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A comparison of methods to determine patent foramen ovale size

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Abstract

Background: Patent foramen ovale (PFO) is implicated in the pathogenesis of clinical conditions such as cryptogenic stroke and migraine with aura. This study evaluated the challenges of sizing a PFO with different contemporary imaging modalities and assessed the relationship between PFO size and severity of the right-to-left shunt (RLS).

Methods: Patients who were referred to interventional cardiology with the diagnosis of a PFO and had undergone intra-procedural balloon sizing (*n* = 147), transesophageal echocardiogram (TEE) imaging (*n* = 67), or intracardiac echocardiogram (ICE) imaging (*n* = 73) at the time of workup were included in this study. TEE and ICE were used to obtain PFO length and height during normal respiration. A sizing balloon was used to obtain PFO width and height after the septum primum was opened with balloon inflation.

Results: The mean PFO length measured by TEE and ICE differed significantly (*n* = 27, 13.0 ± 4.1 vs. 9.9 ± 3.2 mm, *p* = .001). The mean PFO height measured by TEE and ICE (*n* = 27, 1.4 ± 0.6 vs. 1.7 ± 0.6 mm, *p* = .04), TEE and sizing balloon (*n* = 56, 1.5 ± 1.2 vs. 10.5 ± 4.2 mm, *p* < .0001), and ICE and sizing balloon (*n* = 66, 1.7 ± 0.7 vs. 9.1 ± 3.7 mm, *p* < .0001) also differed significantly. A poor correlation existed between anatomic PFO length or height and functional Spencer TCD grade RLS flow with Valsalva, irrespective of the imaging modality used.

Conclusions: The determination of a PFO size is dependent on the imaging modality used. Sizing balloon demonstrates a larger width or height than ultrasound imaging methods, such as TEE and ICE, because a PFO remains closed most of the time, leading the echocardiogram to underestimate the potential PFO size. Additionally, PFO length and height correlate poorly with the functional RLS grade. These findings imply that ultrasound-based size characterization should not be used to determine whether a PFO should be closed.

KEYWORDS

patent foramen ovale, intracardiac echocardiogram, sizing balloon, transcranial Doppler, right-to-left shunt

1 | INTRODUCTION

A patent foramen ovale (PFO) results from incomplete fusion of the septum primum and septum secundum and is the most common congenital cardiac lesion, present in 20% of the adult population.[1] A PFO produces a potential communication between the right and left atria.[2] Although most patients with a PFO are asymptomatic, a variety of clinical conditions are associated with PFO, including cryptogenic stroke[3–6] migraine with aura,[7] decompression illness,[8] altitude illness,[9] and platypnea-orthodeoxia syndrome.[10] Given the multiple pathologies associated with PFO, there has been interest in determining the predictors of a symptomatic PFO, including PFO size, degree of right-to-left shunt (RLS), and presence of an atrial septal aneurysm (ASA). Several methods for measuring a PFO are available, including non-invasively with a transesophageal echocardiogram (TEE) and invasively with either an intracardiac echocardiogram (ICE) or direct balloon sizing. The PFO dimensions may influence which PFO closure device is used. However, the method chosen for PFO sizing, TEE versus ICE versus sizing balloon, is operator-dependent. Further complicating the fact that different imaging modalities exist for determining the size of a PFO is that the anatomical dimensions (length, height, and width) are often defined imprecisely and used interchangeably, yielding conflicting results for the defect size. This retrospective analysis assessed the differences in measuring the dimensions of a PFO with TEE, ICE, and sizing balloon, and it evaluated the relationship between PFO length and height to shunt grade by transcranial Doppler (TCD).

2 | METHODS

2.1 | Patient population

Of the 997 patients with a suspected PFO who were seen at UCLA Medical Center between 2001 and 2018, 147 had adequate sizing balloon images, 67 had adequate TEE images, and 73 had adequate ICE images. Of the 147 subjects with adequate sizing balloon images, 56 had adequate TEE images and 66 had adequate ICE images for direct comparison. Of the 67 subjects with adequate TEE, 27 had adequate ICE images for direct comparison. The remaining patients in each imaging modality cohort did not undergo the stated imaging, had the imaging performed post-PFO closure, had inadequate images for accurate measurements (i.e., inability to clearly visualize or measure the PFO by both observers), or had images that were irretrievable from the online archive. The sizing balloon was primarily used on larger-appearing PFOs until 2017 and sequentially since.

2.2 | Transesophageal echocardiography and intracardiac echocardiogram

TEE images were reviewed using Syngo software (Siemens Inc., Erlangen, Germany). ICE images, obtained using the ACUSON AcuNav Ultrasound Catheter (Biosense Webster Inc, Irvine, California), were reviewed using Centricity Universal Viewer (GE Healthcare, Chicago, Illinois). Measurements were made using the caliper ruler included in the images, using the built-in ultrasound ruler for calibration. All outside hospital TEE studies (n = 9) were uploaded into the Syngo system and analyzed in the same manner. TEE and ICE still frames that optimally demonstrated the maximal PFO length and height were chosen. The PFO length was defined as the maximum distance of overlap between the septum primum and septum secundum (Figure 1). The PFO height was defined as the maximum distance between the septum primum and septum secundum (Figure 1). Of note, the echocardiogram definition of PFO height corresponds to the balloon waist diameter of the sizing balloon image in the left anterior oblique (LAO) projection (Figure 2). Although 125/147 (85%) sizing balloon images were taken in the left anterior oblique (LAO) angiographic projection
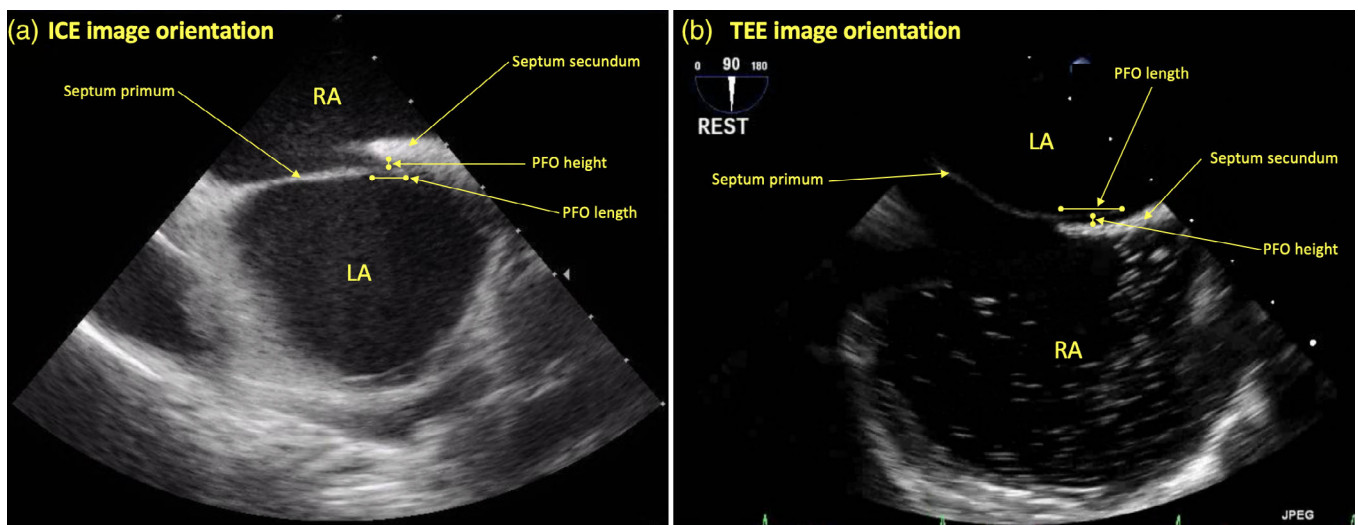

FIGURE 1 ICE and TEE of PFO from the same patient. (a) ICE image. Note that the RA is on top. PFO length = 11.8 mm, PFO height = 1.5 mm. (b). TEE with bubble study. Note that the LA is on top. PFO length = 15.5 mm, PFO height = 1.5 mm. IC, intracardiac echocardiogram; LA, left atrium; PFO, patent foramen ovale; RA, right atrium; TEE, transesophageal echocardiogram
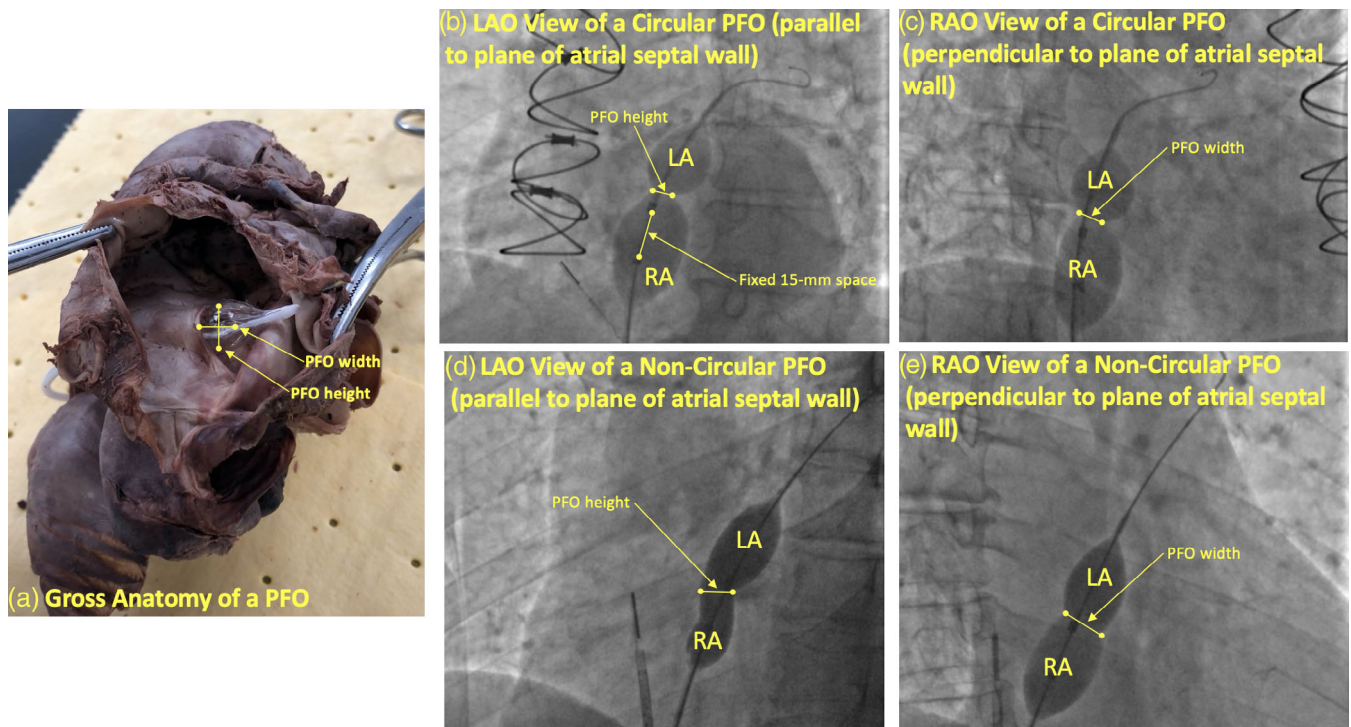
FIGURE 2 PFO Height and Width. (a) An anatomical picture of an inflated Amplatzer sizing balloon going through a PFO at autopsy. (b) and (c) LAO and RAO projections of the sizing balloon through a circular PFO from the same patient, with PFO height (8.3 mm) approximately equal to PFO width (8.2 mm). The LAO view demonstrates how measurements were made (i.e., the PFO height and fixed 15-mm space between the two markers on the sizing balloon were measured using the caliper ruler included with the imaging software and then the PFO height, in pixels, was converted to mm). (d) and (e) LAO and RAO projections of the sizing balloon through a non-circular PFO from the same patient, with PFO height (12.0 mm) unequal to PFO width (14.6 mm). LAO, left anterior oblique; LA, left atrium; mm, millimeters; PFO, patent foramen ovale; RA, right atrium; RAO, right anterior oblique

only, it was assumed that PFO height by sizing balloon was roughly equivalent to PFO width by sizing balloon ($r = 0.91$) because most PFOs transform, with gentle inflation of the balloon, from a slit-like orifice, where height is less than width, to a circular form, where height is equal to width (Figure 2).[11] Routine TEE and ICE imaging do not visualize the PFO width because this requires a three-dimensional enface view of the right atrial septum. The excursion of the atrial septum into the right and left atria was measured, and the presence of an atrial septal aneurysm (ASA) was identified if the distance of septum primum excursion into either atrium was ≥10 mm or the total excursion distance was ≥15 mm (Figure 3).[12]

2.3 | Sizing balloon

The PFO width, defined as the balloon waist diameter in the right anterior oblique (RAO) angiographic projection, was determined using a 24-mm Amplatzer sizing balloon (Abbott Vascular, Chicago, IL). The PFO height, defined as the balloon waist diameter in the LAO projection, was similarly measured. In those cases where only an LAO projection was obtained ($n = 125$), the PFO width was estimated to be equal to the PFO height during balloon stretching based on the observation that most PFOs are nearly circular when stretched by a balloon.[11] Sizing balloon images were reviewed using Centricity Universal Viewer (GE Healthcare, Chicago, Illinois). The caliper ruler
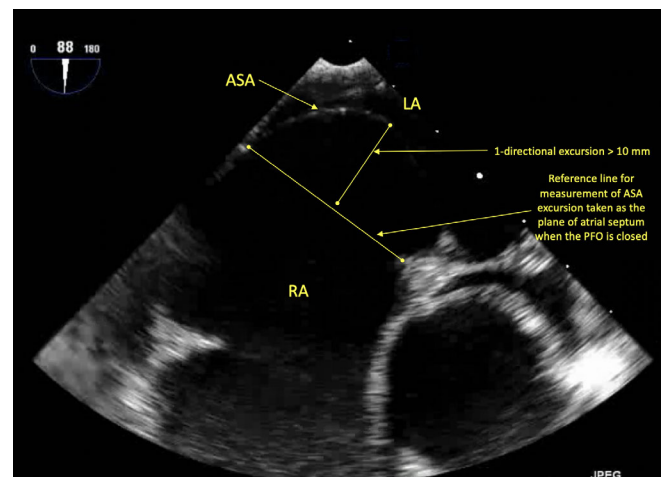

FIGURE 3 TEE demonstrating the presence of an ASA. ASA, atrial septal aneurysm; LA, left atrium; RA, right atrium; TEE, transesophageal echocardiogram

included in the imaging software was used to measure both the balloon waist diameter and the fixed 15-mm space between the two markers on the sizing balloon and then the resulting measurements, in units of pixels, were converted to millimeters (Figure 2).
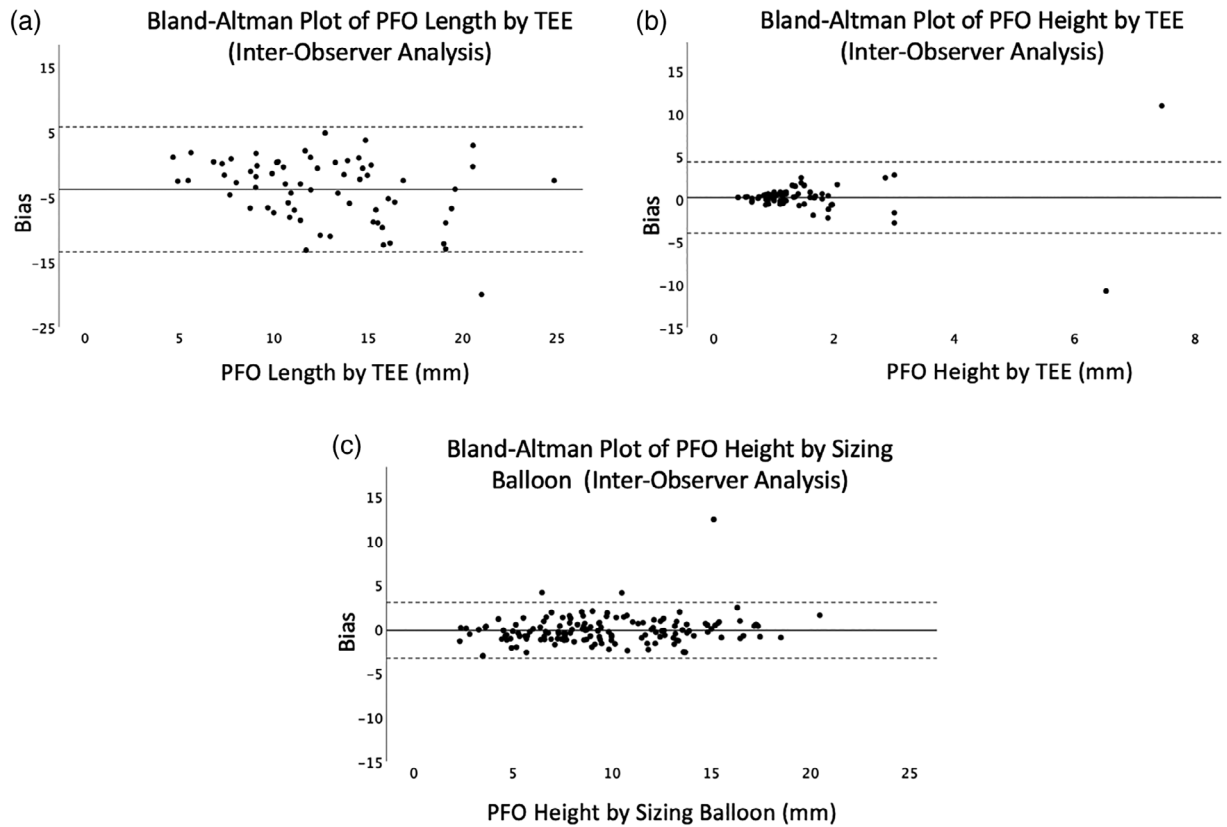
(a) Bland-Altman Plot of PFO Length by TEE (Inter-Observer Analysis)

(b) Bland-Altman Plot of PFO Height by TEE (Inter-Observer Analysis)

(c) Bland-Altman Plot of PFO Height by Sizing Balloon (Inter-Observer Analysis)

FIGURE 4 Inter-observer analyses of PFO measurements by TEE (a–b) and Sizing Balloon (c). Outliers, defined as any value that falls outside the limits of agreement, are minimal, implying good inter-observer reproducibility. PFO, patent foramen ovale; TEE, transesophageal echocardiogram

TABLE 1 PFO size

Imaging modality	Dimension	
Average PFO length (mm)		
TEE (n = 27)	13.0 ± 4.1	p = .001
ICE (n = 27)	9.9 ± 3.2	
Average PFO height (mm)		
TEE (n = 27)	1.4 ± 0.6	p = .04
ICE (n = 27)	1.7 ± 0.6	
TEE (n = 56)	1.5 ± 1.2	p < .0001
Sizing balloon (n = 56)	10.5 ± 4.2	
ICE (n = 66)	1.7 ± 0.7	p < .0001
Sizing balloon (n = 66)	9.1 ± 3.7	

Note: The average PFO length by TEE and ICE and average PFO height by TEE, ICE, and sizing balloon significantly differ from each other.
Abbreviations: ICE, intracardiac echocardiogram; PFO, patent foramen ovale. TEE, transesophageal echocardiogram.

2.4 | Transcranial Doppler

An agitated saline bubble study was conducted at rest and with Valsalva prior to PFO closure to evaluate the degree of RLS. The agitated saline mixed with 1 mL of blood and 0.5 mL of air was administered by injection into an antecubital vein, and the number of bubbles seen in the middle cerebral arteries over 1 min was recorded. The Spencer Logarithmic Scale criteria was used to classify PFO shunt grade[13]: no bubbles (grade 0), 1–10 bubbles (grade 1), 11–30 bubbles (grade 2), 31–100 bubbles (grade 3), 101–300 bubbles (grade 4), and ≥ 300 bubbles (grade 5).

2.5 | Statistical analysis

Two individuals independently completed measurements for the available images and then inter-observer Bland–Altman analyses were performed to assess the reproducibility of the PFO dimensions between observers. Outliers, defined as values that fell outside the limits of agreement (average of the difference between the two measurements ±1.96 × standard deviation), were adjudicated by a third individual, and the average of the three values was taken to be the final value. PFO length by TEE and ICE and PFO height by TEE, ICE, and sizing balloon were compared using paired Student's t-test, and p < .05 was considered statistically significant. The relationship between PFO length by TEE and ICE and height by TEE, ICE, and sizing balloon and Spencer TCD grade with Valsalva pre-PFO closure was analyzed using a linear regression model and then the Pearson correlation
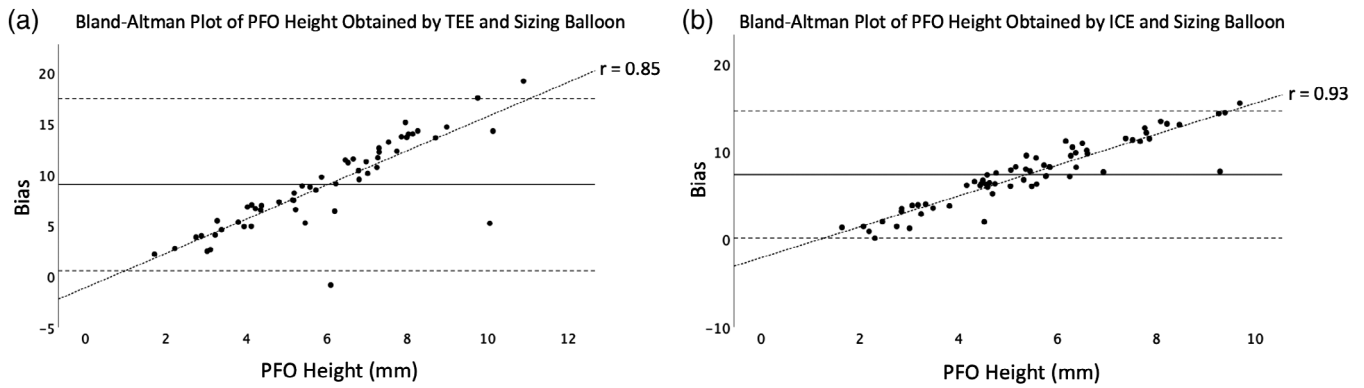
FIGURE 5 Bland–Altman Plots of PFO Height by Sizing Balloon versus TEE (a) and ICE (b). Regression modeling revealed a linear and positive relationship between PFO height and bias, implying that the larger the anatomic size of a PFO obtained with a sizing balloon, the more TEE and ICE underestimate the PFO size. ICE, intracardiac echocardiogram; PFO, patent foramen ovale; TEE, transesophageal echocardiogram
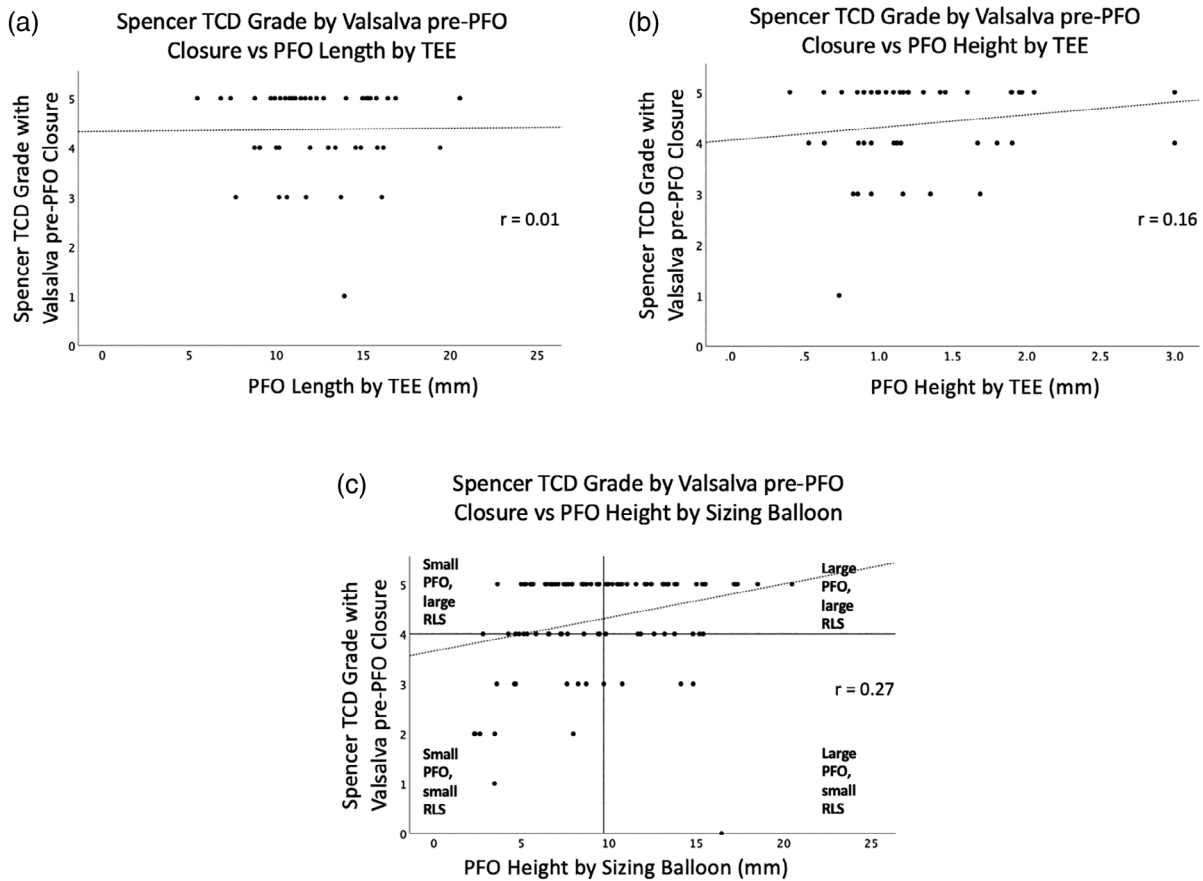

FIGURE 6 Relationship between PFO Size by TEE (a–b) and Sizing Balloon (c) and Spencer TCD Grade with Valsalva Pre-PFO Closure. (a) and (b) PFO length and height by TEE did not correlate with RLS severity. (c) PFO height by sizing balloon correlated in a weak and positive manner with RLS severity. After dividing the distribution into four quadrants by drawing a line on the x-axis that reflects the mean PFO diameter by sizing balloon (9.7 mm) and another line on the y-axis that reflects the Spencer TCD grade with Valsalva pre-PFO closure that defines a "significant" PFO,[4] it becomes evident that small PFOs can be associated with either a small or large RLS whereas large PFOs are most often associated with large RLS. PFO, patent foramen ovale; TCD, transcranial Doppler; TEE, transesophageal echocardiogram

TABLE 2 ASA data

Imaging modality		Average PFO length (mm)		Average PFO height (mm)		Average Spencer TCD grade with Valsalva pre-PFO closure	
TEE (n = 67)	ASA+ (n = 11)	12.4 ± 3.7	p = .81	2.3 ± 2.4	p = .21	4.1 (n = 7)	p = .65
	ASA− (n = 56)	12.7 ± 4.5		1.3 ± 0.5		4.4 (n = 39)	
ICE (n = 73)	ASA+ (n = 10)	8.3 ± 2.4	p = .20	1.9 ± 0.4	p = .14	3.7 (n = 7)	p = .75
	ASA− (n = 63)	9.4 ± 2.9		1.6 ± 0.7		4.0 (n = 42)	

Notes: The average PFO length, PFO height, and Spencer TCD grade with Valsalva prior to PFO closure did not differ significantly between the ASA and non-ASA cohorts by TEE or ICE.

Abbreviations: ASA, atrial septal aneurysm; ICE, intracardiac echocardiogram; PFO, patent foramen ovale; TCD, transcranial Doppler; TEE, transesophageal echocardiogram.

coefficient, r, was calculated. All analyses were conducted using SPSS Statistics v26.

3 | RESULTS

Inter-observer analyses of the PFO length and height measurements are shown in Figure 4. The assessments revealed 1/67 (1.5%) outlier in the TEE length cohort, 2/67 (3%) outliers in the TEE height cohort, 4/73 (5.5%) outliers in the ICE length cohort, 4/73 (5.5%) outliers in the ICE height cohort, and 3/147 (2.0%) outliers in the sizing balloon cohort.

TEE, ICE, and sizing balloon measurements of the anatomic components of the PFO are shown in Table 1. The average PFO length measured by TEE was 13.0 ± 4.1 mm, compared to 9.9 ± 3.2 mm by ICE (n = 27, p = .001). The average PFO height measured by TEE, ICE, and sizing balloon was also statistically different. In the TEE and ICE cohort (n = 27), the average PFO height by TEE was 1.4 ± 0.6 mm, compared to 1.7 ± 0.6 mm by ICE (p = .04). In the TEE and sizing balloon cohort (n = 56), the average PFO height by TEE was 1.5 ± 1.2 mm, compared to 10.5 ± 4.2 mm by sizing balloon (p < .0001). In the ICE and sizing balloon cohort (n = 66), the average PFO height by ICE was 1.7 ± 0.7 mm, compared to 9.1 ± 3.7 mm by sizing balloon (p < .0001).

Bland–Altman plots of PFO height by sizing balloon compared to TEE and to ICE are shown in Figure 5. Linear regression modeling of these plots revealed that PFO height significantly correlated with bias in a linear and positive direction (r = 0.85 for sizing balloon versus TEE and r = 0.93 for sizing balloon versus ICE).

Linear regression modeling of PFO length by TEE and PFO height by TEE and sizing balloon versus Spencer TCD grade with Valsalva pre-PFO closure are shown in Figure 6. PFO height by sizing balloon correlated the most, but still poorly, with Spencer TCD grade (r = 0.27).

ASA data are presented in Table 2. Of the 67 patients with adequate TEE imaging for making PFO measurements, 11 (16.4%) had an ASA. Similarly, of the 73 patients with adequate ICE imaging for making PFO measurements, 10 (13.7%) had an ASA. The average PFO length, PFO height, and Spencer TCD grade with Valsalva pre-PFO closure did not differ significantly between the ASA and non-ASA cohorts by TEE or ICE.

4 | DISCUSSION

The major findings of this study are: (a) PFO size measurements have good inter-observer reproducibility, (b) TEE and ICE yield minor but significantly different results for PFO length and height, (c) TEE and ICE significantly underestimate PFO dimensions (defined as height on ultrasound) compared to balloon sizing, and (d) PFO dimensions by ultrasound or balloon sizing correlate poorly with Spencer TCD grade at rest or with Valsalva.

Inter-observer reproducibility, a method employed to assess the degree to which different observers give consistent estimates of the same observation, is important for data validation.[14] The Bland–Altman plots obtained in this study show a minimal number of outliers, demonstrating good agreement between the measurements obtained by the two independent observers. Furthermore, the measurements obtained for PFO height by TEE in this study (1.4 ± 0.6 mm) are similar to those obtained by Tanaka et al., at 1.5 ± 1.1 mm, but different compared to Lee et al., at 2.0 ± 1.2 mm.[15,16] Similarly, the measurements obtained for PFO length by TEE in this study (13.0 ± 4.1 mm) are similar to those reported by Vitarelli et al., at 11.3 ± 5.6 mm, but different compared to Tanaka et al., at 2.2 ± 0.9 mm, who used a slightly different definition for PFO length (=overlap of the septum primum and secundum).[15,17] The discrepancies can be due to different study populations, different definitions for PFO dimensions, and different planar views for obtaining measurements, which highlights the importance of clearly defining these.

Accurate determination of PFO size is important for successful PFO closure.[18] An undersized PFO closure device could result in residual RLS, leading to recurrent thromboembolic events or migraine,[19] or suboptimal anchorage to the surrounding structures, increasing the risk of device embolization.[20] The use of an oversized PFO closure device, conversely, could predispose to atrial wall erosion and aortic injury.[21] Current methods for sizing a PFO include non-invasive ultrasound (TEE),[22] invasive ultrasound (ICE),[23] and invasive fluoroscopy (sizing balloon).[11] Since non-invasive imaging is most practical, TEE has become the standard arbiter of PFO size determination. The results of the current comparison study suggest that TEE and ICE yield similar but statistically different measurements for the size of a PFO. This is in

accord with a study by Vigna et al., who measured PFOs using TEE and ICE in 45 patients and found a significant disagreement between the two imaging modalities.[24]

Compared to the dimensions of a PFO stretched by a sizing balloon, the PFO size by TEE is 7.5 times smaller, and the size by ICE is 5 times smaller. In a landmark autopsy study of 965 normal hearts assessing the incidence and size of PFO over 10 decades of life, there were 263 (27%) PFOs. The difference in PFO prevalence by autopsy (27%) and clinical methods (TCD = 20%) is different because pathologists use a 1 mm probe to define the presence of a PFO, but these small PFOs are not clearly defined by functional testing with agitated saline bubble studies. The maximal PFO diameter, measured using stretched calibrated probes, ranged between 1 and 19 mm, a range more similar to the PFO height by sizing balloon (2.3–20.5 mm) than by either TEE (0.47.5 mm) or ICE (0.6–5.4 mm).[1] Neither TEE nor ICE provides as large a measurement of the PFO compared with sizing balloon because inflation of the sizing balloon with diluted contrast medium opens the PFO to its maximal anatomical size and shape. This observation challenges a common assumption that a PFO that is small by TEE measurements could not be the responsible pathway for a paradoxical embolism.[25]

Sievert et al. evaluated the incidence of residual RLS in 281 patients who underwent PFO closure with the aid of a sizing balloon and found that a residual shunt was present in 5.5% of patients at a mean follow-up of 12 ± 16 months.[26] Scacciatella et al. reported that among 231 patients who underwent PFO closure under TEE guidance, a severe residual shunt was present in 8% of patients at the time of echocardiographic follow-up and Moon et al. found that, among 38 patients who had their PFO closed with intraprocedural TEE guidance, 26% had a significant residual shunt at the 9-month follow-up mark.[27,28] Similarly, Rigatelli et al. observed that among 1,000 patients who underwent PFO closure with the assistance of ICE, 6.2% of patients had a residual shunt at follow-up.[29] The authors suggest that sizing balloon-guided PFO might result in lower rates of residual RLS compared to TEE and ICE. However, device characteristics also play a significant role in the frequency of residual shunt (data submitted for publication).[30]

Not only do TEE and ICE underestimate PFO size but they underestimate the size of larger PFOs more than smaller ones. From a clinical perspective, the larger the stretched PFO size by sizing balloon, the greater the PFO size underestimation by TEE and/or ICE. This is consistent with studies that identified risk factors for residual RLS following PFO closure. Shafi et al. found that among 51 consecutive patients with PFO-associated stroke or TIA who underwent TEE-guided PFO closure, a larger baseline PFO size was the only independent predictor of a residual shunt.[31]

Our group previously reported that there is only a mild correlation between the size of the embolic stroke by volumetric MR brain imaging and PFO height ($r = 0.03$) or length ($r = 0.09$) by TEE, or shunt grade by TCD ($r = 0.21$).[32] The current study shows that there is also no significant correlation between RLS grade by TCD and PFO length by TEE, or PFO height by TEE or balloon

sizing. It is reasonable to assume that a larger PFO would permit a larger flow of blood from the right atrium to the left atrium. However, paradoxical embolization does not rely solely on the size of the PFO tunnel between the septum primum and septum secundum but rather on a combination of morphological and functional parameters of the PFO.[33] This concept is supported by the observation that of the six randomized clinical trials that assessed the efficacy of PFO closure in preventing recurrent cryptogenic stroke, only DEFENSE-PFO used PFO size as an inclusion criterion.[34–39]

5 | LIMITATIONS

The main limitations of this study are its retrospective design, the assumption that most PFOs are nearly circular, a small sample size of ASA patients, lack of ≥1 imaging type for all patients being assessed, and measuring PFO without Valsalva maneuver. Investigators stratify a PFO as high-risk if it is associated with an ASA because it is assumed that the presence of an ASA increases the anatomic size or functional degree of RLS and therefore the risk of recurrent embolic events.[12,40] The current study did not find a significant difference in PFO length, PFO height, or Spencer TCD grade between those with or without an ASA by TEE or ICE. Given the small sample size of ASA patients (11 by TEE and 10 by ICE), it is difficult to reach any reliable conclusions.

6 | CONCLUSIONS

This article shows that PFO measurements obtained from ultrasound images, whether non-invasively with TEE or during a right heart catheterization with ICE, do not correspond with the measurements of the anatomic opening of a PFO tunnel with a sizing balloon. These findings indicate that ultrasound measurements by TEE and ICE underestimate the anatomic size of a PFO. Additionally, PFO length, height, and width, whether measured non-invasively or invasively, do not correlate with Spencer TCD grade, implying that the degree of RLS is only partially affected by PFO size. Other forces that affect right-to-left flow across a PFO include anatomic factors, such as the presence of a Eustachian valve and/or a Chiari network, and functional factors that influence right atrial pressure, such as the phase of respiration and physiologic maneuvers that increase venous return (e.g., Valsalva maneuver). These observations suggest that PFO anatomic size should not be used as a criterion when deciding whether to close a PFO.

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