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Original Article

Branch-to-Total Pulmonary Artery Area Ratio as a Predictor of Flow Limitation in Tetralogy of Fallot: MRA and Phase Contrast MRI Study

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Abstract

Objective: The severity of branch pulmonary artery stenosis and associated flow restriction can be assessed using catheter angiography and lung perfusion scintigraphy. However, these techniques are time-consuming and have various limitations. This study aims to establish a ratio of the narrowed-to-total pulmonary artery area to assess flow restriction.

Methods: A net flow of the right and left pulmonary arteries was calculated by phase-contrast magnetic resonance imaging (MRI), and the cross-sectional area was calculated at the narrowest point of the branch pulmonary artery using multiplanar reconstruction images from magnetic resonance angiography. A right-to-left pulmonary artery flow ratio between 61/39 and 43/57 was considered normal. The narrowed-to-total pulmonary artery area ratio was calculated to establish a threshold for physiologically significant branch pulmonary artery stenosis.

Results: A total of 272 patients were included in the study. About 136 patients diagnosed with branch pulmonary artery stenosis were compared with 136 patients exhibiting normal branch pulmonary artery flow. The patients with branch pulmonary artery stenosis exhibited a significantly reduced narrowed-to-total pulmonary artery area ratio, with values of 0.46 and 0.38, respectively, showing a statistically significant difference ($P < .00001$). A branch-to-total pulmonary artery area ratio of ≤0.40 exhibited a sensitivity of 67.65% and a specificity of 91.91% in detecting branch pulmonary artery stenosis, as confirmed by the calculated area under the curve of 0.86 with a 95% CI ranging from 0.813 to 0.899 ($P < .0001$). The positive predictive value was 84.79%, and the negative predictive value was 80.99%.

Conclusion: A narrowed-to-total pulmonary artery area ratio of ≤0.40, measured by cross-sectional imaging, can help identify patients who may need catheter angiography, especially when cardiac MRI is unavailable or flow measurement is not possible.

Keywords: Cardiac magnetic resonance imaging, magnetic resonance angiography, phase contrast imaging, pulmonary artery stenosis, tetralogy of Fallot

INTRODUCTION

Tetralogy of Fallot is the most common cyanotic congenital heart disease and usually requires surgical correction during the first years of life.[1] Branch pulmonary artery stenosis, which is one of the most common complications, occurs in 20%-40% of patients after surgical repair, either due to the primary nature of the disease or secondary to surgical interventions.[2]

Evaluating the severity of branch pulmonary artery stenosis following surgical correction is crucial, as branch pulmonary artery stenosis not only exacerbates pulmonary insufficiency but also serves as a key predictor of outcomes and exercise capacity.[3,4]

The current standard care for patients with branch pulmonary artery stenosis involves a series of time-consuming diagnostic procedures, which include catheter angiography and Tc-99-labeled macro-aggregated albumin perfusion scintigraphy. However, both conventional catheter angiography and lung scintigraphy have some limitations in evaluating branch pulmonary artery stenosis. Conventional catheter angiography is not able to assess preferential pulmonary blood flow, while Tc-99 scintigraphy may produce false-negative results in bilateral stenosis or false-positive findings in cases of multi-vessel distal obstructions, parenchymal diseases, or aortopulmonary collaterals.[5]

The anatomic evaluation of the pulmonary artery by echocardiography, computed tomography, and magnetic resonance angiography remains a widely used method for determining the hemodynamic significance of stenoses and assessing the need for angioplasty or stenting.[6-8] However, it was demonstrated that the branch pulmonary artery diameter ratios fail to predict flow discrepancies.[9]

On the other hand, phase-contrast magnetic resonance imaging (MRI) offers a reliable, non-invasive alternative for evaluating branch pulmonary artery stenosis and flow characteristics without ionizing radiation or radionuclides.[10-14] However, long examination time, the requirement for anesthesia, high cost, and the need for trained personnel are the most important limitations to its widespread use. Therefore, this study aims to establish a ratio of the narrowed to the total pulmonary artery cross-sectional area derived from magnetic resonance angiography (MRA) for branch pulmonary artery stenosis that indicates blood flow restriction, using phase-contrast MRI in children following Tetralogy of Fallot repair.

METHODS

Ethics Committee of İstanbul Medeniyet University (Date 25.12.2019, Approval Number: 2019/052) approved this retrospective, single-center study, and the requirement for informed consent was waived.

Study Population

A total of 532 patients who underwent a cardiac MRI with phase contrast MRI and MRA between January 2015 and July 2020 were retrospectively analyzed. Magnetic resonance imaging examinations with poor image quality were excluded. In patients with multiple studies, the most recent eligible examination was used. Patients with right ventricle-to-pulmonary artery conduit, left-to-right shunt, major aortopulmonary collaterals, or those who had pulmonary artery interventions (stenting, balloon dilatation, or pulmonary valve replacement) were excluded.

The patients who had total surgical correction with a native right ventricular outflow tract and a branch pulmonary artery higher than 20 mmHg were accepted as the branch pulmonary artery stenosis group.

Patients with no branch pulmonary artery stenosis, with a Doppler gradient lower than 20 mmHg reported within 6 months before the MRI examination, were accepted as a control group.

The demographic data and the surgical information for these patients were obtained from the national health information system. The inclusion and exclusion criteria of the study are presented in the flowchart (Figure 1).

Magnetic Resonance Imaging Protocol and Evaluation

All cardiovascular MRI examinations were conducted using a 1.5-Tesla scanner (Signa HDx; GE Medical Systems, Milwaukee, WI, USA, and Siemens Avanto, Erlangen, Germany) equipped with a 32-channel phased-array abdominal coil and electrocardiographic gating. Intravenous sedation was not administered during the examination. The images were acquired during 1 or 2 breath-holds of 8-12 seconds duration, depending on the heart rate during the end-expiratory breath-hold. The duration of the examination varied between 15 and 30 minutes.

The examinations and evaluations were conducted by a radiologist with at least 10 years of experience in congenital cardiac imaging. A 3-plane localizer was initially obtained through the thorax using a steady-state free precession sequence. Subsequently, cine steady-state free precession sequences were acquired for 2-chamber, 4-chamber, and short-axis views for all patients.

Time-resolved contrast-enhanced MRAs were obtained using a gradient echo inversion recovery sequence with Electrocardiography (ECG) gating following injection of a gadolinium-based contrast at a dose of 0.2 mmol/kg. The imaging parameters of the MRA included TR: 4.0-4.4 ms; TE: 2.2-2.3 ms; flip angle: 15°; receiver bandwidth: 31.25 kHz; field-of-view: 360-440 × 360-440 mm^2; acquisition voxel size: 2 × 2 × 2-2.2 × 2.2 × 2.2 mm^3; number of excitations: 4, hyperkat acceleration = 6-8× and temporal resolution 31-63 milliseconds.

Phase contrast MRI was performed for flow measurements through the right and left branch pulmonary arteries. Each image set was obtained with retrospective gating and comprised 25 reconstructed cardiac phases according to the heart rate. The optimal velocity encoding value for the pulmonary artery was calculated using the Bernoulli equation based on the gradients reported in the echocardiography report. The phase contrast MRI was performed with retrospective ECG gating and the following imaging parameters: TR/TE, 25/6 milliseconds; slice thickness, 6 mm; flip angle, 30°; receiver bandwidth, 31.25 kHz; rectangular field of view, 260 to 400 mm; matrix, 256 × 256; and number of excitations, 2. The phase contrast MRI of the right and the left pulmonary arteries is prescribed at the midpoint perpendicular to the vessels by the double-oblique technique. The slice location was determined by the reconstructed multiplanar images of MRA. To decrease the turbulent artifact, the imaging planes were located distal to the stenotic area if present.

The subjects' weights and height were recorded to calculate the body surface area, and all measurements were indexed.

Branch Pulmonary Artery Magnetic Resonance Imaging/ Magnetic Resonance Angiography Measurements

Multiplanar reconstructions of the MRA on the pulmonary artery phase were used to measure branch pulmonary artery cross-sectional areas in 2 orthogonal dimensions at the narrowest point on a dedicated workstation. The pulmonary artery phase of the MRA was used for measurements. The cross-sectional diameter of the branch pulmonary artery was determined at its narrowest point using multiplanar reconstruction images derived from MRA. The longest and the shortest diameters of the vessel were measured and recorded for both pulmonary arteries from the inner-to-inner contour of the vessel. The formula for calculating the cross-sectional area of the branch pulmonary artery is provided below. This formulation is derived based on the area calculation of the ellipse.

$$\text{Area} = [\pi \times R_S \times R_L] / 4$$

R_S = minor radius,

R_L = major radius,

$\pi \sim 3.14$

MAIN POINTS

- Accurately detecting significant branch pulmonary artery stenosis in cross-sectional imaging remains challenging when flow assessment by phase-contrast magnetic resonance imaging is unavailable, delaying appropriate intervention.
- A narrowed-to-total pulmonary artery area ratio of ≤ 0.40 reliably distinguished significant stenosis, with almost 68% sensitivity and 92% specificity.
- Measuring the narrowed-to-total pulmonary artery area ratio on cross-sectional imaging provides a rapid, noninvasive tool to identify clinically relevant stenosis, guiding timely referral for intervention and potentially improving patient outcomes.

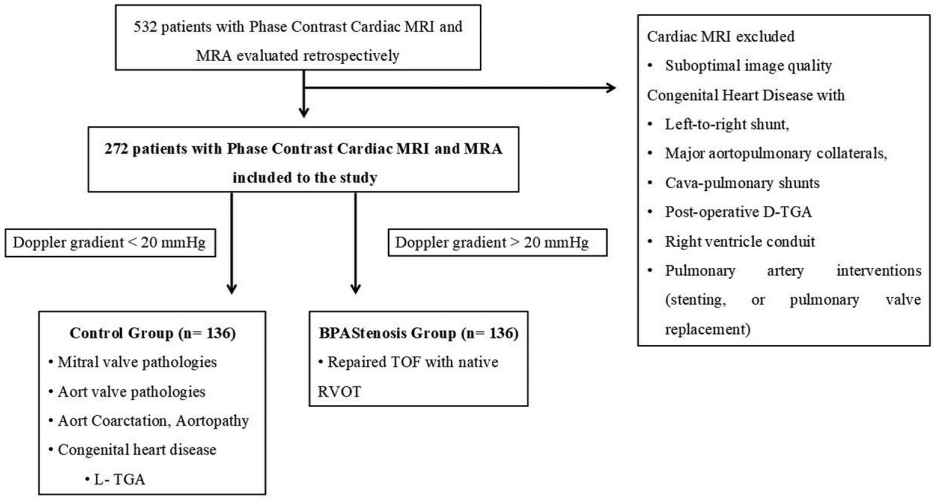

Figure 1. Flow chart showing the patient selection with inclusion and exclusion criteria. BPA, branch pulmonary artery; LPA, left pulmonary artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; TGA, transposition of great arteries; Tetralogy of Fallot, transposition of great arteries.

For the flow analysis of the branch pulmonary arteries, the contours of the left and right pulmonary arteries were automatically contoured and manually corrected, propagated through all cardiac phases. The distribution of blood flow between the right and left pulmonary arteries was calculated as the net right pulmonary artery flow volume divided by the total net flow volume of both pulmonary arteries, expressed as a percentage. A right-to-left pulmonary artery flow ratio was calculated, with a range of 61:39 to 43:57 considered physiologically normal, based on established literature values.[14] The measurement and the calculation are represented in Figures 2 and 3 for the patients in the control and branch pulmonary artery stenosis groups. The patients were divided into 6 groups according to age: Group 1, 1-8 years; Group 2, 8-18 years; Group 3, 19-30 years; Group 4, 30+ years. All the measurements and evaluations were performed using dedicated software (Philips IntelliSpace V 11.0, Philips Medical Imaging Systems, Leiden, the Netherlands).

Statistical Analysis

The obtained data were analyzed using SPSS version 20.0 software (IBM Corporation, Armonk, NY, USA). The median values (interquartile range, 25th–75th percentiles) were used to present the descriptive values. Differences between patient groups were evaluated with nonparametric paired tests to account for data matching (Kruskal–Wallis and Mann–Whitney *U* test). Pearson correlation coefficients were used to assess the correlation of the narrowed-to-total pulmonary artery area ratio with age and gender. Simple linear regression on each set of measurements was used to generate prediction equations relating to the narrowed-to-total pulmonary artery area ratio; goodness of fit was assessed with R^2. A narrowed-to-total branch pulmonary artery area ratio with a discriminatory value suggestive of unilateral branch pulmonary artery stenosis and its receiver operating characteristic (ROC) area under the curve was calculated. A *P*-value of less than .05 was considered significant.

RESULTS

In this retrospective study, 272 patients with a male-to-female ratio of 1.6:1 (105 female and 167 males) were included. The median age was 16 years (11-21). One hundred thirty-six patients (F/M= 83/53) exhibiting normal branch pulmonary artery flow, who served as the control group, with a mean age of 15.5 years (12-22), were included in the study, alongside 136 patients (F/M= 84/52) diagnosed with branch pulmonary artery stenosis, with a mean age of 16 years (11-20), for comparison.

The diameter of the right pulmonary artery and left pulmonary artery was 17 mm (2-20) and 15 mm (5-15) in the control group vs. 15 mm (5-18) and 12.5 mm (5-16) in the branch pulmonary artery stenosis group. The cross-sectional area of the right pulmonary artery and left pulmonary artery was 209.5 mm^2 (73-314) and 176 mm^2 (73-296) in the control group vs. 164 mm^2 (64-314) and 113 mm^2 (52-225) in the branch pulmonary artery stenosis group.

There was a statistically significant difference between control and branch pulmonary artery stenosis groups regarding left pulmonary artery diameter, cross-sectional area, and z-score (P = .006, P=.002, and P < .00001, respectively). However, no statistically significant difference was found in terms of right pulmonary artery diameter, cross-sectional area, and z-score (P = .522, P=.495, and P=.317, respectively). No statistical difference was found for gender in terms of the cross-sectional area of the right pulmonary artery and left pulmonary artery (P=.697 and P= .741, respectively) in the control group and branch pulmonary artery stenosis group (P=.810 and P=.471, respectively). Demographic findings and the details of the measurements are presented in Table 1.

The narrowed-to-total pulmonary artery area ratio was 0.46 vs. 0.38 in the control group and patients with branch pulmonary artery stenosis. There was a statistically significant difference between the control and branch pulmonary artery stenosis group regarding the narrowed-to-total pulmonary artery area ratio (P < .00001). No statistical difference was found between genders in the control group of patients with branch pulmonary artery stenosis (0.44 in boys and 0.43 in girls, P = .968) and (0.37 in boys and 0.36 in girls, P = .794). The difference in the narrowed-to-total pulmonary artery area ratio between control and branch pulmonary artery stenosis groups was statistically significant across all age groups (Table 2).

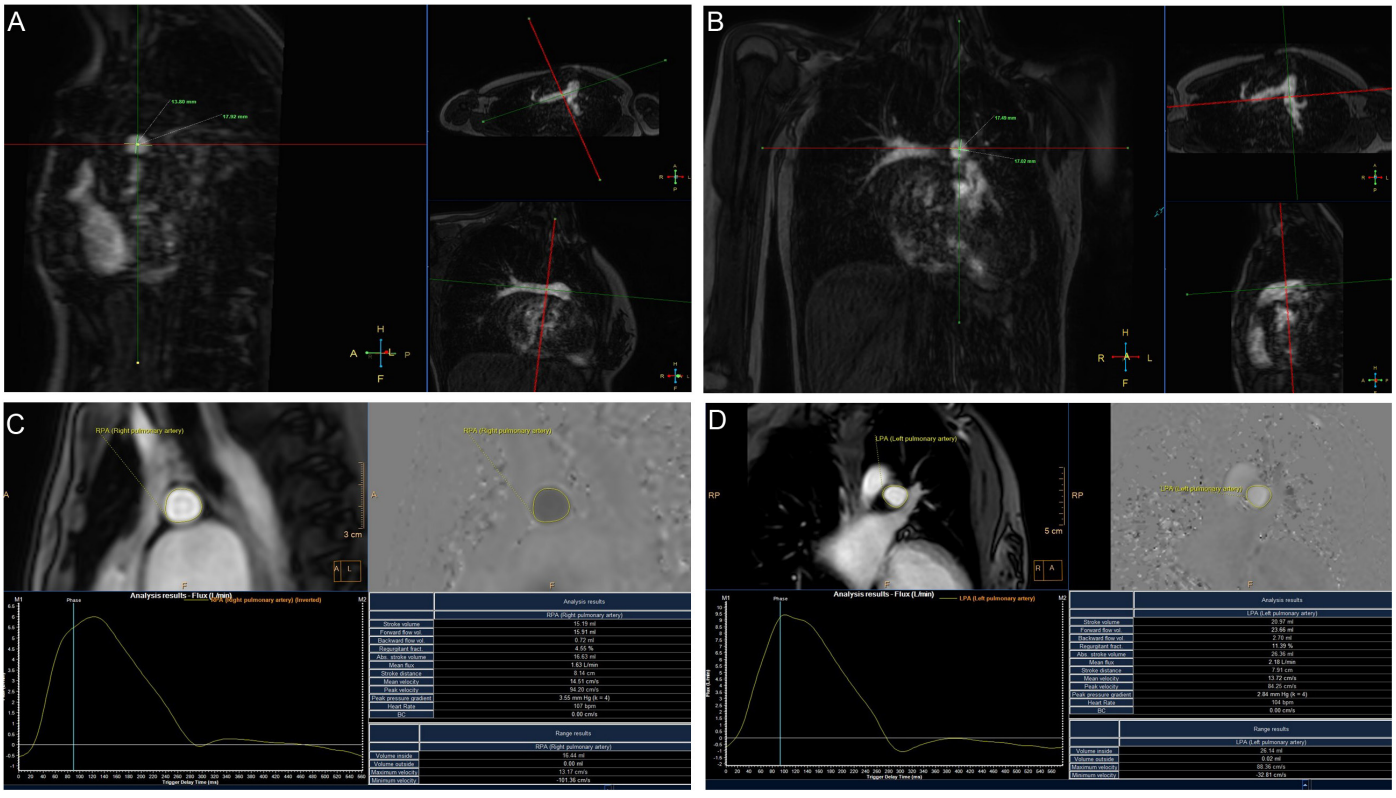

Figure 2. (A-D) A 19-year-old female in the control group. Measurement of the right pulmonary artery (A) and left pulmonary artery (B) in multiplanar reconstructed images of MRA. Phase contrast MRI measurement for the right pulmonary artery (C) and left pulmonary artery (D). The area for the right and left pulmonary arteries are calculated as 194 mm^2 ((3.14 × 13.8 × 17.9)/4) and 234 mm^2 ((3.14 × 17.5 × 17)/4), respectively. The narrowed-to-total pulmonary artery area ratio is calculated as 0.45 (194/428). Net right and left pulmonary artery flows are measured as 15 mL and 21 mL, respectively. The right-to-left pulmonary artery flow ratio is calculated as 42/58%, which is accepted within the normal range.

In the branch pulmonary artery stenosis group, no statistical difference was found in terms of the narrowed-to-total pulmonary artery area ratio between the 4 groups (P=.055). Also, no statistical difference was found between patients younger (0.39, 0.33-0.43) and older (0.37, 0.30-0.41) than 18 years old (P = .173).

The linear regression analysis revealed the following equation: Y=0.3929+−0.001475x. The model's R^2 value was 0.02799 and P=.0516, suggesting that age has a minimal but non-significant effect on the ratio.

A ratio of ≤0.40 exhibited a sensitivity of 67.65% and a specificity of 91.91% in detecting branch pulmonary artery stenosis, as confirmed by the calculated area under the curve (AUC) of 0.86 with a 95% CI ranging from 0.813 to 0.899 and a P-value of <.0001. The estimated positive predictive value (PPV) was 84.79%, and the negative predictive value (NPV) was 80.99 % (Figure 3, 4).

DISCUSSION

This study demonstrated the narrowed-to-total pulmonary artery area ratio as a novel indicator for assessing flow restriction in patients with branch pulmonary artery stenosis. For the first time, this ratio was shown to effectively discriminate patients with clinically significant branch pulmonary artery stenosis without additional diagnostic techniques. A threshold value of 0.4 was identified, enabling the differentiation of patients with physiologically significant stenosis from those without. This finding highlights the potential of this ratio as a simple and non-invasive metric for clinical decision-making in evaluating branch pulmonary artery stenosis.

Different imaging modalities, such as Doppler echocardiography, catheter angiography, or MRI/MRA, have been used to diagnose branch pulmonary artery stenosis. While catheter angiography is considered the gold-standard imaging technique for evaluating anatomical and gradient changes in branch pulmonary artery stenosis and guides the treatment (balloon dilation, stenting) to improve pulmonary blood flow, it carries various limitations, such as exposure to ionizing radiation, the need for iodinated contrast agents, and the inability to quantify flow and cardiac function effectively.[5,15]

Tc-99m-labeled macro-aggregated albumin perfusion scintigraphy is accepted as a gold-standard non-invasive imaging method for assessing lung perfusion.[5,16] However, it is prone to false-negative results in cases of bilateral BPA stenosis or false-positive findings in patients with multi-vessel distal stenosis, parenchymal diseases, or aortopulmonary collaterals.[17,18] Additionally, in patients with cavopulmonary connections, preferential drainage of caval blood into the right or left pulmonary artery can limit the accuracy of this technique.[19] In recent years, phase-contrast MRI has emerged as an effective alternative to radiation-containing perfusion scintigraphy for precisely quantifying differential pulmonary blood flow.[10] As reported by Fratz et al[19], phase-contrast MRI has been shown to provide more accurate evaluations of pulmonary perfusion ratios compared to lung perfusion scintigraphy, particularly in patients with congenital heart disease, such as those with

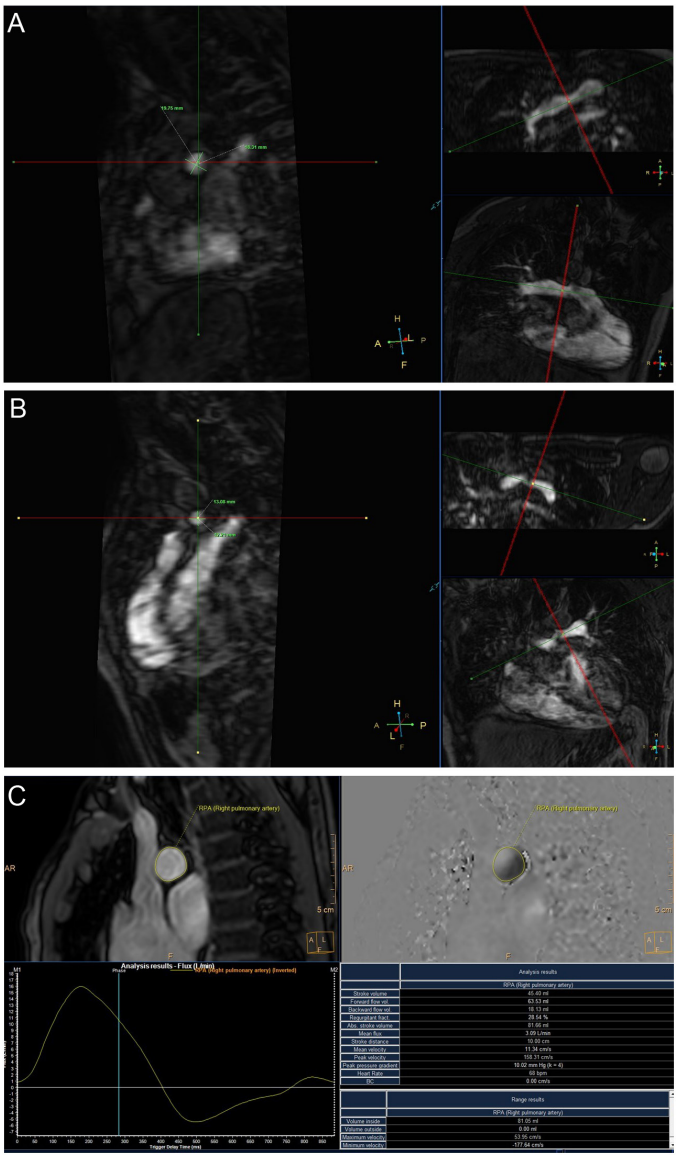

Figure 3. (A-D) A 13-year-old male patient with repaired tetralogy of Fallot. Measurement of the right pulmonary artery (A) and left pulmonary artery (B) in multiplanar reconstructed images of MRA. Phase contrast MRI measurement for the right pulmonary artery (C) and left pulmonary artery (D). The area for the right and left pulmonary arteries are calculated as 283 mm^2 ((3.14 × 19.7 × 18.3)/4) and 125 mm^2 ((3.14 × 12.2 × 13.1)/4), respectively. The narrowed-to-total pulmonary artery area ratio is calculated as 0.31 (125/407). Net right and left pulmonary artery flows are measured as 45 mL and 21 mL, respectively. The right-to-left pulmonary artery flow ratio is calculated as 68/32%, accepted as a diminished preferential pulmonary flow towards the left lung.

Fontan-like circulation. The role of phase-contrast MRI and other non-invasive imaging techniques in diagnosing branch pulmonary artery stenosis is growing in importance.[12] Studies have demonstrated the accuracy of phase-contrast MRI in correlating differential blood flow with lung scintigraphy in adults with normal branch pulmonary artery anatomy.[13] Furthermore, recent research has provided robust documentation of branch pulmonary artery blood flow in patients with pulmonary incompetence, highlighting its value in this population.[14,20,21]

Although MRA has demonstrated a strong correlation with the gold-standard invasive catheter angiography in assessing the great vascular

Table 1. Demographic Findings and the Details of the Branch Pulmonary Artery Measurements of the Study Cohort

Parameters	Control Group	BPA Stenosis Group	*P*
Number of Patients (n)	136	136	–
Male: Female Ratio	83:53 (1.5:1)	84:52 (1.6:1)	–
Median Age (years)	15.5 (12-22)	16 (11-20)	–
Pulmonary Artery Diameter			
RPA Diameter (mm)	17 (2-20)	15 (5-15)	.522
LPA Diameter (mm)	15(5-18)	12.5(5-16)	.006*
Pulmonary Artery Cross Sectional Area			
RPA Area (mm^2)	209.5 (73-314)	164 (64-314)	.459
LPA Area (mm^2)	176 (73-296)	113 (52-225)	.002*
Pulmonary Artery Diameter *Z*-score			
RPA *Z*-score	1.96 (1.08-2.23)	1.57 (0.89-2.80)	.317
LPA *Z*-score	1.49 (0.45-2.12)	1.96 (-0.53-1.57)	<.00001

Results are presented as median (Interquartile range, 25th–75th percentiles). *P* is the *P*-value of Mann–Whitney *U* test analysis.

BPA, branch pulmonary artery; LPA, left pulmonary artery; RPA, right pulmonary artery.

**P* value is significant if <.05.

structures, offering the benefit of avoiding both radiation exposure and iodinated contrast agents.[11] Ordovás et al[9] also demonstrated that the right-to-left pulmonary artery diameter ratio fails to predict flow discrepancies. Greenberg et al[22] suggested that branch pulmonary arteries are usually oval-shaped, potentially leading to inaccuracies in single-diameter measurement methods. The non-circular shape of the branch pulmonary artery and the findings of Greenberg et al[22] provide methodological support for using cross-sectional area measurements in this study, ensuring greater accuracy in evaluating stenosis severity. The current study introduces a more robust approach: the BPA-ratio, calculated as the narrowed-to-total pulmonary artery cross-sectional area, to establish a clinically useful threshold for intervention.

This ratio serves as a reliable indicator of branch pulmonary artery stenosis, offering a clear threshold that can be used to determine the need for intervention. The results indicate that negative test outcomes demonstrate high accuracy in excluding branch pulmonary artery stenosis, which reduces the need for phase-contrast MRI and its associated technical limitations, thereby preventing unnecessary invasive

Table 2. Comparison of Narrowed-to-Total BPA Area Ratio of the Control and the BPA Stenosis Groups by Age Groups

Study Groups		N	Narrowed-to-Total BPA Area Ratio	*P*
Total	**Control**	136	0.46 (0.43-0.48)	<.00001
	BPA stenosis	136	0.38 (0.32-0.42)	
Group 1 (2-8 years)	**Control**	9	0.48 (0.44-0.50)	.002
	BPA stenosis	9	0.34 (0.28-0.41)	
Group 2 (9-18 years)	**Control**	81	0.45 (0.43-0.48)	<.00001
	BPA stenosis	81	0.39 (0.34-0.43)	
Group 3 (19-30 years)	**Control**	32	0.45(0.43-0.48)	<.00001
	BPA stenosis	32	0.37 (0.32-0.42)	
Group 4 (31- years)	**Control**	14	0.45 (0.43-0.47)	.00016
	BPA stenosis	14	0.34 (0.24-0. 38)	

Results are presented as median (Interquartile range, 25th–75th percentiles). *P* is the *P*-value of Mann–Whitney *U* test analysis.

BPA, branch pulmonary artery; LPA, left pulmonary artery; RPA, right pulmonary artery.

**P* value is significant if <.05.

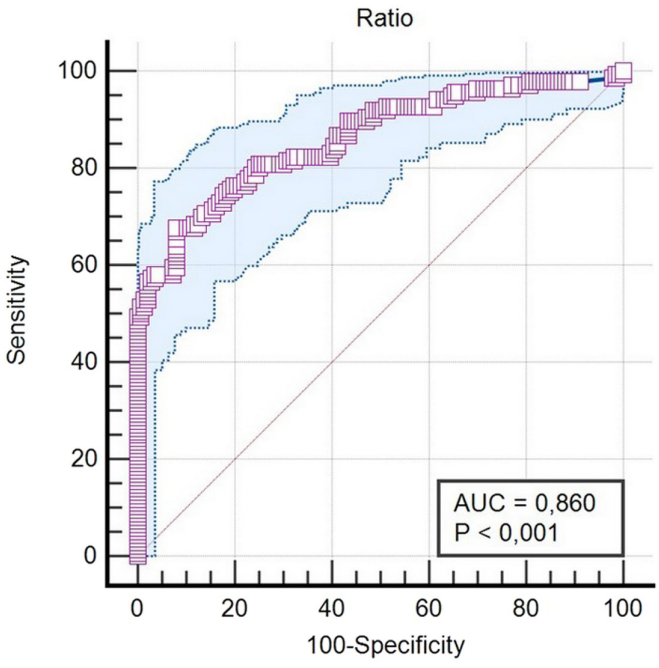

Figure 4. A discriminative narrowed-to-total pulmonary artery area ratio ≤ 0.40 demonstrates a positive predictive value of 70.5% and a negative predictive value of 80.99% for identifying branch pulmonary artery stenosis in repaired tetralogy of Fallot. This threshold's receiver operating characteristic (ROC) curve yields an area under the curve (AUC) of 0.85, indicating its strong utility in ruling out branch pulmonary artery stenosis.

procedures. Conversely, positive results are clinically significant and should be corroborated with confirmatory tests, such as phase-contrast MRI or perfusion scintigraphy. The ratio provides valuable support in classifying patients and enhancing the treatment process. By establishing a precise ratio that correlates with clinically significant stenosis, the study offers a useful tool for clinicians, enabling them to make informed decisions regarding the timing and treatment options.

Another significant contribution of this study is the introduction of the branch-to-total pulmonary artery area ratio as a practical diagnostic metric. MRA offers a non-invasive alternative to evaluate the severity of branch pulmonary artery stenosis without ionizing radiation or radionuclides, making it a practical tool in routine radiology practice.

Magnetic resonance imaging is an appropriate cross-sectional imaging modality for long-term follow-up, particularly in patients with congenital heart disease, as it enables comprehensive evaluation of simultaneous anatomical and physiological changes without radiation exposure. Additionally, it allows for monitoring disease progression and assessing intervention effectiveness over time, thereby supporting long-term patient management.

The study has several limitations, including its retrospective nature, single-center, and small sample size study population. Further research involving prospective data from multiple institutions in large patient cohorts would be valuable in various populations. Another limitation is the lack of confirmation of branch pulmonary artery stenosis through cardiac catheterization or lung scintigraphy. However, obtaining such confirmation would be particularly challenging, especially for the control group, as these procedures involve deep sedation or anesthesia in young children and exposure to radiation and radionuclides. These ethical considerations could render such a study unfeasible. Furthermore, the study population was inherently selective, as all participants had congenital pulmonary arterial stenoses and were referred for MRI to assess hemodynamic significance. The inter- or intraobserver variability was not assessed in this study as phase-contrast MRI is a well-validated technique.[13,14] Additionally, all cardiac MRI examinations were performed using an institutionally approved clinical protocol and evaluated by experienced radiologists in cardiovascular imaging.[21,23] Another limitation of this study is that the estimated area was calculated using the ellipse area formula based on 2 diameters. However, area measurements obtained from multiplanar reconstructions would increase the software dependence. In a busy radiology practice, calculating the area using the ellipse formula may offer a more practical alternative.

In conclusion, a narrowed branch-to-total pulmonary artery area ratio of 0.40, measured using cross-sectional imaging, can assist in identifying patients who may require catheter angiography, mainly when cardiac MRI is unavailable or flow measurement is not feasible. This study refines an existing methodology by incorporating both morphological and flow-based parameters in stenosis evaluation. It can serve as a valuable reference in daily radiology practice, guiding the referral of patients for further investigations without the need for radiation exposure or advanced traditional imaging techniques.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İstanbul Medeniyet University (Date 25.12.2019, Approval Number: 2019/052).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - SO; Design – SO, IKY; Supervision - IKY; Resources - MK; Materials - SO; Data Collection and/or Processing - MK; Analysis and/or Interpretation – TB,ÖA, BT, MFK, MK; Literature Search - AFT; Writing Manuscript - AFT; Critical Review - SO; Other –MK

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Declaration of Interests: The authors declare that they have no competing interests.

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