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Role of transthoracic echocardiography in the detection of atrial septal aneurysm and intracardial shunts of PFO type in ambulatory practice

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SOUHRN

Cíl: Tato studie hodnotí použitelnost transtorakální echokardiografie (TTE) jako screeningové metody k detekci aneurysmatu septa síní na souboru pacientů vyšetřených v období jednoho roku.
Metodika: V období od ledna 2019 do ledna 2020 bylo ambulantně echokardiograficky vyšetřeno 769 pacientů. U 87 % z těchto pacientů s dobrou nebo velmi dobrou vyšetřitelností byla posouzena přítomnost aneurysmatu septa síní (ASA). Pokud bylo nalezeno ASA a pacient projevil zájem, byla provedena kontrastní transtorakální echokardiografie (CTTE).
Výsledky: Nalezli jsme 80 pacientů s ASA, z nichž 37 podstoupilo kontrastní vyšetření. 34 z nich bylo pozitivních na přítomnost pravolevého zkratu. Kolem 18 % pacientů s ASA mělo symptomy z možné nebo z pravděpodobné kardioembolizace. Ti, jejichž symptomy byly suspektní z kardioembolizace, byli léčeni protidestičkovými léky (n = 6) nebo implantací okludéru a protidestičkovou léčbou (n = 2).
Závěry: Dle této studie je prevalence ASA kolem 10 % v běžné kardiologické populaci.
Podíl intrakardiálních zkratů na úrovni septa síní ve skupině pacientů s ASA byl téměř 90 %. V našem vzorku pacientů s ASA bylo kolem 18 % pacientů se symptomy z možné nebo pravděpodobné paradoxní embolizace. Na základě těchto výsledků doporučujeme zhodnotit přítomnost ASA během každého echokardiografického vyšetření a u každého pacienta s ASA provést nějakou formu kontrastního vyšetření. Všichni symptomatičtí pacienti by měli podstoupit transezofageální echokardiografii (TEE) a kontrastní transezofageální echokardiografii (CTEE).

Keywords:
Atrial septal aneurysm
Contrast echocardiography
Occluder
PFO

ABSTRACT

Aims: This study evaluates the usage of TTE as a screening method to detect ASA as is demonstrated on the population of patients examined within the period of one year.
Methods: From January 2019 to January 2020, 769 patients underwent TTE on outpatient basis. 87% of these with either good or very good image quality were analyzed for the presence of ASA. In the presence of ASA, and in the case of patient's interest, CTTE was performed.
Results: We have identified 80 patients with ASA out of which 37 underwent contrast examination. 34 of these were positive for the presence of R-L shunt. Around 18% of patients with ASA exhibited symptoms, which were likely or possibly of embolic origin. Those, whose symptoms were suspicious of cardioembolism were treated with antiplatelet medication (n = 6) or PFO occluder together with antiplatelet medication (n = 2).
Conclusion: According to this study the prevalence of ASA is around 10% in the general cardiologist's population. The proportion of interatrial shunting, detected by CTTE, in the group of patients with ASA was nearly 90%, which is significantly higher than in most of the works published to date. The percentage of patients with possible or probable cardioembolic symptoms was around 18%.
On the basis of these results we suggest to assess the presence of ASA during every echocardiographic examination and to perform some form of contrast examination in all patients with ASA. All symptomatic patients should undergo TEE-CTEE.

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Introduction

Patent foramen ovale (PFO) is, with the prevalence of approximately 25%,[1] a common abnormality of the heart and it is often found together with atrial septal aneurysm (ASA). However, the data about prevalence of ASA vary quite a lot in different publications (its range is between 1,9 and 10%)[2–5] and so do the data on prevalence of interatrial shunting in the presence of ASA (see Discussion). There is also no unity in the definition of ASA, and the criteria used in the literature are arbitrary. In our area, the most often used definition is that of Hanley et al. from the year 1985 – i.e. excursions of atrial septum of at least 15 mm (Fig. 1).[6] Other authors use the definition of 10 mm excursions or more.[7] Mügge et al.[4] used cut-off criteria similar to those reported in an autopsy study by Silver and Dorsey,[7] i.e. a protrusion of the aneurysm >10 mm beyond the plane of the atrial septum into either the right or left atrium, in the series of cases of ASA diagnosed by transesophageal echocardiography (TEE).

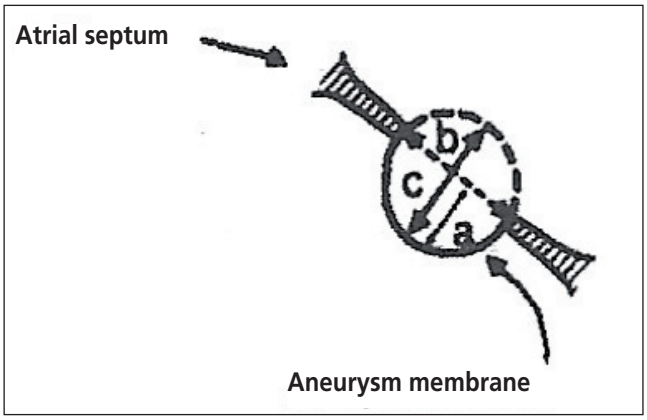

Fig. 1 – Diagnosis of atrial septal aneurysm. ASA was considered to be present when: 1. Atrial septum or part of it exhibited excursions at least 1.5 cm beyond the plane of the atrial septum (a ≥1.5 cm) or exhibited phasic excursions exceeding 1.5 cm (c ≥1.5 cm), and 2. the base of the aneurysmal protrusion was at least 1.5 cm in diameter (b ≥1.5 cm). Adjusted according to Hanley et al.[6]

There is well known association between PFO and paradoxical thromboembolism,[8–12] between PFO, ASA and higher risk of cryptogenic stroke or transitory ischemic attack (TIA)[13,14] and between PFO and migrainous cephalea as well.[15–17] But the results of the PREMIUM study, concerning the possibility of treatment of migraine with PFO occluder were inconclusive.[18] Finally, there is also a known relation between PFO and decompression illness.[19–23]

The results of extensive study published in New England Journal of Medicine in 2017[24,25] suggest, that patients with PFO and concomitant cryptogenic stroke or TIA benefit from antithrombotic treatment combined with PFO occlusion. Having written that PFO frequently coexists with ASA, it is obvious, that ASA is not clinically unimportant.

In this study we have analyzed a group of patients, partly comprising of asymptomatic individuals, without another cardiologist's diagnosis, coming for a preventive consultation and the remainder consisting of people with all kinds of heart diseases or any risk for heart disease.

The aim of this work was to investigate:

1. What is the percentage of patients with ASA.
2. In how many patients with ASA a right to left (R-L) shunt would be detected with the use of contrast transthoracic echocardiography (CTTE).
3. How many patients with ASA and intraatrial shunt had symptoms suspicious of cardioembolism or possible cardioembolism.
4. What proportion of these patients would be, on the basis of transthoracic echocardiography (TTE) and CTTE, indicated for pharmacological prevention of cardioembolism – paradoxical embolisation and how many of them would be referred for TEE and subsequently for occluder implantation.

Ultimately, we wanted to assess the significance of TTE and CTTE in the detection of ASA and PFO.

Methods

In the period from January 2019 to January 2020, 769 patients were examined. Some of them were healthy asymptomatic individuals, coming to the outpatient department of cardiology for preventive consultation whilst others had specific complaints or illness related to cardiology. All examinations were divided, according to image quality, into four groups. A scale of four degrees was used for this purpose: 1° – excellent, 2° – good, 3° – limited and 4° – poor image quality. In 100 examinations (13%) the image quality was rated as limited or poor and these were not included into the study. The rest of the examinations (669) were rated as good (361 patients – 47%) and excellent (308 patients – 40%) image quality. In this population of patients, with good or excellent image quality, we have prospectively searched for ASA presence and this way a sample of 80 patients was collected. Of this group a subgroup A of 47 patients fulfilled the stricter Hanley criteria of ASA[6] and subgroup B of 33 patients, met the milder criteria of other authors.[13,14,26] All 80 patients signed their informed consent for inclusion in the study. A simple analysis was made separately for both subgroups and for the whole group. An example of ASA displayed by TTE is shown in Figure 2. Exclusion criteria were: patient's disagreement, heart failure with left ventricular ejection fraction (LVEF) of less than 45%, de-

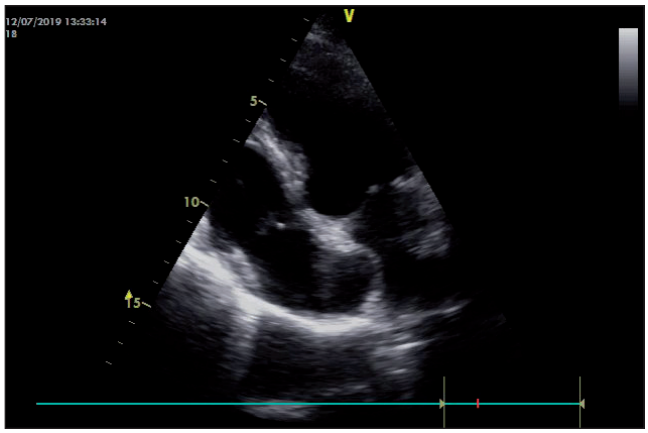

Fig. 2 – ASA in the 2D transthoracic imaging – apical four chamber view (A4C).

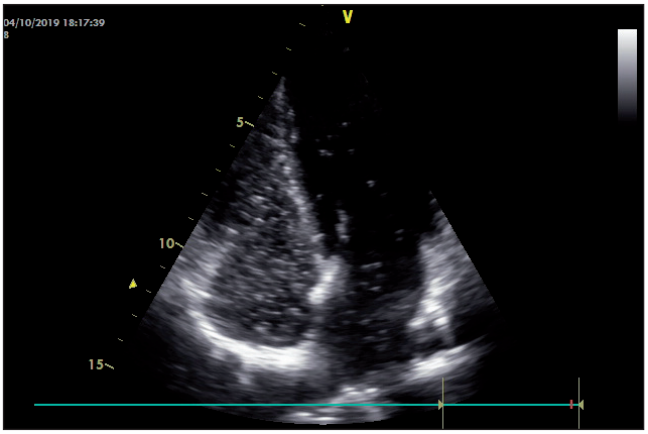

Fig. 3 – Positive bubble test for the presence of shunt in the level of atrial septum. From this picture it is not clear, that ASA is present. TTE A4C view.

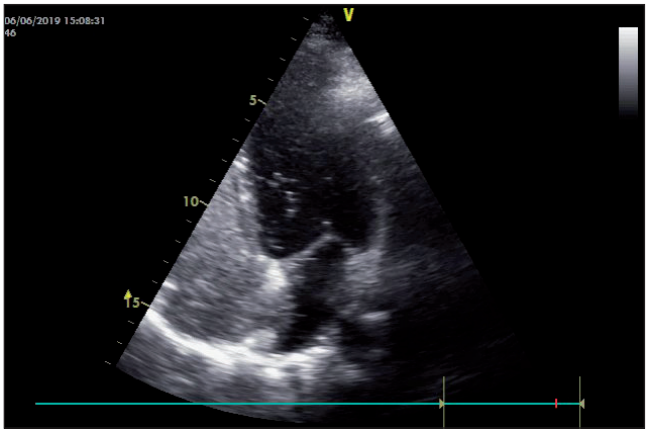

Fig. 4 – Atrial septum aneurysm with positive bubble test. TTE A4C view.

compensated arterial hypertension (arterial blood pressure of >160/90 mm Hg), elevated left ventricular end-diastolic pressure (LVEDP) (according to E/E´ ratio) and significant pulmonary hypertension with pulmonary artery systolic pressure (PASP) of more than 45 mm Hg. Nonetheless none of the patients with ASA met any of the mentioned exclusion criteria.

All patients were examined transthoracically with the GE Vivid S6 machine and in the case of good or excellent image quality, the presence of ASA was assessed. All the transthoracic examinations were done by a single physician. In all patients all standard views were performed (parasternal long and short axis, apical four and two chamber, and subcostal views) and the presence of ASA was explored from parasternal short axis (PSAX), apical four chamber (A4C) and subcostal views. The excursions of the septum were measured from the longitudinal axis of interatrial septum. In the presence of ASA, the 37 patients who expressed interest underwent CTTE – so called bubble test – with the use of agitated saline containing microbubbles administered into the peripheral vein while the patient was examined transthoracically and the Valsalva manoeuvre was performed. The test was considered positive when at least three microbubbles appeared in the left atrium and ventricle (Figs 3 and 4). Some patients underwent TEE – contrast transesophageal echocardiography (CTEE) examinations, which was made on Vivid E9 and Philips Epic 7C machines.

We have used the same criteria of positivity as the authors of the French PFO-ASA study[27] having known that others[28] had used the presence of at least two bubbles as a criterion. Microbubbles were defined as echocontrast points in the heart chambers exhibiting movement. Patients with a positive test and symptoms of suspected or possible embolisation, or with findings of lesions compatible with embolisation on computed tomography (CT) / magnetic resonance imaging (MRI) of the brain underwent TEE and then were referred for occluder implantation.

Results

The results are summarized in Tables 1–3. In the population of 669 patients we have found 47 (7%) patients,

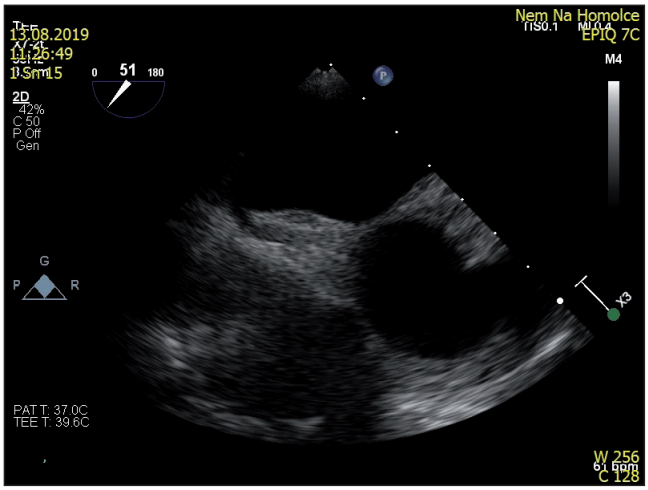

Fig. 5 – TEE during the implantation of Figulla Flex II occluder, displays its proper position immediately after implantation.

who met the stricter Hanley's criteria for ASA – group A. Ten (21%) of these patients had symptoms of probable or possible embolic etiology.

Another 33 (4.9%) pts. fulfilled the milder criteria (group B), out of which 6 patients (18.1%) had symptoms presumably or possibly of embolic origin.

Altogether there were 80 patients in both groups – 27 men and 53 women. Out of these, 8 patients (10%) had symptoms of probable and 7 pts. (8.75%) of possible embolic events. In 2 of these 8 symptomatic patients, occluder implantation was indicated and performed (occluder Figulla Flex II – Fig. 5). These were cases of two women, one from subgroup A and one from subgroup B. The other six symptomatic patients received antiplatelet therapy although occluder implantation was considered as well. Five of them either refused or hesitated to agree with the intervention and in one of these patients occluder implantation was declined by the interventional cardiologist due to unsuitable anatomy.

In the group of patients with symptoms, likely caused by embolizations, there were 7 women and one man. Altogether in the both groups of symptomatic and possibly

Table 1 – Subgroup A (one female patient, who is not accounted into the table had positive CTEE for PFO in the past)

Gender M/F	Avg age	L-Avg	R-Avg	L + R Avg	MVP	Regurgitation ° 1–4 on 1 or more valves	CTTE positive/ negative	Symptoms of probable/possible cardioembolism	Antithrombotic therapy /AT therapy + occluder
16/31	56.43	1.20	1.05	2.17	10	38	19/2	4/6	6/1

L-Avg – average left excursion of the interatrial septum; R-Avg – average right excursion; L + R Avg – average total (left and right excursion). Note: these total excursions were not always measurable – depending on the image quality.

Table 2 – Subgroup B

Gender M/F	Avg age	L-Avg	R-Avg	L + R Avg	MVP	Regurgitation ° 1–4 on 1 or more valves	CTTE positive/ negative	Symptoms of probable/possible cardioembolism	Antithrombotic therapy /AT therapy + occluder
11/22	50,8	1,12	1,15	1,43	9	12	10/1	4/1	7/1

Table 3 – Both subgroups (A+B) together (*3 patients were taking warfarin for AFib but these had no history embolic events)

Gender M/F	Avg age/ Median	L-Avg/ Median	R-Avg/ Median	L + R Avg/ Median	MVP	Regurgitation ° 1–4 on 1 or more valves	CTTE positive/negative	Symptoms (probably/possibly of cardioembolisation)	AT therapy /occluder + AP therapy
27/53	54,6/53,0	1,17/1,12	1,07/1,06	2,13/2	19	50	33/3	8/7	12*/2

symptomatic patients, there were 12 women and 3 men. Average age in the symptomatic group was 52.1 years.

In 37 of 80 patients with ASA (groups A + B), CTTE was performed and 33 were positive for the presence of the trace right to left shunt during CTTE. In one additional female patient of this group, PFO was found earlier in the past during TEE. Altogether 89.5% were positive, including both women indicated for occluder. Only in 10.5% the bubble test was negative.

The indication for occluder implantation was always evaluated by noninvasive cardiologist, interventional cardiologist and neurologist.

The other patients with positive CTTE for the presence of trace R-L shunt were instructed, how to minimize the risk of thromboembolic events in specific situations. Specifically, in situations of long immobility of the legs (e.g. long trips by plane or bus), in women thromboprophylaxis before and after delivery. Women were also discouraged from taking hormonal contraceptives and from smoking. All these patients were also warned about the risks of scuba diving.

As for the coincidence with other structural abnormalities, we found significantly higher occurrence of mitral valve prolapse (MVP): In our group of 80 ASA patients we found 19 mitral valve prolapses (23.8%), approximately 10 times more than in the general population according to the Framingham Heart study.[29,30]

Also, there was often a coincidence of ASA with mitral and tricuspid regurgitations. The mitral regurgitations were either of degenerative etiology (fibrosis and calcifications) caused by ageing of the heart or associated with MVP and most of the tricuspid regurgitations were associated with mild pulmonary hypertension (PASP up to 45 mm Hg).

Out of other structural abnormalities, there were three bicuspid aortic valves, three patients with dilated ascending aorta and two cases of a mild form of the Ebstein anomaly.

Discussion

In most other publications, the prevalence of ASA is significantly lower than in our study: Hanley[6] found 80 out of 36 000 (2.2%), Yetkin et al.[2] 2.4% out of 16 570 patients, Schneider et al.[31] 3% of patients examined transoesophageally, but only 0.16% transthoracically.

The superiority of TEE over TTE in the detection of ASA is well known.[32,33] But because it is an invasive procedure, bound to monitoring and therapeutic background, it is usually performed only in a case of suspected cardioembolism or paradoxical embolisation. TTE, on the other hand, as a noninvasive examination, available in every outpatient department of cardiology, can be used as a screening method very easily with the awareness of its lower sensitivity – according to some authors, as much as 60% of ASAs can escape detection.[32] But it is necessary to add, that the golden diagnostic standard is missing and that TEE is not a reference method.[4] Therefore, we did not try to compare sensitivity of CTTE and CTEE in the detection of ASA. Besides that, out of 37 patients, in whom CTTE was performed, only 3 were negative and thus, it would be impossible to draw any relevant conclusions on sensitivity, should these 3 patients undergo CTEE, whatever the result would be. Nevertheless the significantly improved image quality with modern echocardiographic machines since the 80's and 90's, when most cited works originated, must have inevitably brought an improvement of sensitivity of TTE in the detection of ASA. In this respect, there was one, rather anecdotal case, of a young woman (39 years) with inherited thrombophilia and stroke in the year 2008 with originally a negative CTEE ten years ago, then positive CTTE at our department and subsequently positive – repeated CTEE. In the end, this patient was contraindicated for the occluder implantation due to unsuitable anatomy. Despite this case, there is enough evidence in the literature about the superiority

of TEE in the detection of ASA and PFO[32,33] and it is very likely, that a certain number of ASAs out of the group of "good" image quality have been missed and this is one of the limitations of this study.

The high percentage of positive bubble tests (89.5%) suggests, that increased redundancy of interatrial septum, regardless of the criteria used, represents a significant predictor of the presence of right to left shunt and that the percentage of these shunts in patients with ASA might be even higher than stated in some publications: In fact, the differences in the reported prevalence of shunting in the presence of ASA are quite substantial: In the study of Mügge et al.[4] in 106 patients (54%) ASA was associated with interatrial shunting (atrial septal defect, n = 38; patent foramen ovale, n = 65; sinus venosus defect, n = 3). Albers et al.[34] reported, that twenty (61%) of the 31 patients with atrial septal aneurysms also had interatrial shunts. Schneider et al. found interatrial shunts in 44% of TTE and 77% of TEE studies.[31] Belkin et al. reported a prevalence of 90% of interatrial shunts in patients with ASA in a sample of 36 patients with ASA.[35] Yetkin et al.[2] recorded a prevalence of 2.4% (n = 393) in a large population of 16 570 patients, collected over a period of 4.5 years. In this group of patients with ASA there was only 8% prevalence of PFO. In accordance with our study there was a strong female preponderance. Interestingly, authors of this study did not find increased prevalence of MVP, like authors of other studies. This common association has actually led to a concept of inherent connective tissue deficiency in patients with ASA.[36]

To summarize, the prevalence of interatrial shunting in patients with ASA in different publications ranges from 8% to as much as 90% in smaller studies.

The proportion of symptomatic patients was similar in both groups, regardless of the criteria for ASA.

Among symptomatic patients, there was significant portion, in whom the indication for occluder insertion was weak or who denied the intervention. In these patients it may not be necessary to perform TEE and it might be sufficient to perform the noninvasive TTE and CTTE and CTEE in case of negative CTTE. When the presence of intracardial shunt is known, the preventive measurements may prevent cardioembolic event. That is why it seems reasonable and advisable to actively search for ASA during routine and preventive TTE examinations and in its presence indicate CTTE or CTEE.

According to the guidelines of the European Stroke Organization (ESO) for management of ischemic stroke and transient ischemic attack, it is recommended that endovascular closure of PFO be considered in patients with cryptogenic stroke and high-risk PFO. These guidelines were published in 2008[37] and thus it can be anticipated, that new guidelines would reflect results of the mentioned randomized studies.[24,25] Based on the results of these studies it should be recommended, that in all patients with ASA, P-L shunt and clear embolic events, occluder implantation should be considered additionally to antiplatelet drugs. Treatment of patients with symptoms, ASA and negative bubble test should probably be individualized – depending on the likelihood of thromboembolism and other comorbidities.

Conclusion

In our sample of 669 transthoracically examined patients with good or very good image quality, there were, depending on the criteria used, 47–80 patients with ASA. In other words, we have proved a prevalence of 7–11.9% in general cardiologist's population. Women clearly prevailed (66.3%) and even more in the group of symptomatic patients (82.6% female patients). Two women received, besides antiplatelet medication, a septal occluder.

Out of 37 patients, in whom CTTE was performed, 34 (89.5%) were positive for the presence of trace R-L shunt at the level of atrial septum, which is significantly more than in the works of most of other authors. However, the very wide range of data on prevalence of ASA and ASA with PFO only shows, that the real prevalence is simply unknown and it seems that the clinical significance of ASA with PFO warrants further investigation of its epidemiology.

In our group of 80 patients with ASA, there were around 18% patients with symptoms of possible or probable paradoxical embolization: 8 patients (10%) had symptoms probably and 7 (8.75%) possibly caused by embolisations or microembolisations.

On the basis of these results we recommend to search for ASA during every TTE examination and in its presence to perform some form of contrast echocardiographic examination (CTTE or CTEE) in order to exclude R-L shunt.

It is emphasized that with the use of TTE, diagnosis of ASA can be reliably made only in a case of excellent image quality and TTE should only be regarded as a screening method.

All symptomatic patients should undergo transesophageal examination (TEE and CTEE), which is necessary in the case of occluder implantation.

This study suggests that there might be a significant proportion of patients in whom CTTE might substitute CTEE, i.e. patients without symptoms and those who have symptoms but deny the intervention or the TEE.

This study also confirms the findings of other authors that the occurrence of ASA correlates significantly with the occurrence of mitral valve prolapse.[26]

Conflict of interest
None declared.

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