Anomalous Mitral Arcade in Twin-Twin Transfusion Syndrome

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Background—Echocardiography has documented acquired pulmonary stenosis and cardiomyopathy in recipient fetuses in twin-twin transfusion syndrome. At autopsy, we also have identified anomalous mitral arcade, a rare valve deformity associated with mitral regurgitation.

Methods and Results—To identify a profile for anomalous mitral arcade, we compared clinicopathological data from 11 sets of autopsied twin-twin transfusion syndrome fetuses, including 4 twin pairs in whom the recipient had anomalous mitral arcade (affected) and 7 pairs in whom both had structurally normal mitral valves (unaffected). Anomalous mitral arcade was characterized by a thick fibrous band at the free margin of the leaflets tethering papillary muscles and absent/short tendinous cords. One affected recipient also had pulmonary stenosis and tricuspid valve dysplasia. In all 11 sets, recipient hearts were larger than paired donor hearts. All 11 recipients had moderate to severe cardiac dysfunction by echocardiography. Echocardiography disclosed left atrial enlargement in all affected recipients but none of the unaffected recipients. Mitral regurgitation was present before demise in all affected recipients evaluated with color Doppler. Progressive decrease in mitral leaflet mobility was noted in those affected recipients with serial echocardiography.

Conclusions—Previously unreported in twin-twin transfusion syndrome, anomalous mitral arcade was identified in 4 of 11 recipient fetuses (36%) in this autopsy series. Ultrasound or echocardiographic evidence of left atrial dilation, mitral regurgitation, and decreased leaflet mobility in recipients should raise suspicion for anomalous mitral arcade. Development of anomalous mitral arcade in twin-twin transfusion syndrome recipients suggests that the lesion is an acquired valve deformity in this setting, not a malformation. (Circulation. 2010;122:1456-1463.)

Key Words: echocardiography □ heart defects, congenital □ heart failure □ pathology □ twins □ valves

Twin-twin transfusion syndrome (TTTS) occurs in 10% to 20% of monozygous twin gestations and is an important cause of perinatal mortality in monochorionic twins with very high mortality rates if untreated.1-2 The syndrome is characterized clinically by polyhydramnios in 1 twin and oligohydramnios in the other. The pathophysiology of the syndrome is incompletely understood; however, it has been speculated that an imbalance in net blood supply to the recipient fetus resulting from abnormal placental vascular connections, combined with exposure to circulating abnormal vasoactive mediators, produces the syndrome.2-4

Clinical Perspective on p 1463

In the recipient twin, TTTS can lead to cardiovascular compromise, which can be detected antenatally by ultrasound.3-5,6 On echocardiography, the most common abnormalities seen in recipient twins are ventricular hypertrophy (18% to 49% of cases), increased cardiothoracic ratio (as high as 47%), ventricular dilation (17% to 31%), tricuspid regurgitation (35% to 52%), and mitral regurgitation (13% to 15%).2 In addition, cases of acquired pulmonary stenosis/valve atresia in the recipient twin have been reported.3,6,7 Other than rare case reports,8 there are no autopsy studies of hearts in this population. Thus, the great majority of cardiac abnormalities identified echocardiographically have not been corroborated. As a regional referral center for TTTS, our institution manages a large number of pregnancies with this condition. Furthermore, we have performed a significant number of autopsies in this high-risk population. Although many of the above cardiac abnormalities have been seen at autopsy, we also have identified cases of anomalous mitral arcade, a rare deformity of the mitral valve associated with regurgitation.9-11 Anomalous mitral arcade refers to a thick band of fibrous tissue at the free margin of one or both mitral leaflets; this fibrous band arcs between the anterolateral and posteromedial papillary muscles of the left ventricle. As part of this arch-like configuration, the tendinous cords are shortened and thickened or even absent, and the papillary muscles come in...
delivered at a tertiary referral institution (University of California). This was a retrospective clinicopathological correlation study of TTTS fetuses whose mothers had been followed and autopsied. The specific aim was to define a clinical profile that can be used to raise clinical suspicion for anomalous mitral valve arcade in the setting of severe TTTS. The hypothesis was that anomalous mitral arcade may explain many of the hemodynamic and structural cardiac abnormalities identified echocardiographically. The specific aim was to define a clinical profile that can be used to raise clinical suspicion for anomalous mitral valve arcade in the setting of severe TTTS. Direct contact with the leaflet tissue. The papillary muscles are tethered by the fibrous band, and valvular insufficiency and sudden death may result. The pathogenesis of this rare cardiac lesion is poorly understood.

The present clinicopathological correlation study was undertaken to investigate the occurrence of anomalous mitral arcade in fetuses with TTTS undergoing autopsy at our institution and to examine whether echocardiography can be useful in detecting this rare lesion during fetal life. Our hypothesis was that anomalous mitral arcade may explain many of the hemodynamic and structural cardiac abnormalities identified echocardiographically. The specific aim was to define a clinical profile that can be used to raise clinical suspicion for anomalous mitral valve arcade in the setting of severe TTTS.

**Methods**

This was a retrospective clinicopathological correlation study of autopsied TTTS fetuses whose mothers had been followed and delivered at a tertiary referral institution (University of California, San Francisco Medical Center) from 1999 to 2009. The study was approved by the University of California, San Francisco Committee on Human Research, and the patients gave informed consent.

**Autopsy Evaluation**

The archives of the Autopsy Service were searched for fetuses from cases of TTTS. During this 10-year period, there had been an average autopsy rate of 37%, and the autopsied hearts had been analyzed by a single cardiac pathologist (P.C.U.), usually with the aid of a dissecting microscope. Medical records, including clinical histories, ultrasound, and echocardiographic studies, and detailed pathology reports were reviewed. Fetal hearts had been dissected in standard fashion along the lines of blood flow, and when available, the formalin-fixed specimens were reexamined for the present study. For histological evaluation, a tissue cross section from one recipient’s affected mitral valve and a similar section from that of the corresponding donor were taken in the long axis of the papillary muscle extending into the valve leaflet. Paraffin-embedded tissue sections (5 μm thick) were stained with hematoxylin and eosin and Gomori trichrome according to standard methods.

**Ultrasound and Echocardiographic Evaluation**

Obstetric records, ultrasound reports, and when possible, ultrasound images were reviewed independently by a pediatric cardiologist.
(A.J.M.-G.) and a maternal-fetal medicine specialist (D.W.). The following information was collected: gestational age at the time of examination, estimated fetal weight and percent weight discordance, presence of effusions or edema, Quintero stage as previously described,12 cardiothoracic ratio, subjective assessment of cardiac chamber sizes, and subjective assessment of biventricular cardiac systolic function as normal or decreased. Echocardiographic images were reviewed (A.J.M.-G.) and evaluated for recipient cardiomegaly, hypertrophy, dilation, impaired systolic or diastolic function, atrioventricular valve regurgitation, pulmonary valve structural or Doppler abnormalities, venous Doppler abnormalities, presence or absence of arterial Doppler abnormalities, and presence or absence of hydropic changes, all of which have previously been described in evaluations of cardiac status in TTTS.13,14 In addition, all echocardiograms in the present study were evaluated for the presence of structural mitral valve abnormality and for mitral regurgitation, as well as for the presence of subjective right and left atrial enlargement consistent with moderate to severe atrioventricular valve regurgitation. Clinical records were reviewed for gestational age at presentation, additional obstetric issues, therapies (amnioreduction, laser photocoagulation), and pregnancy outcomes.

To obtain information on the total number of fetuses with TTTS evaluated at our institution by ultrasound and echocardiography during the time period addressed in this autopsy series, we conducted queries of our Fetal Echocardiography and Fetal Treatment Center databases. Information on pregnancy outcomes and cardiovascular evaluation, including the presence or absence of mitral and tricuspid valve regurgitation and structural abnormalities, had previously been entered into this database.

**Statistical Analysis**

Data are expressed as median value and interquartile range; nonparametric statistics were used because of the small sample size. Comparisons of the gestational age at diagnosis, gestational age at death, weight discordance at autopsy, weight discordance by last ultrasound, and heart weight between the affected and unaffected groups were performed by Wilcoxon rank-sum test. Measurements were considered significantly different at a value of $P<0.05$.

**Results**

**Autopsy Evaluation**

During the 10-year time period, 204 pregnancies affected by TTTS were managed at our center. Eleven sets of twins with evidence of TTTS were identified from our autopsy database. Clinical and autopsy findings are summarized in the Table. Twelve of 22 fetuses (55%) were female; 10 of 22 (45%) were male. Among the 11 sets of twins, anomalous mitral arcade was identified in 4 recipient twins, and these 4 sets of twins make up the affected group. Seven sets of twins with TTTS had hearts with normal mitral valves (unaffected group). In each of the 11 pairs, the recipient twin was the larger twin, and the recipient twin’s heart was larger than the donor’s heart (Figure 1). The body weight discordance at autopsy was greater in the affected twins (median, 49%; interquartile range, 43% to 53%) than in the unaffected twins (median, 38%; interquartile range, 13% to 43%), but the difference did not reach statistical significance ($P=0.17$).

Recipient heart weight was significantly greater in affected pairs (median, 10.65 g; interquartile range, 7.3 to 14.2 g) than in unaffected pairs (median, 6.1 g; interquartile range, 4.6 to 6.7 g, $P=0.03$). For 1 case (case 2R in the Table), an autopsy was performed on only 1 twin from the pair, and weight discordance could not be determined. The affected twins...
ranged from 23 0/7 to 24 5/7 weeks’ gestation; unaffected pairs ranged from 20 1/7 to 24 6/7 weeks’ gestation. In the affected group, 2 of 8 twins (25%) were live born but considered nonviable and not resuscitated, and 6 of 8 (75%) were nonviable at delivery. In the unaffected group, 3 of 14 twins (21%) were live born but considered nonviable and not resuscitated, whereas 11 of 14 (79%) were nonviable at delivery.

In affected recipient twins, anomalous mitral valve arcade was identified by its distinctive appearance at autopsy: The anterior and posterior leaflets of the mitral valve were largely thin and translucent but had a thick fibrous ridge at the free margin (Figure 2). This fibrous band arced between the papillary muscles, retracting their tips toward each other to form an arch-like configuration. In 1 heart (case 4R), the fibrous band obliterated the tendinous cords, so the leaflet tissue appeared to fuse with the papillary muscles. In other affected hearts (cases 1R, 2R, and 3R), the tendinous cords were thick and extremely short. In hearts from paired donor twins in the affected group, the mitral valve anterior and posterior leaflets consisted of thin and translucent tissue without any fibrous thickening at the free margins (Figure 2). Long, thin tendinous cords attached the valve leaflets to the papillary muscles. Histological sections from the mitral valve of a recipient with anomalous mitral arcade (case 3R) confirmed continuity between fibrotic leaflet tissue and the papillary muscle head and disclosed a bulge of loose fibrous tissue at the position of the fibrous band seen grossly (Figure 3). A section of mitral valve from the corresponding donor showed a long, narrow collagen cord intervening between the normal leaflet tissue and papillary muscle.

In 2 recipient hearts with anomalous mitral arcade (cases 3R and 4R in the Table), the tricuspid valve was dysplastic; the tricuspid valve leaflets themselves were thin and translucent but had a thick fibrous band at the free margin. In addition, the tendinous cords were extremely short and thick, and the papillary muscles appeared to insert directly into the tricuspid valve leaflets. Thus, the dysplastic tricuspid valve had features similar to anomalous mitral arcade, as has been described previously.11 Bilateral atrial dilation (cases 1R and 3R) and bilateral ventricular dilation (cases 1R and 4R) also were seen in all 4 recipient twins in the affected group. One heart (case 4R) showed thickened pulmonary valve leaflets suggestive of valvar pulmonary stenosis, but in no other heart could pulmonary stenosis be established anatomically. Among twins in the unaffected group, there was 1 heart with bilateral atrial dilation in a recipient (case 8R in the Table). A small ventricular septal defect was observed in 1 donor twin in the unaffected group (case 3D), and an atrial septal defect was seen in 1 recipient twin in the same group (case 5R). One recipient twin in the unaffected group (case 11R) had hypertrophy of both ventricles.

Ultrasound and Echocardiographic Evaluation

Clinical records and ultrasound reports were reviewed for all cases. Ultrasound images were available for 10 of the 11 twin gestations. Three of the twin pregnancies in the affected group had serial echocardiograms for review, whereas 2 of the twin pregnancies in the unaffected group underwent echocardiography; for the remainder (with no echocardiogram available), cardiothoracic ratio and cardiac chamber size and function were determined by review of the available obstetric ultrasound images. Clinical characteristics at last ultrasound evaluation were compared with autopsy findings (Table). Percent weight discordance by ultrasound was higher among the affected twins (median, 48.0%; interquartile range, 40% to 57%) than among unaffected twins (median, 35%; interquartile range, 18% to 47%); however, the difference did not reach statistical significance (P=0.11). The ultrasound, echocardiographic, and clinical findings are presented in the Table. There was no clear difference with respect to Quintero stage between affected and unaffected recipients. All of the recipient fetuses with anomalous mitral arcade had left atrial enlargement, whereas none of the fetuses without the mitral lesion at autopsy had left atrial enlargement by ultrasound before demise (Figure 4).
Progression of Specific Cardiac Findings in Fetuses With Anomalous Mitral Arcade

Case 1 had a single obstetric ultrasound at 24 5/7 weeks that showed cardiomegaly, hydrops, and biatrial enlargement in the recipient. However, the time course of its development could not be determined.

Case 2 had an obstetric ultrasound at 20 6/7 weeks that showed 33% weight discordance; there was polyhydramnios in the larger twin with normal fluid in the smaller twin. At that time, the 4-chamber view, outflows, and arches were normal. Repeat ultrasound evaluation at 21 4/7 weeks was consistent with TTTS, with development of oligohydramnios in the smaller twin. At 22 3/7 weeks, cardiomegaly and biatrial enlargement had developed in the recipient, but there was no hydrops. At 23 6/7 weeks, echocardiography disclosed hydrops, and there was moderate to severe mitral regurgitation (Figures 4 and 5). The mitral valve appeared thickened and echo-bright and had decreased leaflet mobility.

Case 3 presented to our institution at 22 weeks' estimated gestational age, at which time the obstetric ultrasound showed hydrops, cardiomegaly, and right atrial enlargement in the recipient, with a normal-appearing left atrium and a normal-appearing mitral valve. Repeat ultrasounds between 22 3/7 and 23 0/7 weeks showed progressive left atrial enlargement, and echocardiography at 23 4/7 and 24 0/7 weeks confirmed cardiomegaly, biatrial enlargement, and severe mitral regurgitation. The mitral valve at echocardiography was dysplastic, with decreased leaflet mobility.

Case 4 had an obstetric ultrasound at 18 1/7 weeks that showed 21% body weight discordance, with normal amniotic fluid volume in the larger twin. At that time, there was no evidence of hydrops, and the 4-chamber view of the recipient heart was normal. After the diagnosis of TTTS, serial echocardiography disclosed cardiomegaly without left atrial enlargement and a normal-appearing mitral valve with trace mitral regurgitation at 19 3/7 weeks. One week later, there was worsening cardiomegaly and evidence of left atrial enlargement. Between weeks 20 4/7 and 23 5/7, there was progression of mitral regurgitation from moderate to severe (Figure 5). Furthermore, the initially normal-appearing mitral valve became progressively thickened and echo-bright and showed decreased leaflet mobility during the observation period. Pulmonary valve dysplasia also was noted.

Additional Echocardiographic Information From Database Review

Our existing database contained detailed echocardiographic information on all TTTS cases beginning in late 2005, nearly half of the pregnancies cared for in our institution during the 10-year period covered in this report. Of those, 11.5% (10 of 87 recipient fetuses) had mitral regurgitation coded as mild, moderate, or severe. None of the donor fetuses had mitral regurgitation indicated. The presence of more than trivial tricuspid regurgitation was indicated in 39% of recipient fetuses. No structural mitral or tricuspid valve pathology was identified.

Clinical Outcomes of Pregnancies With Fetal Autopsies

Two of the pregnancies with affected twins were treated with laser photocoagulation of placental vascular anastomoses in addition to amnioreduction, and 2 underwent amnioreduction.
alone. None of the procedures was effective. One twin pair was delivered by spontaneous vaginal delivery in the setting of preterm labor; given unfavorable prognoses for their fetuses, the other 10 mothers underwent induction-termination. No pregnancy was terminated for maternal indications alone.

Discussion

The present study documents an association between anomalous mitral arcade and TTTS; previously unrecognized in TTTS, anomalous mitral arcade was identified in 4 of 11 recipient twins (36%) in this autopsy series. Although mitral regurgitation has been noted echocardiographically in 11.5% of fetuses with evidence of TTTS evaluated at our center since 2005 and in 13% to 42% of recipient fetuses with TTTS in previous reports, there have been no previous reports of structural mitral valve pathology in twins with TTTS. Our finding underscores the need for more autopsy studies in this area.

Pathogenesis of Anomalous Mitral Arcade

A rare valvar deformity often associated with insufficiency, anomalous mitral arcade previously has been considered to reflect a cardiac developmental arrest. Morphologically, the affected valve resembles that of a prior developmental stage in that it has lost direct ventricular connections (muscular cords) but shows little attenuation and lengthening of the collagenized tendinous cords. By this explanation, the fibrous band characteristic of anomalous mitral arcade is thought to be a vestige of the thickened leaflet tissue from an earlier stage of development.

The fibrous band, however, could result from remodeling of the valve complex resulting from turbulence across the valve. The relatively high frequency of anomalous mitral arcade in this autopsy series and the documented progressive nature of the lesion are consistent with the hypothesis that the lesion may be a turbulence-related or acquired deformity that does not involve developmental arrest of the mitral valve. However, there are insufficient serial echocardiographic studies in this retrospective cohort to determine whether the development of mitral valve regurgitation preceded, followed, or evolved concurrently with mitral valve dysplasia. Therefore, the role of turbulence across the valve in promoting development of anomalous mitral arcade cannot be determined from the present study.

Alternatively, anomalous mitral arcade could be a result of other conditions in these TTTS recipients. Our finding that recipients in the unaffected group with a degree of heart failure similar to that in the affected group did not develop anomalous mitral arcade suggests that other factors may be involved in the valve lesion. In this regard, recent studies in TTTS have correlated higher concentrations of the vasoactive peptides endothelin-1 and brain natriuretic peptide in recipient amniotic fluid with cardiac dysfunction. Endothelin-1 in particular has been shown to promote fibrosis in various organs, including the heart. It is possible that vasoactive peptides play a role in the development of anomalous mitral arcade. Whatever the cause, anomalous mitral arcade represents a significant fibrotic lesion that even in singleton live-born infants may be severe enough to warrant surgery.
Suspicion for Anomalous Mitral Arcade on Echocardiography

A specific aim of the present study was to define a clinical profile that can be used to raise clinical suspicion for anomalous mitral arcade in TTTS. Body weight discordance at last ultrasound and at autopsy appeared to be greater in the affected sets of twins compared with the unaffected sets. Larger studies of fetuses, however, are needed to substantiate this association. By ultrasound and echocardiographic assessment, more advanced Quintero stages (3 and 4) and moderate to severe degrees of cardiovascular compromise were present in both affected and unaffected twins (Table). The only distinguishing feature of the affected group was the presence of left atrial enlargement, which was progressive in at least 3 recipients, presumably as a result of the mitral regurgitation that is the hallmark of anomalous mitral arcade.9–11

Recently, there has been heightened interest in the cardiomyopathic changes that have been identified echocardiographically in recipient twins. Although anomalous mitral arcade may not be the only basis for heart failure in TTTS, mitral regurgitation, left atrial enlargement, and left atrial hypertension can contribute to the development of fetal hydrops. In addition, because right ventricular systolic performance and diastolic performance are often compromised in recipient fetuses,2,3,6,14,17 the left ventricle may increase its contribution to combined ventricular output to continue to meet the oxygen demands of the growing fetus. Significant alterations in left ventricular performance have also been demonstrated in recipient twins18–20; in this setting, the development of severe mitral regurgitation may significantly limit the ability of the left ventricle to contribute to combined ventricular output. Therefore, the findings from our study underscore the importance of complete echocardiographic evaluation of the fetal heart for evidence of cardiovascular compromise, including color Doppler for evaluation of both mitral and tricuspid valves in pregnancies affected by TTTS. In addition, we suggest that detection of significant regurgitation should raise the index of suspicion for a structural abnormality of the valve. The prognostic significance of this particular finding cannot be ascertained on the basis of this autopsy series and requires further study. Nonetheless, previous reports have demonstrated an association of atrioventricular valve regurgitation with decreased mitral valve mobility should raise suspicion for anomalous mitral arcade. Marked weight discordance on ultrasound might also indicate the development of anomalous mitral arcade. This association, however, needs further study. Although uncommon, acquired mitral arcade is likely a physiologically important lesion that may have prognostic significance in recipient twins, given the previously described association of atrioventricular valve regurgitation with decreased survival in this population.17 Furthermore, this report contributes to accumulating evidence of acquired valve pathology in fetuses. Delineation of factors involved in the development of valve abnormalities in recipient twins in TTTS may provide insight into the mechanisms of development of valvar disease in general, as has been speculated.7

Study Limitations

The retrospective nature of the present study necessitated nonblinded evaluation of the ultrasound images. Not all of the fetuses had echocardiograms before demise, and the detail of the obstetric ultrasounds for evaluation of cardiac pathology was limited. Although we included all fetal autopsies in the setting of TTTS at our institution, the numbers are relatively small, and future studies should include much larger cohorts examined both by echocardiography and at autopsy to confirm these findings. It is possible that our sample was enriched for fetuses with severe mitral valve pathology. The autopsied fetuses likely represent the severe end of the spectrum of cardiac involvement in TTTS, and the perception of poor prognosis, given the echocardiographic appearance of moderate to severe mitral and tricuspid regurgitation in the setting of hydrops, likely played a role in the patients’ decisions to terminate the pregnancies.

Conclusions

Previously unreported in TTTS, anomalous mitral arcade affected 36% of recipient fetuses in this autopsy series. The true incidence of the lesion in this population, however, cannot be determined from this study. Ultrasound/echocardiographic evidence of left atrial dilation, mitral regurgitation, and decreased mitral valve mobility should raise suspicion for anomalous mitral arcade. Larger studies of fetuses, however, are needed to substantiate the true incidence of the lesion in this population, however, cannot be determined from this study. Ultrasound/echocardiographic evidence of left atrial dilation, mitral regurgitation, and decreased mitral valve mobility should raise suspicion for anomalous mitral arcade. Marked weight discordance on ultrasound might also indicate the development of anomalous mitral arcade. This association, however, needs further study. Although uncommon, acquired mitral arcade is likely a physiologically important lesion that may have prognostic significance in recipient twins, given the previously described association of atrioventricular valve regurgitation with decreased survival in this population.17 Furthermore, this report contributes to accumulating evidence of acquired valve pathology in fetuses. Delineation of factors involved in the development of valve abnormalities in recipient twins in TTTS may provide insight into the mechanisms of development of valvar disease in general, as has been speculated.7

Disclosures

None.

References

CLINICAL PERSPECTIVE

Twin-twin transfusion syndrome is an important cause of perinatal mortality in monochorionic twins, often because of cardiovascular compromise associated with increased intravascular volume in the recipient twin. In this autopsy study of 11 sets of twins with the condition, 4 recipient twins had anomalous mitral arcade, a rare fibrotic valve lesion that is associated with regurgitation. Previously unrecognized in twin-twin transfusion syndrome, anomalous mitral arcade may explain many of the progressive hemodynamic abnormalities in this condition. From this retrospective clinicopathological correlation study, ultrasound/echocardiographic evidence of left atrial dilation and significant mitral regurgitation in the recipient should raise suspicion for anomalous mitral arcade, a structural lesion that likely will not reverse after successful laser treatment or delivery of the fetus, as other hemodynamic and functional abnormalities often do. Thus, for perinatologists and fetal echocardiographers who manage patients with twin-twin transfusion syndrome, the present study suggests that acquired mitral arcade is likely a physiologically important lesion that may have prognostic significance in recipient twins. For pediatric cardiologists and scientists who study cardiac development, the occurrence of anomalous mitral arcade in this specific population and the progressive deterioration of hemodynamics in affected recipients militate against developmental arrest as the cause of the valve lesion. Anomalous mitral arcade likely represents a flow-related or acquired valve deformity, not a malformation.
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