

Association Between the Effect of Spontaneous Contrast in the Thoracic Aorta and Recent Ischemic Stroke Determined by Transesophageal Echocardiography

Flavio José Petersen Velho, Fernanda Dotta, Leonora Scherer, Eduardo Bartholomay, Daniela Augusta da Silva, Jefferson Gomes Fernandes, Marco Antonio Rodrigues Torres

Porto Alegre, RS - Brazil

Objective - To assess the independent association between the presence of spontaneous echo contrast in the aorta and recent stroke events.

Methods - Two hundred and twenty-four individuals with a diagnosis of recent stroke and 85 control individuals who were examined due to various present/suspected heart diseases were studied through transesophageal echocardiography. The effects of spontaneous contrast in the aorta and the presence of other potential sources of cardiac embolism associated with them were researched and a questionnaire was completed about patients' clinical risk factors at the time of examination.

Results - The effects of contrast in the aorta was associated with stroke (OR=2.83; CI = 95%, 1.65-4.46; $P<0.001$) in the bivariate analysis. In the multivariate analysis, it remained associated with recent stroke (OR=2.05; CI = 90%, 1.10-3.85; $P=0.06$). Age ≥ 60 years, a history of systemic blood hypertension and smoking, and dyslipidemia were risk factors independently associated with the effects of contrast in the aorta. The presence of a spontaneous contrast effect in the left atrium and Lambl's excrescences were echocardiographic factors independently associated with the effects of contrast in the aorta.

Conclusion - The effect of contrast in the aorta was independently associated with recent stroke and with its clinical risk factors. These results reinforce the hypothesis that the phenomenon is a predictor of several risk factors.

Keywords: transesophageal echocardiography, spontaneous contrast effects on the aorta, stroke

Cerebrovascular diseases are important causes of mortality and disability. In Brazil, despite its medical-social importance as the first cause of death in the country, epidemiological studies are rare¹⁻³.

Cerebrovascular diseases may have many causes, and embolic events, presumably cardiac, are responsible for 20 to 40% of strokes³.

The use of transesophageal echocardiography in the assessment of the heart as an embolic source has been widely accepted because of its greater capacity for spatial resolution of basal cardiovascular structures, such as the left atrium, the left atrial apex, the interatrial septum, and the thoracic artery. Transesophageal echocardiography has enabled the diagnosis of other risk factors associated with an increased risk of stroke.

Thrombi, tumors, and intracavitary vegetations, rheumatic valvular disease (especially mitral stenosis), left ventricle systolic dysfunction, left atrium spontaneous echo contrast, and the complex plaques in the proximal aorta are factors proved to be associated with an increased risk of stroke⁴⁻⁸. Other factors, such as degenerative calcification involving the mitral and the aortic valves; patent foramen ovale with right-left shunt; interatrial septal aneurysm; strands or Lambl's excrescences in the aortic or mitral valve, or both valves; and, more recently, spontaneous echo contrast in the aorta⁶⁻⁹ have been described as potential risk factors; however, some doubts still exist that will certainly be settled with future research in this area.

The meaning of the presence of spontaneous echo contrast in the aorta has been questioned, and recently it was linked to coronary artery disease and to ischemic events in general¹⁰.

The objective of the study was to assess the independent association between the presence of echo contrast in the aorta and recent stroke events.

Methods

The study group of 224 individuals with a recent diagnosis of stroke and the control group of 85 individuals un-

Centro de Diagnóstico por Imagem – Hospital São Lucas da PUCRS
Mailing address: Flavio José Petersen Velho – Av. Ipiranga, 6690/515
Cep 90610-000 – Porto Alegre, RS, Brazil - E-mail: flaviove@terra.com.br
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derwent transesophageal echocardiography for several present or suspected cardiac diseases.

The ethics committee of the institution approved the project, and all patients gave written informed consent.

The study group included individuals with a recent diagnosis of stroke (less than 30 days) treated from November 1997 through November 1999 at the Serviço de Neurologia do Hospital São Lucas da PUC (Neurology Service of the Hospital São Lucas from PUC), in the city of Porto Alegre. These patients underwent transesophageal echocardiography to detect whether the source of emboli was the heart, the thoracic aorta, or both of these.

The control group comprised consecutive individuals studied through transesophageal echocardiography to diagnose various cardiac diseases.

Exclusion criteria for the study and control groups were a descending thoracic aorta diameter > 4 cm; documented thoracic aorta dissection; fractional shortening, obtained through M mode echocardiography, $< 25\%$ or, in cases of segmental systolic dysfunction, ejection fraction (obtained through bi-dimensional transthoracic echocardiography using Simpson's method) of $< 40\%$; definite disagreement on the diagnosis of the effects of contrast in the aorta between 2 echocardiographers; refusing to take part in the study; not signing written informed consent; and, only in the control group, a previous history of systemic or encephalic embolization.

Patients with complete ischemic stroke or transitory ischemic attacks revealed with neurological evaluations were identified as ischemic stroke based on conventional clinical and tomographic criteria.

Diagnosis of the effects of contrast in the aorta was established when an echodense image was observed, moving with the cardiac cycle. When the echodense image observed did not move with the cardiac cycle as defined, we considered it as a technical artifact.

As a methodology, the patient or a relative answered a questionnaire about the patient's current health status and about risk factors for ischemic stroke. All patients underwent transesophageal echocardiography performed by an experienced echocardiographer. Patients were sedated with midazolam before esophageal intubation, with doses ranging from 2 to 15 mg IV. Examinations were performed with XP10 from Acuson-USA, using a multiplanar esophageal transducer with a 5-MHz frequency. For diagnosis of patent foramen ovale, saline solution was injected into a peripheral vein in the study group patients. Examinations were recorded on VCR tapes and assessed by another echocardiographer. The second observer was unaware of the diagnosis. In the cases where disagreement existed regarding the presence or absence of contrast in the aorta, observers tried to reach a consensus, and when they could not, the patient was excluded from the study.

Initially, descriptive statistics were obtained for all study variables, including mean and standard deviation for the quantitative and percentage values for the categorical variables.

To control the confusion effects, a multivariate analysis model was created using the logistic regression technique.

The evaluation of the association between ischemic stroke and the effects of contrast in the aorta was done using contingency tables, and relative risk estimations were obtained using odds ratio (OR) with their respective confidence interval (CI), 95% for bivariate analysis and 90% for multivariate analysis. Statistical significance of the associations was determined using the chi-square test and Fisher's exact test, when necessary. Similar techniques were used in the evaluation of the association between the effects of contrast in the aorta and other factors considered in the study.

The most relevant variables, according to the literature, were included in the mathematical model, regardless of the significance reached in the bivariate analysis.

We did not include all of the potential embolic sources detected through transesophageal echocardiography in the statistical analysis. Variables with an inexpressive prevalence in the sample were not studied in the statistical analysis. Patent foramen ovale was not included in the statistical analysis because its diagnosis was performed, in the majority of cases, through isotonic saline containing microbubbles, which was not routinely performed in the patients from the control group. Mitral valve prolapse and mitral or aortic degeneration calcification were not included in the analysis, because these diagnoses are usually performed using transthoracic echocardiogram.

Statistical significance levels accepted were $\alpha = 0.05$, for bivariate analysis, and $\alpha = 0.1$, for multivariate analysis. Data were processed and analyzed with the SPSS software program (Statistical Package for the Social Sciences) version 6.0 for Windows.

Results

Of 355 individuals who underwent transesophageal echocardiography, 309 were included in the study, 224 in the study group, and 85 in the control group. Forty-six patients were excluded from the study.

Age ranged from 15 to 85 years, with a mean of 62 ± 13 in the study group and 53.1 ± 18.1 in the control group. One hundred and seventy individuals were male.

Table I presents the occurrence of effects of contrast in the aorta and the frequency of clinical and echocardiographic risk factors for ischemic stroke in both groups.

Contrast effects in the aorta were associated with ischemic stroke events (OR = 2.83) in the bivariate analysis (tab. II), which demonstrated an association between ischemic strokes and systemic blood hypertension (OR = 3.79), diabetes mellitus (OR = 2.96), dyslipidemia (OR = 2.77), and with age ≥ 60 years (OR = 2.54). Among the echocardiographic findings, Lambl's excrescences (OR = 6.50) and the presence of complex plaques in the aorta (OR = 3.27) were associated with recent ischemic stroke events.

It was observed, in the multivariate analysis, that the effects of contrast in the aorta remained associated, independently, with recent ischemic stroke events (OR = 2.05, CI 90%, 1.10–3.85, $P = 0.06$) (tab. III).

Table I - Occurrence of spontaneous contrast in the aorta and of echocardiographic and clinical risk factors for ischemic stroke events

Factor	Study Group		Control Group	
	f	%	f	%
ASEC	118	52.7	24	28.2
Age ≥ 60 years	138	63.9	34	41
SBHH	151	67.4	30	35.3
Smoking	65	29	17	20
DM	47	21	7	8.2
Dyslipidemia	70	31.3	12	14.1
Atrial fibrillation	18	8	16	18.8
Vegetation	0	0	3	3.5
Myxoma	1	0.4	1	1.2
ANESIA	7	3.1	1	1.2
LA thrombi	11	4.9	1	1.2
LASCE	28	12.5	13	15.3
DPP	52	23.2	12	14.1
FOSH	56	25	5	5.9
CAOP	68	30.4	10	11.8
EXCVLV	74	33	6	7.1

TASCE- thoracic aorta spontaneous contrast effect; ≥ 60 years old – age equal to or greater than 60 years old; SBHH- systemic blood hypertension history; DM- diabetes mellitus history; IASA- interatrial septal aneurysm; LA Thrombi- left atrium thrombi; LASCE- left atrium spontaneous contrast effect; DPP- discreet proximal plaque in the aorta; FOSH- patent foramen ovale with shunt D-E; CAOP- complex aortic plaque; EXCVLV- Lambl's excrescences in the mitral and/or aortic valve.

Multivariate analysis demonstrated that systemic blood hypertension was the only clinical risk factor (OR = 2.68) associated independently with ischemic stroke events, confirming the independent association between the complex plaques in the aorta and ischemic stroke events (OR = 2.92, CI 1.34-6.67, P=0.02). Lambl's excrescence remained highly associated with recent ischemic stroke events (OR = 6.93, CI = 90% 3.18-15.12, P<0.001) in the multivariate analysis.

Regarding the multivariate analysis of the association between spontaneous echo contrast in the aorta and the presence of other risk factors for ischemic stroke, among the clinical variables, it was observed that age ≥ 60 years, systemic blood hypertension, smoking, and dyslipidemia were associated independently with echo contrast in the aorta. Among the echocardiographic variables, spontaneous echo contrast in the left atrium and Lambl's excrescences remained associated independently with the effects of contrast in the aorta (tab. IV).

Discussion

The spontaneous echo contrast in the left atrium in patients with atrial fibrillation is associated with greater risk of thromboembolism^{5,11-13}, and some evidence exists that echo contrast in the aorta is associated with atherosclerotic coronary disease and with ischemic stroke events^{10,14}.

In our series, the echo contrast in the aorta had an increased prevalence, both in the study group and in the control group (52.7% vs. 28.2%). In the bivariate analysis, an association between echo contrast in the aorta and recent ischemic stroke events was demonstrated (OR = 2.83, CI =

Table II - Bivariate analysis

Factor	Study Group		Control Group		RC	CI 95%	P
	f	%	f	%			
TASEC	118	52.7	24	28.2	2.83	1.65 - 4.46	<0.001
≥ 60 years	138	63.9	34	41	2.54	1.52 - 4.28	<0.001
SBHH	151	67.4	30	35.3	3.79	2.24 - 6.41	<0.001
Smoking	65	29	17	20	1.63	0.98 - 2.99	0.11
DM	47	21	7	8.2	2.96	1.28 - 6.84	0.008
Dyslipidemia	70	31.3	12	14.1	2.77	1.41 - 5.41	0.002
Atrial fibrillation	18	8	16	18.8	0.38	0.18 - 0.78	0.007
CAOP	68	30.4	10	11.8	3.27	1.59 - 6.71	<0.001
LASEC	28	12.5	13	15.3	0.79	0.38 - 1.16	0.52
EXVALV	74	33	6	7.1	6.50	2.71 - 15.59	<0.001

TASCE- thoracic aorta spontaneous contrast effect; ≥ 60 years old - age equal to or greater than 60 years old; SBHH- systemic blood hypertension history; DM- diabetes mellitus history; CAOP- complex aortic plaque; LASCE- left atrium spontaneous contrast effect; EXVALV- Lambl's excrescences in the mitral and/or aortic valve.

Table III - Multivariate analysis

Factor	OR	CI 90%	P
TASEC	2.05	1.10 - 3.85	0.06
≥ 60 years	1.43	0.80 - 2.54	0.31
SBHH	2.68	1.61 - 4.44	0.001
Smoking	1.70	0.32 - 3.13	0.15
DM	1.52	0.67 - 3.45	0.40
Dyslipidemia	1.27	0.66 - 2.45	0.54
Atrial fibrillation	0.25	0.09 - 0.70	0.02
CAOP	2.92	1.34 - 6.67	0.02
LASEC	0.79	0.30 - 2.05	0.68
EXVALV	6.93	3.18 - 15.12	<0.001

TASCE- thoracic aorta spontaneous contrast effect; ≥ 60 years old - age equal to or greater than 60 years old; SBHH- systemic blood hypertension history; DM- diabetes mellitus history; CAOP- complex aortic plaque; LASCE- left atrium spontaneous contrast effect; EXVALV- Lambl's excrescences in the mitral and/or aortic valve.

95% 1.65 – 4.46, P < 0.001). Multivariate analysis confirms that this association is independent (OR = 2.05, CI = 90% 1.10-3.86, P=0.06).

Although the presence of echo contrast in the aorta is attributed to the *rouleau* phenomenon observed in stagnating flows due to erythrocyte aggregation, other factors, such as anticardiolipin antibody, the increase in erythrocyte sedimentation rate, the increase in fibrinogen plasma levels, and plasma viscosity are also related to the phenomenon. These facts explain its presence even in the absence of stagnating flows.

In our study, we excluded patients with diseases that certainly created stagnating flows in the thoracic artery, such as significant left ventricle systolic dysfunction, aortic dissection, and aortic aneurysm. However, it may be possible that these factors involved in the erythrocyte aggregation (known or unknown) are mainly responsible for the appearance of contrast in the aorta in the study group. On the other hand, the increase in plasma fibrinogen, the increase in blood

Table IV - Multivariate analysis of the association between aortic spontaneous contrast effects and the presence of other risk factors for ischemic stroke events			
Factor	OR	CI 90%	P
Age ≥ 60 years old	5.43	3.23 -9.13	<0.001
SBHH	1.67	1.04 -2.69	0.07
Smoking	2.33	1.33 -3.96	0.009
Diabetes	1.85	0.99 -3.47	0.11
Dyslipidemia	1.75	1.04 -2.96	0.08
Atrial fibrillation	3.51	1.33 -9.28	0.03
LASCE	4.41	1.79 -10.83	0.007
CAOP	0.7	0.40 -1.23	0.31
EXVALV	2.06	1.23 -3.47	0.02

Age ≥ 60 years old – age equal to or superior than 60 years old; SBHH- systemic blood hypertension history; LASCE- left atrium spontaneous contrast effect; CAOP- complex aortic plaques; EXVALV- Lambl's excrescence in the mitral and/or aortic valve.

viscosity, and the increase in erythrocyte sedimentation rate are factors associated with heart diseases and vascular brain diseases¹⁵⁻²⁴. Their concomitant presence may explain the association of echo contrast in the aorta with ischemic stroke events, even in the absence of stagnating flows.

Because the control group comprised nonvolunteer individuals with a suspicion of heart disease, some results of the study may have been influenced. The most frequently observed diseases in the control group were mitral stenosis, ischemic heart disease, atrial fibrillation, and infectious endocarditis, which may be associated with stagnating flows and ischemic stroke events. The control group was formed because transesophageal echocardiography is an invasive investigation method that, although it has minimal risk, may cause discomfort, which prevented us from performing it in healthy individuals. It is very likely that, if the control group had comprised paired volunteers, the prevalence of echo contrast in the aorta would have been significantly lower and the association significantly more intense.

The results of the study demonstrate an intense and independent association between atrial fibrillation and echo contrast in the aorta. Atrial fibrillation is one of the main indications for transesophageal echocardiography,

both for risk stratification in chronic patients and as an additional element after cardioversion, and it was present in 18.8% of the individuals in the control group, much more prevalent than the 8.0% of the study group. This fact was an important influence contrary to our hypothesis and was probably responsible for the numbers obtained in the bivariate and multivariate analysis in which atrial fibrillation was a protective factor in ischemic stroke events. The results pertaining to atrial fibrillation were influenced by the formation of the control group. The presence of atrial fibrillation increases the risk of ischemic stroke 4 to 6 times^{9,12,25-28}. The results regarding spontaneous echo contrast in the left atrium were also influenced by the composition of the control group. The spontaneous echo contrast in the left atrium in this study appears to be a nonsignificant protective factor for ischemic stroke events. This finding is in disagreement with that in the literature, and the reasons for that contrast are the same found when we analyzed the association between atrial fibrillation and ischemic stroke events.

In our study, multivariate analysis did not confirm an independent association between the complex aortic plaques and the spontaneous echo contrast in the aorta. This finding, contrary to what was expected, was explained after the performance of several mathematical simulations, which verified that the complex aortic plaques were intensively and independently associated with the factor age ≥ 60 years (OR=8.4), and this factor was associated with the spontaneous echo contrast in the aorta.

In conclusion, the echo contrast in the aorta is independently associated with recent ischemic stroke events. All clinical risk factors for ischemic stroke events evaluated were independently associated with the echo contrast in the aorta. These results together with the certainty of the independent association between echo contrast in the aorta and ischemic stroke events, reinforce the hypothesis that the phenomenon is a marker of multiple risk factors. Among the echocardiographic variables, the presence of spontaneous echo contrast in the left atrium and Lambl's excrescences were echocardiographic factors independently associated with echo contrast in the aorta.

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