Improved differential diagnosis of intracardiac and extracardiac shunts using acoustic intensity mapping of saline contrast studies

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Received 1 February 2019; editorial decision 4 May 2019; accepted 15 May 2019

Aims

The aim of this study was to test the hypothesis that temporal patterns of saline contrast entry into, and exit from the left heart are significantly different in intra- and extra-cardiac shunts and can be used to differentiate the shunt mechanism when Valsalva manoeuvre cannot be performed, or is of uncertain quality. We propose a novel approach of mapping the temporal changes in acoustic intensity (AI) within the left and right heart to identify and define these unique patterns.

Methods and results

We screened cases of right to left shunting on resting agitated saline contrast echocardiograms with clinical criteria that identified the origin of shunting as either a patent foramen ovale or pulmonary arteriovenous malformation. Acoustic time-intensity curves were generated from the right and left heart chambers that reflected the change in saline contrast density over time. Several novel pre-specified parameters were measured from these curves, in addition to the standard heartbeat counting method, to characterize the entrance (wash-in) and exit (wash-out) patterns of saline contrast in the left heart. Statistical analysis showed that AI mapping provided superior differentiation of the two populations than did the traditional beat counting method.

Conclusion

Diagnosis of shunt mechanism from saline contrast studies can be improved over current methods through the use of AI mapping to define the rapidity that peak contrast effect develops, the speed that the contrast effect decays, and the contrast intensity late in the recording.

Keywords

acoustic intensity mapping • saline contrast echocardiography • patent foramen ovale • pulmonary arteriovenous malformation

Introduction

Detection of right to left cardiac shunts is an increasingly common indication for transthoracic echocardiography (TTE). Because colour Doppler alone has very low sensitivity for shunts, intravenous (IV) injection of agitated saline contrast (ASC) has become the standard approach for shunt detection in patients with stroke or unexplained hypoxaemia. ASC can differentiate between intracardiac shunts due to a patent foramen ovale (PFO) or atrial septal defect (ASD) and extracardiac shunts due to pulmonary arteriovenous malformation (PAVM). Although both shunt mechanisms can cause hypoxaemia and paradoxical embolism, the appropriate subsequent diagnostic testing and the specific treatment for an ASC study positive for right to left shunt differs depending on the mechanism. PAVM can be closed via embolism to reduce neurological event rates. Recent publications have shown that the closure of a PFO in patients with cryptogenic stroke can reduce the risk of recurrent stroke.

Currently, increased post-Valsalva opacification of the left atrium and left ventricle (LALV) compared to resting LALV opacification is regarded as the most reliable finding for PFO or ASD on TTE. Conversely, no change with Valsalva is said to imply PAVM. However the quality of the Valsalva manoeuvre is highly variable and often cannot be performed. Therefore, the time interval between right atrium and right ventricle (RARV) contrast and LALV contrast appearance has been suggested as an alternative method. A short-time interval (≤3 heart beats) implies PFO whereas a long time interval (>6 heart beats) is presumed to be associated with the anatomically longer circuit of an extracardiac shunt and signifies a PAVM.

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data to support these recommendations and little guidance as how to perform this measurement.

To address the limitations of Valsalva manoeuvre and beat counting and improve the diagnostic accuracy of ASC studies, we employed acoustic intensity (AI) mapping technology to register simultaneous RARV and LALV time-intensity curves in ASC studies performed without Valsalva manoeuvre in patients with known or highly probable PFO or PAVM. Our specific objectives were (i) to use AI to quantify any differences in contrast patterns between PFO and PAVM patterns; (ii) to compare the diagnostic accuracy of AI to traditional heartbeat counting; and (iii) to determine the incremental diagnostic power of AI when used in conjunction with traditional heartbeat counting.

Methods

The Barnes-Jewish Hospital Echocardiography database was screened over five years for positive saline contrast studies. Criteria for inclusion and classification of cases were listed below.

PFO cases

One or more of the following: (i) inter-atrial septal aneurysm present defined by right or left septal deviation from midline of >1 cm or total excursion of the inter-atrial septum of >1.5 cm; (ii) Valsalva manoeuvre significantly intensified LALV opacification; (iii) transoesophageal (TOE) or TTE visualization of defect by colour Doppler or 2D.

PAVM cases

One or more of the following findings: (i) known history of hereditary haemorrhagic telangiectasia (HHT); (ii) known end-stage liver cirrhosis; (iii) angiographically documented PAVM present.

All cases

All cases meet the following criteria: (i) images recorded in uncompressed raw digital data format suitable for offline AI analysis; and (ii) recording initiated prior to RARV contrast entry and of sufficient duration to include late evolution of contrast effect.

Exclusion criteria were as follows: (i) irregular cardiac rhythm; (ii) excessive acoustic artefact overlying the cardiac image or excessive cardiac or respiratory motion or poor signal to noise ratio.

All analyses were performed on resting agitated saline studies only and not on acquisitions with Valsalva manoeuvre. Studies were transferred to an offline workstation (Echopac® General Electric, Norway) for AI mapping.

AI analysis

Regions of interest (ROI) were drawn in the apical four-chamber to occupy the largest area of the RA or RV and LA or LV free from overlap of cardiac structures or artefacts from adjacent extracardiac structures. Acoustic time-intensity curves were generated from both ROIs to quantify the brightness of reflected echoes as an indicator of bubble density over the entire time of image recording (Figure 1A and Supplementary data online, Movie SA). Despite 320 Gaussian smoothing, some heartbeat-related sinusoidal intra-beat variation persisted. Therefore, values were measured as the mean of this intra-beat variation (Figure 1B). Although patients were in baseline respiratory state, occasional respiratory variation in contrast intensity was also present in some cases, especially in the RARV curves (Figure 1A, asterisks).

AI quantification and measurement

AI measurement employs a logarithmic scale. Y-axis values of these curves represent a ratio of average pixel intensity within the ROI compared to a reference level, with Y-axis units expressed in decibels (Supplementary data online, Appendix S1).

Parameters measured

Table 1 lists the parameters from the AI curves that were used to define the contrast patterns.

In addition to the traditional heartbeat count from RARV opacity to LALV onset shown in row 1, our new indices are divided into those reflecting the rate of growth of LALV contrast, or ‘wash-in’ phase shown in rows 2–3, and those reflecting the clearance or emptying phase of LV contrast, or ‘wash-out’ phase, shown in rows 4–6. Wash-in was quantified by the time interval or number of beats between LALV onset and peak AI. Wash-out was quantified in three ways: (i) final LALV AI-baseline LALV AI, reflecting how completely contrast had cleared; (ii) LALV contrast clearance as the fraction of the total amplitude of LALV AI increase during wash-in that dissipated during wash-out, or (peak AI-final AI)/(peak AI-baseline AI); and (iii) final interventricular AI ratio calculated as the ratio of LALV AI to RARV AI at the end of the recording regardless of recording length.

Statistical analysis

Due to concerns about possible non-normal distribution of our sample and underlying population values, measurements were summarized by median (first quartile–third quartile) and compared between PAVM and PFO groups for significant differences via the non-parametric two-tailed Mann–Whitney U test.

Receiver operating characteristic and logistic regression analysis

Discrimination was further assessed by comparison of each measure to traditional beat counting using receiver operating characteristic (ROC) curve and area under the curve (AUC). We defined PFO as the ‘diseased’ state and sensitivity at a given threshold value of a parameter as the probability that a PFO case exceeds that value.

The ability of each newly defined measure to identify PFO when added to traditional heartbeat counting was evaluated by building a two-parameter multivariable logistic regression model for each measure that included that particular measure and traditional heartbeat counting as independent predictor variables. The corresponding AUC of the resulting model was tested for statistically significant difference from the AUC of the traditional beat counting alone.

Reclassification index analysis

Recent literature favours use of reclassification indices over ROC-AUC analysis to assess improvement in diagnostic discrimination with addition of new parameters. To further describe the ability of each parameter to improve upon traditional beat counting, the Net Reclassification Improvement (NRI) and the Integrated Discrimination Improvement (IDI) indices were determined (Supplementary data online, Appendix S2). The NRI and IDI results were tested for statistical significance according to the method of Pencina et al. All analyses were conducted in SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

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Results

Population
We identified 20 cases with PAVM and 20 cases with PFO that met our inclusion/exclusion criteria. The average recording duration measured from start to completion of image acquisition and heart rate for PAVM cases was 16.1 s [standard deviation (SD) 6.1, range 8.7–27.5] at 83.6 bpm (SD 15.4, range 55–111) and for PFO cases, 17.9 s (SD 4.4, range 8.5–29.4) at 76.9 bpm (SD 17, range 56–101). This equated to an average of 22.4 cardiac cycles captured for PAVM

Table 1  Definitions

<table>
<thead>
<tr>
<th>Measurement definition</th>
<th>Related contrast dynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional beat counting</td>
<td>Number of beats from full RA opacity to LALV onset</td>
</tr>
<tr>
<td>Wash-in indexes</td>
<td>Time interval from LALV onset to LALV PEAK Al (s)</td>
</tr>
<tr>
<td>Wash-out indexes</td>
<td>Number of beats from LALV onset to PEAK LALV Al</td>
</tr>
<tr>
<td></td>
<td>Difference in LALV Al: final-baseline (dB)</td>
</tr>
<tr>
<td></td>
<td>LALV (peak Al-final Al)/(peak Al-baseline Al)</td>
</tr>
<tr>
<td></td>
<td>Final interventricular Al ratio: LALV/RARV</td>
</tr>
</tbody>
</table>

dB, decibels.
cases (SD 7.3, range 12–36) and 21 cycles (SD 6.5, range 10.5–37) for PFO cases.

**Traditional beat counting**

As expected there were fewer beats between RARV opacification and LALV onset in PFO cases compared to PAVM, with group means 2.2 vs. 4.0 beats, respectively (Table 2, Row 1 and Figure 2A).

Although the difference in beat counts was highly statistically significant (P = 3.56 × 10⁻⁸) by two-tailed Mann–Whitney test, the individual values show considerable overlap, especially evident in the intermediate range of 3–6 beats, noted in the literature, but also some overlap in the ranges <3 and >6 beats is present.¹¹

**Wash-in phase intensity analysis**

The LALV wash-in phase time duration of contrast (Table 2, Rows 2 and 3 and Figure 2B and C) was significantly longer in PAVM than PFO (P = 3.2 × 10⁻⁵) and more statistically significant than heartbeat counting. Mean time from first appearance of LALV contrast to peak opacification was 4 s and 5.7 beats for PAVM compared to 1.38 s and 1.92 beats in PFO. The jitter charts (Figure 2B and C) show that overlap is present, but much less pronounced than for beat counting. From the jitter charts it is seen that greater than 5 beats from LALV saline contrast onset to peak intensity strongly favours PAVM, whereas <3 beats favours PFO.

**Wash-out phase AI analysis**

The wash-out phase was also significantly different between PAVM and PFO. We used three separate measures to analyse wash-out.

**Comparison of final LALV AI to baseline AI (before contrast appeared in the LALV)**

In patients with PFO, LALV AI, on average, fell back to within 1 dB of pre-contrast AI, whereas in PAVM, LALV AI persisted, on average, at 11.3 dB above baseline values (Table 2, Row 4 and Figure 2D) reflecting the persistence of LALV contrast at high-intensity levels in PAVM at the end of recording vs. the rapid decay of intensity in PFO. There is much less overlap of values than for beat counting and the difference in distribution of values reached much greater statistical significance (P = 1.29 × 10⁻⁷ vs. P = 3.56 × 10⁻⁴, respectively).

**Comparison of fractional clearance of LALV AI at end of recording**

There was a significantly smaller decline (P = 9.07 × 10⁻⁶) in LALV AI from its peak value in PAVM cases compared to PFO cases as reflected by the ratio of the difference between peak and final AI divided by the difference between peak and baseline AI values (Table 2, Row 5 and Figure 2E). This measure had the highest statistical significance of all parameters studied and presumably reflects the steady drainage of contrast from the lungs in PAVM vs. the transient episodic nature of shunt across the atrial septum. There was minimal overlap in values as seen in the jitter chart. There is markedly greater fractional clearance of contrast in PFO versus PAVM (0.92 or 92% versus 0.18 or 18%, respectively, Table 2).

**Comparison of the ratio of LALV to RARV contrast intensity at the end of recording**

Continued flow of contrast into the LALV in PAVM results in LALV AI exceeding RARV intensity late in the recording in most PAVM cases (final interventricular ratio >1), whereas this is not observed with PFO. Thus, in our PAVM cases, final LALV contrast intensity averaged 13.2 times greater (1320%) than RARV intensity at the end of image acquisition (Table 2, Row 6 and Figure 2F). By comparison, in patients with PFO, final LALV AI was a small fraction of RARV intensity, averaging only 0.16 or 16% of RARV intensity at end of recording (Supplementary data online, Movie S8). As with the first two new measures, there is visually much less overlap of values than for traditional heartbeat counting. Although the Mann–Whitney P-value was slightly higher than heartbeat counting (P = 5.33 × 10⁻⁴, vs. P = 3.56 × 10⁻⁴, respectively), the ratio was <1 in all PFO cases and was >1 in half the PAVM cases signifying that ratios exceeding one are common (sensitivity in the range of 50% ± 11%) in PAVM and highly diagnostic.

**ROC-AUC analysis**

The ROC-AUC for the five new measures were all statistically significant (P < 0.001, Table 3 and Figure 3). When compared with the AUC for traditional beat counting, the ROC-AUC for the final-baseline AI difference and the AI clearance ratio were significantly greater than

### Table 2  Acoustic time-intensity curve findings

<table>
<thead>
<tr>
<th>Measurement</th>
<th>PFO (n = 20)</th>
<th>PAVM (n = 20)</th>
<th>Mann–Whitney P-value, PFO vs. PAVM (two tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional beat counting</td>
<td>Number of beats from full RA opacity to LALV onset</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Time interval from LALV onset to LALV PEAK AI (s)</td>
<td>0.97</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>Number of beats from LALV onset to PEAK LALV AI</td>
<td>1.24</td>
<td>1.92</td>
</tr>
<tr>
<td>Wash-out indexes</td>
<td>Difference in LALV AI: final-baseline (dB)</td>
<td>0.7</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>LALV (peak AI-final AI)/(peak AI-baseline AI) (dB)</td>
<td>0.95</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Final interventricular AI ratio: LALV/RARV (dB)</td>
<td>0.1</td>
<td>0.16</td>
</tr>
</tbody>
</table>

dB, decibels.
(A) Jitter graph showing results when the traditional beat counting method from initial RARV opacification to initial LALV opacification was used to differentiate PFO from PAVM patients. (B and C) Jitter graphs with assessment of wash-in speed of contrast into LALV based on time and number of beats, respectively. Because of the wide range of values in graphs C and F, the Y-axis is separated into two sections in C and the Y-axis is logarithmic in F in order to make the individual lower values more discrete. (D) Jitter graph with degree of wash-out of LALV contrast is seen as the difference between final and baseline LALV intensity. (E and F) Persistence of LALV contrast is assessed in E as the difference between peak and final LALV acoustic intensity and in F as an LALV/RARV intensity ratio. aMann–Whitney. bLog transformed t-test with unequal variances.
Table 3  ROC-AUC and logistic regression

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Area under ROC curve</th>
<th>P-values, bivariate logistic model vs. ‘beats: opacity to onset’ alone (AUC = 0.831)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional beat counting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of beats from full RA opacity to LALV onset</td>
<td>0.831</td>
<td>NA</td>
</tr>
<tr>
<td>Wash-in indexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time interval, LALV onset to peak intensity</td>
<td>0.896</td>
<td>0.429</td>
</tr>
<tr>
<td>Number of beats, LALV onset to peak intensity</td>
<td>0.888</td>
<td>0.533</td>
</tr>
<tr>
<td>Wash-out indexes</td>
<td></td>
<td></td>
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<tr>
<td>Intensity difference LALV: final-baseline</td>
<td>0.989</td>
<td>0.029</td>
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<tr>
<td>Final interventricular intensity ratio: LALV/RARV</td>
<td>0.821</td>
<td>0.921</td>
</tr>
<tr>
<td>AI clearance ratio: (peak-final)/(peak-baseline)</td>
<td>0.995</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Figure 3  ROC curves for each of the wash-in and wash-out parameters tested (solid lines) compared to heartbeat counting (dashed lines). In the Top 2 graphs and bottom left and right graphs the new parameters show superior AUC compared to heartbeat counting. Legends contain AUC and P-values.
the traditional beat counting AUC. Similarly, in bivariate logistical models, the combination of traditional beat counting in conjunction with final - baseline AI difference or with the fractional clearance ratio showed statistically significant improvement in AUC compared to beat counting alone. The other three measures added to heartbeat counting showed a strong but not statistically significant trend towards improvement in AUC.

Reclassification index analysis
In contrast to the ROC-AUC, for both the NRI and the IDI, the addition of any one of the five new parameters to traditional beat counting led to a statistically significant improvement (all \( P < 0.001 \) except final interventricular ratio \( P = 0.027 \)) in correct classification of cases compared to traditional beat counting alone (Table 4).

For the NRI, correct reclassification of PFO or PAVM occurred in at least 20%, and up to a high of 90% of cases depending on which new parameter was employed. Similarly for the IDI, reclassification ranged from 0.173 to 0.638, values >0 indicating improvement.

### Discussion

#### Main findings
Our results demonstrate that the temporal evolution of LALV AI during wash-in and wash-out phases after IV saline contrast provides highly diagnostic information for differentiation of PFO from PAVM without relying on Valsalva manoeuvre. In fact, the results show that these patterns have substantially greater discriminatory power than the traditional method of heartbeat counting from RARV opacity to LALV appearance, yet they have been overlooked in prior work on interpretation of saline contrast studies. It is possible that exclusive reliance on heartbeat counting alone has resulted in misclassification, or unnecessarily indeterminate readings in saline shunt studies and this can be improved by attention to the LALV wash-in and wash-out patterns. Moreover, since it is often not possible to determine whether a Valsalva is adequate, in cases where there is no difference in LALV contrast pre- and post-Valsalva, these features may help the interpreter avoid misclassification of PFO as a PAVM.

The temporal patterns associated with PAVM and PFO were readily differentiated with AI mapping. The features we found to be diagnostic reflect the unique shunt kinetics of PAVM and PFO and these are due to the marked differences in the anatomy and physiology of PAVM and PFO shunts. The patterns are often so distinctive, as can be seen in the accompanying figures, that the on-screen qualitative visual morphology of the acoustic time-intensity curves are likely to be sufficient for differential diagnosis in most cases in the clinical laboratory, obviating time consuming measurements of the videometric density, reliance on specific quantitative intensity thresholds, or measurement of time intervals that we employed in this study for rigorous statistical analysis. In particular, PAVM is associated with a gradual rise in AI in the LALV (wash-in phase), often a sustained peak, and finally a slow decay (wash-out phase) in intensity (Figure 4A and Supplementary data online, Movie SC). In comparison, PFO shunting resembles more a sudden discrete 'burst' of contrast in the LALV that reaches peak intensity very quickly, followed by rapid and complete or almost complete clearing despite persistent, high contrast remaining in the RARV (Figure 4B and Supplementary data online, Movie SB).

A particularly highly predictive feature of PAVM that we saw in half our PAVM cases (sensitivity 50% ± 11%) is that RARV contrast intensity eventually falls below that of the LALV as the RARV empties but contrast continues to drain into the LALV from the lungs (Figure 4A and Supplementary data online, Movie SA). With longer recording time, this finding may have had an even greater sensitivity for PAVM, a matter for further study. By contrast, in PFO, late LALV contrast intensity is virtually always lower than RARV intensity, usually by several orders of magnitude. Thus, late persistence of LALV contrast despite RARV clearing is essentially diagnostic of PAVM. This suggests that recordings of at least 20 s on a routine basis are preferable, or alternatively a separate late recording could be performed to assess these late patterns of contrast evolution.

These principles are valid in the vast majority of clinical cases, but PFO can occasionally demonstrate a more complex pattern of
multiple separate bursts of LALV contrast related to separate crossovers of the LA and RA pressure gradient. We observed up to 5 separate episodes in a 20 s recording (Figure 5 and Supplementary data online, Movie SD). In smaller PFOs, even though the shunt episodes are widely separated, this could be visually mistaken for late contrast persistence inviting misclassification as PAVM. However, the AI curves, if recorded, are unambiguous in the presence of clearing between episodes and careful visual observation also discloses the LALV contrast clearing in between episodes. Moreover, a sufficiently long recording reveals LALV never exceeds RARV contrast as in PAVM.

With very large PFOs (or ASD) contrast shunt episodes can overlap with an additive effect causing a slow increase and a persistence of LALV contrast intensity, potentially simulating PAVM. However, these cases are readily recognized as there is virtually always immediate LALV opacification as soon as contrast enters the RARV (<2 heartbeats) due to the ease with which shunting occurs in these cases. Moreover, LALV intensity never exceeds RARV contrast intensity and does not persist beyond RARV contrast clearance late in the observation period. These features can be used to reliably differentiate the large PFO/ASD from a PAVM when the time to peak is ambiguous.

We utilized AI technology to objectify and quantify the contrast patterns for rigorous statistical analysis. However, the results show that this approach could be a valuable new technology to improve the differential diagnosis of PFO vs. PAVM in the clinical lab. AI is a well-established technology that has been used extensively for cardiopulmonary investigations but has not yet entered the clinical echocardiographic mainstream possibly because it currently requires an accessory software package to be added to standard imaging review stations. Just as the various modalities of strain imaging can now be displayed in clinical image review stations, AI analysis could similarly be incorporated to permit more accurate and reliable diagnosis of saline contrast studies during routine clinical interpretation. The ability to improve upon the accuracy of differentiating between PAVM and PFO has significant clinical importance in selection of subsequent testing and treatment. Whereas suspicion of a PAVM from a saline contrast study may warrant a pulmonary angiogram, a transoesophageal echocardiogram would be preferred for suspected PFO.

Figure 4 Acoustic intensity curves for two subjects. (A) PAVM: acoustic intensity curve showing a slow sustained rise and persistence in LALV acoustic intensity (blue). (B) PFO: acoustic intensity curve demonstrates a rapid brief rise and rapid fall in LV acoustic intensity. As seen in A, a fall in RV intensity (yellow) below LV intensity may be noted in many if not most PAVM patients and is highly diagnostic of PAVM and is not seen in PFO.
All five of our new measures appear superior to traditional beat counting, yet there is some overlap in the distribution of values in each of the individual measurements we tested (Figure 3). Therefore, it can be necessary in some cases to utilize all the features of contrast evolution together plus beat counting in establishing the diagnosis and even occasional cases in which the totality of findings remains non-diagnostic with IV saline injection alone.

Although we did not directly test visual assessment of these patterns, our findings also provide strong preliminary evidence that support the diagnostic utility of simple visual observation of the LV and RV contrast evolution without employing AI mapping (e.g. Supplementary data online, Movie SB). AI reflects bubble density within the cardiac chambers. As seen in the illustrations, AI varied over a huge range of up to 70 decibels or 6–7 orders of magnitude of 10. Even visually very mild contrast effects, consisting of only scattered LALV bubbles varied by 10–20 decibels (1–2 orders of magnitude), or 10 and 100 times, respectively (Figure 5 and Supplementary data online, Movie SD). These changes in AI correspond to obvious changes in bubble density in a range that should be easily discernible visually. This exclusively visual approach warrants further formal study; however, we have suggested some clinical guidelines for visual interpretation when AI is not available based on our quantitative AI results (Supplementary data online, Appendix S3).

**Limitations of beat counting for differentiating shunt mechanism**

Our findings suggest that beat counting can still be used to differentiate patients with PAVM vs. PFO/ASD but that stricter criteria are required, reducing its sensitivity. Thus, LALV opacification within two beats of RARV contrast appearance is very strongly predictive of PFO, but later appearance is ambiguous. This reflects the overlap in timing of LALV opacification in PFO and PAVM related to the complex interplay of shunt size, shunt location, and haemodynamic and
respiratory changes. For example, HHT and cirrhosis are associated with PAVMs and hyperdynamic circulations and are therefore subject to earlier than expected LALV opacification. Conversely late PFO shunting may occur related to spontaneous respiratory variation during image acquisition (Figure 5 and Supplementary data online, Movie SD). Our findings agree with other reports of overlap between PFO and PAVM patients using beat counting.16

Study limitations
This is a proof of concept study in which we were limited to studying cases where the aetiology of shunting was clearly delineated by clinical history and supporting imaging data and where characteristics of image acquisition allowed for optimal AI mapping. This approach warrants validation in a broader population. Since we screened previously acquired cases from within our laboratory database we were constrained in the number of cases we could identify for study. The most important factors limiting our numbers were inadequate recording length, image acquisition in compressed formats not suitable for EchoPac® analysis and failure to meet our verification criteria to ensure correct diagnosis of shunting mechanism. However, our series is the largest study to date that has systematically assessed saline contrast patterns in patients with evidence of right to left shunt. By using AI, an objective quantitative measurement tool, we were able to demonstrate highly significant statistical differences between PFO and PAVM with a much smaller sample size than would otherwise have been required with subjective qualitative visual observer grading.

We cannot exclude the possibility of misclassification of any of our cases into PAVM or PFO categories since not all cases had pulmonary angiography, TOE or Valsalva confirmation, or known septal defect, but were based on clinical criteria. However, any misclassification would have weakened statistical differences between the groups, so if present at all, our findings would be an underestimate of the true statistical differences in the absence of misclassification. Moreover, the very highly significant statistical differences we found between the PFO and PAVM groups strongly suggest accurate group assignment.

Only two of our four new measures were statistically superior to beat counting by ROC-AUC analysis. However, it has been increasingly recognized that ROC-AUC change is a poor method for assessing the incremental value of adding a new diagnostic factor. Reclassification indices have been shown to be superior in identifying statistically significant improvements in diagnostic classification. In all five parameters, we measured showed statistically significant increasing image acquisition (Figure 5 and Supplementary data online, Movie SD). Our findings agree with other reports of overlap between PFO and PAVM patients using beat counting.16

Conclusions
Through the use of AI curves, we have detailed saline contrast patterns that appear superior in differentiating PAVM from PFO than the current method of heartbeat counting. These distinctive patterns of entrance and exit of saline contrast from the LALV can readily be applied using either AI technology if available, and likely by visual interpretation of the 2D images alone as is currently practiced, although this warrants further study to confirm. Rather than interpret a saline contrast study as either positive or negative for shunt when Valsalva is not possible, the location of the shunt may be inferred, not only on the basis of the number of cardiac cycles from first appearance of saline in the LALV but in conjunction with the entrance and exit patterns of LALV saline contrast. Our quantitative analysis shows that these additional parameters can be highly diagnostic by themselves, are superior to the current method of beat counting, and confer even greater diagnostic accuracy when used together with beat counting.

Supplementary data
Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

Acknowledgements
The authors would like to acknowledge the assistance with data and statistical analysis of Jacqueline R Rifkin, B.A., Duke University, Durham, NC, USA for review of the article.

Conflict of interest: none declared.

References


