

The role of coronary CT angiography in diagnosis of patent foramen ovale

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PURPOSE

We aimed to examine the incidence of patent foramen ovale (PFO) and atrial septal aneurysms (ASA) in the Turkish population using coronary computed tomography angiography (CTA); assess the feasibility of coronary CTA for PFO diagnosis by conducting a comparison with transthoracic echocardiography (TTE); and determine the diagnostic role and characteristics of the interatrial tunnel, free flap valve (FFV), and shunts.

METHODS

The present study was conducted retrospectively and included a sample of 782 patients. Coronary CTA results for all patients were evaluated for the following parameters: the presence of PFO, the degree of contrast jet (if present due to PFO), ASA existence, free flap valve (FFV) length, and PFO tunnel diameters (1 and 2). Coronary CTA and TTE results for PFO detection were also compared for 19 patients who underwent both procedures.

RESULTS

PFO was present in 118 patients (15%). In 19 patients who underwent both CTA and TTE, the shunt was present in 15 patients on TTE compared with nine patients on CTA. The sensitivity and specificity of CTA for shunt existence were 53% (8/15) and 75% (3/4), respectively. FFV was observed on CTA in 118 patients (15%). No significant relationship was observed between shunt existence and FFV length ($P = 0.148$), or between shunt existence and tunnel diameter-1 ($P = 0.638$) or diameter-2 ($P = 0.058$). ASAs were present in 16 patients (2%), while accompanying PFO was present in three patients (2.4%).

CONCLUSION

Coronary CTA constitutes a more practical and efficient alternative to TTE for PFO diagnosis. Further, it allows the clear visualization of anatomical details of the interatrial tunnel, shunts, and associated abnormalities and detects ASAs.

The interatrial septum consists of a fusion of the two separate leaves of a flap valve system, which provides continued fetal circulation *in utero*. In approximately 70% of the population, the septum primum and secundum in the interatrial septum fuse shortly after birth and form an intact barrier (1). A failure in the fusion of this flap valve system after birth may lead to a patent foramen ovale (PFO). The connection between the right and left atrium (RA and LA, respectively) forms an anatomical tract for cryptogenic stroke caused by paradoxical emboli (2).

Transesophageal echocardiography (TEE) is a semi-invasive imaging modality that is typically preferred for PFO diagnosis. In particular, contrast-enhanced TEE is a reliable method for the identification of PFO patients with right to left shunts. Although contrast-enhanced TEE is utilized in PFO diagnosis as the reference standard, some studies claim that transthoracic echocardiography (TTE), which is a noninvasive procedure, has comparable sensitivity (3–6).

Although coronary computed tomography angiography (CTA) is primarily utilized to image coronary arteries, this technique can also be used to visualize other cardiac structures, at a very high resolution, in a routine coronary artery scan (2). As computed tomography (CT) technology has advanced, clinicians have discovered that PFO is a frequent finding in routine coronary CTA, and interest in this issue has arisen. The high spatial and temporal resolution provided by advancements in CT technology has enabled easy evaluation of the interatrial septum as well (7–9).

Atrial septal aneurysms (ASA) represent another pathologic anatomical condition, with reported incidences of 1% and 4.6%–10% in autopsy studies patients undergoing TEE, re-

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spectively (10). ASAs may also exist in PFO and are related to both PFO and cryptogenic stroke (2).

The present study aimed to examine the incidence of PFO and ASA in the Turkish population using coronary CTA, to assess the diagnostic feasibility of coronary CTA for PFO diagnosis by conducting a comparison with TTE; and determine the diagnostic role and characteristics of the interatrial tunnel, free flap valve (FFV), and shunts.

Methods

Patient selection

The study was approved by the local institutional review board of our hospital. Informed consent was waived by the institutional review board. In our study, a total of 786 coronary CTA examinations performed in our department between October 2012 and August 2014 were reviewed retrospectively to establish PFO and ASA diagnoses. Of these patients, 520 were male (66%) and 266 were female (34%), with ages ranging from 18 to 87 years (mean and standard deviation, 55±14 years). Indications for coronary CTA included the following parameters: suspected coronary artery disease (n=685), anomaly (n=36), stent patency (n=27), and bypass graft assessment (n=42). Four coronary CTAs were also excluded because of severe artifacts created by dense contrast media in the right heart chambers (n=1) and because of motion (n=3). The remaining 782 patients were included in the study.

CT protocol

All CT examinations were performed using 64-detector or 320-detector scanners (Brilliance-64, Phillips Medical Systems or Aquilion ONE, Toshiba Medical Systems). Two hundred forty patients underwent 64-detector CT scans and 542 patients un-

derwent 320-detector CT scans. A bolus of 60–120 mL iodine contrast agent and iomeprol (Iomeron 400, Bracco), followed by 50 mL saline solution, was injected into an antecubital vein through an 18G–20G catheter at a flow rate of 5–6 mL/s. Our department prefers to administer beta-blocker drugs intravenously, instead of orally (tablet form), prior to coronary CTA studies because of their faster onset and improved clinical feasibility. Thus, the beta-blocker drug metoprolol (5–20 mg, Beloc® 5 mg/mL, AstraZeneca) was administered intravenously before CTA if the heart rate was >70 beats/min. In the absence of contraindications, 0.4 mg of sublingual nitroglycerine spray (Nitrolingual® pump spray, Farma-Tek®) was administered immediately before scan initiation.

For the 64-detector CT scanner, data were acquired using retrospective electrocardiography gating with the following parameters: 64×0.625 mm detector collimation, 0.4 s gantry rotation time, pitch of 0.2–0.4 adapted to the heart rate, 120–140 kVp tube voltage, and 600–900 mA tube current. For the 320-detector CT scanner, data were acquired using prospective electrocardiography gating with the following parameters: 320×0.5 mm detector collimation, 0.35 s gantry rotation time, 100–135 kVp tube voltage, and 400–600 mA tube current. The tube voltage and current were adapted to body mass index and thoracic anatomy in all patients. The effective reconstruction slice thickness was 0.9 mm and 0.5 mm for the 64-detector and 320-detector CT scanners, respectively.

Image analysis and measurement

Multipolar reformations of the images (short-axis, two-chamber, and four-chamber views) were rendered and evaluated. Standard axial images were acquired at mid-diastole. Specifically, PFO and ASA existence in the axial sequence crossing the interatrial septum, FFV length, PFO tunnel diameter, and RA jet flow existence, were evaluated in the sagittal oblique images. In cases where clear evaluation could not be performed with axial and sagittal images, coronal oblique images were also utilized.

Williamson et al. (1) established that PFO anatomy on CT was classified by three criteria: criterion 1 (grade 1 PFO): presence of a distinct “flap” in the LA at the expected location of the septum primum; criterion 2 (grade 2 PFO): presence of a continuous “column” of contrast material (interatrial tunnel) between

the septum primum and septum secundum, connecting the left and right atria; criterion 3 (grade 3 PFO): presence of a “jet” of contrast material from the column into the RA. When compared with the TEE diagnosis, the positive predictive value of criterion 1 alone (grade 1 PFO) was 75%, criteria 1+2 together (grade 2 PFO) was 80%, and criteria 1+2+3 together (grade 3 PFO) was 100% (1, 2) (Fig. 1). The maximum length of the contrast material jet was also measured and graded in sagittal oblique reformatted images (grade 1, ≤1 cm; grade 2, 1–2 cm; and grade 3, >2 cm) (Fig. 1) (11).

Further, the length of the FFV and the distance between the FFV and the septum secundum of the PFO tunnel were also measured. FFV length was measured in oblique sagittal images perpendicular to the interatrial septum on four-chamber views. The flap valve was measured from its free margin (Fig. 2). The diameters of the PFO tunnel (diameter-1 and diameter-2) were measured at midpoint and at the entrance to the RA (11). Only diameter-1 measurement was performed in grade 1 PFO. ASA was defined as a redundant and hypermobile portion of the interatrial septum that demonstrated more than a 10 mm excursion from the centerline (2). Measurements of ASA were obtained on four-chamber views.

Transthoracic echocardiography

Nineteen cases that involved clinical complaints were evaluated by TTE using agitated saline (available echocardiography unit: Philips iE33, Xmatrix, X5-Transducer Systems). Standard TTE procedures were performed for patients in accordance with guidelines provided by the American Society of Echocardiography (3, 5). The interatrial septum was used to visualize the apical four-chamber TTE view. Intravenous agitated saline (9 mL of 0.9% NaCl solution shaken with 1 mL of ambient air) was injected at rest during the performance of a Valsalva maneuver for PFO. TTE images were reviewed by two cardiologists. PFO was considered present if any microbubbles were seen in the left cardiac chambers within three cardiac cycles of maximum RA enhancement (Fig. 3).

Statistical analysis

All statistical analyses were performed using commercially available software (Statistical Package for Social Sciences, version

Main points

- Patent foramen ovale (PFO) and atrial septal aneurysm (ASA) are risk factors for cryptogenic stroke.
- According to our study, the incidence of PFO and ASA in the Turkish population is 15% and 2%, respectively, on coronary computed tomography angiography (CTA).
- Coronary CTA is a practical and effective alternative method for PFO diagnosis in selected cases.
- Coronary CTA can be used with high resolution to reveal the interatrial septum during routine coronary examination.



Figure 1. a–d. Reconstructed CT images from different patients show the interatrial septa with patent foramen ovale. CT image of a 66-year-old woman (a) shows the channel-like appearance of the interatrial septum and continuous “column” of contrast material between the septum primum and septum secundum (arrow). Coronal-oblique CT image of a 58-year-old male (b) shows grade 1 jet flow of the contrast material to the right atrium (arrows). Panels (c) and (d) demonstrate grade 2 and grade 3 jet flows (arrows), respectively.

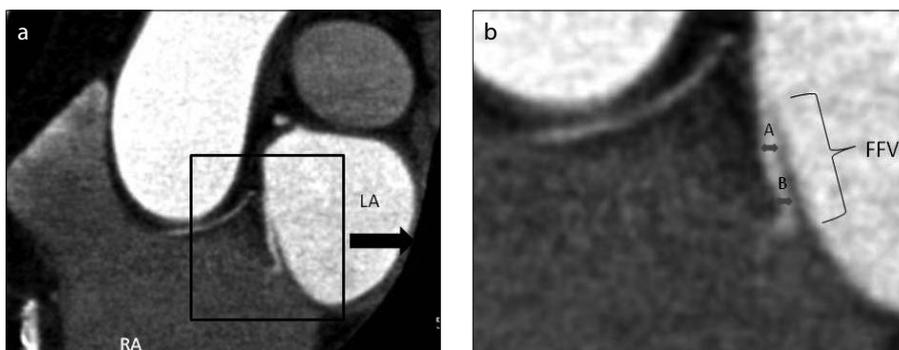


Figure 2. a, b. Sagittal-oblique reformatted CT image (a) of a 66-year-old woman shows the channel-like appearance of the interatrial septum. Panel (b) is a close up view of the square in (a), showing diameters A (2.8 mm) and B (2.1 mm) of the tunnel at midpoint and at the entrance into the right atrium, respectively. LA, left atrium; RA, right atrium; FFV, free flap valve; A, diameter of the tunnel at midpoint

16, SPSS Inc.). Descriptive statistics were presented as median (min–max), frequency, and percent. The Kolmogorov-Smirnov test was used to evaluate whether the continuous variables were normally distribut-

ed. The Mann-Whitney U test and one-way ANOVA were used to compare continuous variables. McNemar test was used to compare categorical variables. Statistical significance was set at $P < 0.05$.

Results

Of 782 patients examined, 118 (15%) had PFO. These patients were further stratified based on PFO grade: 30 (3.8%) with grade 1 PFO, 14 (1.7%) with grade 2, and 74 (9.4%) with grade 3. PFO was detected in 38 patients using a 64-detector CT scanner and 80 patients using a 320-detector CT scanner. Of 118 patients with PFO, 24 (21%) were female and 94 (79%) were male (mean age, 56 ± 15 years; range, 19–85 years). A left-to-right shunt was observed in 74 patients with PFO (62.7%), while no shunt was observed in 44 patients with PFO (37.3%). Fourteen patients (12.2%) displayed no shunt (on CT), but the right atrial end of their channel was patent. The right atrial end was closed in 30 patients (24.5%).

In patients with PFO, no significant relationship was observed between presence of shunt and free flap length ($P = 0.148$). No statistical relationship was observed between presence of shunt and diameter-1 ($P = 0.638$) or diameter-2 ($P = 0.058$).

Of 74 patients with a shunt, 45 (38.1%) had grade-1, 23 (19.5%) had grade-2, and six (5.1%) had grade-3 flow patterns (Table 1). While a minimum FFV length of 4.6 mm was measured at grade-2 jet flow, a minimum of 7.4 mm was measured at grade-3 jet flow. In four patients with a FFV below 4.6 mm, only grade-1 jet flow was observed. No significant relationship was observed between FFV length and shunt grade ($P = 0.128$). The minimum, maximum, and mean FFV lengths were determined as 2.8 mm, 26.9 mm, and 12.1 ± 1 mm, respectively. The minimum, maximum, and median jet flow lengths were determined as 2.4 mm, 27 mm, and 8 mm, respectively.

Nineteen patients in whom PFO was detected (on CT) were evaluated by TTE using agitated saline. Of the patients in this group, while no shunt (jet flow from the PFO channel towards the RA) was observed on CT in 10 patients, grade 1 jet flow was observed in five, grade 2 jet flow in two, and grade 3 jet flow in two (Table 2). Of these 19 patients, shunt existence was determined in 15 patients on TTE (Table 3). No significant association between the presence of a shunt on TTE and presence of a shunt on coronary CTA was observed ($P = 0.07$). When the CT images of the patients with a shunt, as detected by TTE, were evaluated, no statistically significant association between shunt existence and FFV length, and shunt existence and PFO diameters (tunnel diameter-1 and diameter-2) was observed ($P = 0.647$, $P = 0.517$, and $P = 0.548$,

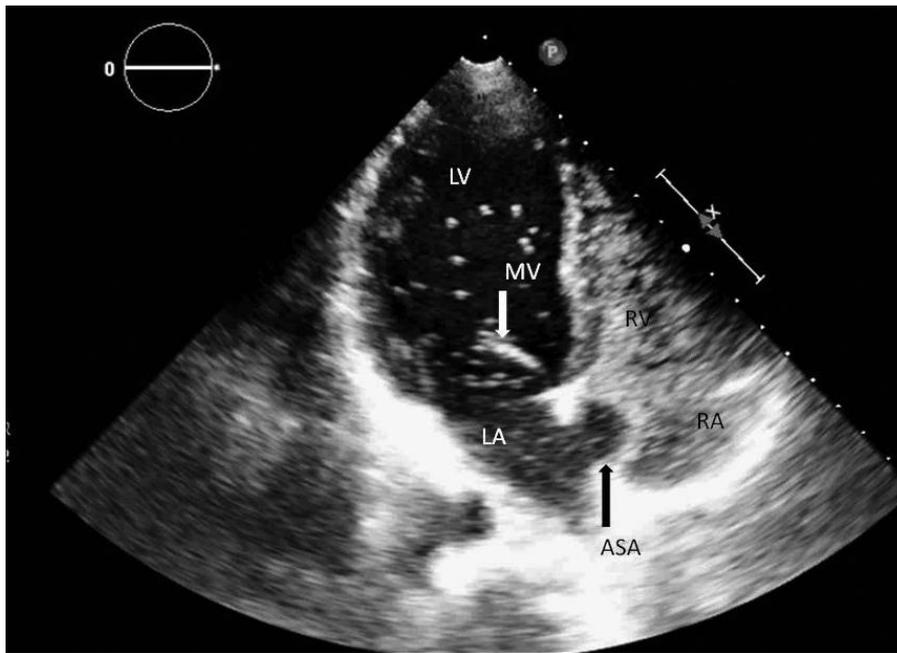


Figure 3. Transthoracic echocardiography four-chamber view with intense contrast in the right and left ventricle-atrium and bubbles in the left ventricle. A saccular atrial septal aneurysm (ASA) of the interatrial septum is also shown. MV, mitral valve; LV, left ventricle, LA, left atrium; RV, right ventricle; RA, right atrium.

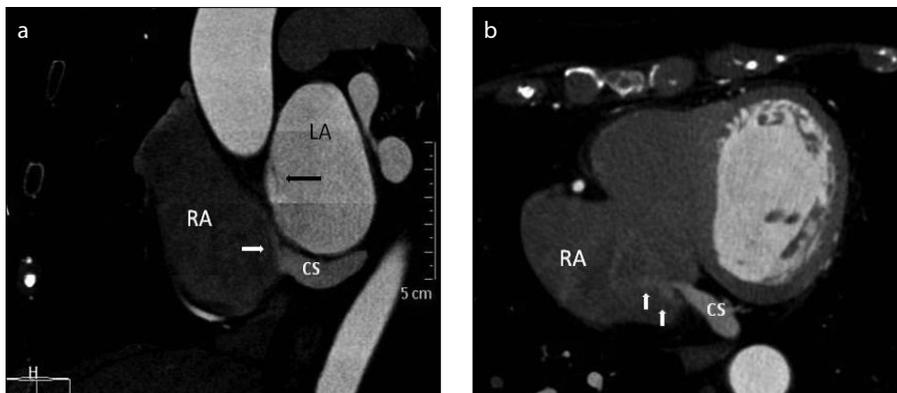


Figure 4. a, b. Sagittal-oblique reformatted CT image (a) shows that the coronary sinus drains into the right atrium with contrast jet (white arrow). The free flap valve (FFV) in the interatrial septum is also seen in the same patient (black arrow). Axial CT image (b) shows a jet flow (white arrows) that does not belong to the patent foramen ovale. RA, right atrium, LA, left atrium; CS, coronary sinus.

respectively). While a tunnel was present in all patients who underwent TTE (n=19), PFO was absent in only four of these patients; it was determined that for tunnel existence only, the sensitivity and specificity were 100% and 78%, respectively. While there was a shunt in the CT scan of one patient, no flow was observed in the TTE of this patient. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of detecting shunt and tunnel existence on CT examination (for PFO diagnosis) were 53%, 75%, 88%, 30%, and 57%, respectively.

ASAs were detected in 16 patients (2%). They were detected in only three (2.4%) of the patients with PFO. The diagnosis was

confirmed by echocardiography in two patients. No shunt flow was observed in these patients on CT. However, a right-to-left shunt was demonstrated in the echocardiographs of these patients. TTE was not performed in the other patient, and the diagnosis was based on CT. The left-to-right shunt flow was demonstrated in this patient on CT.

Discussion

The present study aimed to examine the incidence of PFO and ASA in the Turkish population, using coronary CTA, in order to determine the feasibility of using coronary CTA for PFO diagnosis and assess the diagnostic

feasibility of coronary CTA by conducting a comparison with TTE. The statistical analyses showed high coronary CTA sensitivity, particularly for the presence of an interatrial tunnel, for PFO diagnoses. Thus, we underscore the need for additional assessment of the presence of ASA and tunnels in patients undergoing routine coronary CTA. Also, in selected patients, coronary CTA may also represent a practical and beneficial screening modality for PFO diagnosis, compared with other imaging techniques.

Embryologic interatrial septum consists of the fusion of the septum primum and secundum. The septum primum appears first and leaves behind a window referred to as the ostium secundum. Subsequently, the septum secundum develops at the right atrial side of the septum primum and covers the ostium secundum. The foramen ovale stays between these two septa and carries blood from the inferior vena cava to the LA *in utero*. After birth, the foramen ovale normally closes by the fusion of these two septa. In some individuals, this window stays open and the septum primum remains as a flap-like valve over the foramen ovale (12). An image appearing as a channel in the CT represents the nonfusion of these two embryogenic septa.

The prevalence of PFO is up to 27% in the healthy population (3). It is the most frequently observed cardiac phenomenon in patients aged below 55 years. In addition to being considered as an etiology of cryptogenic stroke, particularly large PFOs are also related to unexplained decompression disease, resulting from paradoxical gas embolism (3). TEE is accepted as the gold standard to evaluate the right-to-left shunt, and some coronary CTA studies comparing the two methods have been performed (1, 11, 13, 14). However, TEE has some disadvantages, including being semi-invasive and making it difficult for the patient to perform the Valsalva maneuver while under sedation. There are studies reporting a comparable sensitivity for TTE and TEE with regard to PFO detection and diagnosis (3–6).

In a retrospective study of 152 stroke patients who underwent cardiac CT and TEE, Kim et al. (13) found left-to-right shunts on CT in 73.1%; this ratio is in good agreement with that reported in our study (62.7%). They also emphasized that when TEE is considered as the gold standard, the appearance of a shunt on CT is a more valuable criterion in PFO diagnosis than the appearance of a channel. On the other hand, the appearance of a channel on CT and of a shunt on

Table 1. Free flap valve and tunnel diameter measurements

Flow groups	Patients with FFV, n (%)	FFV length ^a (mm)	Diameter-1 ^b (mm)	Diameter-2 ^a (mm)	Distance of jet flow ^b (mm)	Grade of jet		
						1	2	3
Total (n=782)	118 (15)	12.1±1 (2.8–26.9)						
Grade 1+2 PFO ^c (n=44)	44 (5.54)	13.2±5.7	2 (0.6–4) ^d	2±0.7 ^e				
Grade 3 PFO (n=74)	74 (9.46)	11.7±5.2	2 (0.9–4.7)	1.7±0.6	8 (2.4–27)	45	23	6

FFV, free flap valve; PFO, patent foramen ovale.
^aFFV length and diameter-2 are presented as mean±standard deviation.
^bDiameter-1 and distance of jet flow are presented as median (min–max).
^cGrade 1 PFO in 30 patients and grade 2 PFO in 14 patients.
^dMeasurement of patients with both grade 1 and grade 2 PFO.
^eMeasurement of patients with grade 2 PFO only.

Table 2. List of patients who underwent transthoracic echocardiography

Patient no.	TTE	FFV (mm)	Jet flow (mm)	Jet grade	Diameter-1 (mm)	Diameter-2 (mm)
1	+	22.1	24	3	3.2	1.9
2	+	14.3	20.5	3	4.7	3.6
3	+	20.2	4.6	1	2.8	2.1
4	-	21.7	0	0	2.8	3.3
5	+	17.9	5.3	1	1.4	1.1
6	+	16.8	0	0	2.1	2.4
7	+	11.5	0	0	3.4	1.9
8	-	6.9	0	0	1.9	1.4
9	+	15.5	12.5	2	1.1	1.3
10	+	4.6	0	0	0.9	0.6
11	+	15.7	0	0	3.4	2.2
12	+	12.8	0	0	1.9	1.8
13	-	17.5	5	1	3.8	2.5
14	+	5.6	8.7	1	0.8	1
15	+	14.9	12.9	2	2.4	1.8
16	-	13.4	0	0	1.7	1.6
17	+	7.8	0	0	2	2.3
18	+	9	0	0	1.8	1.8
19	+	10.7	9	1	1.9	1.6

TTE, transthoracic echocardiography; FFV, free flap valve.

Table 3. Numbers and percentages of patent foramen ovale shunt on CT and TTE

Shunt on CT	Shunt on TTE		Total
	Present	Absent	
Present	8 (42)	1 (5)	9 (47)
Absent	7 (36)	3 (15)	10 (53)
Total	15 (78)	4 (21)	19 (100)

CT, computed tomography; TTE, transthoracic echocardiography.

echocardiography had a higher correlation in our study. When the presence of a tunnel alone on CT was considered as an indicator of PFO, the sensitivity and specificity were

100% and 78%, respectively. These findings suggest that coronary CTA screen may be a useful diagnostic technique, particularly in certain patients.

Saremi et al. (11) examined the length and diameter of the PFO tunnel, whether or not the entry of the flap valve from the right atrial end was patent, and ASA and shunt existence in 264 patients who underwent coronary CTA. In addition, PFO presence was also evaluated in 23 patients who underwent coronary CTA and TEE. A flap valve was detected in 101 patients (38.3%); the right atrial entry was found to be patent in 62 (23.5%) of these patients. A left-to-right shunt was detected in 44 patients (16.7%). While the mean PFO tunnel length was 7.1 mm in patients with a shunt (44 patients), it was found to be 12.1 mm in patients with no detected shunt (57 patients). A shunt was detected in 92.6% of patients with a tunnel length of ≥6 mm, and it was reported that a left-to-right shunt is more frequent in PFO patients with a short tunnel length. A shunt was detected in seven of 23 patients who underwent coronary CTA and TEE. In the present study, a free flap was detected on the CT scan in 118 of 782 patients (15%) who underwent coronary CTA. No significant relationship could be detected between the jet flow existence (shunt) and its degree and FFV length. This finding is not compatible with the findings reported by Saremi et al. (11).

For one patient, a shunt was present on CT, but no flow was observed on TTE. Although TEE is considered as the gold standard for PFO diagnosis, only right-to-left shunts can be evaluated with this technique (11, 15). In general, a left-to-right shunt simultaneously occurs with a right-to-left shunt (bidirectional); however, there may be cases that do not coincide with this condition (11).

CT images should be evaluated at the workstation in different planes to detect the presence of a shunt. Contrast jet flow of the coronary sinus to the RA may be misdiagnosed as a PFO shunt in patients with FFV (Fig. 4). It should also be borne in

mind that absence of an allergy to the iodine-containing contrast medium and renal failure are prerequisites for a coronary CTA. On the other hand, no such requirements are applicable to TTE and TEE. In this regard, echocardiography can be made available to larger patient populations.

It is advantageous to be able to detect shunts in TEE and TTE by increasing the pressure in the RA of the heart with the Valsalva maneuver, depending on the patient's performance. However, it is difficult to evaluate the anatomical characteristics of the interatrial channel by echocardiography, due to its short and angled conduit (16). During coronary CTA, anatomical properties of the PFO channel, including the length and diameter can be examined, and it can also provide functional information regarding the flow of contrast from the LA to the RA. Left-to-right shunts are yet to be fully explored and understood (13). Although the Valsalva maneuver cannot be performed during coronary CTA, as per the results emphasized by Castro et al. (16), interatrial shunt existence carries a risk for cerebral ischemia in patients with PFO, even in the resting state. Nevertheless, it is emphasized in these studies that shunts which appear only with an augmentation maneuver are of little clinical significance, and several activities of daily life are equivalent to performing the augmentation maneuver (e.g., lifting weights, coughing, various sports) (17). Studies have reported that in routine cardiac examinations, the interatrial shunt can be visualized best during the end-systole and mid-diastole (7, 13). Kim et al. (13) have stated that there is no difference between determining the existence of PFO during end-systole and mid-diastole. We have evaluated the reconstructed images in the mid-diastolic phase.

The enhanced activity of the membrane of the fossa ovalis in patients with PFO can mechanically direct the blood in the atrium to the fossa ovalis and the channel. This condition may play a role in the formation of a paradoxical shunt (16). While ASA was defined as the sum of the excursion of the interatrial membrane between the RA and LA ≥ 11 mm in the TEE study performed by Pearson et al. (18) in 410 patients, a protrusion of ≥ 10 mm of the interatrial membrane towards a single (right) atrium on CT, was considered as an ASA in the coronary CTA studies (11, 14).

In a study performed using TEE, the frequency of ASA was found to be 4%–8% in cases without stroke, and 15%–18% in cases with stroke (19). However, we observed a lower ratio in the present study (2%). In patients with PFO, we detected ASA in three patients (2.4%). Among these patients, a passage was

observed in two on TTE, and a shunt was observed in one on CT. It is accepted that approximately 33% of adults with an ASA also have PFO (2, 20). In our study, the prevalence of ASA in cases with (2.4%) and without PFO (1.9%) was still lower than the prevalence reported in the existing literature.

There are some limitations in this study. We evaluated the left-to-right shunt by CT, and the right-to-left shunt by echocardiography. There may be situations where a shunt is determined by CT but not by echocardiography, as in our study. This condition limits the usage of echocardiography as the gold standard for diagnosing PFO. A second limitation to our study is that the Valsalva maneuver cannot be performed in coronary CTA. Right-to-left shunts may be evaluated in the future using cine-CT imaging together with the Valsalva maneuver. The third limitation is that CT data analyses were performed by two radiologists in tandem. Therefore, interobserver variability could not be evaluated. In addition, it might have been better to use the gold standard TEE for comparison, instead of TTE. Finally, we did not perform TTE in all cases with PFO diagnosed by coronary CTA. TTE was performed only when clinically indicated.

In conclusion, high resolution coronary CTA can be used to reveal the interatrial septum during routine coronary examination. Anatomic details of interatrial channel shunts and associated abnormalities (e.g., ASA) can be clearly visualized. Thus, caution should be exercised to account for the possibility of interatrial septum abnormalities on coronary CTA. Additionally, coronary CTA can be used as an alternative method to echocardiography to demonstrate the existence of the interatrial channel and shunt. Coronary CTA constitutes a more practical and efficient alternative to TTE for PFO diagnosis in specific cases.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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