

Fetal atrioventricular valve insufficiency associated with nonimmune hydrops: a two-dimensional echocardiographic and pulsed Doppler ultrasound study

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ABSTRACT Of 466 fetuses who underwent cardiac ultrasound examination with cross-sectional and M mode echocardiography and pulsed Doppler ultrasound and in whom we were able to follow the natural history, 12 were found to have atrioventricular valve insufficiency and nonimmune hydrops. Eleven fetuses (all of whom had structural heart disease) died either in utero or during the early postnatal period. In the one surviving hydropic fetus with supraventricular tachyarrhythmia and atrioventricular valve regurgitation but without structural heart disease, all the abnormalities disappeared on treatment with digoxin and verapamil. Seven fetuses who had atrioventricular valve insufficiency but did not develop nonimmune hydrops all survived pregnancy and the early neonatal period. The syndrome of atrioventricular valve insufficiency, nonimmune hydrops, and structural heart disease has a poor prognosis. The hydrops in this instance reflects fetal cardiac failure related to venous hypertension and low colloid oncotic pressure.

Circulation 72, No. 4, 825-832, 1985.

ADVANCES in ultrasound technology have made it possible to examine human fetal cardiac development and function in utero¹⁻¹³ and have even permitted the study of early embryogenesis in experimental animals.¹⁴ Structural and functional heart disease in utero has been examined by a number of investigators applying M mode and cross-sectional echocardiographic imaging techniques to the examination of the human fetus during the second and third trimesters of pregnancy.¹⁻¹³ This information has been used to counsel prospective parents and, in several instances, to formulate management for the remainder of pregnancy, during delivery, and in the neonatal period.¹⁵⁻²³

Recently several workers have applied range-gated pulsed Doppler ultrasound to quantitate fetal de-

scending aortic and/or umbilical blood flow by measuring mean flow velocity and cross-sectional vessel area.^{11, 12, 24-28} This method has also been used to provide qualitative information about intracardiac blood flow.^{11, 12, 24, 25, 28}

We used the combination of cross-sectional echocardiography and pulsed Doppler ultrasound to evaluate 466 fetuses referred to our centers for evaluation of the presence of congenital heart disease. We detected atrioventricular valve insufficiency in 23 of these 466 fetuses in the second and third trimesters of pregnancy. Of these fetuses, 16 had associated nonimmune hydrops. Four of the pregnancies were terminated. Eleven of the 12 fetuses with structural heart disease either died in utero or within the first week after birth. Seven fetuses with atrioventricular valve insufficiency and structural heart disease but without nonimmune hydrops survived pregnancy and the neonatal period.

Methods

Four hundred sixty-six fetuses, ranging from 16 to 40 weeks gestational age, whose mothers had been referred to the fetal echocardiographic laboratories of the University of California San Francisco Medical Center or the Yale University School of Medicine underwent cross-sectional and M mode echocardiographic studies as described in previous reports, with either

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Supported in part by a grant from the March of Dimes Birth Defects Foundation.

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Received Dec. 11, 1984; revision accepted June 27, 1985.

Presented in part at the Society of Pediatric Research Meeting, May 1984, San Francisco.

Advanced Technologies Laboratories MK-500 or MK-600 ultrasonographs.^{4, 7, 9, 10, 15, 29}

The two-dimensional equipment was interfaced with 3.5 or 5 MHz transducers. Range-gated pulsed Doppler examination was guided from the cross-sectional image where the Doppler carrier frequency was 3.0 or 5 MHz. The sample volume was always kept to minimum size, 1.5 mm in axial direction, and could be placed at any position within the 90 degree sector arc up to a depth of 16 cm. The direction of flow was depicted on the videomonitor as a "positive" deflection when flow was toward the transducer, whereas flow away from the transducer face was depicted as a "negative" deflection with respect to the baseline. The Doppler frequency shift was analyzed by fast Fourier transform algorithm with the intensities of the spectral frequencies depicted in shades of gray. Doppler interrogation was usually performed at 5 to 14 cm distance from the transducer. Atrioventricular valve insufficiency was recognized by the audio output and from the characteristics of the spectral output with reference to the systolic portion of the visible atrioventricular valve motion on the simultaneous M mode display. In the normal heart this period was quiet in systole but showed either disturbed flow consistent with the direction of tricuspid insufficiency or marked systolic aliasing (figure 1). The type of signal displayed depended to some extent on the distance from the transducer. We attempted to obtain flow signals by placing the sample volume as parallel as possible to the direction of blood flow.

In all 466 fetuses we examined, atria, ventricles, and great arteries and veins were defined in each study. Characteristic flow signals were defined in each location.²⁶ Doppler, M mode signals, and cross-sectional images were recorded on videotape. The Doppler signals were also recorded on paper at speeds of 75 mm/sec for a permanent record with a Tektronix page printer.

Tricuspid or atrioventricular valve insufficiency was assessed

as mild, moderate, or marked based on multiple serial positioning of the sample volume in the atria to define how localized the regurgitant jet was and how far from the valve this jet could be recorded.

Results

Among the 466 fetuses we studied, using a combined two-dimensional echocardiographic/Doppler approach, we found 16 fetuses with a combination of atrioventricular valve insufficiency and nonimmune hydrops. Four pregnancies were terminated and therefore excluded from this report. This report is concerned with the 12 remaining fetuses and their natural history. The relevant history, findings, and outcome are summarized in table 1. In addition there were seven fetuses with atrioventricular valve insufficiency without associated hydrops whose data are displayed in table 2. Although the pathologic spectrum is similar to that in table 1, there was no associated nonimmune hydrops and most of the infants survived the first week of life. There were an additional 26 fetuses with non-immune hydrops in whom there was no atrioventricular valve insufficiency. Results from many of these fetuses have been reported previously.^{10,30}

Of the 12 instances of atrioventricular valve insufficiency associated with nonimmune hydrops, 11 with structural heart disease died either in utero or shortly

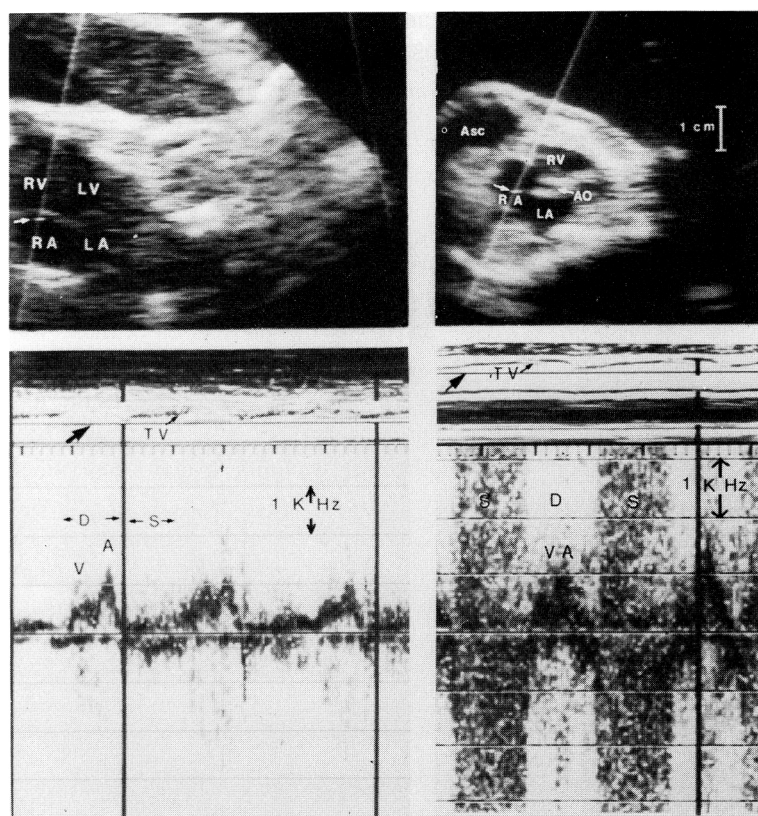


FIGURE 1. Top panels, Cross-sectional echocardiographic images showing the Doppler cursor and sample volume within the atria (small arrows). Bottom panels, M mode tracing with the sample volume (large arrow) located behind the echo of the tricuspid valve (TV) (small arrow). Below the M mode recordings the spectral Doppler output is shown. The scale marker is 1 kHz per division. Flow above the central baseline represents flow toward the transducer, flow below the baseline represents flow away from the transducer. Left, The top frame is an apical four-chamber view of a normal 20 week fetus with the Doppler cursor directed through the right heart and the sample volume placed behind the tricuspid valve within the right atrium (RA). In the bottom panel, the characteristic pattern with forward flow in diastole (D). The A peak from atrial contraction is higher than the V peak of venous filling. In systole (S), there is no flow signal. Right, Image from fetus 3, short-axis plane through the right heart. The sample volume is proximal to the tricuspid valve in the right atrium (RA). AO = aorta; Asc = ascites; LA = left atrium; RV = right ventricle. A 1 cm marker is shown. At bottom right, the systolic portion of the image (S) shows marked flow disturbance with aliasing (the dominant negative direction away from the right ventricle and the transducer). The diastolic V and A points are present but less clearly separated than in the normal patient.

TABLE 1

Presentation and outcome of fetuses with atrioventricular valve insufficiency and nonimmune hydrops

Fetus No.	Weeks gest.	Presenting problem	Findings	Outcome
1	20	Lithium ingestion	20 wk: tricuspid insufficiency and questionable valve displacement; 24 wk: definite displacement of tricuspid valve characteristic of Ebstein's anomaly; 34 wk: hydrops	Vaginal delivery, born cyanotic, maintained on PGE ₁ , presented with low blood pressure, died at 30 hr, autopsy confirmed diagnosis of Ebstein's anomaly
2	36	Arrhythmia	Complex bradyarrhythmia, AV canal defect, AV valve insufficiency, interrupted IVC, polysplenia, hydrops	Vaginal delivery, presented with low blood pressure and cardiac failure, died at 20 hr, autopsy confirmed diagnosis
3	20	Twin pregnancy with hydropic twin	Tricuspid valve insufficiency, no recordable pulmonary valve, small main pulmonary artery segment, 1 twin hydropic, 1 normal	Twin died and pregnancy aborted spontaneously, autopsy refused
4	35	Hydropic fetus	Aortic atresia, diminutive left ventricle and mitral valve, tricuspid insufficiency, hydrops	Vaginal delivery, died within 20 hr, autopsy confirmed diagnosis
5	34	Lithium treatment for depression, hydrops noted 24 wk gestation	Ebstein's anomaly noted on echo and tricuspid insufficiency by Doppler exam	Died on second day of life, autopsy confirmed diagnosis
6	38	Polyhydramnios and hydrops	Right atrial and right ventricular dilatation, pulmonary outflow not clearly seen, tricuspid insufficiency	Died at 4 hr, autopsy confirmed dysplastic pulmonary valve
7	29	Polyhydramnios, sustained tachycardia (240/min)	Normal cardiac anatomy, hydrops, mother given digitalis, verapamil, and eventually furosemide	Hydrothorax and ascites, resolved 14 days after treatment, born at 38 wk gestation
8	26	Fetal hydrops, bradycardia, Sjogren's syndrome, arthritis, ANA positive to 1:160	Complete heart block with ventricular rate of 55/min, hydrops, AV valve insufficiency	Spontaneous abortion at 30 wk, at postmortem tricuspid valve thickened and right ventricle hypertrophied
9	23	Nonimmune hydrops at 23 wk gestation	AV canal defect, mild AV valve insufficiency, pulmonary atresia, asplenia	Died on first day of life, could not be resuscitated, postmortem refused
10	25	Ascites, pericardial effusion; mother has Ebstein's anomaly at 24 weeks	Ebstein's anomaly, same degree as maternal disorder, nonimmune hydrops, moderate AV valve insufficiency	Born with hydrops, severe tricuspid valve insufficiency after birth with right-to-left atrial shunt, died at 5 days
11	29	Bradycardia (45–50/min)	Ambiguous atrial situs, AV canal defect, double-outlet right ventricle and pulmonic stenosis, mild atrioventricular valve insufficiency by Doppler exam	Maintained on terbutaline to prevent premature labor, heart rate increased to 70/min, AV valve regurgitation increased, nonimmune hydrops developed, baby died on first day of life, autopsy confirmed right isomerism and other in utero findings
12	31	Maternal polyhydramnios and nonimmune fetal hydrops	AV canal defect and AV valve insufficiency	Amniocentesis showed trisomy 21, baby delivered at term, died on first day of life

ANA = antinuclear antibody; AV = atrioventricular; IVC = inferior vena cava.

after delivery. The sole survivor was a 29 week fetus with sustained supraventricular tachycardia whose tachyarrhythmia, atrioventricular valve regurgitation, and hydrops fetal resolved in utero after transplacental therapy with digoxin and verapamil.

Our first fetus discovered to have atrioventricular valve insufficiency was a 20 week product of a 42-year-old gravida IV para III who had received high-dosage lithium for depression during the first trimester.

The examination showed an enlarged right atrium and probable displacement of the tricuspid valve. Doppler insonation of the right atrium from a four-chamber view showed marked tricuspid insufficiency. The diagnosis of Ebstein's anomaly was suspected (figure 2). At 24 weeks gestation the degree of tricuspid insufficiency appeared qualitatively unchanged but there had been further enlargement of the right atrium and the umbilical vein, possibly reflecting venous hy-

TABLE 2

Presentation and outcome of fetuses with atrioventricular valve insufficiency and without nonimmune hydrops

Fetus No.	Weeks gest.	Presenting problem	Findings	Outcome
1	34	Severe growth retardation	Pulmonary insufficiency, tricuspid insufficiency	Cesarean section undertaken, severe growth retardation with birth weight 1250 g, postnatal echocardiogram confirmed pulmonary and tricuspid insufficiency, infant alive and well
2	34	Bradycardia (85/min)	Right isomerism, AV canal defect, double-outlet right ventricle and pulmonary stenosis, AV valve insufficiency	Prenatal findings confirmed after birth, Blalock-Taussig shunt performed, patient alive at 2 mo of age
3	38	Intermittent bradycardia to 50/min, anti-Rho antibody positive	Complete heart block at echocardiography, mild AV valve insufficiency	Epicardial pacemaker inserted, baby doing well
4	26	Bradycardia to 60/min, mother had hepatitis during pregnancy	Complete heart block with AV valve insufficiency	No problem with heart block since delivery
5	34	Dermatomyositis, bradycardia	Complete heart block and mild AV valve insufficiency	Situs inversus, baby born with dextrocardia, catheterization showed small atrial septal defect and patent ductus arteriosus, asymptomatic at 6 mo
6	32	Bradycardia	Isolated levocardia, atrial isomerism, complete AV canal defect, severe subpulmonary stenosis, mild AV valve insufficiency, sinus bradycardia	Delivery at 36 wk gestation, cardiac catheterization showed right isomerism and mild AV valve regurgitation, child alive after Blalock-Taussig shunt
7	32	General ultrasound exam showed duodenal atresia	Complete AV canal defect with mild AV valve insufficiency, chromosome analysis showed normal complement	Small for dates, operation to bypass duodenal atresia, echocardiography after birth confirmed in utero findings

AV = atrioventricular.

pertension. The tricuspid valve showed obvious displacement of its septal leaflet. Examination at 35 weeks gestation showed fetal hydrops in addition to the atrioventricular valve insufficiency. Analysis of the amniotic fluid showed fetal pulmonary maturity. Labor was induced and the infant delivered. She was cyanotic (Pao₂ 34 mm Hg) and had marked hydrops and poor peripheral perfusion, with an arterial blood pressure of only 40/20 mm Hg. Postnatal echocardiographic and Doppler examination confirmed the prenatal findings. Contrast echocardiography showed marked right-to-left atrial shunting.

Despite administration of prostaglandin E₁, isoproterenol, and dopamine, the baby died 30 hr after delivery. Autopsy confirmed the diagnosis of Ebstein's anomaly.

The second fetus we encountered was the product of a gravida II para I referred for evaluation of a fetal cardiac arrhythmia at 35 weeks gestation. The fetus was noted to be hydropic with atrioventricular valve insufficiency on Doppler examination and complex congenital heart disease consisting of an atrioventricular canal defect associated with left atrial isomerism

(figure 3). Labor was induced and delivery was uneventful. Neonatal ultrasound examination confirmed the prenatal diagnosis of atrioventricular valve insufficiency. The blood pressure was low and could not be maintained despite infusion of isoproterenol and dopamine. The infant died 32 hr after birth and autopsy confirmed the findings.

The next case involved a 23 week monoamniotic twin pregnancy. Nonimmune hydrops was noted during an obstetric ultrasound examination and the patient was referred for cardiac ultrasound study, which showed the presence of pulmonary atresia. The right ventricle and right atrium appeared enlarged in the four-chamber view (figure 4). Doppler insonation of the main pulmonary artery showed no forward flow into the pulmonary artery. There was no observable pulmonary valve motion. Pulsed Doppler insonation of the right atrium showed marked tricuspid insufficiency (figure 1, *right*). The other twin was morphologically normal. The pregnancy terminated spontaneously 4 weeks later. Both fetuses were stillborn and severely macerated. Postmortem examination was refused.

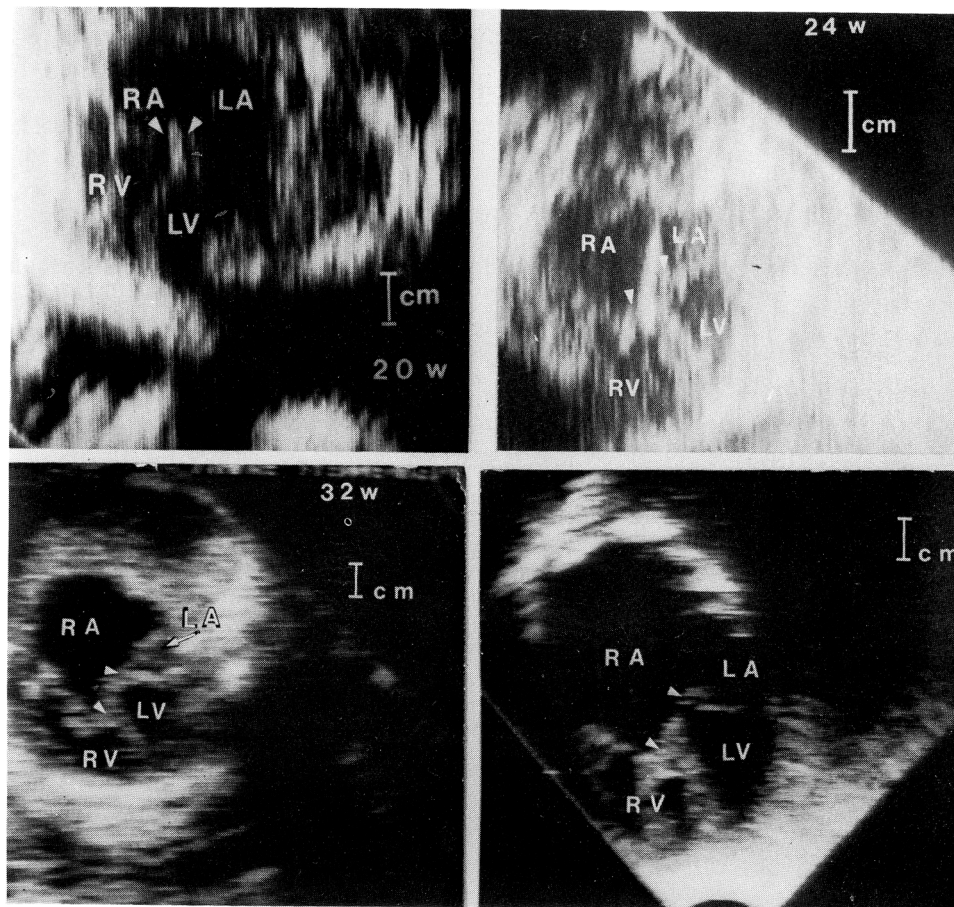


FIGURE 2. Four frames in equivalent orientation, four-chamber plane, from fetus 1 with Ebstein's anomaly, showing the findings at 20 weeks (*top left*), 24 weeks (*top right*), 32 weeks (*bottom left*), and after birth at 35 weeks (*bottom right*). The four chambers identified are the right atrium (RA), right ventricle (RV), left atrium (LA), and left ventricle (LV). The arrows indicate the septal insertion of the tricuspid and mitral valves. At 20 weeks the heart appears structurally normal (although other views suggested right atrial enlargement). At 24 weeks right atrial enlargement and tricuspid displacement are apparent. At 32 weeks the tricuspid displacement is marked, the right atrial enlargement has progressed, and pleural effusions are noted. After birth there is a similar pattern to that at 32 weeks. A large right-sided pericardial effusion can be seen.

The fourth fetus was examined at 32 weeks of gestation and was found to have nonimmune hydrops with marked ascites and pericardial effusion. Fetal echocardiography confirmed the presence of aortic atresia, a minute ascending aorta, and a diminutive mitral valve and left ventricle (figure 5). Doppler flow study showed marked systolic flow disturbance within the enlarged right atrium with aliasing indicating tricuspid insufficiency. The jet could be recorded only toward the lateral atrial wall, suggesting that the insufficiency was mild. The baby died within 6 hr of delivery. The autopsy findings confirmed the sonographic observations in utero. Data pertaining to the other fetuses in this study are summarized in tables 1 and 2.

Discussion

These cases demonstrate the ability of range-gated pulsed Doppler echocardiography to detect flow dis-

turbances in fetuses with cardiovascular compromise related to abnormalities either of cardiac structure or of rhythm.

Hydrops fetalis was present in all 12 fetuses who demonstrated atrioventricular valve regurgitation. The 11 fetuses with structural heart disease died in utero or during the first few days of life.

We encountered an additional seven fetuses who had atrioventricular valve insufficiency without non-immune hydrops. The prognosis appears somewhat better than that of the group in whom there was atrioventricular valve insufficiency and nonimmune hydrops (table 2). Although the prognosis of nonimmune hydrops in general is poor, 82% mortality,³⁰ our series suggests that nonimmune hydrops associated with atrioventricular valve insufficiency makes the prognosis even poorer.

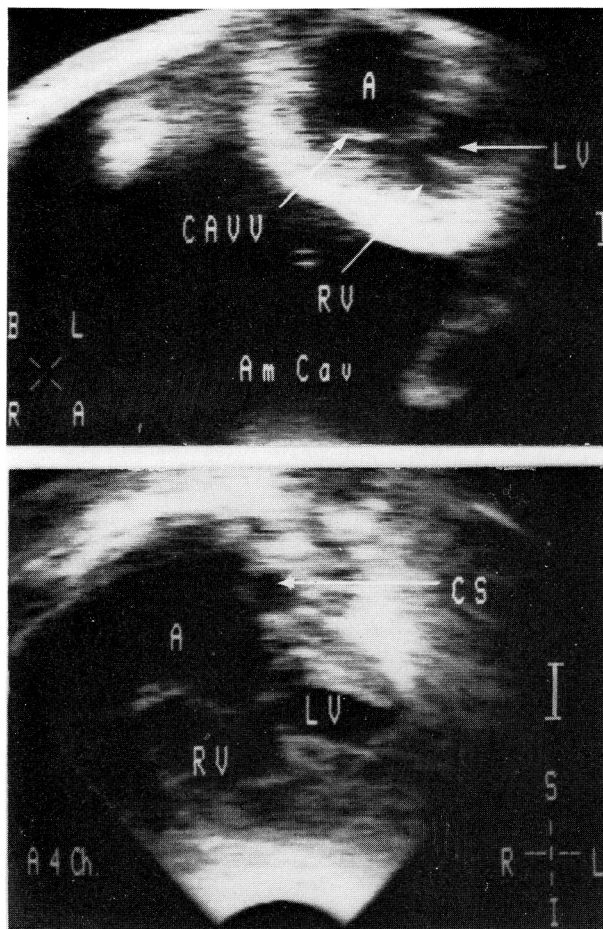


FIGURE 3. Four-chamber view taken from the examination in utero (*top*) and after birth (*bottom*). The top panel shows the single large common atrium (A) and the common atrioventricular valve (CAVV). The left ventricle (LV) and right ventricle (RV) are separated by the ventricular septum and a large ventricular septal defect. There is polyhydramnios filling the amniotic cavity (Am Cav). A 1 cm scale marker is shown. A = apex; B = base; L = left; R = right. The bottom panel shows the same intracardiac anatomy after birth except a large coronary sinus (CS) can be seen. I = inferior; L = left; R = right; S = superior.

The high incidence of cardiac pathology in the presence of nonimmune fetal hydrops has been recognized,^{9, 30} suggesting that hydrops fetalis represents end-stage fetal cardiac decompensation in some cases.

It has been assumed that hydrops is the result of fetal systemic venous hypertension. The response of the fetal circulation to obstructive lesions such as hypoplastic left heart syndrome with aortic atresia or pulmonary atresia is to redistribute flow, thereby bypassing the obstruction. Thus cardiac failure and fetal hydrops appear to be uncommon findings in the presence of valvular stenotic lesions at birth. However, atrioventricular valve insufficiency is associated with a mandatory increased volume load on the heart. The fetal heart has only a limited ability to increase its output in response to an increase in ventricular filling

pressure. Several studies in fetal lambs have shown that the ventricular output is near the peak at ventricular end-diastolic pressures that are present in the normal resting state; any further increase in preload has a limited effect on stroke volume.^{31–33} This could be the result of either myocardial immaturity with limited inotropic reserves or reduced compliance of the fetal ventricles.³⁴ Because the foramen ovale provides a large communication between the left atrium and systemic veins, the volume loading causes systemic venous hypertension regardless of whether there is insufficiency of a mitral, a tricuspid, or a common atrioventricular valve.

The elevated systemic venous hypertension coupled with low colloid osmotic pressure during fetal life

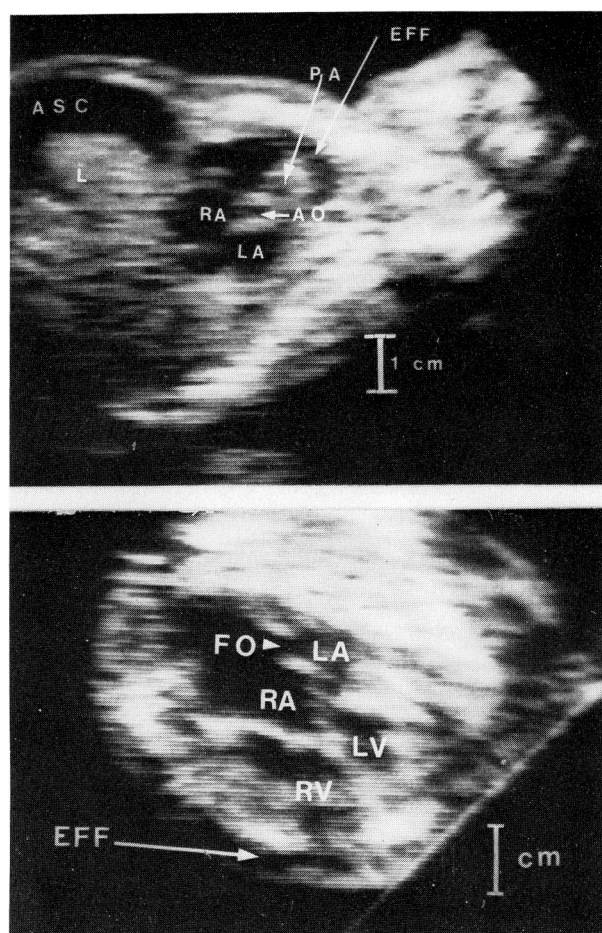


FIGURE 4. *Top*, Longitudinal view through one twin fetus at 23 weeks showing the finding of hydrops with skin edema, ascites (Asc), and pericardial effusion (EFF). The heart orientation is in a plane equivalent to a short-axis plane showing a large right atrium (RA), smaller left atrium (LA), aorta (AO), and pulmonary artery (PA). The pulmonary valve leaflets did not open and there was no recordable Doppler signal within the pulmonary artery. L = liver. A 1 cm marker is shown. *Bottom*, A four-chamber plane with the enlarged right atrium (RA) and right ventricle (RV). The fossa ovalis (FO) is patent (arrow) and the smaller left atrium (LA) and left ventricle (LV) are seen.

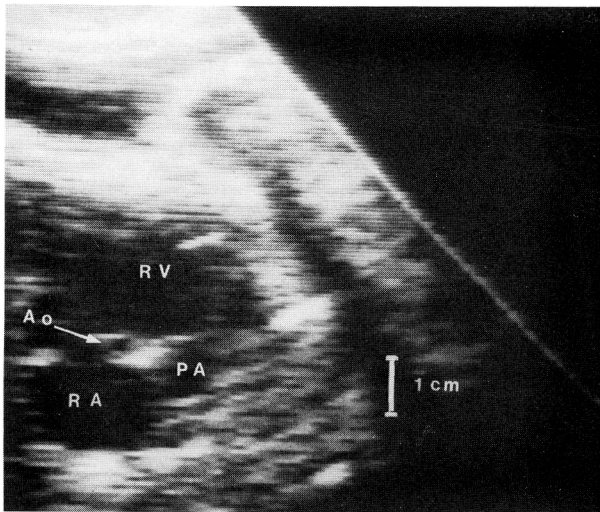


FIGURE 5. Short-axis projection in fetus 4 shows a minute aortic root (Ao) and large right atrium (RA). Right ventricle (RV) and pulmonary artery (PA). A 1 cm marker shows the aorta to be no larger than 4 mm. RV = right ventricle; PA = pulmonary artery.

leads to the presence of edema and hydrops in the fetus. The physiologic low serum albumin level may be further aggravated by decreased hepatic albumin formation in the presence of retrograde inferior vena caval flow and loss of albumin into the extravascular space. The venous pressure could not be measured in our fetuses, but the atrium receiving regurgitant flow was usually large and the umbilical vein dilated when compared with the umbilical artery cross-sectional area.

Pulsed Doppler ultrasound has provided the means to ascertain the presence of atrioventricular or semilunar valve regurgitation and would seem to confirm the postulate that the severity of the venous hypertension load attending such valve dysfunction may be the factor that distinguishes the hydropic fetus from the nonhydropic fetus with the same underlying cardiac lesion. We have been able to follow the natural history of seven other fetuses with similar lesions and atrioventricular valve insufficiency without nonimmune hydrops, all of whom have survived through pregnancy and the early neonatal period (table 2). The atrioventricular valve insufficiency appears to have been less severe by the limited methods we were able to use to define severity.

The difference in the clinical manifestations of the fetuses with atrioventricular valve insufficiency could be related to the severity of the lesion. However, it could also be the result of the duration of the insufficiency, as well as changes in the degree of insufficiency associated with growth. This is exemplified in fetuses 1 and 11, in whom atrioventricular valve insuf-

ficiency was noted before hydrops was observed. The increasing severity of the hemodynamic disturbance could well be related to increase in heart size with increasing valvular insufficiency occurring in association with increased size of the valve anulus caused by growth and dilatation.

A relatively small subgroup of patients with congenital heart disease develop hydrops fetalis (i.e., absent pulmonary valve syndrome, Ebstein's malformation of the tricuspid valve, as well as atrial isomerism with atrioventricular canal defects) largely secondary to atrioventricular or semilunar valve insufficiency rather than systolic pump failure.

The findings in our patients suggest that early identification of atrioventricular valve regurgitation in utero may, in selected cases, identify the fetus with structural or functional cardiac impairment who may be at risk for the development of hydrops fetalis. In such cases, prompt transplacental medication or early delivery may be considered.

The detection of atrioventricular valve insufficiency may be used to direct efforts at in utero therapy of arrhythmias and may be used to formulate plans for delivery of the affected fetus and, in the future, may be useful for identifying fetuses who may be candidates for cardiac surgery in utero. The detection of tricuspid insufficiency in aortic atresia, which occurred in one fetus in this series, may suggest that palliative surgery would not make these infants appropriate candidates for a subsequent Fontan operation.³⁵

Although it is possible to criticize this study on the basis of not assessing interobserver and intraobserver error, we kept the exposure of the fetuses to ultrasound to a minimum in accordance with recent recommendations.³⁶

These studies suggest that the detection of atrioventricular valve insufficiency provides practical information of value for managing the high-risk pregnancy. The combined ultrasound technique augments our understanding of the pathophysiologic nature of the human fetus affected with congenital heart disease.

We thank Ms. Martha Prince for preparation of the manuscript and photographic material, Ms. Mary Helen Briscoe for the artwork, Mr. Rick Soloway for the photography, and Mrs. Heather Silverman for editorial assistance.

References

1. Sahn DJ, Lange LW, Allen HD, Goldberg SJ, Anderson C, Giles H, Haber K: Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. *Circulation* 62: 588, 1980
2. Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C, Giles H: Quantitative real-time cross-sectional echocardiographic imag-

- ing of the human fetus during the second half of pregnancy. *Circulation* **62**: 799, 1980
3. Allan LD, Tynan MJ, Campbell S, Wilkinson JL, Anderson RH: Echocardiographic and anatomical correlates in the fetus. *Br Heart J* **44**: 444, 1980
 4. Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS: Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics* **65**: 1059, 1980
 5. Allan LD, Tynan M, Campbell S, Anderson RH: Identification of congenital cardiac malformations by echocardiography in midtrimester fetus. *Br Heart J* **46**: 358, 1981
 6. Allan LD, Tynan MJ, Campbell S, Anderson RH: Normal fetal cardiac anatomy — a basis for the echocardiographic detection of abnormalities. *Prenatal Diagn* **1**: 131, 1981
 7. DeVore GR, Donnerstein RL, Kleinman CS, Platt LD, Hobbins JC: Fetal echocardiography. I. Normal anatomy as determined by real-time-directed M-mode ultrasound. *Am J Obstet Gynecol* **144**: 249, 1982
 8. Allan LD, Joseph MC, Boyd EG, Campbell S, Tynan M: M-mode echocardiography in the developing human fetus. *Br Heart J* **47**: 573, 1982
 9. Kleinman CS, Donnerstein RL, DeVore GR, Jaffe CC, Lynch DC, Berkowitz RL, Talner NS, Hobbins JC: Fetal echocardiography for evaluation of in utero congestive heart failure. *N Engl J Med* **306**: 568, 1982
 10. Kleinman CS, Donnerstein RL, Jaffe CC, DeVore GR, Weinstein EM, Lynch DC, Talner NS, Berkowitz RL, Hobbins JC: Fetal echocardiography. A tool for evaluation of in utero cardiac arrhythmias and monitoring of in utero therapy: analysis of 71 patients. *Am J Cardiol* **51**: 237, 1983
 11. Wladimiroff JW, McGhie J, Vosters R: Fetal cardiac activity. In Rijsterborgh H, editor: *Echocardiology*. The Hague, 1981. Martinus Nijhoff Publishers, p 417
 12. Eik-Nes SH, Brubakk AO, Ulstein MK: Measurement of human fetal blood flow. *Br Med J* **280**: 283, 1980
 13. Redel DA, Hansmann M: Fetal obstruction of the foramen ovale detected by two-dimensional Doppler echocardiography. In Rijsterborgh H, editor: *Echocardiology*. The Hague, 1981. Martinus Nijhoff Publishers, p 425
 14. Loeber C, Goldberg SJ, Hendrix MJC, Sahn DJ: Dynamic mammalian cardiogenesis investigated by high-resolution ultrasound in guinea pigs. *Circulation* **68**: 841, 1983
 15. Silverman NH, Snider AR, Golbus MS, Stanger P: Perspectives in fetal echocardiography. In Dellenbach P, editor: *Ler symposium international d'echocardiologie foetale*. Strasbourg, 1982. Milupa Dietique, p 95
 16. Redel DA, Hansmann M: Prenatal diagnosis and treatment of heart disease. In Dellenbach P, editor: *Ler symposium international d'echocardiologie foetale*. Strasbourg, 1982. Milupa Dietique, p 127
 17. Hansmann M, Redel DA: Prenatal symptoms and clinical management of heart disease. In Dellenbach P, editor: *Ler symposium international d'echocardiologie foetale*. Strasbourg, 1982. Milupa Dietique, p 137
 18. Nesser HJ, Redel DA, Salzer HR: Echocardiography in utero of tricuspid atresia. In Dellenbach P, editor: *Ler symposium international d'echocardiologie foetale*. Strasbourg, 1982. Milupa Dietique, p 248
 19. DeGeeter B, Nisand I, Kohler A, Durand JL, Dellenbach P, Kieny R: Etude du coeur foetale en routine. In Dellenbach P, editor: *Ler symposium international d'echocardiologie foetale*. Strasbourg, 1982. Milupa Dietique, p 87
 20. Leslie J, Shen SC, Strauss L: Hypertrophic cardiomyopathy in a midtrimester fetus born to a diabetic mother. *J Pediatr* **100**: 631, 1982
 21. Sahn DJ, Shenker L, Reed KL, Valdes-Cruz LM, Sobonya R, Anderson C: Prenatal ultrasound diagnosis of hypoplastic left heart syndrome in utero associated with hydrops fetalis. *Am Heart J* **104**: 1368, 1982
 22. Sharf M, Abinader EG, Shapiro I, Rosenfeld T, Eibschitz I: Prenatal echocardiographic diagnosis of Ebstein's anomaly with pulmonary atresia. *Am J Obstet Gynecol* **147**: 300, 1983
 23. Silverman NH, Enderlein MA, Golbus MS: Ultrasonic recognition of aortic valve atresia in utero. *Am J Cardiol* **5**: 20s, 1985
 24. Berman WJ, editor: *Pulsed Doppler ultrasound in clinical pediatrics*. Mount Kisco, NY, 1983. Futura Publishing Co.
 25. Kurjak A, Rajhvajn B Jr: Ultrasonic measurements of umbilical blood flow in normal and complicated pregnancies. *J Perinat Med* **10**: 3, 1982
 26. Maulik D, Nanda NC, Saini VD: Fetal Doppler echocardiography: methods and characterization of normal and abnormal hemodynamics. *Am J Cardiol* **53**: 572, 1984
 27. Hata T, Hata K, Kitao M: Fetal intracardiac blood-flow patterns assessed by pulsed Doppler and B-mode ultrasound. *J Cardiovasc Ultrasonogr* **3**: 101, 1984
 28. Tonge HM, Struijk PC, Wladimiroff JW: Blood flow measurements in the fetal descending aorta: technique and clinics. *Clin Cardiol* **7**: 323, 1984
 29. Silverman NH, Golbus MS: Echocardiographic techniques for assessing normal and abnormal fetal cardiac anatomy. *J Am Coll Cardiol* **5**: S20, 1985
 30. Mahoney BS, Filly RA, Callen PW, Chinn DH, Golbus MS: Severe nonimmune hydrops fetalis: sonographic evaluation. *Radiology* **151**: 757, 1984
 31. Heymann MA, Rudolph AM: Effects of increasing preload on right ventricular output in fetal lambs in utero. *Circulation* **48**(suppl IV): IV-37, 1983
 32. Gilbert RD: Effects of afterload and baroreceptors on cardiac function in fetal sheep. *J Dev Physiol* **4**: 299, 1982
 33. Thornburg KL, Morton MJ: Filling and arterial pressures as determinants of RV stroke volume in the sheep fetus. *Am J Physiol* **244**: H656, 1983
 34. Friedman WF, Lesch M, Sonnenblick EH: *Intrinsic physiologic properties of the developing heart in neonatal heart disease*. New York, 1972. Grune & Stratton, p 27
 35. Lang P, Norwood WI: Hemodynamic assessment after palliative surgery for hypoplastic left heart syndrome. *Circulation* **68**: 104, 1983
 36. Diagnostic ultrasound imaging in pregnancy. U.S. Dept. of Health & Human Services. Public Health Service and National Institutes of Health. N.I.H. Publication No. 84-667. U.S. Government Printing Office, Washington, DC, pp 21-56