Right Atrial Dysfunction in the Fetus with Severely Regurgitant Tricuspid Valve Disease: A Potential Source of Cardiovascular Compromise

Lisa W. Howley, MD, Nee Scze Khoo, MBChB, Anita J. Moon-Grady, MD, Sonali S. Patel, MD, PhD, Fayeza Alrais, MBBS, FRCSC, Wayne Tworetzky, MD, Timothy Colen, MBBS, Paul Brooks, MBBS, Jean Trines, RDCS, Tiina Ojala, MD, PhD, and Lisa K. Hornberger, MD, *Edmonton, Alberta, Canada; San Francisco, California; Aurora, Colorado; and Boston, Massachusetts*

Background: In severe right heart obstruction (RHO), redistribution of cardiac output to the left ventricle (LV) is well tolerated by the fetal circulation. Although the same should be true of severely regurgitant tricuspid valve disease (rTVD) with reduced or no output from the right ventricle, affected fetuses more frequently develop hydrops or suffer intrauterine demise. We hypothesized that right atrium (RA) function is altered in rTVD but not in RHO, which could contribute to differences in outcomes.

Methods: Multi-institutional retrospective review of fetal echocardiograms performed over a 10-year period on fetuses with rTVD (Ebstein's anomaly, tricuspid valve dysplasia) or RHO (pulmonary atresia/intact ventricular septum, tricuspid atresia) and a healthy fetal control group. Offline velocity vector imaging and Doppler measurements of RA size and function and LV function were made.

Results: Thirty-four fetuses with rTVD, 40 with RHO, and 79 controls were compared. The rTVD fetuses had the largest RA size and lowest RA expansion index, fractional area of change, and RA indexed filling and emptying rates compared with fetuses with RHO and controls. The rTVD fetuses had the shortest LV ejection time and increased Tei index with a normal LV ejection fraction. RA dilation (odds ratio, 1.27; 95% CI, 1.05–1.54) and reduced indexed emptying rate (odds ratio, 2.49; 95% CI, 1.07–5.81) were associated with fetal or neonatal demise.

Conclusions: Fetal rTVD is characterized by more severe RA dilation and dysfunction compared with fetal RHO and control groups. RA dysfunction may be an important contributor to reduced ventricular filling and output, potentially playing a critical role in the worsened outcomes observed in fetal rTVD. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Atrium, Ebstein's anomaly, Tricuspid, Right atrial function, Velocity vector imaging, Fetal echocardiography

Fetal tricuspid valve disease with significant tricuspid valve regurgitation (rTVD), including both Ebstein's anomaly and tricuspid valve dysplasia, is commonly associated with cardiovascular compromise that can lead to evolution of hydrops, sudden fetal demise, or hemodynamic instability in the neonatal period even in the absence of frank hydrops.[1,2] Despite improvements in prenatal detection of rTVD, management of affected fetuses before and after birth remains an ongoing challenge, with an overall perinatal mortality reported as high as 83%.[3-5] Even in the most recent surgical era, fetal mortality from rTVD remains high.[6,7] Currently, the pathophysiology of fetal rTVD that contributes to the dismal outcome of these fetuses remains incompletely defined.

It has long been recognized that most structural heart defects are well tolerated by the fetal circulation. In cases of severe right heart obstruction (RHO) including tricuspid atresia and pulmonary atresia (PA)/intact ventricular septum, redistribution of systemic venous return across the patent foramen ovale to the left heart permits maintenance of the combined fetal cardiac output. Interestingly, although venous Doppler changes that suggest increased central venous

From the Fetal & Neonatal Cardiology Program, Division of Cardiology, Department of Pediatrics (L.W.H., N.S.K., T.C., P.B., J.T., T.O., L.K.H.), and Department of Obstetrics & Gynecology, Women & Children's Health Research Institute and Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada (L.W.H., N.S.K., T.C., P.B., J.T., T.O., L.K.H.); Pediatric Cardiology, University of California, San Francisco, San Francisco, California (A.J.M.-G., F.A.); Pediatric Cardiology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado (S.S.P.); and Pediatric Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (W.T.)

The first two authors should be considered the same in author order.

Reprint requests: Lisa K. Hornberger, MD, Pediatric Cardiology, Stollery Children's Hospital, 4C2 WCMC, 8440 112th Street, Edmonton, Alberta T6G2B7, Canada (E-mail: *lisa.hornberger@albertahealthservices.ca*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2017.01.002

Abbreviations

APF = Antegrade pulmonary blood flow

ET = Ejection time

IVC = Inferior vena cava

IVCT = Isovolumic contraction time

IVRT = Isovolumic relaxation time

LV = Left ventricle, ventricular

PA = Pulmonary atresia

RA = Right atrium, atrial

RHO = Right heart obstruction

rTVD = Regurgitant tricuspid valve disease

RV = Right ventricle, ventricular

TR = Tricuspid regurgitation

VTI = Velocity time integral

VVI = Velocity vector imaging

UA PI = Umbilical artery pulsatility index

pressure are common in fetal RHO, evolution of cardiovascular compromise is rare.[8,9] While fetal rTVD represents right heart pathology and in the most severe cases requires redistribution of the entire cardiac preload to the left heart, these fetuses may be less able to maintain a normal cardiac output, resulting in hemodynamic instability before and after birth. This suggests a unique pathophysiology for fetal and neonatal rTVD. Past studies have identified features potentially attributable to the cardiovascular compromise of fetal rTVD including impaired left ventricular (LV) function and reduced LV preload and output.[10-13] It has been postulated that altered LV filling and function in fetal and neonatal rTVD is a consequence of the mechanical influence of a dilated right atrium (RA) and ventricle (RV) and altered ventricular septal position.[6]

The importance of atrial function on cardiac performance has been previously examined in both adult populations and animal models.[14-16] The atria modulate ventricular filling through three phases: (1) a reservoir or expansion phase during systole, (2) a conduit phase during early diastole, and (3) an active contractile "booster" phase during late diastole.[16,17] Abnormalities in atrial function are known to directly impact ventricular filling and, consequently, cardiac output.[18,19] The role of the atria in ventricular performance and output may be even more important before birth.[20] During fetal life, the RA, in particular, plays an integral role in the circulation, receiving blood from the systemic and umbilical veins and redistributing the venous return to both the RV and LV. However, the RA in rTVD is often massively dilated, while it is not in RHO and in normal fetuses. In the current investigation, we sought to determine whether there exists an inherent difference in RA function between fetuses with rTVD, those with critical RHO, and normal healthy fetuses. We hypothesized that in fetal rTVD, but not in RHO, intrinsic RA function is abnormal, which may result in ineffective blood flow redistribution, decreased LV filling and output, and increased RA and central venous pressures, ultimately contributing to worse outcomes.

METHODS

Study Patients

Following receipt of ethics approval, we retrospectively identified from existing hospital databases all cases of rTVD diagnosed in utero between January 2001 and February 2010 at three major tertiary care institutions in North America: Stollery Children's Hospital, Edmonton, Alberta, Canada; the University of California San Francisco Benioff Children's Hospital, San Francisco, California; and the Children's Hospital, Boston, Massachusetts. All cases of fetal cardiac anomalies were initially referred following abnormal obstetrical ultrasounds with concern for structural cardiac disease. We included fetuses with tricuspid valve dysplasia and Ebstein's anomaly that were identified on prenatal ultrasound to have significant tricuspid valve regurgitation with apical displacement of the tricuspid valve septal leaflet or dysplastic leaflets. We also searched the existing fetal cardiac pathology databases of Stollery Children's Hospital and University of California San Francisco Benioff Children's Hospital to identify all encountered pregnancies with fetal RHO within the study period including fetuses with PA and intact ventricular septum, severe pulmonary stenosis with exclusively retrograde flow in the ductus arteriosus, and tricuspid atresia with normally related great vessels. Fetuses with rTVD or RHO associated with more complex heart disease or extracardiac anomalies were excluded. A cohort of normal fetuses from uncomplicated singleton pregnancies was identified for comparison purposes from the Stollery Children's Hospital fetal database. Referral indications for the normal controls included suspicion of arrhythmia and family history of congenital heart disease. Prenatal and postnatal medical records were reviewed for clinical information, including perinatal outcome for both pathologies and control patients.

Image Acquisition

Detailed prenatal echocardiographic examinations, including anatomic assessment and Doppler interrogation, were performed with the following ultrasound systems: Siemens C512 (Mountain View, CA) and General Electric Voluson E8 imaging systems (General Electric, Milwaukee, WI). All data images were digitally recorded and stored as standard Digital Imaging and Communication in Medicine images for offline analysis. In cases where multiple evaluations of the same fetus were available, only the initial patient ultrasound study or the earliest serial study in which images for offline analysis were sufficient was analyzed. Fetuses were excluded if image format or quality was inadequate for offline velocity vector imaging (VVI) analysis.

Right Atrial Velocity Vector Imaging

RA functional parameters were measured using offline commercially available software (Syngo Velocity Vector Imaging, Siemens Medical Solutions, Malvern, PA). All digitally stored fetal echocardiogram images were reexamined, and VVI measures were performed offline by a single investigator (L.W.H.). The fetal cardiac cycle was determined using the anatomic M-mode by detecting fetal atrioventricular valve motion. Using a standard four-chamber view, a single-frame tracing of the RA endocardial border was performed to obtain a velocity vector profile of native atrial wall motion and area, with extrapolated volume data (Figure 1). In fetuses with Ebstein's anomaly and "atrialization" of a portion of the RV, the VVI tracing included only the native RA to the level of the tricuspid valve annulus and did not include the atrialized ventricular component as the ventricular interaction (atrialized RV and LV) often results in dyssynchronous motion. When septum primum was challenging to visualize in its entirety, the estimated plane of the atrial septum was used in the measurement. The software generated time-volume curves, providing data regarding the RA maximum and minimum calculated volumes as well as RA filling and emptying rates. To adjust for the differences in atrial volumes between gestations, both RA filling and RA emptying rates were indexed by dividing each value by the maximum RA