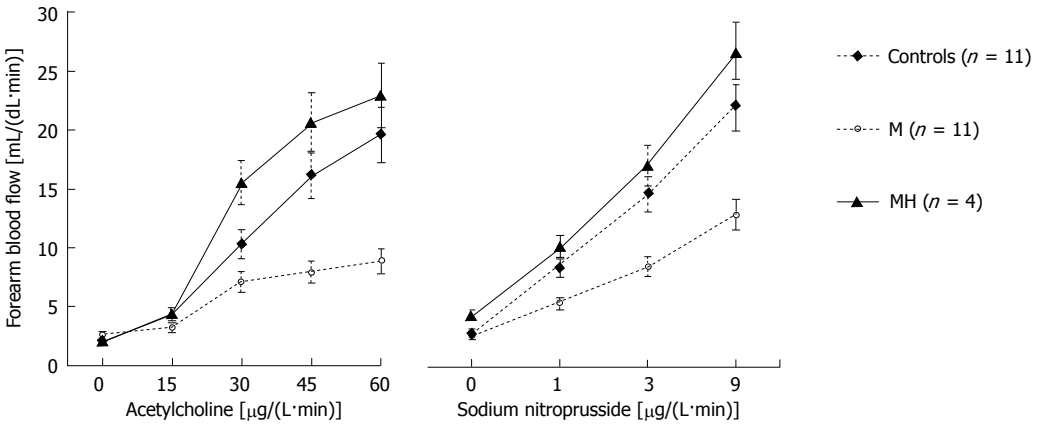

Figure 1 Forearm blood flow response to infusion of acetylcholine or sodium nitroprusside into the brachial artery in patients with migraine during or free from headache, and control subjects. The patients with migraine were studied during the interictal period (group M) or the headache attack (group MH). Data (mean ± SE) were analyzed by analysis of variance for repeated measures. $P < 0.05$ for the effect of migraine in the acetylcholine (Ach) test and $P < 0.05$ for the interaction between migraine and Ach. $P < 0.005$ for the effect of migraine in the nitroprusside test and $P < 0.05$ for the interaction between migraine and nitroprusside.

showed a near half-maximal fall in FBF. The investigators making the measurements of vascular reactivity were blind to the clinical status of the subjects undergoing the experiments.

Calculations

Based on previously published data[4], we computed the minimum sample size with respect to a two-tailed Student *t* test, considering: (1) a difference for the slope of the dose response curve to Ach to be detected between controls and migrainers as $\delta \geqslant 0.25$ mL/(dL·min·μg); (2) a value of SD = 0.156 mL/(dL·min·μg); and (3) a type I error probability = 0.05 and a power = 0.90. This results in a minimum sample size of $n = 9$ subjects for group. Since no data are available in the literature regarding the response to norepinephrine of FBF in migrainers, we decided to increase the number of subjects to be recruited to 11 per group.

Statistical analysis

The differences in clinical and metabolic parameters between the three study groups were analyzed by the unpaired Student's *t* test with Bonferroni correction for multiple comparisons. Vascular reactivity data are expressed as absolute values of FBF. Comparison between migraine and control subjects was performed by a two-way analysis of variance for repeated measures (General Linear Model, version 13.0, SPSS Inc., Chicago, IL, United States) and Least Significant Difference test was used for post hoc analysis. Comparison between baseline and NE infusion data was performed by the paired Student's *t* test. Results are expressed as mean ± SE.

RESULTS

The baseline values of FBF were similar in the three groups (Figure 1). Infusion of ACh, an endothelium-dependent vasodilator, elicited a progressive vasodilatory response in all groups ($P < 0.001$). However, in patients with migraine studied during the interictal period, FBF response was lower than that of control subjects ($P < 0.05$). In contrast, patients studied during the headache attack showed a more intense response to Ach infusion ($P < 0.02$ *vs* M; Figure 1). In response to the highest dose of Ach, FBF rose to 19.6 ± 3.1, 8.8 ± 2.4, and 22.9 ± 2.2 mL/dL per minute in controls and migraine patients without or with headache attack, respectively ($P = 0.036$ for M group *vs* C and $P < 0.02$ *vs* MH). The response to ACh was also analyzed using the slope of the dose-response curves. In the patients with migraine without headache the average slope was markedly less steep than in controls (0.11 ± 0.05 and 0.31 ± 0.05 mL/(dL·min·μg), respectively; $P = 0.03$). In contrast, the slope of the dose response curve to Ach in migraine patients during the headache attack was similar to controls (0.39 ± 0.04 mL/(dL·min·μg), $P < 0.02$ *vs* M, P = NS *vs* C).

The dose-response curve to NP, an NO donor directly acting on VSMCs, is shown in Figure 1. As compared with controls, patients with migraine without headache showed a significantly lower response at all infusion rates ($P = 0.004$ *vs* C). In contrast, patients with migraine during the headache attack showed a response to NP similar to controls and markedly increased when compared to migrainers studied during the interictal period (P = NS *vs* C and $P = 0.002$ *vs* M). The maximal response of FBF to NP was 22.2 ± 1.9, 12.8 ± 1.9 and 26.6 ± 3.8 mL/dL per minute in controls and migraine patients without or with headache attack, respectively ($P < 0.02$ for M group *vs* C and MH). The response to NP was also analyzed using the slope of the dose-response curves. In the patients with migraine without headache the average slope was markedly less steep than in controls [1.05 ± 0.19 and 1.96 ± 0.20 mL/(dL·min·μg), respectively; $P < 0.01$]. In contrast, the slope of the dose response curve to NP in migraine patients during the headache attack was similar to controls [2.29 ± 0.29 mL/(dL·min·μg), $P < 0.02$ *vs* M, $P > 0.05$ *vs* C].

In Figure 2, we report the dose response curves to

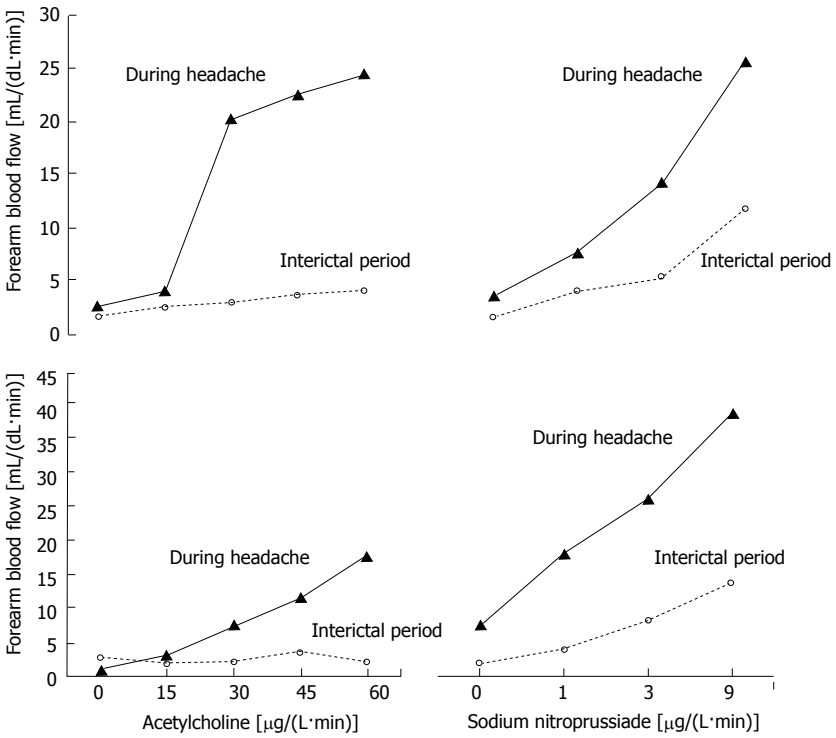

Figure 2 Individual forearm blood flow response to infusion of acetylcholine or sodium nitroprusside into the brachial artery in two patients with migraine studied during or free from headache.

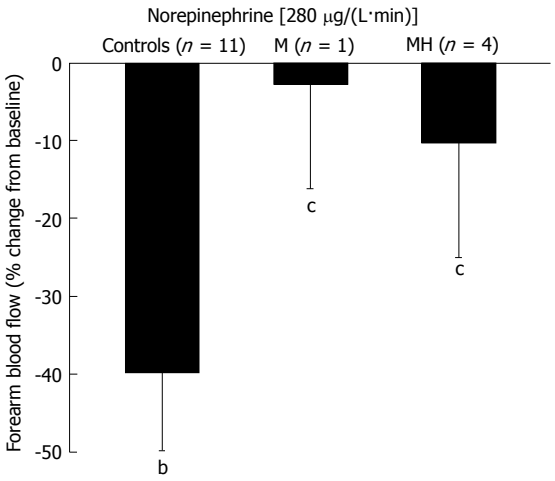

Figure 3 Forearm blood flow response to infusion of norepinephrine at the rate of 280 μg/L per minute into the brachial artery in patients with migraine during or free from headache, and control subjects. The patients with migraine were studied during the interictal period (group M) or the headache attack (group MH). Data (mean ± SE) were analyzed by paired *t* test *vs* baseline and unpaired *t* test among groups. $^{b}P < 0.01$ *vs* baseline; $^{c}P < 0.05$ *vs* controls.

Ach or NP infusions for the two patients who gave us a unique opportunity to study the phenomenon both during the interictal period and the headache attack. It is striking how potently the response to both Ach and NP was enhanced by the headache attack as compared with the basal response.

Figure 3 shows the data on the effect of NE infusion. FBF was reduced by 1.19 ± 0.17 mL/dL per minute by NE infusion in C (-40% ± 6%, $P = 0.001$ *vs* baseline). In contrast, NE infusion was unable to elicit a vasoconstrictory response in migraine patients either when studied in the headache-free period or during the headache attack (-0.29 ± 0.23 and -0.66 ± 0.69 mL/dL per minute, accounting for a reduction by 3% ± 13% and 10% ± 15% in M and MH, respectively; $P > 0.05$ *vs* baseline and $P < 0.05$ *vs* C).

DISCUSSION

In the present study, we measured vascular reactivity in patients with migraine without aura either during the interictal period or during a headache attack. We confirm our previous finding that patients with migraine studied in the interictal period suffer from impaired vasodilation in response to acetylcholine and sodium nitroprusside. Furthermore, we extend our observation to the vasoconstrictory response to an adrenergic agonist and show that in these patients a defect in the response to NE also coexists. In addition, we studied a group of patients with migraine during the headache attack. Under these circumstances, the marked defect in vasodilation completely reverted, as documented by the normal responses to Ach and NP. In contrast, the vasoconstrictory response to the sympathetic agonist NE remained blocked.

Although patients with migraine during the headache-free period have a normal postural increase compared to control subjects, they are also characterized by a 50% reduction of absolute circulating NE levels in both supine and orthostatic position[12-14], suggesting an abnormal regulation of the sympathetic nervous system activity. Because in these patients NE intravenous administration

induces more prolonged elevation in blood pressure (BP) than in control subjects, an adrenergic receptor supersensitivity was invoked[12]. In addition, the observation of greater and more prolonged BP response to phenylephrine led to the conclusion that an alpha-adrenergic receptor increased sensitivity was implicated[15]. However, it must be considered that the intravenous administration of NE or phenylephrine does not trigger only the receptors localized in the vessel wall, but can potentially unleash more complex, systemic mechanisms. In addition, indirect data obtained by administering the beta-blocker propranolol to patients with migraine, suggested that beta receptors distribution in the radial artery might be abnormal[16]. To the best of our knowledge, the current study is the only one in which NE is directly infused into the brachial artery in patients with migraine. The agonist was infused locally in very small amounts that were unable to induce systemic perturbations of NE circulating levels, given its very short half-life. This is also supported by the lack of any change in FBF of the contralateral arm in control subjects or in systemic BP (data not shown). Therefore, under the current circumstances, any confounding involvement of indirect sympathetic mechanisms secondary to changes in circulating NE levels can be excluded, and the observed effects only reflect the direct action of NE on the forearm resistance vessels. It must be also stressed that NE stimulates both the alpha-receptors (vasocostrictory response) and the beta-receptors (vasodilatory response). Therefore, the response to NE infusion represents the net balance of two opposite forces. In normal subjects, however, the vasoconstrictory response clearly prevails, whereas in patients with migraine the resistance vessels are unable to respond to the sympathetic agonist. We cannot dissect whether the block of the vasoconstrictory response in migraine patients is due to a relative reduction of the NE effect through the alpha-receptors or an increase of the beta-receptor response or a combination of the two. Unfortunately, no information is available in the literature regarding the adrenergic receptor relative distribution in the cell membranes of peripheral arterial vessels.

Given the inability of VSMCs to relax in response to endothelial NO in the interictal period, were the vasoconstrictory ability of NE intact rather than severely impaired, patients with migraine would experience constantly raised vascular resistance and systemic hypertension. Therefore, the defective NE-induced vasoconstriction observed in patients with migraine might represent a chronic hemodynamic adjustment to compensate for the reduced vasodilatory response to NO by the VSMCs. The hypothesis of a compensatory down-regulation of the vasoconstrictory response of VSMCs would be well in agreement with the generalized reduction of sympathetic nervous system activity previously reported in migraine patients[12].

We have previously demonstrated the presence of impaired vascular reactivity in patients with migraine during the interictal period, entirely attributable to VSMCs dysfunction[4,5]. The impaired vasodilatory response to Ach was associated with normal NO production by endothelial cells. Moreover, the hemodynamic response to NP, a direct stimulator of VSMCs, was markedly impaired. In the current study, we confirm the observation that in patients with migraine studied free from headache the response to Ach and NP is severely impaired. Data in the literature have provided divergent results, either when flow-mediated dilation or forearm perfusion technique associated with plethysmography or other approaches were used[17-23]. In previous studies, migraine patients have not been discriminated with regard to the presence of aura and different vascular beds (micro- *vs* macrovascular and intra- *vs* extra-cranial) have been explored. The possibility exists that the two types of migraine might be characterized by a different vascular reactivity. Accordingly, the cardiovascular risk profile of the two types of migraine appears to be different, suggesting that the intimate mechanism of vascular function diverge and our findings lend support to the hypothesis that migraine without aura is not associated with dysfunction of the endothelial cells potentially triggering atherosclerotic processes[1,2,24-28].

In patients with migraine during the headache attack, basal FBF was similar to that measured off the pain attack and to that of control subjects. In contrast, the impaired vasodilation in response to the infusion of Ach and NP of the interictal period was fully restored. Taken together, our data indicate that the patients with migraine in the interictal period have a reduced sensitivity of their VSMCs to the NO released by the endothelial cells. In contrast, during the headache attack, the response to NO, as suggested by the NP infusion data, becomes similar to that measured in the controls, indicating a restored sensitivity of VSMCs. We have previously demonstrated that during Ach infusion in patients with migraine during the interictal period the release of NO is normal and that endothelial function is intact[4,5]. Interestingly, when in previous studies systemic nitroglycerin, an NO donor, was administered to patients with migraine, an approach used to induce headache in migraine patients or to measure non-endothelial-mediated vasodilation, an increased sensitivity to NO was demonstrated in intra-and extracranial vessels[19-25]. Further studies are necessary to clarify the intriguing issue about the mechanisms that come into play during the migraine attack to redirect VSMC sensitivity towards normal.

Study limitations

A potential limitation of the current study is the small sample of patients studied during the headache attack. The forearm perfusion technique requires the cannulation of the brachial artery and, in general, this approach precludes the possibility to study large patients groups. In addition, it is quite hard to perform a forearm study that lasts several hours in patients who during the headache attack abstain from taking analgesics for the potential drug impact on vascular reactivity.

As compared with ultrasonographic techniques, such as the flow mediated dilation, the forearm technique bears much less variability. Indeed, the effects observed in our patients during the headache attack were very clear-cut, providing solid statistics despite the small sample. A final consideration is that we studied patients with spontaneous headache attack. This is a point of great strength of our work, since confounding factors linked to experimental stimuli used to trigger a headache attack were not operative.

In conclusion, patients with migraine without aura studied in the interictal period are characterized by VSMCs impaired ability to relax in response to NO and to contract in response to NE. We hypothesize that the two defects compensate for each other and this provides for the maintenance of normal vascular resistance and blood pressure homeostasis. In contrast, during the headache attack, due to mechanisms still unclear, the VSMCs regain their ability to respond to NO, but remain unresponsive to NE. Such differential effect of the migraine attack is not surprising, given that NO and NE activate different intracellular signaling pathways in VSMCs.

COMMENTS

Background

Migraine has been associated with an increased risk of cardiovascular events. However, authors have recently demonstrated that patients with migraine without aura, studied during the interictal period, do not present peripheral endothelial dysfunction, which is classically associated with a worse cardiovascular risk profile, but rather an abnormal relaxation of the vascular smooth muscle cells (VSMCs). It is unclear whether the inability of VSMCs to respond to vasodilators is an isolated abnormality or, rather, reflects a more complex hemodynamic alteration and whether persists during the headache attack.

Research frontiers

The demonstration that the vascular abnormality observed in migraine are not due to endothelial dysfunction, but rather to VSMCs impairment might result in novel therapeutic approachs. Furthermore, life style intervention useful to improve endothelial dysfunction might be ineffective to correct the defects in VSMCs dysfunction.

Innovations and breakthroughs

This is the first study to demonstrate that patients with migraine without aura studied in the interictal period are characterized by VSMCs impaired ability to relax in response to nitric oxide (NO) and to contract in response to norepinephrine (NE). Authors hypothesize that the two defects compensate for each other and this provides for the maintenance of normal vascular resistance and blood pressure homeostasis. In contrast, during the headache attack, due to mechanisms still unclear, the VSMCs regain their ability to respond to NO, but remain unresponsive to NE.

Applications

Elucidation of the vascular response in patients with migraine both free of and during the headache episode would be of great importance to the authors' understanding of the mechanisms involved in the pathogenesis of the disease and to better design appropriate therapeutic approaches.

Terminology

Vascular dysfunction is mainly attributable to endothelial dysfunction. In migraine patients without aura, the inability of VSMCs to respond to nitric oxide can be considered a novel mechanism of vascular dysfunction.

Peer review

The authors studied peripheral vascular function in patients with migraine without aura. the patients were studied both during and free of the headache attack. Vascular dysfunction in these patients involves both impairment of vasodilation and vasoconstriction, both due to an abnormal functioning of VSMCs. The results are very interesting.

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BRIEF ARTICLE

Low-dose CT coronary angiography using iterative reconstruction with a 256-slice CT scanner

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Abstract

AIM: To explore whether computer tomography coronary angiography (CTCA) using iterative reconstruction (IR) leads to significant radiation dose reduction without a significant loss in image interpretability compared to conventional filtered back projection (FBP).

METHODS: A consecutive series of 200 patients referred to our institution to undergo CTCA constituted the study population. Patients were sequentially assigned to FBP or IR. All studies were acquired with a 256-slice CT scanner. A coronary segment was considered interpretable if image quality was adequate for evaluation of coronary lesions in all segments ⩾ 1.5 mm.

RESULTS: The mean age was 56.3 ± 9.6 years and 165 (83%) were male, with no significant differences between groups. Most scans were acquired using prospective ECG triggering, without differences between groups (FBP 84% *vs* IR 82%; $P = 0.71$). A total of 3198 (94%) coronary segments were deemed of diagnostic quality. The percent assessable coronary segments was similar between groups (FBP 91.7% ± 4.0% *vs* IR 92.5% ± 2.8%; $P = 0.12$). Radiation dose was significantly lower in the IR group (2.8 ± 1.4 mSv *vs* 4.6 ± 3.0 mSv; $P < 0.0001$). Image noise (37.8 ± 1.4 HU *vs* 38.2 ± 2.4 HU; $P = 0.20$) and signal density (461.7 ± 51.9 HU *vs* 462.2 ± 51.2 HU; $P = 0.54$) levels did not differ between FBP and IR groups, respectively. The IR group was associated to significant effective dose reductions, irrespective of the acquisition mode.

CONCLUSION: Application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose.

Key words: Low-dose computer tomography coronary angiography; Iterative reconstruction

Core tip: A consecutive series of 200 patients referred to our institution to undergo computer tomography coronary angiography (CTCA) were sequentially assigned to filtered back projection (FBP) or iterative reconstruction (IR). The percent assessable coronary segment was similar between groups. Radiation dose was significantly lower in the IR group. Image noise and signal density levels did not differ between FBP and IR groups. The IR group was associated to significant effective dose reductions, irrespective of the acquisition mode. Our findings suggest that application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose.

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INTRODUCTION

With a large body of evidence accumulated within the past decade, computer tomography coronary angiogra-

phy (CTCA) has earned a role in diagnostic algorithms of patients at intermediate risk of coronary artery disease[1-3]. However, the high effective radiation dose related to CTCA scans remains a limitation and has been the foundation of most of the criticisms received. Indeed, the recently published Prospective Multicenter Study on Radiation Dose Estimates of Cardiac CT Angiography I and Ⅱ (PROTECTION I and Ⅱ) reported a wide range of effective radiation doses according to the acquisition technique, therefore encouraging the application of dose reduction techniques such as prospective ECG-triggering, tube current modulation, and/or high pitch helical scanning[4,5] .

In the past few years, iterative reconstruction (IR), an alternative to conventional image reconstruction filtered back projection (FBP), has gained interest in order to attempt to attenuate the increase in image noise related to tube current modulation and low tube voltage acquisitions[6]. IR has the ability to reduce image noise by iteratively comparing the images obtained to a modeled projection. Thus, it can be used to reconstruct images with similar image quality despite a significant reduction in tube current, resulting in a reduction in overall radiation dose. This has particular interest in CTCA studies in order to attempt to overcome the main limitation of the technique for cardiovascular purposes[7-11]. The aim of our investigation was to explore whether CTCA using IR can achieve a substantial effective dose reduction without a significant loss in image interpretability.

MATERIALS AND METHODS

The present was a single-centre, investigator-driven, observational, prospective study that aimed to explore whether IR of CTCA scans leads to a significant radiation dose reduction without impairment of image interpretability. For that purpose, a consecutive series of patients referred to our institution to undergo CTCA constituted the study population. Patients were assigned to FBP or, sequentially, to IR. Inclusion criteria included adult patients (≥ 18 years), without a history of contrast related allergy, renal failure, or hemodynamic instability, that were referred to CTCA to exclude coronary artery disease. Baseline heart rate, arrhythmia, or body mass index did not impact the enrollment decision. Patients with pacemakers or implantable devices were excluded. The institution's Ethics Committee approved the study protocol, which complied with the Declaration of Helsinki, and written informed consent was obtained from all patients.

CTCA acquisition

All studies were acquired with a 256-slice CT scanner (Philips Healthcare, Cleveland). Patients with a heart rate of > 65 beats/min received 50 mg oral metoprolol one hour prior to the scan or 5 mg intravenous propralonol if needed in order to achieve a target heart rate of less than 60 bpm. A dual phase protocol with 70 mL of iobitridol (Xenetix 350^{TM}, Guerbet, France) followed by a 50-mL saline flush was injected through an arm vein after administration of 0.4 mg of sublingual nitroglycerin. A bolus tracking technique was used to synchronize the arrival of contrast at the level of the coronary arteries with the start of the scan. Scanning parameters were as follows. Rotation time 270 ms; tube voltage in FBP with body mass index (BMI) < 25 kg/m^2: 100 kV, BMI > 25 kg/m^2: 120 kV; tube voltage in IR with BMI < 20 kg/m^2: 80 kV, BMI 20-30 kg/m^2: 100 kV, BMI > 30 kg/m^2: 120 kV. Tube current was adjusted according to the scan protocol and BMI (range 170-1200 mA). Prospective ECG-triggering axial scanning was used when possible based on heart rate. ECG-based tube current modulation was performed for all helical studies.

CTCA analysis

Image analysis and coronary segment interpretability were assessed by consensus of two experienced level 3-certified coronary CTA physicians using dedicated software (Comprehensive Cardiac Analysis, Philips Healthcare) on a CT workstation (Brilliance Workspace, Philips Healthcare, Cleveland, OH, United States), blinded to the acquisition mode. A coronary segment was considered interpretable if image quality was adequate for evaluation of coronary lesions in all segments ⩾ 1.5 mm.

Slice CT images were reconstructed preferably at end diastole using axial planes, multiplanar reconstructions, and maximum intensity projections at 1 mm slice thickness. Image noise and signal density for both FBP and IR (iDose^{TM}, level 5, Philips Healthcare) reconstruction algorithms were evaluated. The signal density and noise were evaluated using standardized regions of interest of 10 mm^2 within the aortic root at the level of the left main coronary artery on axial images, being the signal density defined as the mean Hounsfield units and the signal noise as the mean standard deviation of the signal density. Studies were evaluated using the previously reported 17-segment model, and effective dose radiation estimates were calculated using the dose-length product[12].

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as mean ± SD, or median (25th, 75th percentile) for variables with non-Gaussian distribution. Comparisons between groups were performed using independent Student's *t* test, or χ^2 tests as indicated. We explored correlations between continuous variables using Pearson correlation coefficients. A two-sided *P* value of less than 0.05 indicated statistical significance. Statistical analyses were performed with the use of SPSS software, version 13.0 (Chicago, IL, United States).

RESULTS

A consecutive series of 200 patients referred to undergo CTCA constituted the study population (FBP, *n* = 100) and (IR, *n* = 100). The mean age was 56.3 ± 9.6 years

Table 1 Demographical characteristics, acquisition parameters, radiation dose and image quality

	FBP	IR	*P* value
Age (yr)	55.6 ± 9.1	56.0 ± 10.1	0.67
Male	85 (85)	80 (80)	0.35
Body mass index (kg/m^2)	27.2 ± 2.7	26.3 ± 3.4	0.03
Body mass index ⩾ 30	15 (15)	13 (13)	0.68
Heart rate (bpm)	58.3 ± 7.0	58.2 ± 6.4	0.88
Acquisition technique			
Prospective (axial)	84 (84)	82 (82)	0.71
Retrospective (helical)	16 (16)	18 (18)	
Tube voltage (kV)	119.0 ± 4.4	109.0 ± 10.4	< 0.0001
Percent 80-100 kV	5 (5)	54 (54)	< 0.0001
mAs in prospective	203.1 ± 15.4	195.7 ± 26.8	< 0.0001
mAs in helical	943.2 ± 119.5	870.1 ± 122.8	< 0.0001
Radiation dose (mSv)			
Total	4.6 ± 3.0	2.8 ± 1.4	< 0.0001
Prospective (axial)	3.4 ± 2.4	2.4 ± 0.7	< 0.0001
Retrospective (helical)	10.3 ± 3.9	5.2 ± 1.6	< 0.0001
Image quality			
Attenuation level (HU)	461.7 ± 51.9	462.2 ± 51.2	0.54
Image noise (HU)	37.8 ± 1.4	38.2 ± 2.4	0.20
Signal to noise ratio	12.2 ± 1.4	12.1 ± 1.4	0.28
Coronary assessment (%)	91.7 ± 4.0	92.5 ± 2.8	0.12

Data are expressed as absolute numbers (percentage) or mean ± SD. FBP: Filtered back projection; IR: Iterative reconstruction.

and 165 (83%) were male, with no significant differences between groups. The mean heart rate was 58.3 ± 7.0 bpm for the FBP group and 58.2 ± 6.4 bpm for the IR group (P = 0.88). Patients assigned to IR had a significantly lower body mass index (26.3 ± 3.4 kg/m^2 *vs* 27.2 ± 2.7 kg/m^2; P = 0.03), despite both groups had similar proportion of patients with BMI ⩾ 30 kg/m^2 (Table 1). Most scans were acquired using prospective ECG triggering, without difference between groups (FBP 84% *vs* IR 82%; P = 0.71).

A total of 3198 (94%) coronary segments were deemed of good diagnostic quality. The percent of assessable coronary segments was similar between groups (FBP 91.7% ± 4.0% *vs* 92.5% ± 2.8%; P = 0.12). Image noise (37.8 ± 1.4 HU *vs* 38.2 ± 2.4 HU; P = 0.20) and signal density (461.7 ± 51.9 HU *vs* 462.2 ± 51.2 HU; P = 0.54) levels did not differ between FBP and IR groups, respectively. The median effective radiation dose was 3.35 mSv (interquartile range 2.45-3.35). The IR group was associated to significant effective dose reductions, irrespective of the acquisition mode (helical or axial). Prospective scans with IR exhibited the least radiation doses (Table 1).

We found no significant relationships between radiation dose and the percent of interpretable segments (r = -0.01, P = 0.85). In turn, we found a significant, albeit weak, correlation between the effective radiation dose (mSv) and the signal to noise ratio (r = 0.25, P < 0.001), as well as between the mA and the signal to noise ratio (r = 0.31, P < 0.001).

DISCUSSION

In the past decade, CTCA has rapidly emerged as a non-invasive diagnostic tool with the ability to identify obstructive coronary disease, and has gained a role in different risk stratification and diagnostic algorithms. Moreover, it has demonstrated a significant prognostic value independent of traditional risk factors and functional tests[13-17]. Notwithstanding, one of the main challenges of CTCA is the relatively high radiation dose related to the technique[18-20]. Several different strategies have been proposed in order to attempt to decrease effective radiation dose, including tube modulation and prospective (axial) scanning[21-24]. One of the latest developments aimed at lowering dose radiation is IR.

The main finding of our investigation was that compared to conventional FBP, IR in CTCA preserved image interpretability despite a significant reduction in radiation dose. Compared to FBP, IR achieved a 50% dose reduction in helical scans, and a 29% dose reduction in prospective scans, being these results within the range of previous findings in different populations[7]. Such significant reduction might be attributed to the fact that more than half of the IR scans were performed using low voltage (80-100 kV), whereas within the FBP group only 5% of the scans were performed using 100 kV.

Tube current reduction with FBP, a commonly used dose reduction strategy, leads to an increment in image noise. In turn, IR consists in synthesized projection data that are compared to real data in an iterative manner, resulting in a significant reduction of image noise[6]. By reducing image noise, IR allows tube current reduction and, consequently, effective dose reduction. This explains the significantly larger dose reduction in helical compared to axial scans using IR.

A number of limitations must be recognized. Despite patients were sequentially assigned to FBP or IR, randomization was not performed, leading to an expected significantly higher body mass index of FBP patients, although it should be stressed that no significant differences were observed regarding the number of obese patients (BMI ⩾ 30 kg/m^2). Furthermore, coronary angiography was not performed in order to evaluate the diagnostic accuracy of each technique; therefore our results should do not allow making assumptions in this regard and should be limited to the image interpretability.

Application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose, being this mainly attributed to the use of lower voltage scans.

COMMENTS

Background

In the past decade, computer tomography coronary angiography (CTCA) has rapidly emerged as a non-invasive diagnostic tool with the ability to identify obstructive coronary disease, and has gained a role in different risk stratification and diagnostic algorithms. Moreover, it has demonstrated a significant prognostic value independent of traditional risk factors and functional tests.

Research frontiers

Several different strategies have been proposed in order to attempt to decrease effective radiation dose, including tube modulation and prospective (axial) scanning. One of the latest developments aimed at lowering dose radiation is iterative reconstruction (IR).

Innovations and breakthroughs

The main finding of this investigation was that compared to conventional filtered back projection, IR in CTCA preserved image interpretability despite a significant reduction in radiation dose.

Applications

Application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose, being this mainly attributed to the use of lower voltage scans.

Peer review

In principle, it is a solid work on a state-of-the-art scientific topic. However, there are numerous minor typing errors as well as grammatical mistakes throughout the entire manuscript that need to be corrected prior to possible publication.

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CASE REPORT

Left ventricular myxoma: Missed *vs* metastatic

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Abstract

Left ventricular myxomas account for 2.5% of all cardiac myxoma cases. There are very few case reports on left ventricular myxoma (LVM) presented after complete surgical resection of left atrial myxoma. Here we report a case of a 58-year-old male presented to the hospital for transient limb weakness, numbness and dysarthria. Magnetic resonance image of the brain revealed multiple thromboembolic cerebrovascular accidents. Transthoracic echocardiogram (TTE) revealed a left atrial myxoma. It was resected completely with good surgical margins. After one and half year he started having dizziness, and transient right sided weakness. Computer tomography scan of the head revealed a progression of thromboembolic disease. TTE revealed a LVM that was confirmed by transesophageal echocardiogram. It was resected with good surgical margins 3 wk after recurrent cerebrovascular accident.

Key words: Left ventricular myxoma; Metastatic myxoma; Left atrial myxoma; Recurrent myxoma

Core tip: Left ventricular myxoma (LVM) after surgical resection of left atrial myxoma is very rare. Etiologies for recurrent LVM after left atrial myxoma resection are incomplete surgical resection, metastasis, totipotent multicentricity and missed. Here we are describing a case that was probably a metastatic LVM as it is uncommon statistically for it to be a recurrent myxoma in the left ventricle after complete resection from left atrium. If there is a progression of the cerebral hemorrhagic lesions it would confirm our diagnosis of the metastatic process.

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INTRODUCTION

Left ventricular myxomas account for 2.5% of all cardiac myxoma cases. There are very few case reports on left ventricular myxoma (LVM) presented after complete surgical resection of left atrial myxoma.

CASE REPORT

A 58-year-old male with a past medical history of hypertension and diabetes went to see a primary care physician with complaints of multiple episodes of transient limb weakness, numbness and dysarthria lasting less than 1 h. A magnetic resonance image (MRI) of the brain was obtained revealing multiple bilateral, supra, infratentorial, cortical and sub-cortical infarctions in watershed areas consistent with multiple thromboembolic strokes. Upon admission to the hospital, routine lab work (complete blood count, complete metabolic profile, lipid panel, thyroid function tests, coagulation studies), and carotid doppler failed to reveal any significant abnormalities other than poorly controlled diabetes, and a serum cholesterol of 113 mg/dL. A transthoracic

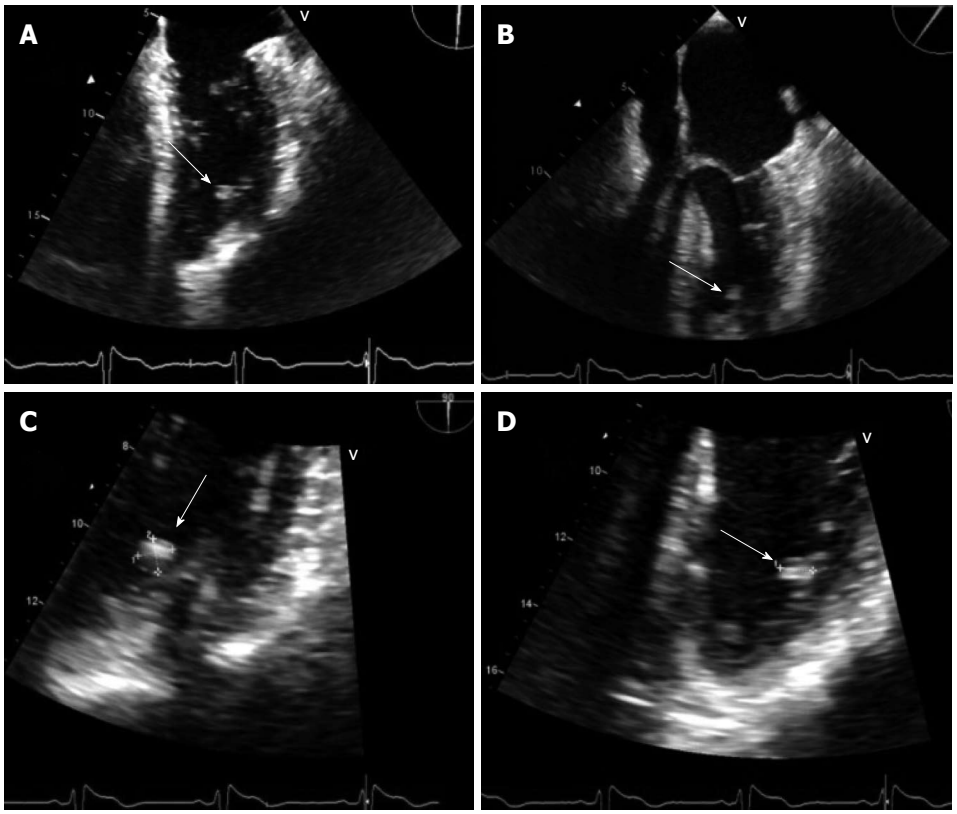

Figure 1 Transesophageal echocardiogram. A: Mid esophagus view of the transesophageal echo (TEE) revealing left ventricular myxoma; B: TEE, four chamber view showing Left ventricular myxom; C: Magnified view showing a myxoma, size 1 cm x 2 cm; D: Magnified view showing a myxoma of 1 cm in horizontal direction. Showing its close proximity to trabecular muscles.

echocardiogram (TTE) demonstrated a 3.5 cm homogenous mass in the left atrium with mild dilation and a normal left ventricle (LV). A pre-operative coronary angiogram failed to reveal any significant coronary artery disease. The left atrial mass was subsequently resected with good surgical margins and a small incidental patent foramen was successfully closed. Final pathology of the mass confirmed it to be a transparent myxoma. Patient was discharged home in stable condition and did well for few months without any major symptoms other than generalized weakness.

Nearly one year later the patient was diagnosed with generalized partial seizures following an episode of right-side weakness and was started on antiepileptic medication, which he refused to take. Over the next 2-3 wk he experienced two more episodes of right sided weakness associated with dizziness and admitted for non-adherence with medication. He then presented to our institution with near syncope and atypical chest pain. Routine cardiac evaluation was negative and he was discharged after 2 d. Later, he again presented to the emergency department, this time for intermittent right-sided weakness and transient dizziness. A computer tomography (CT) scan of the head revealed interval progression of thromboembolic disease. An MRI confirmed the CT scan findings; multiple small hemorrhagic lesions were subsequently identified and later confirmed by cerebral angiography. Multiple mycotic aneurysms were ruled out by blood cultures. TTE was performed and it revealed a 0.94 cm × 0.74 cm mass attached to lateral wall of LV. A transesophageal echo (TEE) then confirmed the presence of a mobile, round homogenous mass attached to the anterolateral wall of the LV (Figure 1). Three weeks after the recurrent cerebrovascular accident (CVA) the mass was resected. Initially, a left atrial and then aortic approach was attempted to locate and isolate the mass. Both approaches were unsuccessful. Eventually, an anterolateral approach located the mass buried in trabecular muscles of the posteroapical area without any valvular attachment. Excision was done without a difficulty. Pathology confirmed a LVM and the patient was discharged 1 wk later.

DISCUSSION

Primary cardiac tumors are rare and have an average incidence of 0.02%[1,2]. Of these, cardiac myxomas account for 88% of cases and are primarily benign in nature[3]. Myxomas constitute 0.23% of all the open heart surgical procedures[2]. The most common location for myxoma is the left atrium followed by the right atrium. A biatrial location is occasionally seen but all other locations are quite uncommon[3]. Myxomas found in the left ventricle account for only 2.5% of cases[3,4]. Myxomas are primarily sporadic while familial cases

constitute up to 10%[2]. Familial myxomas have unusual locations and recurrences, and some are associated with Carney's Complex (myxomas of the heart, and skin, spotty skin pigmentation, blue nevi, and endocrine over activity)[3].

Most myxomas are either asymptomatic or produce non-specific symptoms such as malaise, fatigue or heart failure symptoms. Embolic events are one of the major clinical presentations of myxomas. The risk of embolization is mostly determined by the morphology of the myxoma rather than its size. As in this case, semi-transparent polyploid myxomas carry a high risk for embolization compared to round myxomas[2]. Valvular myxomas carry high risk of embolization[2,5]. This variation in prevalence of emboli seen in published series can be explained by the fact that valvular myxomas carry a high risk of embolization compared to myxomas located elsewhere. Even though the final embolic destination is commonly the cerebrovascular territory other arterial territories such as the pulmonary or coronary circulation can be involved[1-4] .

The other common mechanisms of symptom production with myxomas are mechanical obstruction and arrhythmias when cardiac conducting system is involved[1-4].

Most myxomas are diagnosed with TTE, but are often missed when located in unusual places. In this case, locating the LV myxoma was difficult both on TTE and intraoperatively was difficult due to its concealment by trabecular muscle. TEE and MRI are best studies for localizing and characterizing myxoma. In all cases of suspected myxomas TEE should be performed[3].

Surgical resection is the treatment of choice for myxomas and should be performed as early as possible as there is a risk of embolization. In the presence of a recent CVA, surgical resection may be delayed for up to 4 wk and should be performed on pump with systemic heparinization[6]. Even though surgical technique is changing constantly, resection should include clean surgical margins to reduce the likely of recurrence[7,8]. There are very few cases myxoma has recurred in the LV after the resection of the tumor in LA[7]. In this case the myxoma recurred in the LV one year after the initial resection. The index TTE and the initial surgery did not give reason to suspect a LV myxoma. Possible mechanisms for the LVM in this case are recurrence (incomplete surgical resection or new growth of reserve cell or implantation from original tumor), or missed during initial evaluation, or metastasis. During the index diagnosis, neither MRI nor TEE was performed thus raising the possibility of LV myxoma was initially missed. However, though limited, neither TTE nor cardiac cauterizations have identified any LVM.

Recurrent myxomas often grow faster than primary tumors and can occur in 3% of sporadic cases and 20% of familial cases[9]. Incomplete surgical margins is one of the major reason to have recurrences[7]. The tumor recurs near the original resection site in 85% of cases with an atrial location in 97%[7]. In this case initial sporadic myxoma had good surgical margins during the index surgical resection. The site of recurrence however, was LV making the recurrence secondary to incomplete resection much less likely. Metastatic seeding of myxoma cells is well described in the literature. The malignant nature of myxomas is defined based on growth rate behavior rather than histological features. Malignant myxoma may be identified by high interleukin 6 levels, presence of constitutional symptoms, elevated gamma globulins, and a high erythrocyte sedimentation rate (ESR) after complete resection of the tumor[9]. In this case, the patient reported some constitutional symptoms malaise and generalized weakness but lack of specificity of these symptoms and the failure to obtain a post-operative ESR make supporting malignant potential of the tumor problematic. Multiple cerebral hemorrhagic lesions (probably secondary to small aneurysms) were noted in this patient and may support the idea of metastatic process. A malignant nature may be confirmed in future if the tumor is subsequently found at other distant sites. We excluded the probability of familial disease by taking a good family history, and there were no signs or symptoms of Carneys Complex[9]. At this time, it is believed that this recurrent LV myxoma case is most likely due to a metastatic process. Careful follow up has been planned for this patient to monitor for recurrence of myxoma as well as any worsening of neurological symptoms.

Follow up echocardiography is required to evaluate for recurrence. It is highly crucial in familial cases and in those cases where good surgical margins cannot be achieved[6].

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CASE REPORT

Medical management of connector pin thrombosis with the Amplatzer cardiac plug left atrial closure device

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Abstract

Transcatheter closure of the left atrial appendage with the Amplatzer™ cardiac plug device and double antiplatelet treatment for 3 mo has become an alternative treatment for patients with atrial fibrillation at high embolism risk and contraindications for chronic oral anticoagulation. The inadequate implantation of the left atrial appendage closure device and the discontinuation of double antiplatelet therapy are well-known as factors related to device thrombosis. Nevertheless, device thrombosis after adequate implantation requiring surgical treatment or restarting chronic oral anticoagulation has been reported and can reach 15% of patients. The connector pin thrombosis of the Amplatzer™ cardiac plug, despite a good adherence to antiplatelet treatment, has been recently described as a potential mechanism for device thrombosis. Our clinical case reports the management of this condition for the first time, showing that the early detection of thrombotic complications by transesophageal echocardiography permits solving this serious complication with medical treatment only.

Key words: Atrial fibrillation; Oral anticoagulation; Left atrial appendage closure; Amplatzer cardiac plug; Device thrombosis

Core tip: Percutaneous closure of the left atrial appendage has become an alternative treatment for patients with atrial fibrillation and with contraindications for chronic oral anticoagulation. Recently, the first case of connector pin thrombosis of the Amplatzer™ cardiac plug device for percutaneous left atrial appendage closure was described. Our work describes the management of this serious problem for the first time.

Fernández-Rodríguez D, Vannini L, Martín-Yuste V, Brugaletta S, Robles R, Regueiro A, Masotti M, Sabaté M. Medical management of connector pin thrombosis with the Amplatzer cardiac plug left atrial closure device. *World J Cardiol* 2013; 5(10): 391-393 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i10/391.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i10.391

INTRODUCTION

Transcatheter closure of the left atrial appendage (LAA) with the Amplatzer™ cardiac plug (ACP) device has become an alternative treatment for patients with atrial fibrillation (AF) at high embolism risk and with contraindications for chronic oral anticoagulation (OAC)[1,2]. The inadequate implantation of ACP and the discontinuation of double antiplatelet treatment (DAPT) are well-known as factors related to device thrombosis[1,3]. Furthermore, device thrombosis after adequate implantation, requiring surgical treatment or restarting chronic OAC, has been reported[4,5] and can reach 15% of patients[6]. The connector pin thrombosis of the ACP, despite a good adherence

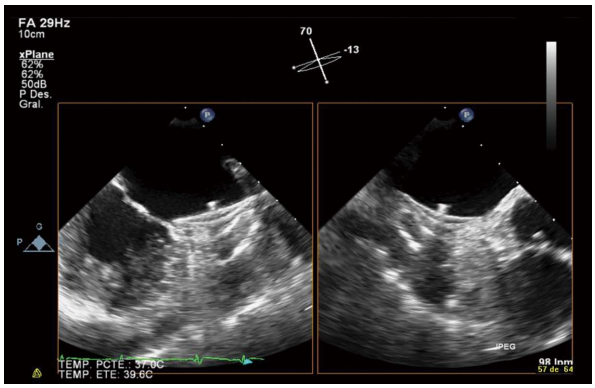

Figure 1 Forty-five day control. Transesophageal echocardiography two-dimensional X-plane processing, simultaneous visualization at 70° (left) and 13° (right). Successful Amplatzer™ cardiac plug implantation: completely covering the left atrial appendage ostium by the occluder disk and no evidence of device thrombosis.

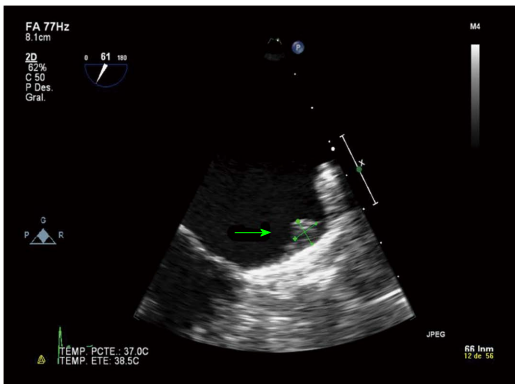

Figure 2 Four month control. Transesophageal echocardiography two-dimensional image. Adequate covering of the left atrial appendage ostium but little thrombus (7 mm × 7 mm) is observed at the top of the button of the Amplatzer™ cardiac plug.

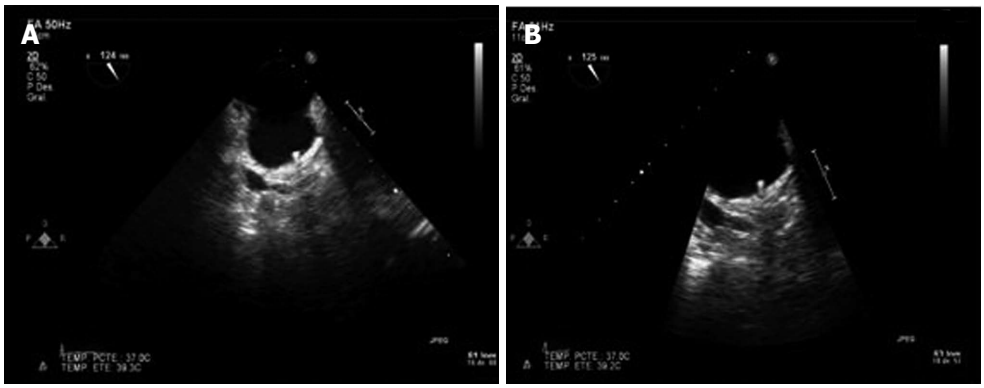

Figure 3 Transesophageal echocardiography two-dimensional image. A: Control after 2 wk of intravenous sodium heparin treatment. Complete resolution of button thrombosis and correct device positioning; B: 6 mo control. Correct device positioning and absence of button thrombosis.

to antiplatelet therapy, has been recently described as a potential mechanism for device thrombosis[7]. The aim of this work is to describe the management of this serious complication after ACP device implantation.

CASE REPORT

A 79-year-old woman with ischemic heart disease, hypertension and diabetes mellitus presented with paroxysmal AF. The patient was under OAC because of a high embolism risk (CHADS2 score of 4 points) but had multiple admissions because of gastrointestinal bleeding (GIB) of unknown cause, despite an intensive etiological study. To avoid long-term OAC, a percutaneous closure of the LAA with a 26-mm ACP device was performed and the patient was discharged under DAPT (aspirin 100 mg and clopidogrel 75 mg) until the 6th month. The post procedural transesophageal echocardiography (TEE) and the 45 d TEE revealed correct device positioning and the absence of thrombosis of the ACP (Figure 1). The patient remained asymptomatic with the absence of any GIB. The 4 mo transthoracic echocardiography (TTE) demonstrated correct device positioning without thrombotic complications but the 4 mo TEE detected a thrombus over the connector pin of the ACP despite the DAPT (Figure 2). Intravenous anticoagulation with heparin was started and TEE 2 wk later showed thrombosis resolution (Figure 3A). The patient continued with DAPT for two more months. The 6 mo TEE showed the absence of thrombus (Figure 3B), allowing the withdrawal of clopigrel. The 12 mo TTE confirmed the thrombus resolution and the patient remained uneventful, with no GIB or cardioembolic events after 2 years.

DISCUSSION

Four major points about thrombosis of the ACP could be drawn from our report. Firstly, the incomplete endothelization of the connector pin of the ACP during the initial 6 mo can contribute to the development of thrombosis of the ACP device. Our clinical case is in accordance with the first description of the connector pin thrombosis in correctly implanted ACP devices[7]. For that reason, a second generation of the ACP (ACP 2 or Amulet™) with a modified connector pin has been designed[8]. Secondly, the role of TEE and TTE in detecting device-related complications remains controversial[1]. The correct positioning can be detected with both techniques

but TEE is the only method that permits the correct diagnosis of residual or emerging device thrombosis. So, the strict monitoring with TEE is mandatory until the 6th month because of the considerable proportion of device thrombosis. Thirdly, recommended antiplatelet therapy for prevention of thrombotic events varies with the type of device used for transcatheter closure of the LAA. The ACP manufacturer recommends DAPT for 3 mo, based on porcine models[1], but button thrombosis in ACP successfully implanted devices in humans beyond 3 mo suggests the possibility of extending the DAPT until the 6th month with complete exclusion of thrombotic complications by TEE. For these reasons, we recommend a strict echocardiographic follow-up protocol in order to detect any thrombotic complication early (1 d, 45 d, 3 mo and 6 mo TEE and 12 mo TTE). Fourthly, the case illustrates the adequacy of our management of thrombotic complications of ACP. After ACP implantation, DAPT is administered and anticoagulation is stopped due to the contraindication of long-term OAC. If thrombotic complications are detected by a strict TEE monitoring during the follow-up, the early initiation of intravenous anticoagulation can remove the thrombus, preventing serious thrombotic complications if not detected early and avoiding the need of long-term OAC in patients at high risk of complications under OAC treatment.

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Circle of Willis atherosclerosis, Alzheimer's disease and the Dean number

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Abstract

The important role of atherosclerosis in pathophysiology of Alzheimer's Disease has become evident. Mechanisms such as hyperlipidemia, inflammation, abdominal obesity and insulin resistance are important yet they may not fully explain the specific involvement of the Circle of Willis in these pathologies. The Circle of Wills is a complex geometrical structure which has several areas with different curvature as well as various branching angles of vessels composing the circle. The hemodynamics in this region should take into account the Dean number which indicates the influence of curvature on the resistance to blood flow. Thus, areas with various curvature and angles may have different hemodynamics and there are certain areas in the Circle of Willis that are more likely to develop atherosclerotic changes. Therefore, this could suggest the novel pathophysiological pathway resulting from the geometric peculiarities of the Circle of Willis. One of the directions of future research is to examine whether specific areas of the Circle of Willis are more likely to develop atherosclerotic changes compared to other ones. Selective areas of the Circle of Willis affected by atherosclerotic changes could indicate the primary role of atherosclerosis promoting Alzheimer's disease although other pathophysiological mechanisms suggesting the opposite direction should be also examined in prospective studies.

Key words: Circle of Willis; Alzheimer's disease; Atherosclerosis; Mechanism; The Dean number

Core tip: The Dean number can become an important local pathophysiological mechanism that can help to explain the specific involvement of the Circle of Willis in atherosclerosis and Alzheimer's Disease as anatomically different parts of the Circle of Willis would exhibit various degree of the curvature which would predispose to Alzheimer's disease. This could possibly explain some sporadic cases of Alzheimer's disease in the presence of minimal damage from atherosclerosis as well as open up new avenues for prevention of sporadic Alzheimer's disease.

Ismailov RM. Circle of Willis atherosclerosis, Alzheimer's disease and the Dean number. *World J Cardiol* 2013; 5(10): 394-396 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i10/394.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i10.394

TO THE EDITOR

The important role of atherosclerosis in pathophysiology of Alzheimer's disease has become evident. Studies that examined an association between the Circle of Willis atherosclerosis, Alzheimer's disease and some other neurodegenerative conditions are examples of important research directions focused on probable influence of various vascular factors on Alzheimer's disease[1,2]. On the other hand, those studies suggest that these pathologies could share some common pathophysiological mechanisms that yet need to be investigated. Some of such mechanisms such as hyperlipidemia, inflammation, abdominal obesity and insulin resistance were described by authors as prob-

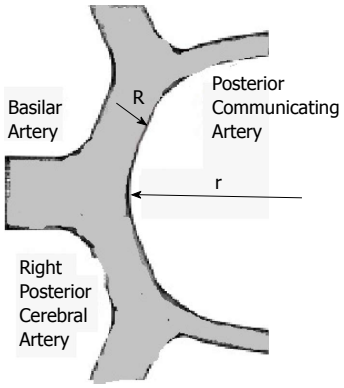

Figure 1 The Circle of Willis: The values of curvature (R and r).

able candidates[1,2]. However, although all these factors are very important, they may not fully explain the specific involvement of the Circle of Willis in these pathologies.

The Circle of Wills is a complex geometrical structure which has several areas with different curvature as well as various branching angles of vessels composing the circle. On the other hand, there are multiple anatomical variations of the Circle of Willis[3]. When a fluid runs through branching pipes a change of the its direction happens and similarly, when blood flows through the branching area in the Circle of Willis it changes direction. In general, taking into account that blood flow in the cardiovascular system is mostly laminar and the fact that branching areas of many arterial bifurcations have various angles, several hemodynamic factors (*i.e.,* radius of curvature of internal wall at branching area, Reynolds number, diameters of bifurcating vessels, *etc.*) should be taken into account[4]. One of them is the degree of curvature or the Dean number (Di). The Dean number indicates the influence of curvature on the resistance to blood flow[4,5]. If flow is laminar, then the Dean number is determined as:

$$D = 0.5\ Re\{[R(\frac{R}{r})^{1/2}]\}$$

Where Re indicates Reynolds number, R is a radius of the vessel, r is a radius of the curvature[4] (Figure 1).

Thus, areas with various curvature and angles may have different hemodynamics. For example, hemodynamics in the area where the degree of curvature is substantial could be described by the so called "hemodynamic shade" zone[6]. This zone can be characterized by a secondary flow and a boundary, therefore, there is a significant deterioration of mass exchange due to the attachment of stacks of erythrocytes (rouleaux) to the vascular wall[6]. This could deteriorate the permeability of the endothelium and decrease the rate of removal of various particles such as lipids and lipoproteins, which in turn can lead to the formation of lipid stripes directed along the blood flow and located in the "hemodynamic shade" of the original attached rouleaux. This could also explain why hyperlipidemia could be one of the non specific yet contributing pathophysiological mechanisms in the development of the Circle of Willis atherosclerosis. Therefore, there are certain areas in the Circle of Willis that are more likely to develop atherosclerotic changes. As mentioned earlier, other factors such as hyperlipidemia or abdominal obesity should be taken into account as well.

Subsequently, with the development of atherosclerosis, vascular wall in the certain areas of the Circle of Willis (*i.e.,* with substantial curvature) becomes less elastic and more rigid. This could result in the deterioration in the cyclic changes in the vascular wall deformation produced by cardiac contractions, and, therefore, in the performance of a "deformation pump"[7]. The operating principle of this pump is in the cyclic creation of the boundary layer and its separation[7]. This deformation pump is important to consider as it could influence the dynamics of the regional brain extravascular extracellular fluid which was previously studied with regard to amyloid beta-protein, amyloid-beta building blocks for plaques and subsequent involvement in neurodegeneration[8]. Such consideration of regional brain extravascular extracellular fluid dynamics is also particularly important in light of the fact that certain waste products such as glutamate or calcium can accumulate there causing degradation of certain cellular components thus playing an important role in the pathogenesis of Alzheimer's disease[9,10]. A consideration of both the deformation pump and extravascular extracellular fluid could become an important link between Alzheimer's disease and atherosclerosis.

All this could suggest the novel pathophysiological pathway resulting from the geometric peculiarities of the Circle of Willis. One of the directions of future research is to examine whether specific areas of the Circle of Willis are more likely to develop atherosclerotic changes compared to other ones. Selective areas of the Circle of Willis affected by atherosclerotic changes could indicate the primary role of atherosclerosis promoting Alzheimer's disease. On the other hand, other pathophysiological mechanisms that could explore local factors (*i.e.,* the Dean number) and suggesting the opposite direction should be also examined in prospective studies. For example, anatomically "different" parts of the Circle of Willis (*i.e.,* narrowed branching areas) would exhibit various degree of the Dean number and this would predispose to Alzheimer's disease. This could possibly explain some sporadic cases of Alzheimer's disease in the presence of minimal damage from atherosclerosis in this area. More importantly, this would open up new avenues for prevention of sporadic Alzheimer's disease in the light of the fact that this is an emerging health concern in the elderly. In addition, certain rheological factors such as blood viscosity should be taken into account as a contributing pathophysiological mechanism as well. In conclusion, more studies are needed to examine the common pathophysiological mechanisms related to both Alzheimer's disease and various vascular pathologies. Such common pathophysiological pathways should take into account multiple factors such as hyperlipidemia, insulin resistance, certain local rheological and hemodynamic

factors as well as potentially new contributing factors established in future research.

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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