

Submitted:
25.07.2019
Accepted:
16.10.2019
Published:
31.12.2019

Fetal cardiac function by three-dimensional ultrasound using 4D-STIC and VOCAL – an update

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DOI: 10.15557/JoU.2019.0043

Keywords

fetal heart,
cardiac function,
three-dimensional
ultrasound,
spatio-temporal
image correlation,
virtual organ
computer-aided
analysis

Abstract

Three- and four-dimensional (3D/4D) ultrasonography with spatio-temporal image correlation (4D-STIC) allows obtaining fetal cardiac volumes and their static and real-time analysis in multiplanar and rendering modes. Cardiac biometrics and Doppler-echocardiographic parameters for evaluation of fetal heart function, including cardiac output and stroke volume, can be analyzed using M-mode, two-dimensional (2D), and 3D/4D cardiac ultrasound. In recent years, functional echocardiography has been used to study fetuses without a structurally cardiac defect but who are at risk of heart failure due to the presence of extra-cardiac conditions, such as, fetal growth restriction, tumors/masses, twin-to-twin transfusion syndrome, fetal anemia (Rh alloimmunization), congenital infections, or maternal diabetes mellitus. The assessment of cardiac function provides important information on hemodynamic status and can help optimize the best time for delivery and reduce perinatal morbidity and mortality. Since 2003, with the advent of the 4D-STIC software, it is possible to evaluate the fetal heart in multiplanar, and rendering modes. This technology associated with virtual organ computer-aided analysis (VOCAL) enables determining the ventricular volume (end-diastole, end-systole), the stroke-volume, the ejection fraction, and the cardiac output of each ventricle. Since 2004, several studies demonstrated that the 4D-STIC and VOCAL had good reproducibility to measure cardiac volumes. This study reviews published studies that evaluated the fetal cardiac function by 3D ultrasound using 4D-STIC and VOCAL software.

Introduction

Congenital heart disease (CHD) occurs in one to two newborns per 100 live births and is an important cause of perinatal morbidity and mortality^(1–4). Prenatal screening and diagnosis of anatomical and functional heart malformations are possible by ultrasonography and fetal

echocardiography, allowing for planning of delivery and, in some cases, prenatal therapy, favoring the postnatal prognosis of CHD^(5–7).

Cardiac function is routinely evaluated in fetuses with anatomical malformations. In recent years, functional echocardiography has been used to study fetuses with

a structurally normal heart but who are susceptible to hemodynamic changes due to the presence of extra-cardiac conditions, including, among others, fetal growth restriction, tumors/masses, twin-to-twin transfusion syndrome, fetal anemia (Rh alloimmunization), congenital infections, or maternal diseases such as diabetes mellitus, systemic arterial hypertension, and Graves' disease⁽⁸⁻¹¹⁾.

The assessment of cardiac function provides critical information on hemodynamic status and the cardiovascular adaptation of the fetus and can help optimize the best time for delivery and reduce perinatal morbidity and mortality. Various myocardial parameters can be analyzed in combination considering specific applications for different diseases.

The systolic function of the fetal heart can be evaluated by measuring the ejection fraction (EF), shortening fraction (SF), cardiac output (CO), cardiac volume (CV), maximal displacement of the valve ring (tricuspid or mitral), myocardial performance index (MPI), and myocardial strain parameters⁽⁸⁻¹³⁾. Cardiac function, including SF, CO, and CV, can be analyzed by one-dimensional (M-mode), 2D, and 3D/4D ultrasound. The measurement of ventricular volumes during diastole and systole by 3D/4D ultrasound combined with virtual organ computer-aided analysis (VOCAL) allows calculating the EF and CO of each ventricle (left ventricle and right ventricle) and both (combined CO)^(14,15).

The objective of this study is to review the published studies that assessed systolic function using 3D ultrasound combined with spatio-temporal image correlation (4D-STIC) and VOCAL.

Analysis of systolic function

Many techniques are available to evaluate cardiac function in fetuses, including Doppler blood flow, measurement of the heart chambers (cardiac biometrics) and of each interval of the cardiac cycle, CV by 3D/4D ultrasound, or the



Fig. 1. Myocardial performance index (MPI) or left ventricular Tei index calculated by the formula: $MPI = \text{isovolumetric contraction time (IVCT)} + \text{isovolumetric relaxation time (IVRT)} / \text{ejection time (ET)}$. The ventricular outflow and inflow values should be obtained by Doppler to measure MPI

combination of several parameters. Therefore, MPI, stroke volume (SV), CO, SF, and EF may be used to assess systolic function.

MPI is a quantitative, non-invasive method used for the assessment of systolic and diastolic cardiac function. It is calculated for each ventricle using spectral Doppler and the following formula: isovolumetric contraction time (ICT) + isovolumetric relaxation time (IRT)/ejection time (ET) (Fig. 1). Myocardial dysfunction may lead to prolonged isovolumetric intervals and decreased ET, resulting in increased MPI. MPI values higher than 0.52 were highly sensitive and specific to predict adverse events during pregnancy and the neonatal period⁽¹⁶⁻¹⁹⁾.

The atrioventricular annular movement determined using the M-mode ultrasound/echocardiogram (mitral annular plane systolic excursion [MAPSE] and tricuspid annular plane systolic excursion [TAPSE]) is easy to obtain and has a good correlation with tissue Doppler measurements for evaluating the longitudinal systolic function of the fetal myocardium⁽²⁰⁾ (Fig. 2 A, B, and C). Moreover, TAPSE can be determined in the 4D-STIC M-mode with good reproducibility, and reference curves for TAPSE by gestational age (GA) have been validated⁽²⁰⁻²¹⁾.

In recent years, the advancements of tissue Doppler with speckle tracking enable the accuracy of the measurements of myocardial strain indexes (strain and strain rate), which are important for assessing left ventricle (LV) function (Fig. 3). Despite the high potential of 2D speckle tracking, its applicability in fetal cardiac analysis needs to be validated⁽¹⁰⁻¹³⁾.

SV can be calculated for each ventricle in the 2D mode, multiplying the valve area of the outflow tract by the mean velocity-time integral (VTI) of the ventricular outflow: $SV = \text{area} \times \text{VTI}$ (Fig. 4). SV can be determined by 3D/4D ultrasonography using the following formula: end-diastolic volume (EDV) – end-systolic volume (ESV) (Fig. 5). The combined CO can be calculated by multiplying the sum of the SV of the two ventricles by the heart rate (bpm) ($CO = RV\ SV + LV\ SV \times HR$). Similarly to the SV, the CO can be calculated for each ventricle and also increases with GA. The SVs of the LV and right ventricle (RV) are positively correlated with GA, and after 24 weeks of gestation, the RV CO predominates over the LV CO. Several z-scores and percentile curves were developed for CO as a function of GA using 2D ultrasound⁽²²⁻²⁶⁾. CO values below the 5th percentile or below -2.0 are considered low, and CO values above the 95th percentile or above +2.0 are considered high in reference curves by GA. The CO of the fetus may increase in cases of arteriovenous malformations of the central nervous system (Galen's aneurysm), teratomas, and twin-to-twin transfusion syndrome, or decrease in cases of low cardiac contractility, including myocarditis and fetal cardiomyopathy^(8,9,26).

The EF reflects the percentage of blood ejected from the ventricles and can be calculated in each ventricle by 3D ultrasound with 4D-STIC using the following formula: $EDV - ESV / EDV$. EDV and ESV can be measured by 3D

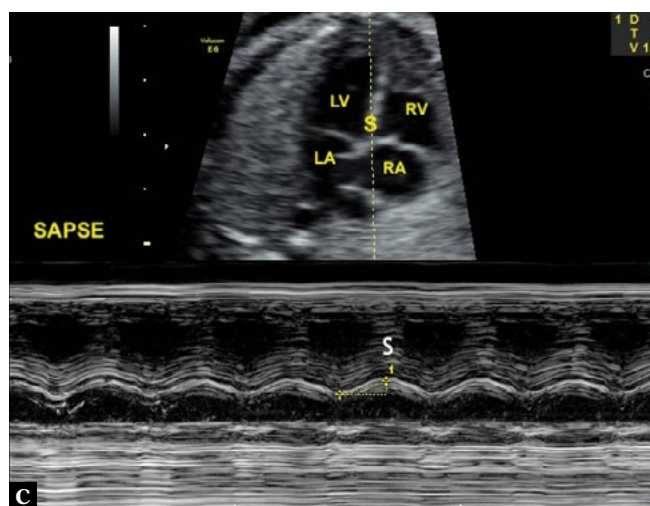
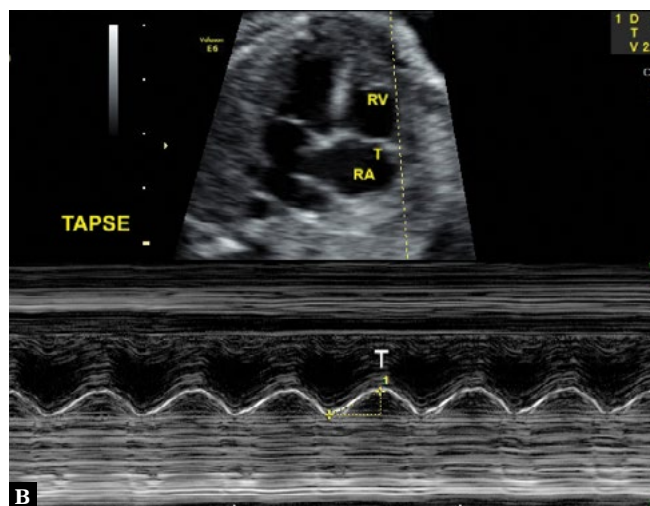
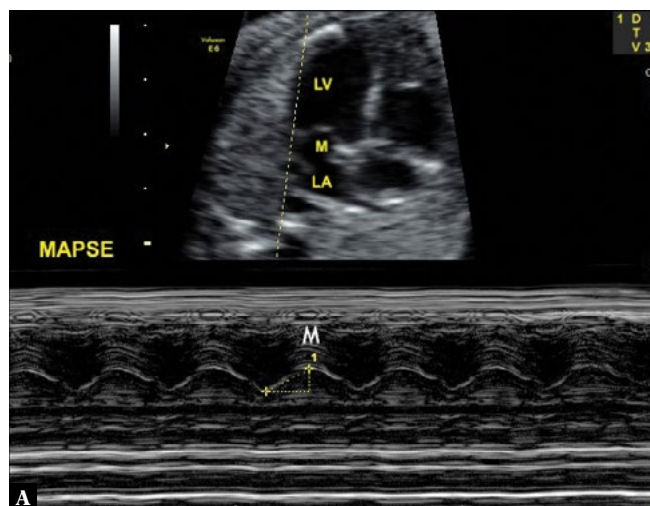


Fig. 2. Evaluation of the atrioventricular annular movement in the uni-dimensional mode (M-mode) of the echocardiogram. **A.** MAPSE, mitral annular plane systolic excursion; **B.** TAPSE, tricuspid annular plane systolic excursion; **C.** SAPSE, septal annular plane systolic excursion. LA – left atrium; LV – left ventricle; M – mitral valve; RA – right atrium; RV – right ventricle; S – interventricular septum; T – tricuspid valve

ultrasound using 4D-STIC with VOCAL (Fig. 5). SF is an index that evaluates reduction of ventricular diameter from end-diastole to end-systole. Using the M-mode with 2D and 3D ultrasound (4D-STIC M-mode), the maximum and minimum diameters of each ventricle can be measured in the four-chamber plane. SF can be calculated separately for each ventricle using the following formula: maximal or end-diastolic diameter (EDD) – minimum or end-systolic diameter (ESD)/EDD. SF below 28% on M-mode and EF below 63% on 3D/4D mode without changes by GA are considered altered^(27–29).

Assessment of fetal cardiac function by 3D ultrasonography with 4D-STIC

Since 2003, with the advent of the 4D-STIC software, it is possible to evaluate the fetal heart in multiplanar, and rendering modes. This technology, initially described by De Vore *et al.*, allows measuring fetal CVs using a volumetric transducer during a scan of 7.5–15.0 s, with the acquisition of 150 2D images per second. The reconstruction of these images in time-correlated 3D volumes (4D-STIC) enables simulation of cardiac movements

(cinelop). Moreover, this technique enables anatomical and functional analysis of the fetal heart in the absence of the patient (off-line) and the delivery of CV data using an internet link for analysis in tertiary centers (tele-STIC) (30–34).

The quantification of ventricular volumes during diastole and systole by 4D-STIC and VOCAL enables calculating the ESV, CO, and EF, combined or not with other modalities, including the inversion mode, Color Doppler, and power Doppler^(14,15). The 4D-STIC M-mode also allows measuring the EF and SF of the ventricles by determining their end-diastolic and end-systolic diameters, and



Fig. 3. Analysis of myocardial deformity by speckle tracking, which tracks acoustic markers (speckle) and improves the accuracy of the measurements

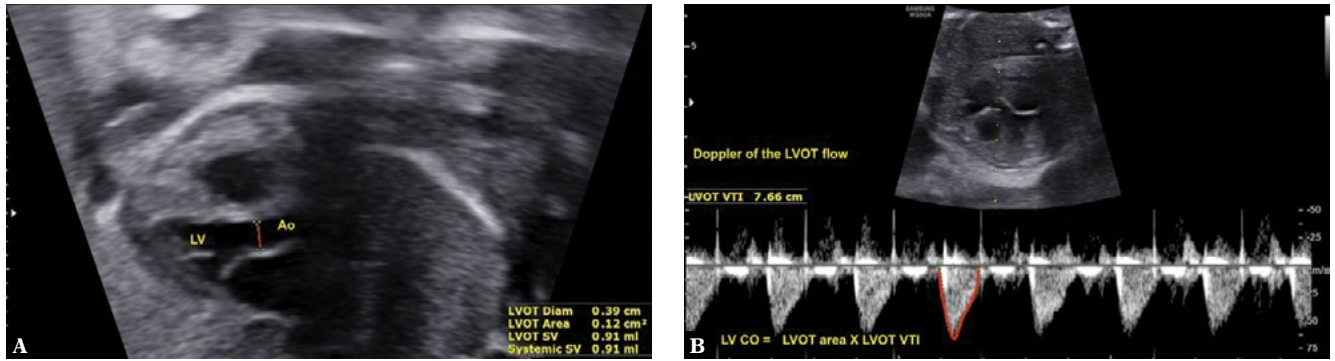


Fig. 4. The stroke volume (SV) can be calculated for each ventricle in the 2D mode by multiplying the valve area of the outflow tract by the mean velocity-time integral (VTI) of the ventricular outflow: $SV = \pi r^2 \times VTI$. Ao – aorta; LV – left ventricle; LVOT – left ventricle outflow tract

its effectiveness in fetuses with hydrops has also been demonstrated⁽²²⁾.

Methods

For this review, a search strategy was carried out at the PubMed database to identify articles published in English between 2004 and 2019. The objective of this approach was to identify relevant studies on the functional assessment of a human fetal heart by 3D ultrasonography and 4D-STIC and VOCAL. The following MESH terms were used: “fetal heart,” “cardiac volumes,” and “virtual organ computer-aided analysis.” A total of 18 articles were found. Only studies that performed functional analyses of the normal fetal heart by 3D ultrasound using 4D-STIC and VOCAL were included in the review. The titles and abstracts of these articles were obtained. Four of the 18 studies were excluded for the following reasons: use of VOCAL in hypoplastic left heart syndrome (one study), use of VOCAL for measuring thymus volume (one study), and use of 4D-STIC without VOCAL (two studies). Three other articles were added after analyzing the selected articles and their references. Consequently, 17 articles were analyzed (Tab. 1).

Measurement of CO and EF using 4D-STIC and VOCAL

Although 4D-STIC was initially used *in vivo* for the analysis of CHD, Bhat *et al.* performed the first study to quantify the ventricular mass using 4D-STIC combined with VOCAL. In this study, the obtained values of the chamber volumes were multiplied by the myocardial density (1050 g/cm³) to determine ventricular mass in mesodiastole. This study was performed *in vivo* with 90 normal fetuses between 15 and 37 weeks of gestation and *in vitro* using pulsating balloons, which simulated the four cardiac chambers. There was a positive correlation between the mass of both ventricles and GA⁽³⁵⁾.

Rizzo *et al.* demonstrated that the use of 4D-STIC and VOCAL for measuring ventricular CVs presented a good agreement with 2D Doppler measurements. Messing *et al.* (2007) acquired cardiac images in mesodiastole using

4D-STIC and VOCAL with inversion mode to quantify ventricular volumes and the EF of fetuses without structural changes. The study included 100 normal fetuses between 20 and 40 weeks of gestation. The results demonstrated that the mean ESV ranged from 0.17 to 1.56 cm³ for the LV and from 0.26 to 2.29 cm³ for the RV. The mean LV-RV SV ratio was 1.4, and the EF ranged from 42.5% to 86%⁽³⁶⁾.

Hamill *et al.* analyzed 44 fetuses between 19 and 40 weeks of gestation and found good reproducibility in the quantification of CVs by VOCAL, in agreement with previous studies^(33,36,37). Molina *et al.* analyzed SV and CO in 140 normal fetuses between 12 and 34 weeks of gestation using 4D-STIC with VOCAL. The CVs were smaller than those obtained in previous studies in 2D mode, and there was a positive correlation of SV and CO with GA⁽¹⁴⁾.

Uittenbogaard *et al.* carried out an *in vitro* study in which small balloons connected to a pump system were used to mimic fetal heart chambers. In this study, 76 fetal CVs were acquired by 4D-STIC using three methods: 3D slice, VOCAL, and VOCAL with inversion mode. These authors concluded that 4D-STIC was a viable and accurate method for calculating volumes from 0.30 mL. *In vitro*, the 3D slice method was more accurate, less

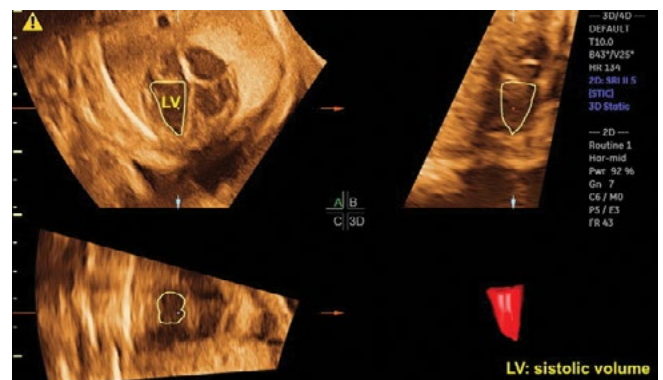


Fig. 5. Measurement of the LV cardiac output and ejection fraction using the 4D-STIC and VOCAL software. LV – left ventricle

Tab. 1. Studies evaluating ventricular cardiac function – cardiac output, stroke volume, and ejection fraction – using three-dimensional ultrasound with 4D-STIC and VOCAL

Author	Total number of cases	Gestational age (weeks)	Conclusion
Bhat <i>et al.</i> (2004) ⁽³⁵⁾	90 (in vitro)	15–37	There was a positive correlation between ventricular mass and gestational age.
Rizzo <i>et al.</i> (2007) ⁽³³⁾	56 (16 with intrauterine growth restrictions and 40 controls)	20–34	There was good agreement between the measurements of the ventricular cardiac volumes using 4D-STIC with VOCAL and 2D- ultrasound with Doppler.
Messing B <i>et al.</i> (2007) ⁽³⁶⁾	100	20–40	It was demonstrated that 4D-STIC was simple, highly reproducible, and could be used for assessing fetal cardiac function. Nomograms for ventricular volume, stroke volume, and ejection fraction were established by gestational age. The ratio between RV and LV volumes was 1.4. The stroke volume ranged from 0.78 to 5.50 cm ³ , and the ejection fraction ranged from 42.5% to 86.0%.
Molina <i>et al.</i> (2008) ⁽¹⁴⁾	140	12–34	There was a positive correlation of stroke volume and CO of both ventricles with gestational age.
Hamill <i>et al.</i> (2009) ⁽³⁷⁾	44	19–40	VOCAL had good reproducibility for measuring cardiac volumes.
Uittenbogaard <i>et al.</i> (2010) ⁽³⁸⁾	76 (in vitro)		4D-STIC was shown to be a viable and accurate method for calculating volumes from 0.30 mL. In vitro, 4D-STIC combined with the 3D slice method was more accurate, less time-consuming, and more reliable than VOCAL.
Rizzo <i>et al.</i> (2010) ⁽³⁴⁾	45 (15 with congenital heart disease and 30 healthy controls)	19–32	The authors compared ventricular volumes obtained by 4D-STIC with VOCAL and with sonography-based automated volume count (SonoAVC). The time necessary to measure volumes using SonoAVC was significantly shorter than that of the two other methods. However, SonoAVC and VOCAL results were similar. One limitation of the study was the small sample size.
Simioni <i>et al.</i> (2011) ⁽³⁹⁾	265	20–34	Reference curves were constructed for stroke volume, CO, and ejection fraction according to GA. Stroke volume and CO were positively correlated with GA.
Hamill <i>et al.</i> (2011) ⁽²⁸⁾	184	19–42	RV diastolic and systolic volumes were larger than LV volumes. LV ejection fraction was larger than RV ejection fraction. Stroke volume and CO increased with GA, without significant differences between the LV and RV.
Schoonderwald <i>et al.</i> (2012) ⁽⁴⁰⁾	30 (84 acquired volumes – 54 excluded volumes)	20–34	Cardiac volume, stroke volume, and ejection fraction were compared using Simpson's and VOCAL methods, and both methods were highly reproducible. The small sample size was considered a limitation to use 4D-STIC in clinical practice. *Strict criteria were adopted to include high-quality images of cardiac volumes.
Simioni <i>et al.</i> (2012) ⁽⁴¹⁾	216 (108 fetuses of each sex)	20–24	There were no significant sex differences in CO and ejection fraction.
DeKoninck <i>et al.</i> (2012) ⁽⁴²⁾	15	16, 24, and 24	There was good reproducibility of 3D ultrasonography with 4D-STIC for measuring CO when compared to 2D- Doppler ultrasonography. 4D-STIC combined with SonoAVC and the inversion mode showed higher intra- and interobserver reproducibility than 4D-STIC combined with VOCAL.
Hamill <i>et al.</i> (2013) ⁽⁴³⁾	34	20–36	There was an inverse correlation between ventricular CO and vascular resistance of the umbilical artery using 4D-STIC and VOCAL.
Rolo <i>et al.</i> (2015) ⁽⁴⁴⁾	200	18–33	4D-STIC with VOCAL was highly reproducible and was used to calculate the volumes of the IVS by GA.
Barros <i>et al.</i> (2015) ⁽⁴⁵⁾	371	20–33	4D-STIC and VOCAL was highly reproducible and was used to construct reference curves for the volumes of the ventricular walls of the fetal heart by GA.
Araujo Júnior <i>et al.</i> (2016) ⁽⁴⁶⁾	170	20–33	4D-STIC and VOCAL was used to construct reference curves for atrial wall volumes of the fetal heart.

CHD – congenital heart disease; EF – ejection fraction; SV – stroke volume; RV – right ventricle; LV – left ventricle; CO – cardiac output; IVS – interventricular septum; GA – gestational age.

time-consuming, and more reliable than the two other methods⁽³⁸⁾.

Rizzo *et al.* compared the ventricular volumes of 15 fetuses with CHD and 30 fetuses without CHD. The CVs were obtained by 4D-STIC at end-systole and end-diastole and quantified using VOCAL and sonography-based automated volume count (SonoAVC). The time required to measure the ventricular SV was significantly shorter using SonoAVC; however, SonoAVC and VOCAL results were similar. Although it was possible to determine CVs with good intra- and interobserver reproducibility even in fetuses with CHD, the small number of cases was a limitation of this study⁽³⁴⁾.

Messing *et al.* used 4D-STIC with VOCAL and inversion mode in 106 fetuses between 21 and 38 weeks of gestation and quantified the ventricular wall mass with good reproducibility, and this parameter was altered in fetuses with CHD. The authors concluded that this technique was important to assess cardiac function in cases involving anatomical and structural changes⁽³⁶⁾. Simioni *et al.* constructed reference curves for SV, CO, and EF for 265 fetuses between 20 and 34 weeks of gestation. SV and CO increased with GA, whereas EF remained constant (approximately 0.63)⁽³⁹⁾. Hamill *et al.* compared the LV and RV volumes using 4D-STIC and VOCAL and concluded that, although the RV volume was larger than the LV volume, and the LV EF was higher than the RV EF, there were no significant differences in CO and SV⁽²⁸⁾.

Schoonderwaldt *et al.* measured CVs of 84 fetuses between 20 and 34 weeks of gestation by 4D-STIC and used the Simpson's and VOCAL methods to determine the EDV, ESV, EV, and EF of the LV. The authors compared the two methods and concluded that both presented good reproducibility. However, of the 84 CVs, 54 were excluded because of low-quality images. Consequently, the authors emphasized that the small number of samples with high-quality images limited the use of 4D-STIC in clinical practice. Furthermore, the authors explained that the number of samples was small due to the strict criteria adopted, which considered only the CVs whose endocardial borders were clearly delineated and without shadowing artifacts in all six planes⁽⁴⁰⁾.

Simioni *et al.* performed a cross-sectional study with 216 fetuses (108 females and 108 males) between 20 and 24 weeks of gestation using 4D-STIC and VOCAL. The CO and EF were calculated using the formulas for CO for each ventricle, and the EF was determined from the measured volumes. There were significant differences in CO and EF. The mean values of combined CO, left CO, right CO, right EF, and left EF in male and female fetuses were 240.07 mL/min, 122.67 mL/min, 123.40 mL/min, 72.84%, 67.22%, 270.56 mL/min, 139.22 mL/min, 131.34 mL/min, 70.73%, and 64.76%, respectively⁽⁴¹⁾.

DeKoninck *et al.* demonstrated that the use of 3D ultrasonography with 4D-STIC for calculating CO had good reproducibility compared to 2D Doppler ultrasonography. Three different techniques were used to determine CO by 3D ultrasonography with 4D-STIC: VOCAL, SonoAVC, and the inversion mode. SonoAVC and the inversion mode presented higher intra- and interobserver reproducibility. The combined CO values by weight (mL/kg/min) were 177.2, 160.7, and 174.0 mL/kg/min using VOCAL, SonoAVC, and inversion mode, respectively (all at $p < 0.0001$)⁽⁴²⁾. However, the sample size of the study was small ($n = 15$, Tab. 1).

Hamill *et al.* determined the relationship between umbilical vascular impedance and CO using 4D-STIC and VOCAL. The study included 34 fetuses between 20 and 36 weeks of gestation and found that the ventricular volumes were lower in fetuses with increased resistance of the umbilical artery when compared to normal fetuses with a relatively higher decrease in LV volume⁽⁴³⁾.

Rolo *et al.* measured the volume of the interventricular septum (IVS) of 200 fetuses between 18 and 33 weeks gestation. The mean IVS values ranged from $0.13 \pm 0.03 \text{ cm}^3$ to $1.33 \pm 0.37 \text{ cm}^3$ ⁽⁴⁴⁾. Barros *et al.* calculated the cardiac wall volumes in 371 fetuses between 20 and 33 weeks gestation and created reference curves using 4D-STIC and VOCAL⁽⁴⁵⁾. In both studies, the authors demonstrated that the technique presented good intra- and interobserver reproducibility.

Araujo Júnior *et al.* calculated atrial wall volumes in 170 fetuses between 20 and 33 weeks and 6 days of gestation using 4D-STIC and VOCAL. The mean right atrium volume varied from $0.45 \pm 0.16 \text{ cm}^3$ to $2.17 \pm 0.62 \text{ cm}^3$, and the mean left atrium volume ranged from $0.54 \pm 0.21 \text{ cm}^3$ to $2.17 \pm 0.3 \text{ cm}^3$ ⁽⁴⁶⁾.

Conclusion

Since 2004, several studies demonstrated a positive correlation of ventricular and atrial volumes with GA using 4D-STIC and VOCAL. Similarly, the CO calculated using these methods showed a positive correlation with GA, and RV volumes were larger than LV volumes. The retrieved studies demonstrated that 4D-STIC and VOCAL had good reproducibility to measure cardiac volumes and developed reference curves for this parameter by GA. Therefore, 4D-STIC and VOCAL are crucial for evaluating cardiac function parameters, including end-systolic volume, CO, and EF.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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