

**Prenatal diagnosis of tetralogy of Fallot with pulmonary atresia using
Fetal Intelligent Navigation Echocardiography (FINE)**

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Case 2

A 28-year old woman (G3, P2002) was referred to our research ultrasound unit at 22 weeks of gestation. Her past medical history was significant for pseudotumor cerebri, asthma, chronic hypertension, iron deficiency anemia, and seizure disorder. In addition, her grandfather had an unspecified heart defect as a child that required surgery. The patient had a body mass index of 33, which is classified as obese [1]. Earlier on the same day, she underwent a clinical ultrasound examination in which a cardiac defect was suspected, but the specific diagnosis could not be determined. We performed four-dimensional sonography with spatiotemporal image correlation (STIC), in which volume datasets of the fetal heart containing gray-scale and color Doppler information were acquired from the apical four-chamber view by transverse sweeps through the fetal chest. The acquisition time was 10 seconds, while the acquisition angle was 30 degrees. Two STIC volume datasets (gray-scale and color Doppler each) considered to be of highest quality were chosen for analysis by the Fetal Intelligent Navigation Echocardiography (FINE) method [2].

For this case, it is noteworthy that when attempting to mark the pulmonary valve using Anatomic Box® in the gray-scale STIC volume, a clear valve could not be identified. Yet, it was still possible to estimate the location for marking due to two technologic features of FINE: 1) *pulmonary valve* alert [3,4], which was automatically activated during the marking process because the fetal spine in the STIC volume was located between 4- and 5-o'clock; and 2) *intelligent cursor placement*. The pulmonary valve alert is a type of *marking alert* (i.e. movie) which notifies the sonologist that fetal anatomical structures for marking (e.g. pulmonary valve) may be in different locations than what is expected [3,4]. Such movie depicts a reference image example to guide and teach the sonologist how to mark the anatomic structure of interest. Another feature of

FINE which simplifies the marking process for the user is “intelligent” cursor placement, in which the system automatically places the cursor near, or at the location to be marked. Intelligent cursor placement occurs for four anatomic structures (right atrial wall, pulmonary valve, superior vena cava, and transverse aortic arch).

For the gray-scale STIC volume, six echocardiography views were abnormal (Supplementary Figure S5, Supplementary Movie 3). The three vessels and trachea view showed a large transverse aortic arch without a pulmonary artery identified. The four-chamber view appeared normal. However, when Virtual Intelligent Sonographer Assistance (VIS-Assistance®) was activated, a ventricular septal defect (VSD) with overriding aorta became visible. In the five-chamber view, the anteriorly malaligned VSD was visualized with overriding of the ventricular septum by the dilated aortic root. The left ventricular outflow tract view showed similar findings. Movement of the aortic valve leaflets in this fetus appeared normal. In the short-axis view of great vessels/right ventricular outflow tract, the main pulmonary artery and valve, branch pulmonary arteries, and ductus arteriosus could not be identified. Similarly in the ductal arch view, the main pulmonary artery and valve, as well as the ductus arteriosus could not be visualized. The aortic arch view showed a dilated aortic root and a prominent ascending aorta. Importantly, automatic labeling of the cardiac anatomy was correct for all nine echocardiography views. Moreover, labeling of the pulmonary artery by FINE (Supplementary Figure S5, Supplementary Movie 3) was in the “appropriate” location, even though an actual main pulmonary artery and valve could not be visualized. When the color Doppler STIC volume was analysed by FINE [5], multiple echocardiography views demonstrated color flow in the aorta, but absent flow in the area of the main pulmonary artery, confirming the diagnosis of pulmonary atresia.

The patient underwent second trimester amniocentesis and the karyotype was 46XY. Microarray studies were normal, including testing for 22q11.2 deletion syndrome. At 30 weeks of gestation, a STIC volume dataset was obtained with color Doppler information and FINE demonstrated color flow exiting both ventricles into the large overriding aorta (Supplementary Figure S6). The fetus was appropriately grown for gestational age and the amniotic fluid volume was normal.

Delivery and Postnatal course (Case 2)

At 39 5/7 weeks of gestation, the patient underwent induction of labor due to anhydramnios and delivered a viable male infant weighing 3530 grams vaginally. The Apgar scores were 8 and 9 (at 1 and 5 minutes, respectively). Given the known prenatal diagnosis of pulmonary atresia, the neonate was started on continuous prostaglandin E1 infusion shortly after birth and was clinically well with acceptable saturations. The postnatal echocardiogram at day one of life confirmed the diagnosis of tetralogy of Fallot with pulmonary atresia (TOF/PA), with a large anterior malaligned VSD and overriding aorta (Supplementary Figure S7). Although the initial postnatal echocardiogram suggested a ductus arteriosus supplying confluent pulmonary arteries, subsequent studies determined the presence of discontinuous pulmonary arteries (Supplementary Figure S8) with bilateral large major aorto-pulmonary collateral arteries (MAPCAs) – each providing complete blood supply to its respective lung.

Cardiac catheterization obtained in the first few days of life confirmed a non-confluent pulmonary arterial system. Angiographic imaging showed a major systemic-to-pulmonary collateral artery (i.e. MAPCA) originating from the right innominate artery to supply the entire right lung, and an additional large MAPCA arising from the underside of the aortic arch to supply the entire left lung (Supplementary Figure S9). Given the overall normally-sized pulmonary arteries, early surgical correction was

performed on day 5 of life, consisting of VSD closure, unifocalization of the pulmonary arteries, and placement of a right ventricle-to-pulmonary artery conduit. The neonate was discharged home in good clinical condition after an uneventful postoperative course. At the time of this writing (13 months of age), the right ventricular systolic function was normal and the neonate was doing well overall, except for some intermittent complaints of mild exercise intolerance.

Supplementary Discussion

FINE as a method to diagnose congenital heart disease

We report herein for the first time, two different cases of TOF/PA with variable sources of pulmonary blood flow in which the diagnosis was made successfully using the FINE method. This is relevant because of the complex and heterogeneous nature of this cardiac defect. In addition, supralvalvar aortic stenosis was evident for Case 1 using FINE, but was not the case on real-time fetal echocardiography.

FINE is a novel method which automatically generates and displays nine standard fetal echocardiography views in normal hearts by applying “intelligent navigation” technology to STIC volume datasets [2,3,5-7]. As a result, such method considerably simplifies examination of the fetal heart and reduces operator dependency [2]. When FINE was first developed, we proposed using this technology to examine the fetal heart in the population at large, instead of diagnosing congenital heart disease [2]. However, since that time our group has reported that FINE: 1) demonstrates abnormal fetal cardiac anatomy successfully [2,4,5,8,9]; and 2) has high accuracy (95%) in detecting a broad spectrum of congenital heart disease [4]. Moreover, we have recently shown that the implementation of color Doppler FINE successfully demonstrates abnormal fetal cardiac anatomy and hemodynamic flow in cases of cardiac anomalies [5]. For Case 2, color Doppler FINE was especially helpful, because it confirmed the

absence of pulmonary blood flow and the presence of antegrade color flow into the overriding aorta for multiple echocardiography views.

For both cases herein, there were several specific features of the FINE method that were very helpful in making the prenatal diagnosis of TOF/PA: 1) VIS-Assistance®; and 2) automatic labeling. VIS-Assistance® allowed automatic navigation and exploration of each cardiac diagnostic plane, thus confirming a severely hypoplastic pulmonary artery with closed pulmonary valve (Case 1), as well as non-visualization of the main pulmonary artery and valve, branch pulmonary arteries, and ductus arteriosus (Case 2). It is noteworthy that automatic labeling (anatomical structures, diagnostic planes, left and right sides of the fetus, and cranial and caudal ends) was correct in all nine fetal echocardiography views for both cases. This is possible because the system “infers” the actual location of structures in space [6].

Tetralogy of Fallot with pulmonary atresia: variable anatomy of the pulmonary arterial circulation

TOF/PA (also known as pulmonary atresia with VSD) comprises approximately 20% of all tetralogy of Fallot cases [10]. It is a rare form of congenital heart disease (10/100,000 live born infants) [11], and is characterized by atresia of the pulmonary valve, pulmonary artery hypoplasia, VSD, and an overriding aorta. The aortic root often has a greater diameter than that seen in tetralogy of Fallot, because all of the right ventricular stroke volume exits into the overriding aorta. Pulmonary atresia can vary from complete muscular separation between the right ventricular outflow tract and pulmonary trunk, to separation of these two structures by an imperforate pulmonary valve [12]. The pulmonary trunk itself may be patent up to the level of an imperforate valve, can originate blindly above an area of muscular atresia (Supplementary Figure S10), or can be thread-like throughout its length [12]. In other cases, the pulmonary

trunk may be completely absent, along with the intrapericardial pulmonary arteries. As a consequence, patients with TOF/PA are dependent on a patent ductus arteriosus or systemic aortopulmonary collateral arteries for pulmonary blood flow. The two cases reported herein demonstrate the heterogeneity of this cardiac defect – specifically, the presence or absence of native confluent pulmonary arteries (Cases 1 and 2, respectively), as well as varied sources of pulmonary blood flow in the form of a patent ductus arteriosus or MAPCAs. The clinical presentation of neonates depends upon the amount and source of pulmonary blood flow. Specifically, the severity of cyanosis relates to the progressive narrowing and closure of the ductus arteriosus, and adequacy of the systemic-to-pulmonary collateral vessels [12].

The differential diagnosis includes tetralogy of Fallot, common arterial trunk (or truncus arteriosus), double outlet right ventricle with pulmonary stenosis or atresia, and single ventricle with pulmonary stenosis or atresia. Yet, features which distinguish TOF/PA from classic tetralogy of Fallot include an absent right ventricular outflow tract and severe abnormalities in the pulmonary circulation, in which the pulmonary blood supply may be entirely from the systemic arterial circulation. Since the four-chamber view typically appears normal on ultrasound, TOF/PA is unlikely to be recognized during fetal cardiac screening if the outflow tracts are not evaluated.

Although TOF/PA can be diagnosed in the prenatal period [13-17], it can be difficult to determine the morphology of the central pulmonary arteries (i.e. size and anatomy) and locate the source of pulmonary blood supply [16]. Indeed, Volpe et al. reported that two-dimensional and color Doppler echocardiography failed to assess the anatomy of the central pulmonary arteries and source of pulmonary blood supply in 33% and 25% of 12 fetuses, respectively [14]. On the other hand, the authors reported that the combination of STIC and B-flow imaging (which uses digitally encoded

sonographic technology to provide direct visualization of blood echoes in gray scale) successfully did so for a different set of five fetuses [14]. Since TOF/PA is often a ductal-dependent cardiac defect, the fetus should ideally be born at a center in which prostaglandins can be administered immediately after birth.

Once TOF/PA has been diagnosed prenatally, both the counseling and prognosis are influenced mainly by the morphology of the central pulmonary arteries and sources of pulmonary blood supply, as well as the presence of genetic and extracardiac abnormalities [14,16]. The main source of variability among patients is the anatomy of the pulmonary arteries, ranging from well-formed and confluent pulmonary artery branches to completely absent pulmonary arteries. Sources of pulmonary blood flow may be from the ductus arteriosus, systemic-pulmonary collateral circulation, or a combination of both [14,18], as seen in the first case. Typically, when the pulmonary arterial supply is derived from the ductus arteriosus, the intrapericardial pulmonary arteries are confluent [12,18]. However, the solitary ductus may be right or left-sided, and bilateral ducti can supply non-confluent pulmonary arteries with a normal distribution [12].

Collateral arteries from the descending aorta to the lungs (i.e. MAPCAs) represent remnants of the embryonic ventral splanchnic arteries and normally regress when the normal pulmonary arterial system forms early in gestation [19]. However, major collateral arteries may persist when there is early maldevelopment of the pulmonary valve or central pulmonary arterial system, as in TOF/PA [19]. MAPCAs are present in 20-25% of patients with TOF/PA [20,21], and may be identified prenatally in 44% of cases [16]. Gomez et al. reported that of their fetuses with TOF/PA, MAPCAs were present in 50% [13]. Yet, the prenatal identification of MAPCAs is challenging, since they can vary greatly in size, number (usually two to six), site of origin (e.g.

ascending aorta, descending aorta, head and neck vessels, coronary arteries), structure, and course within the mediastinum [17]. Moreover, as MAPCAs have a serpiginous course, they may not be visualized in a single plane. Identification of such arteries in the prenatal period is enhanced by color Doppler imaging with low velocity settings, as well as pulsed Doppler velocimetry [17]. For Case 2, color Doppler FINE (in which a high velocity scale was used for STIC volume acquisition) did not demonstrate evidence of MAPCAs. In the postnatal period, echocardiography is typically followed by diagnostic cardiac catheterization (considered the gold standard) to delineate the number of MAPCAs, their diameter, origin, course, and supplied lung lobes [22,23]. Such information is important for surgical planning and repair, as well as prognosis.

A classification system for TOF/PA has been suggested by the Society of Thoracic Surgeons and is based on where the pulmonary arterial flow is derived from [24]: 1) Type A: native intrapericardial pulmonary arteries exclusively; 2) Type B: both native intrapericardial pulmonary arteries and MAPCAs (Case 1); and 3) Type C: MAPCAs exclusively (Case 2).

Patients with relatively normal-sized confluent central pulmonary arteries usually receive pulmonary blood flow from the ductus arteriosus, rarely have incomplete distribution of the right and left pulmonary arteries, and rarely have significant MAPCAs [16,25]. The majority of TOF/PA cases have confluent native pulmonary arteries (Case 1), but they are hypoplastic; flow into them is derived from MAPCAs, usually through small intrapulmonary communications [26]. More than 80% of those with non-confluent or hypoplastic central pulmonary arteries have incomplete distribution of one or both pulmonary arteries, with MAPCAs supplying the non-connected pulmonary arterial segments [16,27]. Non-confluent or severely hypoplastic central pulmonary arteries and an extensive collateral aortopulmonary arterial

circulation have a major impact on surgical treatment and can substantially increase risk [16]. Less commonly, the native central pulmonary arteries are completely absent, and all pulmonary blood flow is derived from MAPCAs [26], as seen in Case 2.

Associated findings, prognosis, and outcome

In 20-50% of TOF/PA cases, there is a right-sided aortic arch [28]. Moreover, the presence of MAPCAs is significantly associated with a right aortic arch [13]. A secundum atrial septal defect or patent foramen ovale is seen in approximately 50% of cases postnatally [28]. In addition, an absent ductus arteriosus may be seen in about half of all cases [29].

Chromosomal abnormalities have been reported in 8.3% of children with TOF/PA [10]. Moreover, there is an important association of this cardiac defect with deletions in the chromosomal region 22q11. Indeed, the prevalence of 22q11.2 deletion is found in 26% of fetuses with TOF/PA [16]. The 22q11 microdeletion is more common in cases of TOF/PA with major collateral arteries when compared to tetralogy of Fallot with pulmonary stenosis [19]. Some investigators have also reported that for fetal TOF/PA, the incidence of 22q11.2 deletion is higher in the subgroup with MAPCAs (50%) than in the subgroup without MAPCAs (10%), although this did not reach statistical significance [13]. The interstitial deletion 16q21-q22.1 has also been reported in a newborn with TOF/PA, MAPCAs, dysmorphic craniofacial features, failure to thrive, and severe psychomotor developmental delay [30]. Taken together, prenatal testing should be offered to all women carrying a fetus with TOF/PA.

The prognosis and long-term survival of TOF/PA primarily depend upon the underlying distribution and size of the pulmonary arteries, as well as any associated abnormalities. In general, if the ductus arteriosus is the primary source of pulmonary flow, long-term outcome is improved [29]. In addition, patients without intrapericardial

pulmonary arteries but with confluent intrapulmonary arteries have a better outcome than those with nonconfluent pulmonary arteries [19].

The surgical management of patients with TOF/PA and MAPCAs includes establishing antegrade pulmonary blood flow via a conduit from the right ventricle to the pulmonary arteries, and unifocalization of the aortopulmonary collateral vessels to the pulmonary arteries [22,31] (as in Case 2). In some cases, a complete repair cannot be performed, and staged unifocalization is required, with the goal of recruiting as many lung segments as possible (Case 1). Unifocalization broadly refers to procedures that join the multifocal sources of arterial supply (whether intrapericardial arteries or collateral arteries) into a single source that has a uniform flow and pressure for each bronchopulmonary segment [12,19]. In general, however, the surgical approach to accomplish the goals described above is quite variable, depending on the individual anatomy of each neonate, and frequently requires more than one surgical procedure [19,22,23,32]. For example, in cases of severely hypoplastic pulmonary arteries, a staged approach is preferred to allow pulmonary arterial growth [33]. An issue that is controversial is the timing, if ever, of VSD closure [32]. The final goal of surgery is to construct completely separated pulmonary and systemic circulations. In addition, preserving perfusion to as many lung segments as possible and avoiding irreversible changes in the pulmonary vascular bed is desired [26].

Cho et al. reported that of 160 patients with TOF/PA who did not undergo complete surgical repair, the early and late mortality were 16.3% and 23.1%, respectively [34]. The presence of MAPCAs was a significant risk factor of late mortality. However, for the 335 patients who did undergo complete surgical repair, the early and late mortality was 4.5% [34].

Despite advances in the surgical and interventional treatment of TOF/PA, inadequate growth of the pulmonary vasculature is still apparent in a fraction of patients even after optimal treatment [19]. Further discussion about the surgical treatment of TOF/PA is beyond the scope of this article, and the interested reader is referred to the scientific literature on this subject.

Acknowledgments

An application for a patent (“Apparatus and Method for Fetal Intelligent Navigation Echocardiography”) has been filed with the U.S. Patent and Trademark Office, and the patent is pending. Dr. Lami Yeo and Dr. Roberto Romero are co-inventors, along with Mr. Gustavo Abella and Mr. Ricardo Gayoso. The rights of Dr. Yeo and Dr. Romero have been assigned to Wayne State University, and NICHD/NIH, respectively.

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Declaration of Interest

The authors report no declarations of interest.

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Supplementary Figure Legends:

1. **Supplementary Figure S2: Transthoracic echocardiogram of the parasternal long-axis view at day one of life (Case 1).** A large perimembranous ventricular septal defect and overriding aorta is seen. The aortic valve leaflets are also thickened and dysplastic (white arrow), with narrowing of the supra-valvar area (yellow arrow). The atretic pulmonary valve is not seen in this plane. *Asc Ao*, ascending aorta; *LV*, left ventricle; *RV*, right ventricle; *VSD*, ventricular septal defect.

2. **Supplementary Figure S3: Transthoracic echocardiogram of the apical four-chamber view at day one of life (Case 1).** Color Doppler flow is seen exiting both ventricles through the ventricular septal defect into the overriding aorta. Color Doppler aliasing is present (white arrow) due to turbulent flow across the aortic valve and supra-valvar area. The ascending aorta past the level of the aortic valve is not visualized in this image. Note that the color Doppler bar orientation does not correspond to the orientation of blood flow depicted in the heart, because the image has been flipped for illustrative purposes. *LV*, left ventricle; *RV*, right ventricle; *VSD*, ventricular septal defect.

3. **Supplementary Figure S4: Cardiac catheterization at day five of life (Case 1).** Right upper pulmonary vein wedge angiogram shows contrast filling the upper lobe of the right lung (white star). Contrast then travels retrograde into the native pulmonary arteries, demonstrating the presence of confluent, but severely hypoplastic native pulmonary arteries (white arrows) supplied by a small patent ductus arteriosus (yellow arrow) to perfuse both the right and left lungs. These native pulmonary arteries (although severely hypoplastic) appear to provide almost complete blood supply to the lung fields. An additional major collateral artery (not seen in this image) was seen originating from an anomalous right subclavian artery to provide dual blood supply to the right lung. *PDA*, patent ductus arteriosus.

4. **Supplementary Figure S5: Application of the Fetal Intelligent Navigation Echocardiography (FINE) method to a spatiotemporal image correlation volume dataset of a fetus with tetralogy of Fallot and pulmonary atresia at 22 gestational weeks (Case 2)** (also see Supplementary Movie 3). Diagnostic planes or Virtual Intelligent Sonographer Assistance (VIS-Assistance®) with automatic labeling are shown, in which six echocardiography views are abnormal. The three-vessels and trachea view shows a large transverse aortic arch without a pulmonary artery identified. The four-chamber view appears normal. However, when VIS-Assistance® is activated, a ventricular septal defect with overriding aorta became visible (not shown here). In the five-chamber view, the anteriorly malaligned ventricular septal defect is visualized with overriding of the ventricular septum by the dilated aortic root. The left ventricular outflow tract view shows similar findings. Movement of the aortic valve leaflets is normal. In the short-axis view of great vessels/right ventricular outflow tract view, the main pulmonary artery and valve, branch pulmonary arteries, and ductus arteriosus cannot be identified. Similarly in the ductal arch view, the main pulmonary artery and valve, as well as the ductus arteriosus cannot be visualized. The aortic arch view shows a dilated aortic root and a prominent ascending aorta. It is noteworthy that automatic labeling was correct for all nine echocardiography views. Labeling of the pulmonary artery by FINE is in the “appropriate” location, even though an actual main pulmonary artery and valve cannot be visualized. *A*, transverse aortic arch; *Ao*, aorta; *Desc.*,

descending; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; P, pulmonary artery; PA, pulmonary artery; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; S, superior vena cava; SVC, superior vena cava; Trans., transverse

5. **Supplementary Figure S6: Spatiotemporal image correlation volume dataset of Case 2 acquired with color Doppler imaging at 30 gestational weeks and analysed by color Doppler Fetal Intelligent Navigation Echocardiography (FINE).** In the left ventricular outflow tract view, there is a color signal (blue) exiting from both ventricles into the overriding aorta. Automatic labeling by FINE (left ventricle, and name of echocardiography view) is depicted. *LV, left ventricle.*

6. **Supplementary Figure S7: Transthoracic echocardiogram of the parasternal long-axis view at day one of life (Case 2).** 7A. Gray scale image shows a large anterior malaligned ventricular septal defect and overriding aorta. 7B. Color Doppler imaging demonstrates blood flow exiting both ventricles (blue color signal) into the large overriding ascending aorta. *LA, left atrium; LV, left ventricle; RV, right ventricle; VSD, ventricular septal defect.*

7. **Supplementary Figure S8: Transthoracic echocardiography from the suprasternal notch at day one of life (Case 2).** 8A. Major aortopulmonary collateral (MAPCA) originating from the proximal brachiocephalic artery (white arrow) to form the right pulmonary artery distally, coursing to the neonate's right side to supply the right lung. 8B. Another large MAPCA originates from the underside of the aortic arch and courses to the neonate's left side to form the left pulmonary artery and supply the left lung. The mid-portion of the right pulmonary artery is also visualized in this image. *Asc Ao, ascending aorta; LPA, left pulmonary artery; RPA, right pulmonary artery.*

8. **Supplementary Figure S9: Cardiac catheterization at day two of life (Case 2).** 9A. **Anterior-posterior view.** Angiography in the proximal descending aorta demonstrates a right-sided MAPCA originating from the proximal portion of the right innominate artery (yellow arrow) to supply the entire normally-sized right pulmonary artery. 9B. **Left anterior oblique view.** The left pulmonary artery originates as a large MAPCA from the underside of the aortic arch. No collaterals are seen from the descending aorta. The aortic arch is left-sided with a normal brachiocephalic branching pattern (entire arch is not fully shown in this image). The right pulmonary artery is seen faintly due to the location of contrast injection remote from its origin. *Desc Ao, descending aorta; LCCA, left common carotid artery; LPA, left pulmonary artery; LSCA, left subclavian artery; MAPCA, major aortopulmonary collateral artery; RCCA, right common carotid artery; RPA, right pulmonary artery; RSCA, right subclavian artery.*

9. **Supplementary Figure S10: Pathologic specimen of a different neonate with tetralogy of Fallot and pulmonary atresia.** A metal probe is seen through the large, perimembranous ventricular septal defect. The aorta (opened through a vertical incision) is dilated and overrides the ventricular septal defect. The right ventricle is hypertrophied (black star) and there is muscular pulmonary atresia (no true connection) (red stars). The native main pulmonary artery is present but severely hypoplastic, measuring 1.5 mm (white arrow) and connected to the aorta by the ductus arteriosus (white star). The lungs are seen in the background. *RV, right ventricle.*

Supplementary Movie Legends:

1. **Supplementary Movie 1: Application of the Fetal Intelligent Navigation Echocardiography (FINE) method to a spatiotemporal image correlation volume dataset of a fetus with tetralogy of Fallot and pulmonary atresia at 30 gestational weeks (Case 1)** (also see Figure 1). Diagnostic planes or Virtual Intelligent Sonographer Assistance (VIS-Assistance®) with automatic labeling are shown, in which five echocardiography views are abnormal. The three-vessels and trachea view shows a severely hypoplastic pulmonary artery with dilated transverse aortic arch. The pulmonary valve appears hyperechoic and closed throughout the cardiac cycle. The four-chamber view appears normal. VIS-Assistance® demonstrates two pulmonary veins connecting normally to the left atrium (not shown here). In the left ventricular outflow tract view, there is a subaortic ventricular septal defect with overriding of the ventricular septum by the dilated aortic root. In addition, the aortic valve appears thickened and dysplastic, suggesting aortic stenosis. The short-axis view of great vessels/right ventricular outflow tract view shows pulmonary atresia with a severely hypoplastic pulmonary artery, as well as a tiny ductus arteriosus. The pulmonary valve tissue again appears hyperechoic and closed throughout the cardiac cycle. The ductal arch view demonstrates similar findings. In the aortic arch view, the aortic root is dilated and there is a prominent ascending aorta. It is noteworthy that automatic labeling was correct for all nine echocardiography views. *A, transverse aortic arch; Ao, aorta; Desc., descending; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; P, pulmonary artery; PA, pulmonary artery; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; S, superior vena cava; SVC, superior vena cava; Trans., transverse*

2. **Supplementary Movie 2: Transthoracic echocardiogram with color Doppler of the parasternal long-axis view at day one of life (Case 1)**. Color Doppler flow is seen entering the ventricles through the atrioventricular valves (red color), and then exiting the ventricles through the ventricular septal defect into the overriding aorta (blue color). The ascending aorta past the level of the aortic valve is not visualized in this videoclip. Color Doppler aliasing is present due to turbulent flow across the aortic valve and supralvalvar area.

3. **Supplementary Movie 3: Application of the Fetal Intelligent Navigation Echocardiography (FINE) method to a spatiotemporal image correlation volume dataset of a fetus with tetralogy of Fallot and pulmonary atresia at 22 gestational weeks (Case 2)** (also see Supplementary Figure S5). Diagnostic planes or Virtual Intelligent Sonographer Assistance (VIS-Assistance®) with automatic labeling are shown, in which six echocardiography views are abnormal. The three-vessels and trachea view shows a large transverse aortic arch without a pulmonary artery identified. The four-chamber view appears normal. However, when VIS-Assistance® is activated, a ventricular septal defect with overriding aorta became visible (not shown here). In the five-chamber view, the anteriorly malaligned ventricular septal defect is visualized with overriding of the ventricular septum by the dilated aortic root. The left ventricular outflow tract view shows similar findings. Movement of the aortic valve leaflets is normal. In the short-axis view of great vessels/right ventricular outflow tract view, the main pulmonary artery and valve, branch pulmonary arteries, and ductus arteriosus cannot be identified. Similarly in the ductal arch view, the main pulmonary artery and valve, as well as the ductus arteriosus cannot be visualized. The aortic arch view shows

a dilated aortic root and a prominent ascending aorta. It is noteworthy that automatic labeling was correct for all nine echocardiography views. Labeling of the pulmonary artery by FINE is in the “appropriate” location, even though an actual main pulmonary artery and valve cannot be visualized. *A*, transverse aortic arch; *Ao*, aorta; *Desc.*, descending; *IVC*, inferior vena cava; *LA*, left atrium; *LV*, left ventricle; *P*, pulmonary artery; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *RVOT*, right ventricular outflow tract; *S*, superior vena cava; *SVC*, superior vena cava; *Trans.*, transverse