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Redundancy of foramen ovale flap may mimic fetal aortic coarctation

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KEYWORDS: aortic coarctation; fetal echocardiography; fetus; foramen ovale flap; ultrasound; ventricular disproportion

CONTRIBUTION

What are the novel findings of this work?
This study demonstrates that, in the fetus, the presence of a redundant foramen ovale flap (RFOF) in the absence of a concurrent restrictive foramen ovale may mimic the presence of aortic coarctation. A RFOF may lead to ventricular disproportion, with features identical to those associated with coarctation of the aorta.

What are the clinical implications of this work?
Aortic coarctation is the subject of both false-positive and false-negative diagnoses on fetal echocardiography. Knowing that a RFOF may be a cause of ventricular disproportion may lead sonologists to look out for this anatomic condition, which may, in turn, reduce the false-positive rate of diagnosis of aortic coarctation.

ABSTRACT

Objectives *To assess the relationship between presence of a redundant foramen ovale flap (RFOF), in the absence of a clearly restrictive foramen ovale, and ventricular disproportion, in three groups of fetuses: (1) those with a final diagnosis of aortic coarctation (CoA); (2) those referred for suspicion of ventricular disproportion and/or CoA which did not develop CoA postnatally; and (3) normal fetuses.*

Methods *This was a retrospective study including 73 fetuses: 12 with a final diagnosis of isolated CoA; 30 referred for suspicion of ventricular disproportion and/or CoA, which did not develop CoA postnatally; and 31 normal fetuses. Four-dimensional volume datasets and clips were assessed offline. Maximum diameters of the FOF (FOFD), left atrium (LAD), right atrium, left and right ventricles and, when available, aortic isthmus, were measured, as were areas of the FOF (FOFA), left atrium (LAA) and right atrium. The left/right ratios for all segments of the heart, as well as the FOFD/LAD ratio and FOFA/LAA ratio, were calculated. Regression analysis was performed to assess the relationship between RFOF and ventricular disproportion and means were compared by ANOVA.*

Results *Repeatability was fair, with all variables having an intraclass correlation coefficient* $\geq 83\%$*. In the pooled group of fetuses with no CoA found at birth (normal fetuses plus those with ventricular disproportion (*$n = 61$*)), there was a significant linear correlation between redundancy of the FOF and degree of ventricular disproportion (*$P < 0.01$ *and* $P < 0.05$ *for diameter and area ratios, respectively). Categorizing the FOF redundancy, FOFD/LAD ratio* ≥ 0.65 *was significantly associated with ventricular disproportion (*$P = 0.006$*). Based on the degree of FOF prominence, we described four categories of redundancy, ranging from no redundancy/ventricular disproportion (Stage 0) to severe redundancy/ventricular disproportion with transient obstruction of the foramen ovale or mitral orifice (Stage III). Comparing cases without neonatal evidence of coarctation but FOFD/LAD ratio* ≥ 0.65 vs *those with neonatal evidence of coarctation, there was no statistically significant difference in the degree of ventricular disproportion or in the Z-score of the aortic isthmus maximum diameter.*

Conclusions *This study demonstrates that: (1) there is an association between RFOF and ventricular disproportion, independent of the association with a restrictive foramen ovale, and (2) the presence of a RFOF may mimic CoA. In fact, it causes both ventricular disproportion and a significant reduction in the diameter of the aortic isthmus, associated in some cases also with reversed isthmic flow. Future prospective studies are needed to evaluate whether focusing the sonologist's attention on the appearance of the foramen ovale may reduce the rate of false-positive diagnosis of CoA.*

INTRODUCTION

The foramen ovale (FO) is a crescent-shaped interatrial communication formed by the septum secundum on the right atrial side and the septum primum on the left atrial side. This structure allows the oxygen-enriched blood coming from the ductus venosus to reach the left atrium, contributing substantially to the left-ventricular output.

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The foramen ovale flap (FOF), which derives primarily from the septum primum, partially covers this interatrial communication. The FOF has been defined as redundant (RFOF), in the context of fetal congenital heart disease (CHD), when it herniates into the left atrium for more than 50% of the left atrial diameter[2,4]. In normal fetal hearts, a RFOF has been reported to occur in roughly one third of the cases with a restrictive FO[7]. Restrictive FO has been investigated widely in the presence of CHD, because of the association with poor fetal and neonatal outcome[1–4], while its occurrence in normal fetal hearts and in association with RFOF has been reported less often[5–10]. The fact that ventricular disproportion might occur in cases with RFOF but without evidence of a restrictive FO was not evident from these studies[5–9] and has been described only rarely[10]. This possibly causal relationship is of importance, because ventricular disproportion is one of the indirect sonographic signs possibly associated with coarctation of the aorta (CoA)[11–13].

Our hypothesis was that a RFOF may *per se* lead to ventricular disproportion and, consequently, mimic CoA, in the absence of a clearly restrictive FO. The aim of this study was, therefore, to assess, in the absence of a clearly restrictive FO, the relationships between FOF redundancy and ventricular disproportion in three groups of fetuses: (1) those with a final diagnosis of CoA; (2) those referred for suspicion of ventricular disproportion and/or CoA which did not develop CoA postnatally; and (3) normal fetuses.

METHODS

Study design and population

This was a retrospective study including 73 fetuses, allocated into three groups: (1) fetuses with a final diagnosis of isolated CoA ($n = 12$); (2) fetuses referred for suspicion of ventricular disproportion and/or CoA who did not develop CoA postnatally ($n = 30$); and (3) normal fetuses ($n = 31$). All fetuses had undergone fetal echocardiography at our unit to confirm CoA or exclude cardiac anomalies for a variety of indications. Those that met the following inclusion criteria were retrieved from the database: (1) diagnosis confirmed postnatally; (2) availability of either a four-dimensional dataset or, at least, a clip of a four-chamber view in which the FOF was clearly visible; (3) absence of other major CHD; (4) clips/volume datasets acquired during fetal apnea; and (5), for cases with CoA, absence of hemodynamically significant ventricular septal defects (VSD) (cases with muscular VSD visible only on color Doppler echocardiography were included). Cases referred for fetal echocardiography because of growth restriction were excluded, since it is well known that growth impairment may lead to moderate ventricular disproportion. Similarly, cases with evidence of a restrictive FO were excluded.

Ultrasound methodology and measurements

The software packages 4D View (version 17, GE Healthcare, Zipf, Austria) and ImageJ (NIH, Bethesda, MD, USA) were used to obtain measurements from four-dimensional volume datasets (spatiotemporal image correlation (STIC)) and clips, respectively. For all retrieved cases, the following methodology was used. Images were first processed and measurements taken by a single operator (F.V.). To assess reproducibility, 20 cases were selected randomly and their measurements were taken by a second operator (D.P.), and a second time by the first operator, both blinded to the results of the other evaluations. The first step was to analyze frame-by-frame the four-chamber view, selecting the single frame in which the FOF was most prominent, which corresponds to the end-systolic part of the cardiac cycle. In that

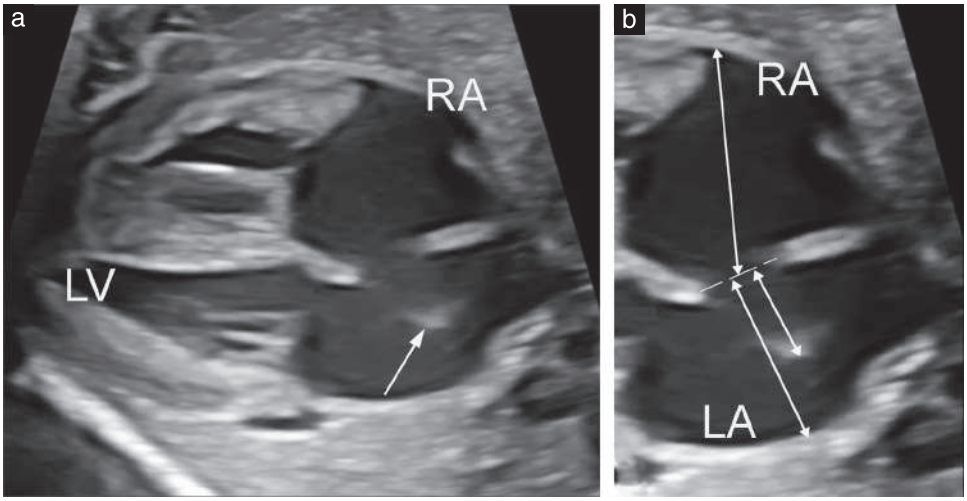

Figure 1 Four-chamber view of fetal heart at 28 gestational weeks illustrating study measurements. (a) Single frame showing maximum excursion of foramen ovale flap (arrow), corresponding to end-systolic phase of cardiac cycle. (b) Magnification of atria shows how measurements of atrial and foramen ovale flap maximum diameters were taken. Dotted line was drawn across foramen ovale, and measurements were taken from this line to lateral atrial walls and flap (double-headed arrows). LA, left atrium; LV, left ventricle; RA, right atrium.

image, the maximum diameters of the FOF (FOFD), left atrium (LAD) and right atrium (Figure 1) and left (LV) and right (RV) ventricles, as well as the areas of the FOF (FOFA), left atrium (LAA) and right atrium, were measured. FOFD was measured from the outer edge of the most prominent part of the FOF to a line drawn along the interatrial septum (on–on). LAD and right atrial maximum diameter were measured above and parallel to the atrioventricular valves. Ventricular maximum diameters were measured below and parallel to the atrioventricular valves. A FOF was defined as being redundant when it herniated into the left atrium for more than 50% of its maximum diameter[2,4]. Table 1 lists the ratios that were then calculated, to normalize the data for gestational age. In addition, the value of the aortic isthmus *Z*-score was evaluated, according to Pasquini *et al.*[14], in all cases in which this parameter could be measured from the volume dataset. This measurement was performed on the three-vessels and trachea view. Finally, ventricular diameters were also compared with normative data published recently for normal fetal hearts[15], in order to assess whether differential ventricular dimensions could help discriminate between RFOF and CoA.

Statistical analysis

Comparison of frequency data was performed by means of the chi-square test or Fisher's exact test as appropriate. The Mann–Whitney *U*-test was used to compare medians. Repeatability was assessed by calculating Pearson's correlation coefficient (intraclass correlation coefficient) for intra- and interobserver reliability[16]. The latter was estimated by comparing measures from the first operator to the average of the two series of available measures from the second one. The Bland–Altman method and Pitman's test were applied to evaluate the corresponding agreement between measures both between and within operators[17]. All analyses were carried out using the SPSS for Windows statistical package (version 21, IBM Corp., Armonk, NY, USA).

Table 1 Summary of proposed ratios developed to assess relationships between redundancy of foramen ovale flap (FOF) and ventricular dimensions

Ratio	*Details*
FOFD/LAD	Ratio between FOF maximum diameter and left atrial maximum diameter
FOFA/LAA	Ratio between area of FOF, traced on outer edge, and left atrial area
LAD/RAD	Ratio between left and right atrial maximum diameters
LAA/RAA	Ratio between left and right atrial areas
LVD/RVD	Ratio between left and right ventricular maximum diameters

RESULTS

The mean gestational age at ultrasound of the fetuses included in this study was 31 + 2 (SD, 2 + 6; range, 27–37) weeks for group with ventricular disproportion and no CoA, 28 + 6 (SD, 5 + 1; range, 21–35) weeks for the CoA group and 30 + 3 (SD, 2 + 6; range, 25–36) weeks for the control group ($P = 0.145$).

Results of the reliability analysis are given in Table 2, with the Bland–Altman plots shown in Figures S1 and S2. Reproducibility was fair for both intra- and interobserver variability, the only exception being the right atrial diameter, for which the Pitman test showed slightly reduced interoperator reproducibility.

The first part of the analysis regards the 61 pooled cases in which there was no CoA found at birth (31 referred for ventricular disproportion and 30 normal controls). In this group, a significant linear relationship between redundancy of the FOF and degree of ventricular disproportion was demonstrated, both for the maximum diameter ratios and for the area ratios ($P < 0.01$ and $P < 0.05$, respectively) (Figure 2). When we assessed degree of FOF prominence not in a continuous way but as a categorical variable, using FOFD/LAD ratio cut-offs of ≥ 0.60 or ≥ 0.65, respectively, the association with ventricular disproportion became significant ($P < 0.05$) or highly significant ($P = 0.006$) (Figure 3). Considering these cut-offs, there were 34 cases with a FOFD/LAD ratio < 0.65 and 27 with a ratio ≥ 0.65, of which 21 showed ventricular disproportion (Figure 3). The cut-off for the ratio of areas to reach similar statistical significance was FOFA/LAA ratio ≥ 0.41 ($P < 0.003$). Based on the prominence of the FOF and its hemodynamic effects, we propose defining four categories of FOF redundancy (Table 3, Figure 4).

Table 2 Intra- and interobserver repeatability for all measured variables in 30 randomly selected cases

	Intraobserver				*Interobserver*			
Variable	*Pearson's ICC*	P	*Pitman test* r	P	*Pearson's ICC*	P	*Pitman test* r	P
FOF max diam	0.98	< 0.001	−0.09	0.63	0.96	< 0.001	0.13	0.5
FOF area	0.99	< 0.001	−0.29	0.15	0.99	< 0.001	−0.35	0.6
LA max diam	0.94	< 0.001	−0.19	0.32	0.83	< 0.001	0.37	0.85
LA area	0.96	< 0.001	0.26	0.18	0.91	< 0.001	−0.13	0.5
RA max diam	0.95	< 0.001	−0.14	0.47	0.92	< 0.001	−0.41	0.03
RA area	0.98	< 0.001	−0.09	0.65	0.95	< 0.001	−0.11	0.56
LV max diam	0.96	< 0.001	−0.28	0.14	0.90	< 0.001	−0.36	0.06
RV max diam	0.97	< 0.001	0.27	0.16	0.94	< 0.001	−0.26	0.16

Following method of Bland and Altman[17]. FOF, foramen ovale flap; LA, left atrium; LV, left ventricle; max diam, maximum diameter; RA, right atrium; RV, right ventricle.

The second part of the analysis compared the 21 cases with a FOFD/LAD ratio ≥ 0.65 and ventricular disproportion, and the 12 with a confirmed diagnosis of CoA. As evident from Figure 5, there was virtually no difference either in the degree of ventricular disproportion or in the reduced caliber of the aortic isthmus (no significant difference). However, in all Category-III and in two Category-II cases, there was reversed blood flow across the isthmus (Figure 6).

Finally, we assessed whether there was any difference in the pattern of ventricular disproportion in the 34 RFOF *vs* the 12 confirmed CoA cases. To this end, we plotted our data on reference charts published recently[15] (Figure 7). The pattern was similar for CoA and RFOF cases, with significantly reduced LV size not associated with an obvious increase in RV size.

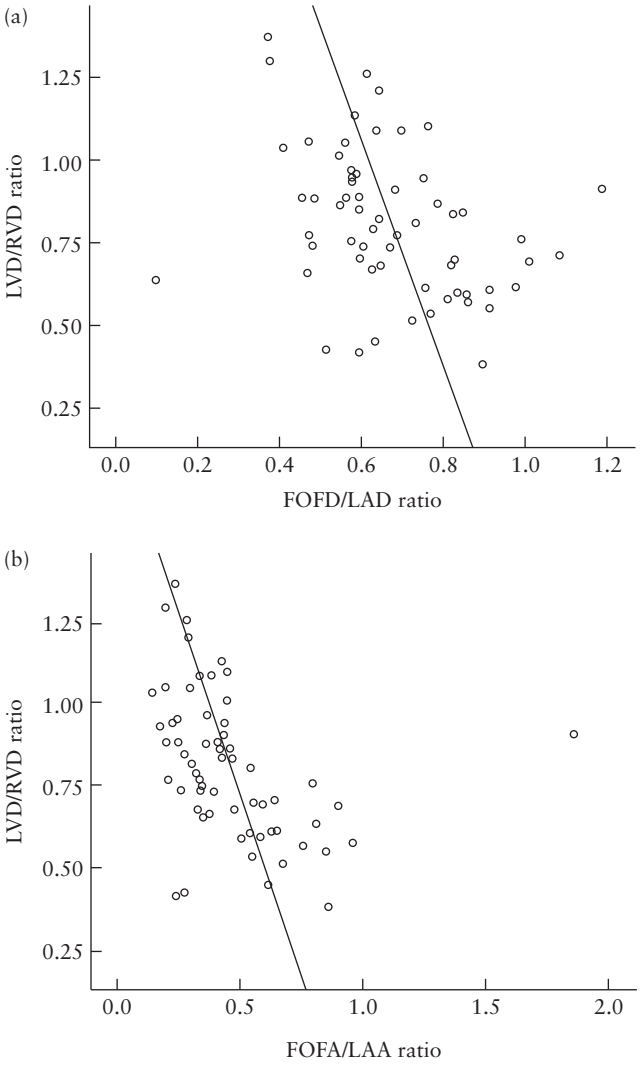

Figure 2 Scatterplots showing linear correlation of foramen ovale flap maximum diameter/left atrial maximum diameter (FOFD/LAD) ratio (a) and of foramen ovale flap area/left atrial area (FOFA/LAA) ratio (b) with degree of ventricular disproportion (expressed as left-to-right ventricular maximum diameter (LVD/RVD) ratio) in 61 fetuses without coarctation of the aorta. (a) $y = 90.93 - 0.29x$; R^2 linear = 0.118; $P < 0.01$. (b) $y = 63.16 - 0.19x$; R^2 linear = 0.084; $P < 0.05$.

DISCUSSION

Since the introduction into clinical practice of fetal echocardiography almost 40 years ago[18,19], CoA has always been something of a weak spot of this otherwise accurate technique[11–13,20–22]. One of the indirect signs potentially pointing to underlying CoA is ventricular disproportion[11], but this is somewhat unspecific, occurring in various other situations, such as growth restriction and restrictive FO[7–10]. Also, right-ventricular dominance increases physiologically in the third trimester of pregnancy, and this is responsible for the higher false-positive rate for CoA when ventricular disproportion is referred late in pregnancy[22]. We have demonstrated in this study that: (1) RFOF causes ventricular disproportion even in the absence of a clearly restrictive FO (Figures 2 and 3), as has also been pointed out by Channing *et al.*[10], and (2) the presence of a RFOF may mimic CoA (Figures 4–6). In fact, RFOF may be associated with both ventricular disproportion and reduced isthmus size, two key features of CoA that are associated, mainly in Category-III cases, with

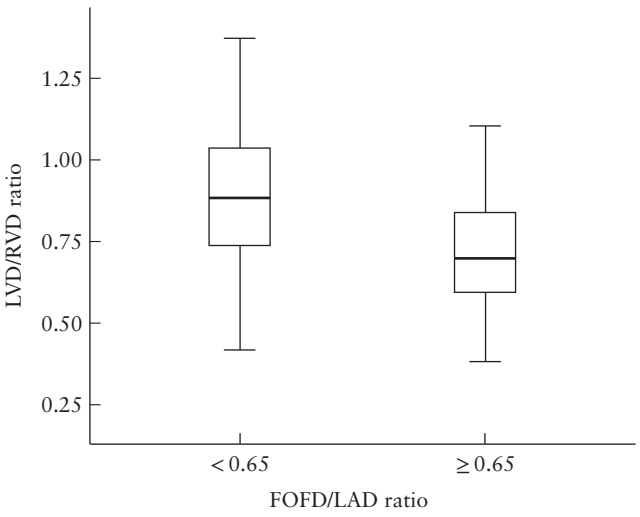

Figure 3 Box-and-whiskers plots showing presence of ventricular disproportion (expressed as left-to-right ventricular maximum diameter (LVD/RVD) ratio) in 34 fetuses with foramen ovale flap maximum diameter/left atrial maximum diameter (FOFD/LAD) ratio < 0.65 and 27 fetuses with FOFD/LAD ratio ≥ 0.65 ($P = 0.006$). Boxes and internal lines show median and interquartile range, and whiskers show range.

Table 3 Proposed categories of redundancy of fetal foramen ovale (FO)

Stage	*FOFD/LAD ratio*	*Ventricular disproportion*	*Other features*
0	< 0.65	Absent	—
I	≥ 0.65	Absent	—
II	≥ 0.65	Present	—
III	≥ 0.65	Present	Transient prolapse into FO or mitral valve orifice

FOFD, foramen ovale flap maximum diameter; LAD, left atrial maximum diameter.

reversed isthmic flow (Figure 6). It is likely that the hemodynamic mechanism behind this association of RFOF with ventricular disproportion is partly shared with that occurring in restrictive FO. In fact, redundancy of the FOF may contribute to a dynamic reduction in mitral valve inflow and perturbation of the stream from the ductus venosus to the left atrium, both because of a modification of the septum primum angle and due to partial obstruction from the flapping membrane of the flap itself. The latter is similar in action to a restrictive FO. Ballooning and redundancy of the FOF has been described to occur in about 30% of fetuses with a restrictive FO (diameter $\leq$ 2.5 mm)[7]. We speculate that these two events, i.e. dynamic obstruction of mitral inflow and obstruction

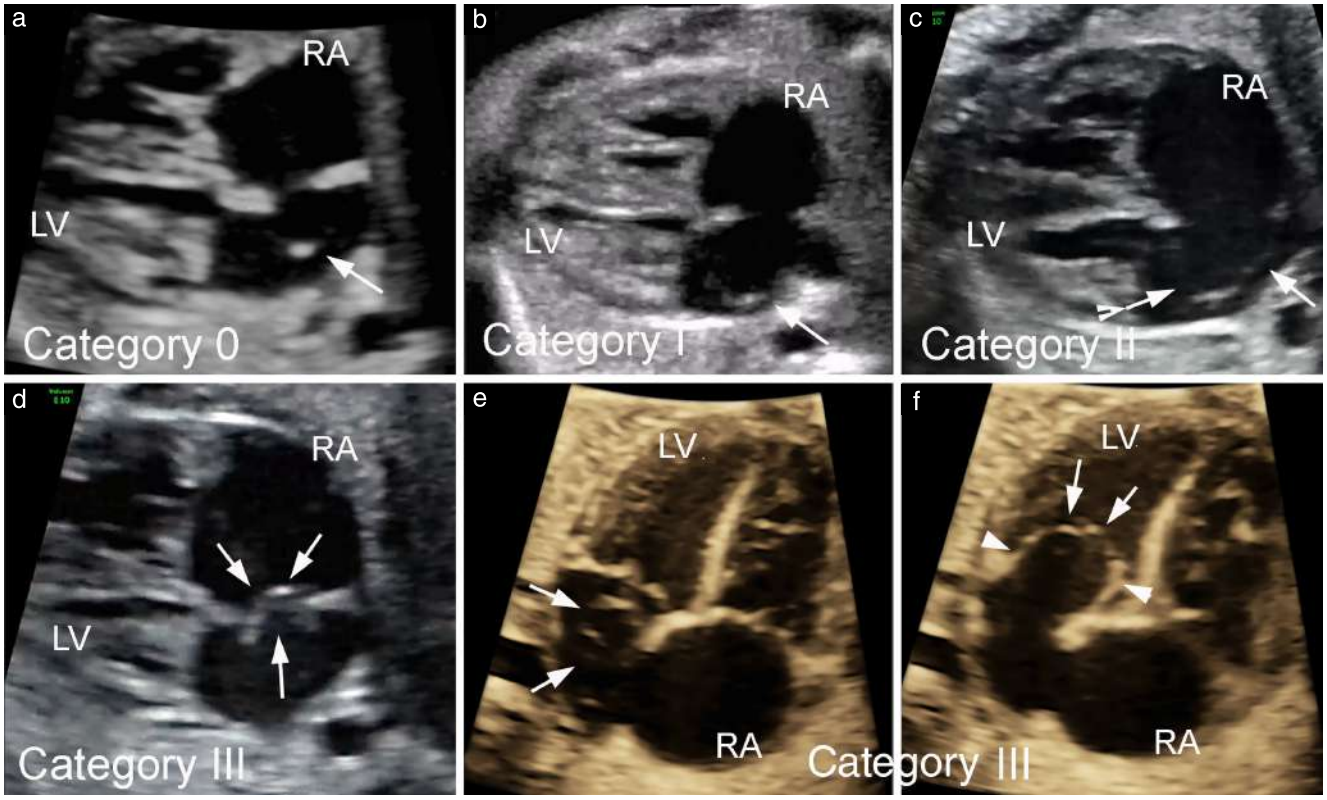

Figure 4 Proposed echocardiographic categorization system for redundancy of fetal foramen ovale flap (Table 3). (a) Category 0: FOFD/LAD ratio < 0.65, no ventricular disproportion. (b) Category I: FOFD/LAD ratio ≥ 0.65, no ventricular disproportion. (c) Category II: FOFD/LAD ratio ≥ 0.65, presence of ventricular disproportion. (d–f) Category III: FOFD/LAD ratio ≥ 0.65, presence of ventricular disproportion, presence of transient prolapse into foramen ovale (d) or mitral valve orifice (e,f); latter images are two frames of cardiac cycle in same fetus, with severe protrusion of flap into left atrium (e) and successive deep prolapse into mitral orifice (f). LV, left ventricle; RA, right atrium.

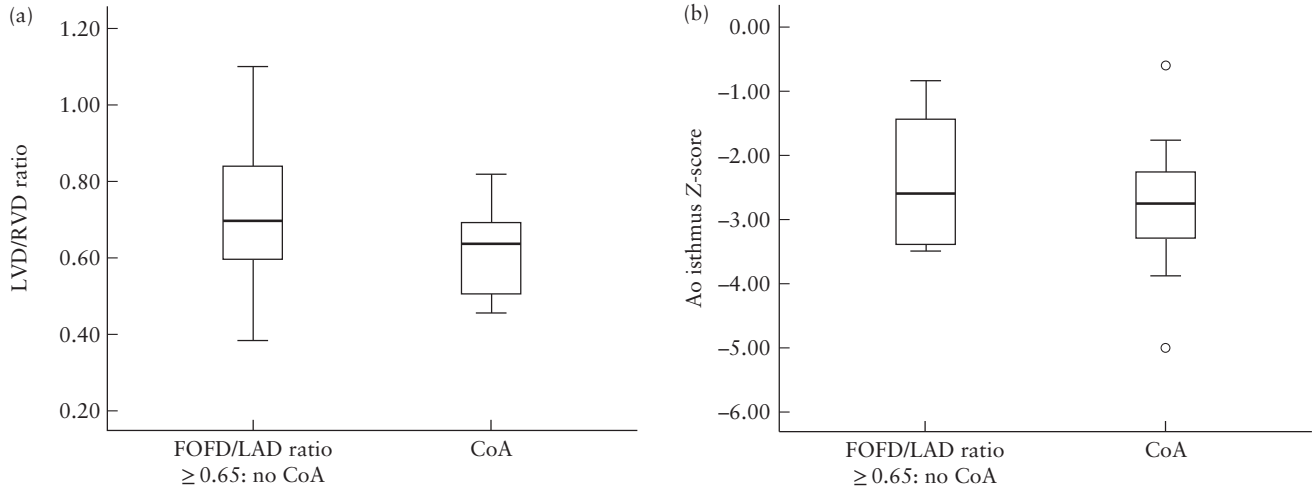

Figure 5 Box-and-whiskers plots showing presence of ventricular disproportion (expressed as left-to-right ventricular maximum diameter (LVD/RVD) ratio) (a) and aortic (Ao) isthmus *Z*-score (b) in 21 fetuses with foramen ovale flap maximum diameter/left atrial maximum diameter ratio ≥ 0.65 and ventricular disproportion and no coarctation of the aorta (CoA) compared with 12 fetuses with ventricular disproportion and CoA (*P* not significant for both). Boxes and internal lines show median and interquartile range, whiskers show range and circles are outliers.

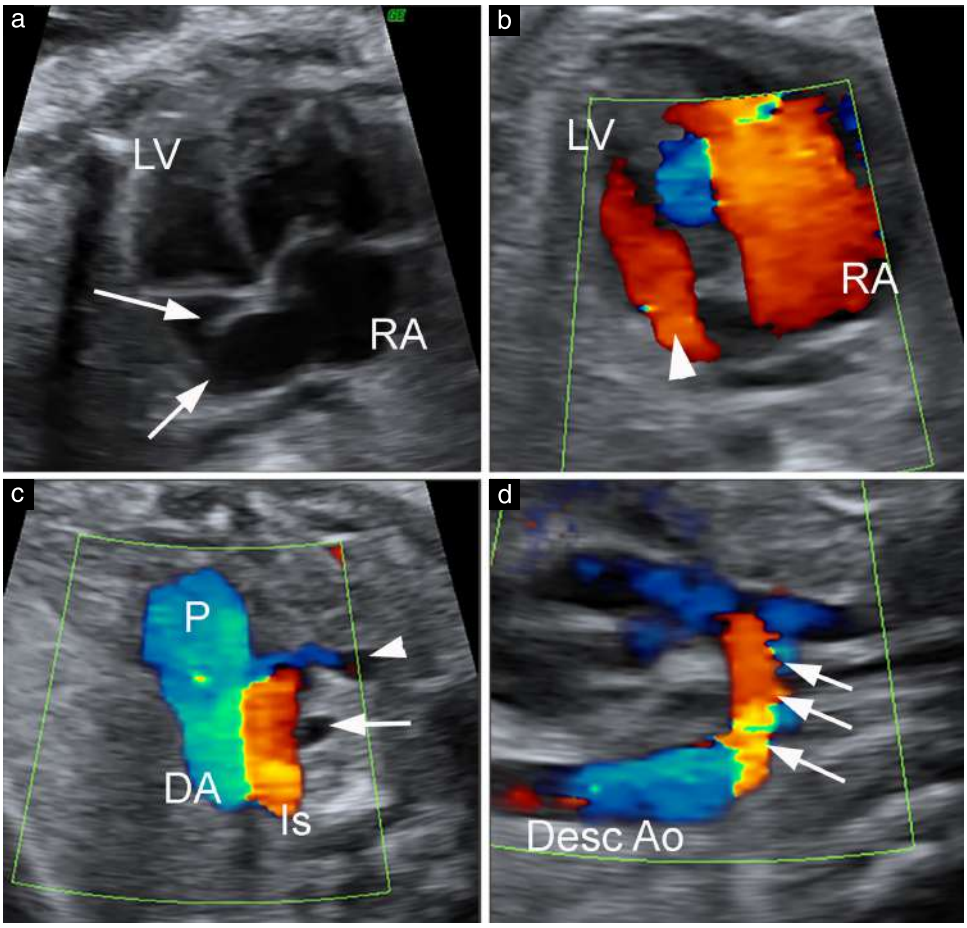

Figure 6 Ultrasound assessment during fetal apnea of single fetus at 35 gestational weeks, confirming pathogenetic hypothesis (see text for details). (a) Four-chamber view, in which significant prominence of foramen ovale flap is demonstrated (arrows; FOFD/LAD ratio ≥ 0.65), together with ventricular disproportion. (b) Color Doppler image, showing significant reduction of mitral inflow (arrowhead), caused by prominence of foramen ovale flap. Note also severe ventricular disproportion. (c) Three-vessels-and-trachea view with color Doppler, demonstrating both small diameter of transverse aortic arch and reversed blood flow across it (trachea (arrow) and superior vena cava (arrowhead) are indicated). (d) Longitudinal view of aortic arch, in which small size of transverse arch, as well as turbulent, reversed blood flow (arrows), are confirmed. DA, ductus arteriosus; Desc Ao, descending thoracic aorta; Is, aortic isthmus; LV, left ventricle; P, pulmonary trunk; RA, right atrium.

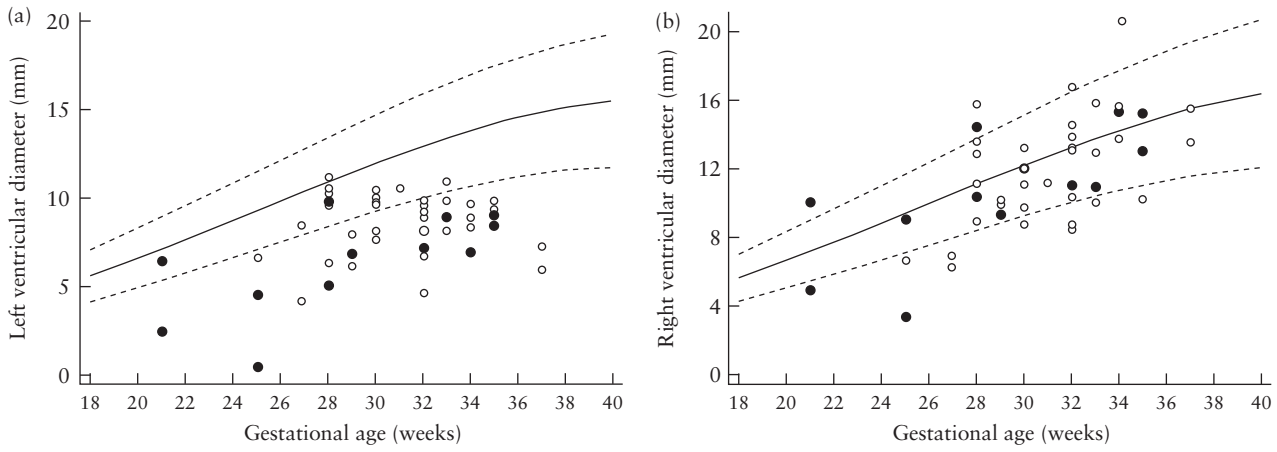

Figure 7 Scatterplots showing left (a) and right (b) ventricular maximum diameters for our 34 cases of redundant foramen ovale flap (○) and 12 cases of aortic coarctation (●), plotted against nomograms published recently[15]. Pattern of reduction in left ventricular dimensions with no clear increase in right ventricular dimensions is similar for both groups, with no statistically significant difference.

of the ductus-venosus right atrium–left atrium stream, determine a significant shift of blood from the left heart to the right heart, in turn leading to the development of moderate-to-severe ventricular disproportion and to an increase in pressure in the right-sided structures. These phenomena are confirmed by color Doppler imaging, which demonstrates both a severely narrowed mitral inflow and, in most severe cases, reversed flow across a small aortic isthmus (Figure 6).

It should be underlined here that all cases in which CoA was not diagnosed after birth, regardless of the FOF redundancy category, had a normal outcome. In no case was a Type-II atrial septal defect diagnosed and in all cases the FO closed between 2 days and 6 weeks following birth, thus excluding a restrictive FO as such, since in this case the closure would have been an early neonatal event. Therefore, a RFOF may indeed be associated with ventricular disproportion *per se*, regardless of a concurrent restrictive FO. Reversing the scenario, if a RFOF is found in a fetus referred for suspicion of CoA or, simply, ventricular disproportion, its recognition reduces the chances of that fetus being affected with CoA at birth. In this regard, it can be considered that the higher the category of FOF redundancy, the more difficult will be its differentiation from CoA.

This study had some limitations. The sample size was relatively small. This is related to the strict selection criteria needed to retrieve reliably all of the measurements from stored clips or STIC volume datasets. Furthermore, the relatively small number of normal cases may have reduced the significance of our findings. To support our conclusions, we therefore compared our measurements with nomograms published recently[15], showing for RFOF a pattern of ventricular disproportion rather similar to that seen in CoA (Figure 7), due mainly to a reduction in LV size.

In conclusion, we have described the association between RFOF and ventricular disproportion and have shown that this atrial paraphysiological condition can mimic CoA both hemodynamically and sonographically, independently of any association with a restrictive FO. Prospective studies are needed to assess whether focusing the sonologist's attention on the appearance of the FO may reduce the rate of false-positive diagnosis of CoA.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figures S1 and S2 Bland–Altman plots for evaluation of intraoperator (left panels) and interoperator (right panels) agreement for analyzed variables: areas (foramen ovale and left and right atria) (Figure S1) and maximum diameters (foramen ovale, left and right atria and left and right ventricles) (Figure S2).