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Ductus venosus Doppler in the assessment of fetal cardiovascular health: an updated practical approach

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Abstract

The ductus venosus has a central role in the distribution of highly oxygenated umbilical venous blood to the heart. Its waveform is related to the pressure-volume changes in the cardiac atria and it is therefore important in the monitoring of any fetal condition that may affect forward cardiac function. The cardiovascular parameters that can influence forward cardiac function include afterload, myocardial performance and preload. Decreased forward flow during atrial systole (a-wave) is the most sensitive and ubiquitous finding when any of these parameters is affected. In contrast, decreased forward velocities during end-systolic relaxation (v-wave) are more specifically related to myocardial performance. The ductus venosus pulsatility index alone does not accurately reflect cardiac function, and in cases of suspected fetal cardiac dysfunction, echocardiography is required to identify the underlying mechanism. The role of ductus venosus Doppler in the assessment of fetal growth restriction, supraventricular tachycardia, fetal hydrops, complicated monochorionic twins and congenital heart disease is discussed with these considerations in mind.

Abbreviations: AV, atrio-ventricular; CHD, congenital heart disease; DV, ductus venosus; FGR, fetal growth restriction; PIV, pulsatility index for veins; SVT, supraventricular tachycardia; TTTS, twin-to-twin transfusion syndrome.

The central role of ductus venosus in fetal cardiovascular assessment

Doppler examination of the fetal venous circulation was introduced into perinatal medicine over 25 years ago to extend cardiovascular functional assessment beyond the capabilities of arterial Doppler. All central and precordial venous vessels share the same flow pattern of forward flow in ventricular systole and diastole and a temporary decrease in forward flow during end-ventricular systole and atrial systole. However, the ductus venosus (DV) has several important characteristics that favor its widespread use in fetal medicine. It is a short vessel with a relatively fixed position, allowing for standardization of the

Key message

The ductus venosus waveform reflects the pressure–volume changes in the heart. Despite the limited specificity of the ductus venosus waveform, its correlation with cardiac forward function makes it of central importance in assessing the overall severity of fetal cardiovascular pathology. Ductus venosus Doppler study has a critical role in directing the clinical management of fetuses at risk of cardiovascular deterioration.

examination. It is the only venous vessel that regulates nutrient delivery of umbilical vein blood between the liver and heart, and therefore has an important physiologic role (1,2). It has the highest forward velocities in the venous system, with antegrade flow throughout the entire cardiac cycle, allowing for semiquantitative, as well as qualitative, waveform analysis (1,3,4). Finally, venous blood flow changes are equally reflected in the DV Doppler parameters, and its use has been validated in a wide range of fetal conditions (4–6).

Physiology of the ductus venosus in the fetal circulation

The DV originates from the umbilical vein. Under normal conditions, 75% of the nutrient-rich umbilical venous blood continues to the liver to reach the heart through the hepatic veins, whereas the remaining 25% reaches the heart directly through the DV (2). The blood entering the DV undergoes significant acceleration in the direction of the foramen ovale. This produces a relative separation of its blood stream from the other venous flow entering the heart and allows nutrient-rich blood to reach the left ventricle instead of flowing through the tricuspid valve to the right ventricle (7). Through this mechanism, the myocardium and cerebral circulations receive blood with a higher nutritional content than could be achieved if there was total venous admixture of blood entering the heart.

Assessing the ductus venosus velocity waveform

The DV is best sampled at the isthmus, near its origin from the umbilical vein. In the absence of fetal movements, color Doppler is applied to identify the isthmus, which is often apparent by its high forward velocities or aliasing, in a mid-sagittal or cross-sectional abdominal plane. The pulsed wave Doppler gate of 2 mm is placed on this area to obtain the waveform with the smallest possible angle of insonation (8). A pulsed Doppler sample >2 mm increases the risk of contamination from adjacent vessels. The use of a high velocity color Doppler scale above 48 cm/s helps to discriminate the DV from adjacent venous vessels with slower flow (9). A high signal-to-noise ratio is required to obtain a good-quality waveform. If the required criteria for vessel sampling are met, a normal waveform will present peak systolic velocities (S) of 48–71 cm/s and peak diastolic velocities (D) of 31–58 cm/s, depending on gestational age (9,10).

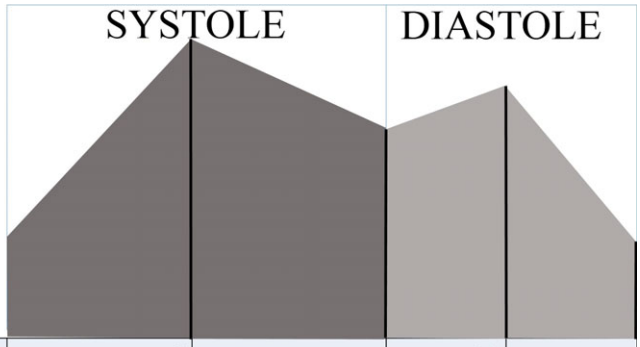
Once a good quality waveform is acquired, it can be assessed qualitatively (such as absent or reversed a-wave), or by obtaining semiquantitative, angle-independent Doppler indices. For semiquantitative analysis, the waveform needs to be outlined from the beginning of ventricular systole to the end of atrial systole, in order to measure the peak velocity during ventricular systole (S-wave), ventricular end-systole (v-descent), ventricular diastole (D-wave), atrial systole (a-wave), and the time-averaged maximum velocity (4,8,11) (Figure 1). The complex nature of the venous flow velocity waveform has led to the development of a number of Doppler indices that are derived by incorporating several velocities (4,9,12–16), in contrast to velocity ratios of relative forward flow during individual phases of the cardiac cycle (Table 1). Of these Doppler ratios, the pulsatility index for veins (PIV) is clinically the most widely utilized.

Normal and abnormal ductus venosus waveforms

The variations in venous forward flow reflect the changes in atrial pressure and volume across the systolic and diastolic phases of the cardiac cycle. Venous forward velocity is highest when intra-atrial pressure is low. This occurs during early systole, when the atrio-ventricular (AV) valve rings descend rapidly, and during early diastole, when the AV valves are open and blood flows passively into the relaxed ventricles. In contrast, forward velocities decrease when atrial pressures are higher. This occurs in end-systole, when the AV rings ascend to their diastolic position, or when the atria contract during atrial systole. The associated cardiac pressure and volume changes correspond to four phases of the DV waveform (Figure 1): (1) during the systolic peak (S), peak velocities increase concurrent with systolic ventricular ejection; (2) at the post-systolic trough (v-descent), venous velocities decrease as the ventricles reach the end of systole; (3) diastolic peak (D) velocities increase as AV valves open during early passive diastolic ventricular filling; (4) a second steep trough (a-wave) corresponds to atrial systole, when the venous forward velocity reaches the lowest point.

The volumes and pressures within the cardiac chambers are determined by cardiac afterload, contractility, compliance of the cardiac muscle, and the pressure exerted by blood volume, commonly referred to as preload. With advancing gestation, cardiac afterload decreases as placental flow resistance declines, whereas cardiac compliance and contractility increase. The increased efficiency of forward cardiac function leads to significant increase in absolute S-, D-, and a-wave blood flow velocities. This produces a steady linear decrease in venous pulsatility and a-wave-related ratios (8,9,17,18).

During atrial systole, the venous blood column is in continuity with the atria and ventricles through the open atrio-ventricular valves. This is the reason why abnormalities in venous forward flow almost universally decrease a-wave velocities (Figure 2) (6). There are two additional



Wave	S	v	D	a
Phase of cardiac cycle	Systole	Ventricular relaxation (late systole)	Early ventricular diastole	Atrial contraction (late diastole)
Event	AV valve rings descend	AV valve rings ascend towards resting position	AV valves open	Active ventricular diastolic filling
Atrial pressure	↓	↑	↓	↑
Effect on venous return to the atria (DV flow velocity)	↑	↓	↑	↓
Effect on DV waveform	First peak (S-wave)	First trough (v-wave)	Second peak (D-wave)	Second trough (a-wave)

Figure 1. Schematization of the four phases of the ductus venosus (DV) waveform and corresponding pressure-volume changes in the heart.

DV waveform patterns that are seen when the forward flow during the entire diastole is reduced. Under these circumstances, D- and a-wave velocities show a relative decline (19,20). The third pattern is observed when there is decreased forward flow during end-systole, creating an "M"-shaped waveform pattern due to decreased v-wave velocity (19) (Figure 2). Although it has been assumed that the DV waveform can be used to assess cardiac function, recent evidence indicates that a-wave velocities in particular are unrelated to individual cardiac performance parameters (13,21,22). Conversely, v-wave-related velocity ratios (such as S/v and v/D) show significant correlation with cardiac function (22). However, abnormalities of these parameters are not reflected by Doppler indices such as the PIV, and if these indices are used, waveform analysis cannot differentiate the underlying pathology. The important clinical implication is that DV Doppler provides an overall but non-specific reflection of cardiac forward function.

An abnormal DV waveform requires a careful examination of all potential cardiovascular contributory aspects. Table 2 shows a simplified approach with a checklist of conditions that should be considered when an abnormal DV waveform is observed. Sometimes multiple mechanisms can coexist, such as in advanced deterioration of growth-restricted fetuses, when there is a combination of increased afterload due to high placental resistance and decreased cardiac contractility due to poor myocardial oxygenation. Therefore, arterial fetal Doppler studies, evaluation of the outflow tracts and atrio-ventricular connections, and examination of myocardial performance may be required to determine specific contributors to the abnormal waveform (19,23,24).

Despite the limited specificity of the DV waveform, its correlation with forward function of the heart makes it of central importance in assessing the overall severity of cardiovascular pathology. It is therefore useful in the clinical management of all fetal conditions that can give rise to cardiovascular deterioration.

Fetal growth restriction

In fetuses with early-onset growth restriction (FGR) before 34 weeks, the combination of arterial and DV

Table 1. Ductus venosus (DV) Doppler indices.

DV preload index	$\frac{\text{Systolic} - \text{Diastolic peak velocity}}{\text{Systolic peak velocity}}$
DV Pulsatility index for veins (PIV)	$\frac{\text{Systolic} - \text{End-diastolic velocity (a)}}{\text{Time average maximum velocity}}$
DV Peak velocity index for veins	$\frac{\text{Systolic} - \text{End-diastolic velocity (a)}}{\text{Diastolic peak velocity}}$
Percentage reverse flow	$\frac{\text{Systolic time averaged velocity}}{\text{Diastolic time averaged velocity}} \times 100$
Velocity ratios	
S/v ratio	Forward flow into the atria during ventricular relaxation
v/D ratio	Early diastolic filling
D/a ratio	Forward flow during passive and active diastolic filling
S/D ratio	Ventricular systolic to early passive diastolic filling
S/a ratio	Ventricular systolic to active diastolic filling
v/a ratio	Late-systolic to late- diastolic filling

Doppler is a widely accepted key component of longitudinal monitoring and the prediction of fetal deterioration (6,25). In these pregnancies, qualitative and semi-quantitative abnormalities in the umbilical artery and middle cerebral artery Doppler waveforms are frequently seen and reflect the underlying increased placental blood flow resistance and fetal hypoxemia, respectively (26–28). Increased placental blood flow resistance to the point of absent or reversed umbilical artery end-diastolic flow places the FGR fetus at risk for late cardiovascular changes that are associated with fetal deterioration and eventually decompensation (15,29). In this setting, an abnormal DV waveform can occur as a result of three mechanisms: (1) the massive increase in placental afterload; (2) the decreased myocardial performance and compliance due to myocardial hypoxia (29,30); (3) the autoregulatory increase in the DV diameter allowing an increase in the fraction of shunting (31,32). Due to this variability in underlying mechanisms, the median time interval between abnormal DV Doppler and loss of biophysical variables ranges between 1 and 8 days (33). When DV forward a-wave is absent or reversed, fetal survival of longer than 1 week is unlikely (34). While long suspected in observational studies, the TRUFFLE study has now demonstrated that in early onset FGR after 26 weeks, DV Doppler, especially in combination with the computerized CTG, guides optimal delivery timing (25,35–38).

The gestational age at detection of FGR also needs to be considered when interpreting the DV waveform. Early-

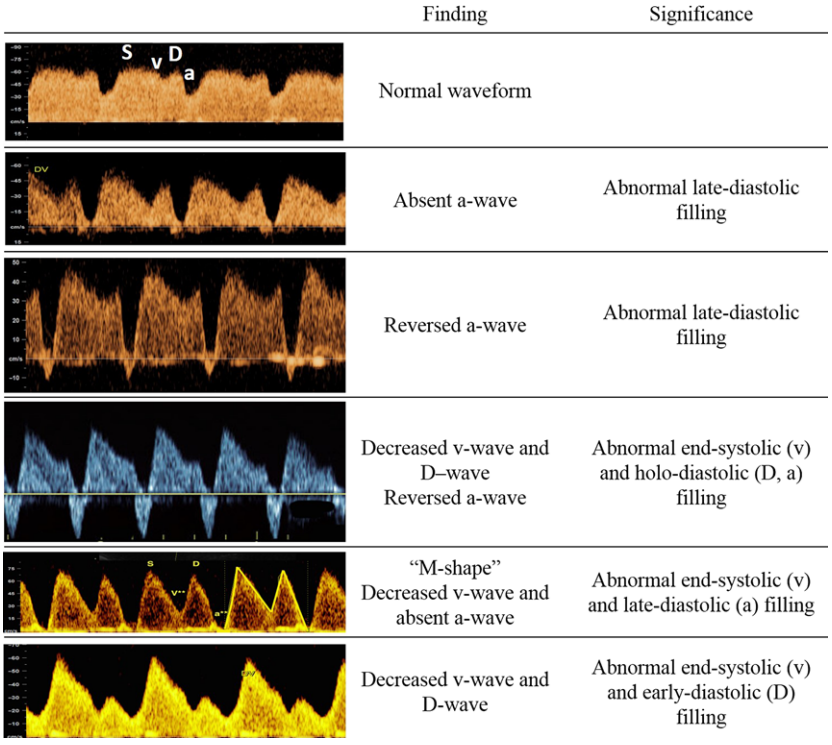


Figure 2. Normal and abnormal ductus venosus waveform patterns.

Table 2. Pathological conditions that produce abnormal ductus venosus waveforms, arranged by their cardiovascular etiology.

Increased cardiac preload	Abnormal cardiac function or structure	Increased cardiac afterload
• Increased venous vascular volume • Valvular disease (such as tricuspid valve regurgitation, Ebstein anomaly)	• Decreased compliance • Decreased contractility • Arrhythmias • Cardiomyopathies • Cardiac tumors	• Placental dysfunction (FGR) • Valvular disease (such as aortic or pulmonary stenosis/atresia) • Vascular disease (such as aortic coarctation, constriction of the ductus arteriosus) • Laser occlusion of placental vascular anastomoses for the treatment of TTTS (donor twin)

FGR, fetal growth restriction; TTTS, twin-to-twin transfusion syndrome.

and late-onset FGR represent two distinct clinical phenotypes of placental dysfunction. In contrast to early-onset FGR, in late-onset disease (after 34 weeks), placental dysfunction is most often characterized by impaired diffusion of oxygen and nutrients, potentially leading to fetal hypoxemia, rather than to an increase in afterload. In this context, an abnormal DV waveform is rarely observed, and sudden unanticipated stillbirth is strongly associated with middle cerebral artery brain-sparing (39).

Hydrops fetalis

Non-immune hydrops represents a clinical end-point for numerous fetal disorders that range from a good prognosis with treatment to lethal conditions. The common etiologies include cardiovascular, chromosomal and hematologic abnormalities, followed by structural fetal anomalies, complications of monochorionic twinning, infection, and placental abnormalities (40). Many of these conditions can affect forward cardiac function and, therefore, the DV waveform. In myocardial dysfunction leading to low-output heart failure and in certain structural heart defects, right heart pressure increases, resulting in increased central venous pressure (preload) (41). In hydrops due to cystic adenomatoid malformation or pulmonary sequestration, the pulmonary masses can obstruct venous or arterial blood flow causing combined impact on cardiac forward function. Fetal arrhythmias can result in inadequate diastolic ventricular filling. Fetal anemia, twin-to-twin transfusion syndrome (TTTS), or sacrococcygeal teratomas can lead to high-output cardiac failure in late stages, which can be presaged by abnormal DV Doppler (42).

Abnormal venous Doppler appears to be more frequent in low-output hydrops than high-output hydrops (43–45). Interestingly, high-output hydropic fetuses with anemia can show normal or even low preload index and PIV in the DV, despite a hyperdynamic circulation or hypervolemia (45). This suggests that hydrops fetalis in the early stages of anemia is not primarily due to high-output cardiac decompensation. Here, the increase in cardiac output leads to a decrease in forward flow resistance in the DV and is an expression of initial fetal compensation. In the anemic fetus, DV Doppler parameters can therefore be helpful in distinguishing the early stage of the disease, when a better prognosis can be expected, from the later stages, when congestive heart failure occurs.

Abnormal venous flow, in both the DV (absent/reversed a-wave) and the umbilical vein (pulsations), is strongly related to perinatal death in pregnancies complicated by fetal hydrops (44,46,47), with perinatal mortality rates as high as 79% (44). In cases of increased hepatic venous pressure, umbilical venous flow may reverse altogether, leading to placental swelling (48). It is for these reasons that DV Doppler is performed in all cases of fetal hydrops, and an abnormal waveform should prompt a detailed evaluation of the fetal anatomy, cardiovascular status, and fetal echocardiography (44,49).

Supraventricular tachycardia

Fetal supraventricular tachycardia (SVT) has immediate and delayed effects on the fetal heart. The immediate effect is that the rapid heart rate leads to ineffective cardiac function, resulting in atrio-ventricular valvular regurgitation, decreased cardiac output, and increased central venous pressure eventually leading to hydrops. The delayed effect of sustained SVT is the development of a reversible fetal cardiomyopathy (50,51). The risk for hydrops and the degree of increased central venous pressure are best assessed by DV Doppler. When the typical multiphasic pattern is replaced by biphasic flow with holodiastolic flow reversal, the central venous pressure rises rapidly by up to 75% (52,53). This is often, but not invariably, observed above heart rates of 210 bpm. However, if this flow pattern emerges, it is a predictor of hydrops that is independent of the heart rate. It is under these circumstances that maternal anti-arrhythmic therapy should be initiated early, before placental hydrops impairs transplacental passage of the medications. Even if response to treatment varies, the initial response to therapy is consistent and is characterized by the restoration of a normal triphasic DV waveform that precedes car-

dioversion (54). Once SVT is resolved, DV Doppler is helpful in monitoring the resolution of SVT-induced cardiomyopathy. Failure to resolve within 2 weeks of cardioversion should raise the suspicion for persistence of paroxysmal SVT episodes that delay the myocardial recovery (52).

Twin-to-twin transfusion syndrome

Twin-to-twin transfusion syndrome (TTTS) develops when the angioarchitecture of the placenta allows unbalanced exchange of blood volume between the donor and recipient twin. It produces complex cardiovascular effects that differ between donor and recipient (55–58). In the donor twin, restrictive high-resistance placentation and myocardial dysfunction related to growth restriction is more typical, with the recipient showing signs of hypervolemia, myocardial hypertrophy, and high output failure potentially inducing fetal hydrops. Staging of TTTS was introduced by Quintero et al. (59) and includes the concurrent evaluation of the umbilical artery, DV, and umbilical vein Doppler. Critical Doppler abnormalities, consisting of absent or reversed umbilical artery end-diastolic velocity, absent or reversed DV a-wave, or umbilical venous pulsations, define stage 3 TTTS. In the donor twin, abnormal DV waveforms are reminiscent of FGR fetuses, with a prominent decrease in the a-wave resulting in an M-shaped pattern when ventricular relaxation is abnormal (Figure 2). In the recipient, DV a-wave and D-wave velocities tend to decrease as a sign of increased preload and impaired ventricular filling (55,56,60). DV Doppler abnormalities at the time of diagnosis occur significantly more often in the recipient than in the donor and have been correlated with development of hydrops and with lower survival in the recipient twin (55), thus indicating the prognostic importance of venous Doppler assessment in TTTS. However, the lack in specificity of the DV waveform in identifying the pathophysiological mechanism is illustrated by the application of cardiovascular scores. As observed for other fetal cardiovascular diseases, there is certainly overlap between abnormal venous Doppler and cardiac dysfunction, but there is no consistent relation between the two. Detailed cardiovascular scoring in TTTS identifies cardiac dysfunction independent of venous Doppler status even in stage 1 disease (61). Therefore, a comprehensive fetal cardiac assessment by echocardiography is an important component of clinical evaluation in pregnancies complicated by TTTS.

Following fetoscopic laser surgery, DV Doppler assessment is required to monitor the response to therapy (62). In recipient fetuses, a significant decrease in DV PIV is frequently observed immediately after the procedure (55,63), and cardiac function, which can be severely abnormal at the time of TTTS, normalizes during a 4-week time span after therapy (64). The recipient is at risk of developing pulmonary valve stenosis secondary to chronic right-sided volume overload and cardiac muscular hypertrophy. In the donor twin, abnormal DV flow and tricuspid regurgitation can be observed postoperatively (55,63,64) and typically regress within 4 weeks (64). Also, hydropic signs after treatment are observed in approximately 25% of donor twins (55,65). These acute hemodynamic changes are probably secondary to the development of a state of relative hypervolemia combined with an abrupt increase in afterload following the surgical occlusion of the vascular anastomoses. They can therefore be considered transient signs of fetal circulatory adaptation after laser coagulation (55,64). These postoperative changes in the donor appear not to be associated with an increase in the myocardial performance index, again suggesting that this parameter is more specific for inherent cardiac muscle characteristics, whereas the DV is also influenced by extra-cardiac variables (64). The postoperative increase in DV pulsatility in donor fetuses after the procedure does not correlate with a decrease in probability of survival (55).

The other important function of DV Doppler in monochorionic pregnancies is the early stratification of patients who are at risk of developing TTTS. At the time of first-trimester ultrasound, discordance of nuchal translucency thickness, as well as DV and tricuspid valve flow abnormalities, may represent the early manifestation of hemodynamic imbalance between donor and recipient, and are related to the clinical progression to TTTS in the second trimester (66,67).

Congenital heart disease

Congenital heart diseases (CHD) can be associated with abnormal venous Doppler waveforms due to the anatomic defect itself or due to the functional impact of the lesion. Accordingly, DV Doppler has a role in the screening, severity assessment and longitudinal monitoring of fetuses with CHD.

Integration of the DV Doppler into first-trimester nuchal translucency screening enhances the early prediction of congenital heart diseases. In fetuses with an elevated nuchal translucency that are found to be chromosomally normal, first trimester absence or reversal of the DV a-wave stratifies fetuses that are at risk for CHD (68–70). In this subgroup of fetuses, DV Doppler potentially predicts 83% of major congenital heart defects (70). However, in fetuses with normal nuchal translucency, the sensitivity is low (70). It is noteworthy that congenital absence of the DV is associated with CHD, including abnormalities of the venous system (71,72). Accordingly, when the DV cannot be identified, or the DV a-wave is abnormal, further

evaluation by first- or second-trimester echocardiography, depending on availability and acuity of clinical suspicion, is recommended.

Congenital heart disease may produce a variety of DV Doppler abnormalities either via obstruction to venous flow or superimposing cardiac dysfunction. Many fetuses with CHD have abnormal DV Doppler waveforms at baseline. Particularly, right-sided CHD with obstructive lesions (such as tricuspid or pulmonary valve stenosis/atresia) are associated with a high rate of DV a-wave flow reversal at baseline. Conversely, fetuses with non-obstructive lesions rarely show flow reversal in the DV at baseline or during distress, even when significant tricuspid regurgitation is present (73). This is most likely attributable to differences in the underlying pathophysiology (74). Obstructive lesions, such as critical pulmonic stenosis, can also lead to myocardial dysfunction. Accordingly, in these fetuses, a high DV-PIV correlates with the risk of intrauterine or neonatal death (75). It is for these reasons and the limitations of DV semiquantitative waveform analysis that the interpretation of DV Doppler results requires special considerations in CHD. In particular, it is useful to record the DV waveform at the time of the initial echocardiogram. If deterioration is suspected, comparing the associated DV waveform pattern with the baseline pattern often provides a more useful assessment than using the Doppler reference range alone. In cases where the DV is markedly abnormal at baseline examination, newly evolving umbilical venous pulsations may be the only venous Doppler sign of changing central hemodynamics. Under these circumstances, functional fetal echocardiography is required to clarify the underlying mechanisms responsible for the changes in venous flow dynamics.

Conclusion

Ductus venosus (DV) Doppler study has a critical role in directing the clinical management and predicting perinatal outcome of many fetal conditions that can give rise to cardiovascular deterioration. Despite the limited specificity of the DV waveform, its correlation with forward function of the heart makes it of central importance in assessing the overall severity of fetal cardiovascular pathology.

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