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IMAGING

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Hemodynamic Assessment of Infants With Congenital Heart Disease Using Ferumoxytol-Enhanced 4D Flow Cardiac Magnetic Resonance

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ABSTRACT

In complex congenital heart disease, characterization of the circulation is necessary to anticipate the clinical course. Four-dimensional cardiac magnetic resonance imaging enhanced by superparamagnetic iron oxide contrast agents (ferumoxytol) enables detailed and efficient assessment of both anatomy and physiology in neonates. We demonstrate this impact in 3 cases of neonates with congenital heart disease. (JACC Case Rep. 2024;29:102559) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Abnormal blood flow is the driving pathophysiology of congenital heart disease. Beyond medical and surgical management of traditional intracardiac shunts, pediatric cardiology practice is challenged by the small infant with congenital heart disease and multiple sources of intracardiac shunting or valvular regurgitation. Modern cardiac magnetic resonance (CMR) allows for time-resolved 3-dimensional phase-contrast (4D flow) analysis to characterize in vivo flows of the entire heart. The use of ferumoxytol (a superparamagnetic iron oxide contrast agent) in particular enhances accuracy and clinical applicability in small infants.[1] We demonstrate 3 cases in infants with congenital heart disease where 4D flow analysis greatly affected decisions on the type of surgical repair by providing deep understanding of anatomy and physiology.

TAKE-HOME MESSAGES

- Hemodynamic assessment of congenital heart disease frequently requires complex interpretation of multiple intracardiac shunts.
- In infants, ferumoxytol-enhanced 4D flow CMR can provide comprehensive flow analysis to guide surgical management.

CASE 1: TETRALOGY OF FALLOT OR EBSTEIN ANOMALY?

A newborn girl (body surface area, 0.21 m^2) with a prenatal diagnosis of dextroversion, tetralogy of Fallot with pulmonary stenosis, and a large omphalocele was intubated after delivery and started on prostaglandin E_1 for hypoxia. The initial echocardiogram demonstrated a large conoventricular-type ventricular septal defect (VSD) with anterior malalignment

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

LV = left ventricular

PA = pulmonary artery

Qes = effective systemic circulation

Qp = pulmonary blood flow

RV = right ventricular

VSD = ventricular septal defect

4D flow = time-resolved 3-dimensional phase-contrast

and a small pulmonary valve. However, Ebstein anomaly was suspected on the basis of abnormal tricuspid valve architecture with moderate to severe regurgitation and a right-to-left atrial shunt. The right ventricular (RV) outflow tract peak velocity was ~1.5 m/s in the setting of a large patent ductus arteriosus. Maintaining oxygenation was challenging, with persistent lower saturations ~80% to 85% and intermittent lactic acidosis despite aggressive respiratory management.

In most congenital heart disease, echocardiography is used by pediatric cardiologists to infer the dominant mechanisms of cyanosis such as RV outflow tract obstruction. However, traditional Doppler metrics may not fully clarify the physiology in patients with multiple sources of intracardiac shunting (eg, the estimated pressure gradient may underrepresent obstruction in the presence of a large ductus arteriosus). Traditionally, cardiac catheterization has been the next diagnostic modality; however, noninvasive flow assessment by CMR offers the potential for determining the significance of both intracardiac shunting and tricuspid regurgitation.

With a single acquisition, 4D flow CMR can provide accurate shunt quantification at multiple levels with good intraclass agreement. In neonates, flow measurements are performed in very small-caliber vessels with low flow rates, with a requirement for general anesthesia and sequences with high spatial resolution and optimal blood pool contrast to maintain accuracy.[2] At our institution (Children's National Hospital, Washington, DC, USA), this is accomplished by using ferumoxytol contrast material in combination with a respiratory-gated, GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) accelerated 4D flow sequence (previously research, now product) on a Siemens 1.5-T machine (scan parameters listed in **Table 1**). This methodology has been validated against 2-dimensional phase-contrast measurements.[1]

The patient subsequently underwent CMR while she was sedated (**Figures 1A to 1D**, Video 1), with a total scan time of 33 minutes (9 minutes for 4D flow). The tricuspid inferior and septal leaflets were dysplastic, with severe insufficiency from the commissure (regurgitant fraction >75%), resulting in severe right atrial dilation and a pocket of atrialized right ventricle. The branch pulmonary arteries (PAs) measured lower limits of normal. The effective systemic circulation (Qes, which is based on systemic venous return) was ~2 L/min/m^2, with higher pulmonary flow (Qp, which is distal branch PA flow) ~3.3 L/min/m^2 (**Figure 2**). The Qp was maintained by left-to-right shunt at the ventricular and ductal level. Meanwhile, there was a net right-to-left atrial shunt ~1.1 L/min/m^2 by direct measurement.

TABLE 1 Laboratory Standard Parameters for 4-Dimensional Flow

Slice thickness, mm	1.3
In-plane field of view, mm	160 × 200
IPAT acceleration factor	1-2
Views per segment	2
In-plane acquisition resolution, mm	1.78 × 1.25
In-plane reconstructed resolution, mm	1.25 × 1.25
In-plane acquisition matrix	90 × 160
In-plane reconstruction matrix	128 × 160
Echo time, ms	2.37-2.55
Temporal resolution, ms	39.28
VENC, cm/s	150-250
Number of reconstructed phases	30

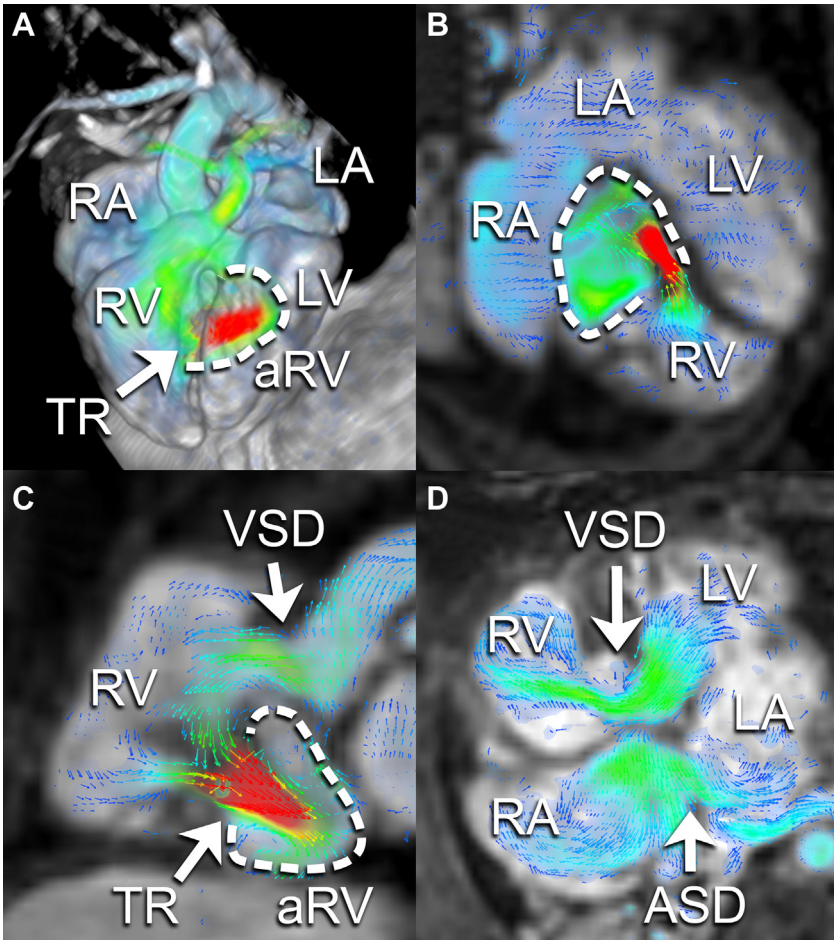
IPAT = integrated parallel imaging techniques; VENC = velocity encoding.

The CMR findings effectively ruled out RV outflow obstruction with right-to-left VSD shunt as the main mechanism for cyanosis (ie, tetralogy of Fallot), instead highlighting tricuspid regurgitation, a right-to-left atrial shunt, and a need for tricuspid valve intervention. Thus, the patient underwent successful repair of the tricuspid valve posterior leaflet, patch closure of the VSD, and pulmonary arterioplasty. This case demonstrates the potential of multiple flow measurements within 1 data set. With traditional 2-dimensional phase-contrast imaging, multiple acquisitions (at least 7 separate acquisitions) would have prolonged scan time, thereby adding physiologic uncertainty to measurements.

CASE 2: SCIMITAR SYNDROME WITH CONTRALATERAL PULMONARY VEIN STENOSIS

A 34-week premature female infant (body surface area, 0.19 m^2) received a diagnosis of anomalous right lower pulmonary vein draining into the inferior vena cava, right lung hypoplasia, dextroposition, and right aortopulmonary collateral vessels consistent with scimitar syndrome. These findings were confirmed by computed tomography. However, given ongoing challenges with ventilation, CMR was performed to assess the hemodynamic burden from the scimitar vein and/or aorta-pulmonary collateral vessels.

FIGURE 1 4-Dimensional Flow of Ebstein Anomaly From Different Planes

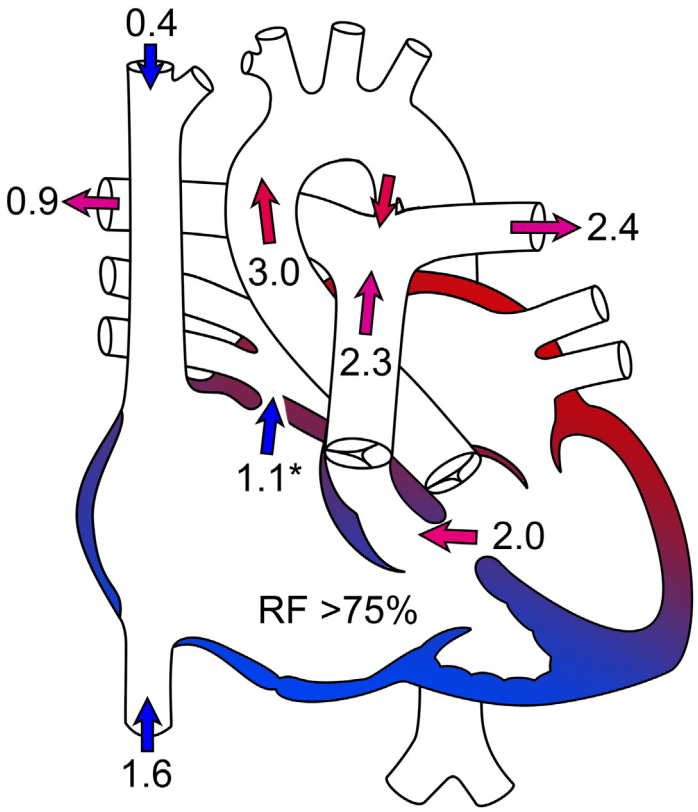


(A) Volume rendering from a left anterior oblique/cranial view. (B) A 4-chamber view. (C) A sagittal view. (D) A short-axis view. Velocity encoding was set to 225 cm/s for this acquisition. As a result of tricuspid regurgitation (TR), there is a small pocket of atrialized right ventricle (aRV, delineated within broken lines) and a severely dilated right atrium (RA). There is left-to-right shunting across the ventricular septal defect (VSD) and right-to-left shunting across the atrial septal defect (ASD). LA = left atrium; LV = left ventricle.

The 4D flow (**Figures 3A to 3D**, Video 2) demonstrated pulmonary venous anatomy and aortopulmonary collateral vessels from the descending aorta to the right lung. The right PA was relatively hypoplastic compared with the left PA, with a 33%/66% flow split. The aortopulmonary collateral vasculature contributed to ~12% of pulmonary venous return, a finding suggesting that the scimitar vein contributed to the majority of the shunt. Meanwhile, prominent flow was noted in the left pulmonary veins, with an abnormal nonphasic flow pattern concerning for venous obstruction (**Figure 4A**). The patient underwent cardiac catheterization (**Figure 4B**), which confirmed significant left pulmonary vein stenosis (mean gradient ~18 mm Hg) and pulmonary hypertension. She underwent surgical repair consisting of a fenestrated baffle of the right veins to the left atrium and a sutureless-type repair of the left pulmonary veins.

Patients with scimitar syndrome have heterogenous presentations of respiratory distress and/or heart failure, on the basis of varying degree of atrial shunt, lung hypoplasia, and aortopulmonary collateral burden. This infant represented the most severe form with contralateral pulmonary vein stenosis and accompany pulmonary hypertension, known to be

FIGURE 2 Quantitative Flow Parameters (Indexed by Body Surface Area) Measured by 4-Dimensional Flow in Ebstein Anomaly



Units are in L/min/m^2. The asterisk indicates that atrial flow is bidirectional with a net right-to-left shunt. RF = regurgitant fraction.

associated with poor outcomes.[3] Unfortunately, this patient died of complications related to pulmonary hypertension, despite aggressive medical therapy and catheterization rehabilitation.

Although cardiac catheterization remains the gold standard in anatomical and hemodynamic definition of pulmonary veins, 4D flow can provide complementary hemodynamic assessment of the various shunts in addition to detecting abnormal venous flow patterns. The ability to visualize discrete flow acceleration adds potential diagnostic value for pulmonary vein stenosis, and the use of 4D flow should be systematically explored in this challenging disease.

CASE 3: THE BORDERLINE LEFT VENTRICLE

A newborn boy (body surface area 0.18 m^2) with a prenatal diagnosis of VSD and a persistent left superior vena cava to the coronary sinus was admitted with ductal-dependent systemic circulation. In addition to a large midmuscular VSD, postnatal echocardiography demonstrated borderline left-sided heart structures, including a hypoplastic mitral annulus and a transverse aortic arch. The left ventricle was borderline small with a narrow subaortic outflow tract, albeit apex forming. There was moderate flow acceleration across the mitral valve with an estimated gradient of ~5 to 10 mm Hg. Partial anomalous pulmonary venous return was also suspected. CMR with the patient under general anesthesia was performed to confirm systemic and pulmonary venous anatomy and assess the potential for biventricular-type repair.

Traditionally, echocardiography has determined viability of a biventricular circulation on the basis of measurements of left ventricular (LV) size, the mitral valve, and the aortic valve. Imaging studies have demonstrated the value of combining of multimodality metrics to improve prediction for viable biventricular repair.[4,5] The performance of these metrics in the presence of anomalous pulmonary venous return adds uncertainty. Thus, accurate characterization of the left-sided atrioventricular inflow by CMR is beneficial in anticipating the growth potential of the left ventricle.

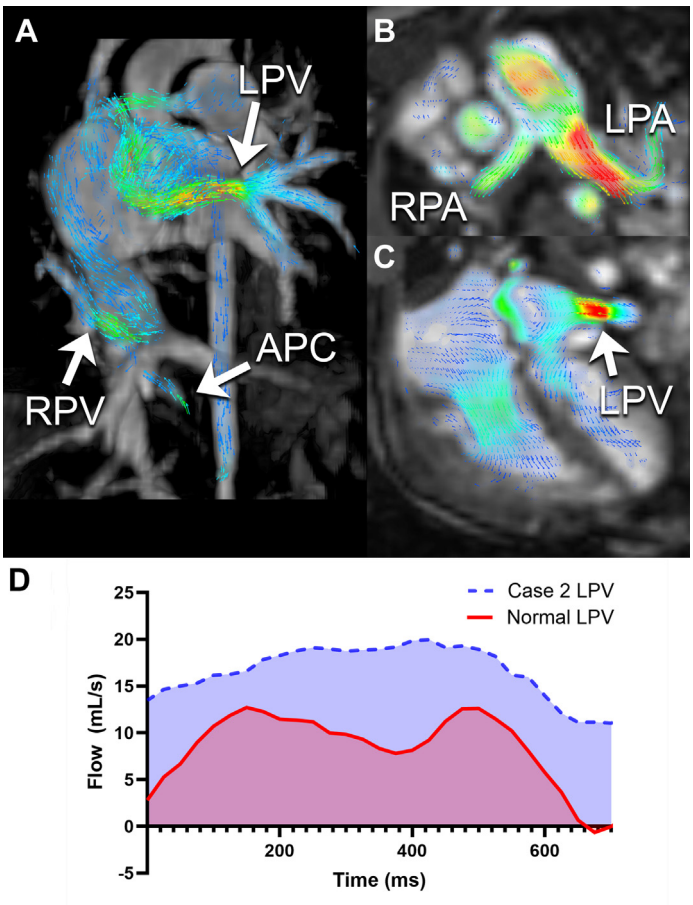
The 4D flow (**Figures 5A to 5F**, Video 3) confirmed an overall large shunt (Qp/Qes >5:1) from both the VSD and the partial anomalous right pulmonary veins into the right atrium. The dilated proximal coronary sinus distorted the orientation and size of the mitral valve. The mitral valve otherwise had normal leaflet motion and was able to accommodate ~2.8 L/min/m^2 flow (**Figure 6**) that contributed to the VSD shunt (1.7 L/min/m^2) and aortic output (1.1 L/min/m^2). The left ventricle had an indexed end-diastolic volume of 34 mL/m^2 with a cardiac index of 2.8 L/min/m^2.

The surgical management for the borderline left ventricle is challenging if the mitral inflow is hypoplastic. Recent operative strategy has considered a staged approach where the atrial shunt is partially diverted into the left ventricle for growth. In this case, the mitral valve appeared sufficient in sustaining an adequate cardiac index. Thus, the patient successfully underwent Warden-type repair of partial anomalous pulmonary veins, VSD patch closure, and aortic arch augmentation. Postoperative imaging demonstrated a mild mitral valve gradient with normal LV size and function.

TECHNICAL CONSIDERATIONS FOR 4D FLOW IN SMALL INFANTS

Beyond logistical considerations of CMR (general anesthesia and transport of a hemodynamically

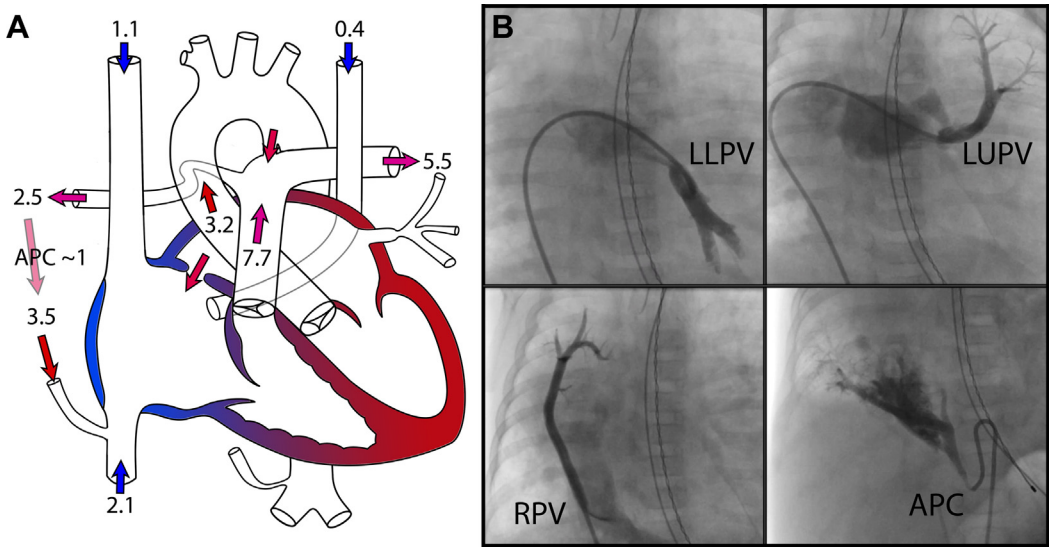
FIGURE 3 **4D Flow in Scimitar Syndrome With Contralateral Pulmonary Vein Stenosis**



(A to C). The 4-dimensional flow of scimitar syndrome from multiple planes. (A) A coronal view. (B) An axial view. (C) A 4-chamber view. Velocity encoding was set to 150 cm/s for this acquisition. The scimitar vein, which receives all right pulmonary veins (RVPs), drains into the inferior vena cava. A single aortopulmonary collateral (APC) vessel supplies the hypoplastic right lung. There is discrete flow acceleration across the left pulmonary veins (LPVs) concerning for obstruction. (D) Flow across the left pulmonary veins demonstrating an abnormal nonphasic pattern (normal left pulmonary vein in an infant for comparison). LPA = left pulmonary artery; RPA = right pulmonary artery.

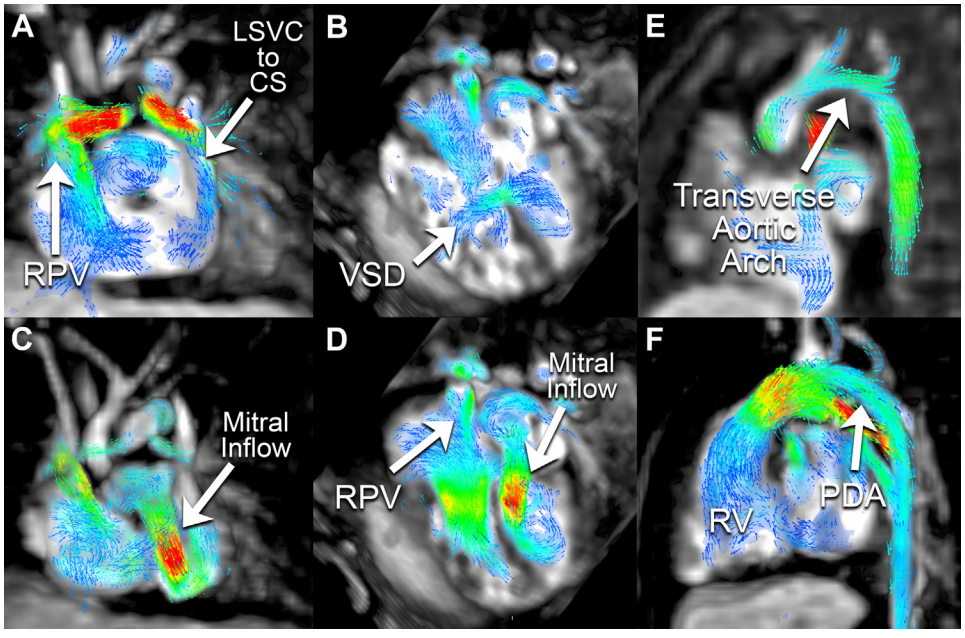
tenuous patient), sequence parameters require a delicate balance of appropriate spatiotemporal resolution, signal strength, and scan time, which may be significantly challenging in very small vessels in neonates with fast heart rates. The 4D flow consensus statements recommend that the spatial resolution in neonates should aim for a 0.75 to 1 mm^3 voxel size,[2] although this recommendation was based on a study using a 3-T magnet.[6] Our clinical experience with a 1.5-T magnet suggests that even with ferumoxytol enhancement, spatial resolutions <1.3 mm^3 risk significant loss of signal strength that affects flow accuracy and interpretation; we recommend the use of coarser 4D flow resolution (≥ 1.8 mm^3) in cases where ferumoxytol use is contraindicated or not available.[1] We also recommend lower VENC than is typically recommended[2] because any aliasing artifact from flow acceleration within a stenotic vessel or valve can be circumvented by measuring in a region proximal to the region of flow acceleration. Moreover, because most intracardiac shunts constitute an increase in volume load, vessels with typically low

FIGURE 4 Flow Parameters and Angiography in Scimitar Syndrome



(A) Quantitative flow parameters (indexed by body surface area) measured by 4-dimensional flow in scimitar syndrome. Units are in L/min/m^2. (B) Catheterization angiography of the pulmonary veins and aortopulmonary collateral (APC) vessel. LLPV = left lower pulmonary vein; LUPV = left upper pulmonary vein; RPV = right pulmonary vein.

FIGURE 5 4-Dimensional Flow of VSD With Borderline Left Ventricle and Mitral Valve Hypoplasia



(A to F) Views from different planes. (A and C) Coronal view in systole and diastole. (B and D) Apical view in systole and diastole. € Arch view. (F) Ductal view. Velocity encoding was set to 200 cm/s for this acquisition. The mitral valve inflow/orientation is distorted by a dilated coronary sinus (CS) because of a persistent left superior vena cava (LSVC). The transverse aortic arch is hypoplastic, and the descending aorta flow is partially provided by a patent ductus arteriosus (PDA) (note that flow is bidirectional with right-to-left shunt in systole). RV = right ventricle; other abbreviations as in Figures 1 and 3.

velocities (eg, pulmonary veins) will have higher flows, such that a VENC range of 150 to 250 cm/s provides reasonable sensitivity to most flow assessment in the heart. In the absence of dual VENC, repeat 4D flow (one set for lower VENC, another set for higher) could also be considered, although this would significantly prolong scan time. Thus, the application of this analysis is most advantageous in cases with ferumoxytol contrast enhancement and multiple adequate-sized vessels or shunts, where different aspects of the heart can be interrogated to address any resolution deficiencies in particularly small vessels (eg, small collateral vessels or coronary artery fistulas <1-2 mm in size).

CONCLUSIONS

4D flow is ready for widespread clinical application in congenital heart disease. Clinical acquisitions are now efficient and reliable, and they can be used to guide management in infants with complex congenital heart disease.

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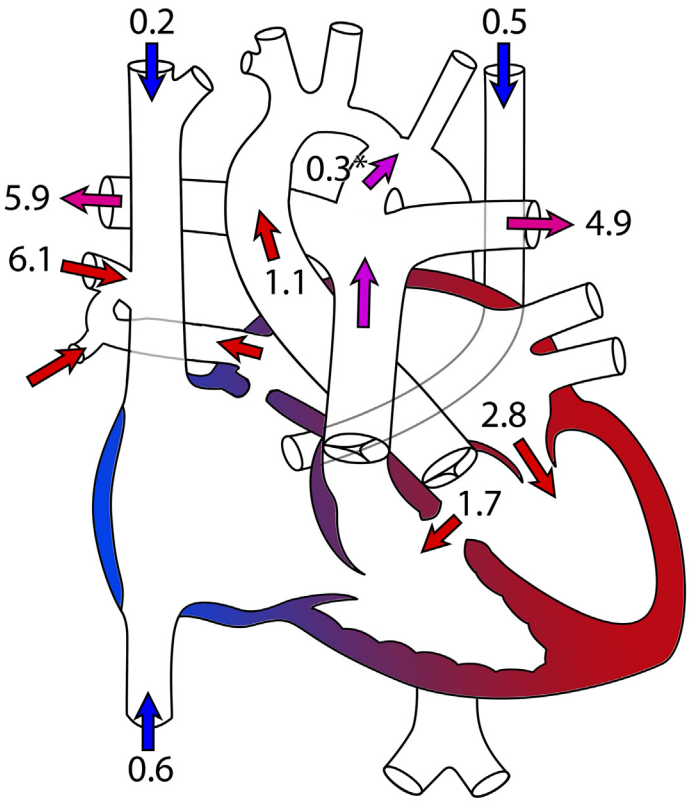
FIGURE 6 Quantitative Flow Parameters (Indexed by Body Surface Area) Measured by 4-Dimensional Flow in Ventricular Septal Defect With Borderline Left Ventricle and Mitral Valve Hypoplasia



Units are in L/min/m^2. The asterisk indicates that ductus arteriosus flow is bidirectional, with a net right-to-left shunt to supply the systemic circulation.

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APPENDIX For supplemental videos, please see the online version of this paper.