REVIEW PAPER

Tissue velocities, strain, and strain rate for echocardiographic assessment of ventricular function in congenital heart disease

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During the last decade tissue Doppler and myocardial deformation imaging has been introduced to quantify myocardial function in patients with congenital heart disease. These methods could have potential benefits for patients where the anatomy makes it difficult to quantify ventricular function using M-mode or two-dimensional volumetric techniques. In this overview, the potential benefits as well as limitations of the techniques are discussed. Looking directly into the myocardium renders the techniques geometry-independent, allowing the quantification of right ventricular as well as univentricular systolic function. The limitations include the influence of variable loading conditions as well as different methodological problems.

KEYWORDS
Congenital heart disease; Tissue Doppler; Strain and strain rate

Introduction

The increased availability of several newer techniques to assess ventricular function has stimulated interest for their use in congenital heart disease (CHD). In this paper we will review the use of myocardial tissue Doppler velocities as well as deformation imaging (strain and strain rate quantification) in CHD.

Why these methods may be useful for assessment of ventricular function in congenital heart disease

Several characteristics of tissue velocity and deformation imaging, make them attractive for assessment of ventricular function in CHD. These methods are independent of ventricular geometry and therefore may be useful for evaluation of ventricles with variable morphology. In CHD particularly, assessment of right ventricular (RV) function and hearts with a functionally single ventricle remains challenging. Subjective functional assessment of these ventricles by 'eyeballing' 2-D echo clips is still the most frequently used technique in routine clinical practice. Methods which quantify ventricular function independent of the underlying geometry would therefore provide a useful adjunct to qualitative assessment. A second advantage of the new myocardial motion and deformation techniques is that they can quantify regional myocardial function in addition to global ventricular function. Regional assessment of function has been especially useful in ischaemic heart disease and this may be important in some congenital lesions where coronary artery anomalies are present or where during cardiac surgery the coronary arteries were re-implanted. Examples are anomalous left coronary artery from the pulmonary artery (ALCAPA), transposition of the great arteries after the arterial switch operation and tetralogy of Fallot (TOF). It is possible to quantify regional myocardial function in different segments and identify regional dysfunction. For CHD it is still uncertain how regional dysfunction affects global function and the role of regional differences during the progression of myocardial dysfunction needs to be defined. The new methods also allow quantification of myocardial motion and deformation in different directions (longitudinal, radial, and circumferential) while conventional methods mainly rely on the assessment of radial function. Quantification of longitudinal function may be especially important when assessing RV function as the RV fibres are predominantly arranged in a longitudinal orientation.

From a practical standpoint the data can be acquired at the bedside using a standard echo system in a relatively short period of time. Tissue Doppler velocities can be

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acquired and analysed on-line using pulsed wave Doppler techniques. Alternatively, colour-Doppler myocardial images (clips) may be stored for on-line/off-line analysis of regional myocardial velocities. This allows quantification of myocardial velocities in different segments during the same cardiac cycle. Strain and strain rate can be calculated based on tissue Doppler velocities or newer 2-D gray-scale-based speckle tracking techniques. The first is more difficult and requires training and experience to obtain reliable and reproducible data but yields high frame-rates which may be important in children with high heart rates. The high inter-observer variability for processing tissue velocities and strain/strain rate imaging derived from colour tissue Doppler imaging loops has hampered its application substantially. Speckle-tracking is based on gray-scale images, is usually easier to perform and allows nearly instantaneous quantification of regional deformation. However, different analysis software currently available yield different results and frame rates are still relatively low. Also, the variability of speckle-tracking techniques is still considerable in the pediatric population. Therefore, it is important for each laboratory to standardize the methodology so that it can be applied to serial follow-up of patients.

**Influence of volume and pressure loading on tissue velocities and deformation parameters: implications for congenital heart disease**

Most types of CHD involve an important component of volume and/or pressure load with variable degrees of remodelling and adaptation to the different loading conditions. While initially it was thought that tissue velocities and strain were relatively independent of loading conditions, subsequent research showed this to be incorrect. Still, isovolumic acceleration (IVA), derived from the early systolic tissue Doppler velocity tracing, and peak systolic strain rate, both of which normally occur during early systole, are relatively independent of loading conditions.

The effects of preload, which at the fibre level is represented by the end-diastolic fibre length and at the ventricular level is often, although with important limitations, taken as the end-diastolic volume; and afterload (the load which the ventricle must overcome to eject blood) on tissue velocities has been investigated in a number of studies. In the clinical realm, increased left-ventricular volume due to ventricular septal defect (VSD) or patent ductus arteriosus affect blood flow Doppler velocities, but have a smaller impact on systolic and diastolic tissue velocities. Following intervention and elimination of the left-to-right shunt, blood Doppler velocities decrease, while tissue velocities remain largely unchanged. However, other studies, both in animals and in humans, have found that tissue velocities decrease when preload is acutely reduced. In acute experiments IVA remained relatively unchanged. This discrepancy can potentially be explained by the difference between acute and chronic changes in preload and their differential effect on tissue velocities. In regards to the effect of afterload on tissue velocities, most studies have shown that increased ventricular pressure, often demonstrated clinically by aortic stenosis, leads to decreased tissue velocities. Chronic adaptation of the left ventricle to pressure loading may be important in this respect. Concentric hypertrophy associated with aortic stenosis may affect longitudinal function and lead to decreased longitudinal myocardial velocities. Consistent with this is that in patients with hypertrophic cardiomyopathy, where ventricular afterload is normal, decreased tissue deformation has been observed.

Strain and strain rate, while influenced by loading conditions, are likely more independent of loading than are tissue velocities. In patients with ASD, RV peak systolic velocities were higher at baseline and returned to normal after closure of the ASD. In contrast, RV strain and strain rate were similar to normal controls and did not change significantly after ASD closure, suggesting that strain and strain rate are relatively load-independent measures of contractile function in the clinical setting (Figure 1).

Further studies are required to study the differential effects of acute vs. chronic volume loading on myocardial velocities and deformation indices. Such information should improve interpretation of observed values in clinical practice in patients with variable loading conditions. Strain-rate imaging has also been used to demonstrate that patients who underwent device closure of an ASD had better LV and RV longitudinal deformation than patients who underwent surgical closure of an ASD. This result is not surprising as the negative effects of cardiopulmonary bypass on myocardial function are well documented.

**Tissue velocities, strain, and strain rate in tetralogy of Fallot**

Tissue velocities, strain, and strain rate hold great potential for assessment of RV function in CHD. This has probably been characterized most in regards to RV function in TOF (Figure 2). Even in asymptomatic young patients after TOF repair, RV free wall longitudinal tissue velocities, strain, and strain rate are decreased. Importantly, this may be especially pronounced in patients who had RV outflow tract reconstruction with a transannular patch compared with those with an infundibular patch.

Pulmonary regurgitation and the timing of RV outflow tract dysfunction with pulmonary valve replacement (PVR)
continue to be a major clinical challenge in the long-term follow-up of patients with TOF. Currently, the most accepted criteria for PVR are based on clinical symptoms, exercise capability, and RV dimensions. Tissue velocities and deformation, as indicators of RV contractile function, have not been well studied in this regard. A number of observational studies have interrogated tissue velocities as well as strain and strain rate after PVR. Following surgical valve replacement, 2-D derived strain and strain rate were decreased at 1 month after surgical PVR with a subsequent increase at 6 months, although to values that were still lower than the pre-procedure values. Subsequent follow-up is not provided, but would be important to determine whether the decreased RV deformation is transient, or whether there is long-term reduction in RV function, possibly as a consequence of the procedure itself. In this respect transcatheter PVR is emerging as a viable alternative to surgical PVR. Acutely after catheter PVR performed for RVOT obstruction, both tricuspid and mitral peak systolic velocities may transiently show mild improvement, although whether this is clinically significant is questionable. So while RV end-diastolic volume decreases, effective stroke volume and ejection fraction increase, patients feel better, and are able to exercise more following PVR, it is difficult to attribute these changes to improvement in RV myocardial contractile function (Figure 3). Also, when transcatheter PVR is performed for pulmonary regurgitation and RV volume load, effective RV stroke volume increases and patients feel better; however, peak systolic tissue velocities and IVA at both the tricuspid and mitral annulus remain unchanged. It may be that the volume-loaded RV may not benefit from PVR to the same degree as the pressure-loaded RV. It may also be that patients with more significant RV dysfunction at baseline are most likely to benefit from PVR, as tricuspid annulus IVA prior to repair has been moderately correlated with change in oxygen consumption (\( \text{VO}_2 \)) after repair. However, data informing us as to the optimal timing of PVR in terms of reversibility of RV function are lacking and we do not know if there is an IVA value below which PVR does not lead to improved exercise capability.

The relationship between pulmonary regurgitation and myocardial function is still not fully elucidated. While some investigators have found an association between PR and lower tissue velocities, IVA, or deformation indices, the degree of overlap in IVA values when plotted against the degree of pulmonary regurgitation is large and may not be clinically useful. Furthermore, others have failed to demonstrate a relation between deformation and the degree of pulmonary regurgitation. It is well recognized that some patients develop LV dysfunction after repair of TOF. Tissue velocities as well as deformation indices would provide an attractive alternative for serial assessment of LV function in this group (Figure 4). However, results regarding deformation of the septum and left ventricle after repair of TOF have been heterogeneous. Some authors have found that IVS deformation is reduced in TOF, while others, using 2-D speckle tracking, have found that it is preserved and may even play a compensatory role for decreased RV free wall function in order to maintain ejection fraction. It would be interesting to correlate functional findings with histological or MRI findings which have shown regions of fibrosis in the IVS, remote from the site of RV infundibulotomy in these patients. Tissue Doppler has also been used to investigate important electro-mechanical interactions in TOF and strain rate has been related to the QRS duration. While most research has focused on RV systolic function in TOF, RV diastolic properties are also important. In adult
patients, early diastolic myocardial velocities have been shown to be reduced in comparison to age-matched controls and this reduction was significantly associated with maximal workload and duration of exercise testing. Therefore, the exercise intolerance experienced by many of these patients may be attributable in part to diastolic dysfunction (Figure 5).

Use of new techniques for evaluation of systemic right ventricular function

In a biventricular circulation, the right ventricle functions as the systemic ventricle in primarily two disorders: transposition of the great arteries (atrio-ventricular concordance and ventricular-arterial discordance) after an atrial switch procedure (Senning or Mustard) and congenitally corrected transposition of the great arteries (atrio-ventricular and ventricular-arterial discordance). Strain and strain rate can be used for assessment of both systolic and diastolic ventricular function in this group of patients and may be preferential to tissue velocities. Following an atrial switch procedure, RV free wall, septal, and LV lateral wall longitudinal strain and strain rate values have been found to be reduced as have systemic RV tissue velocities and IVA. IVA showed moderate correlation with the

Figure 3 (A and B) Right ventricular strain derived from speckle tracking at the basal septum (red) and basal lateral right ventricular wall (yellow) before (A) and post (B) transcatheter pulmonary valve placement in a patient after repair of Fallot. Strain is not significantly changed in either location after the procedure.
invasive reference of end-systolic elastance, albeit with considerable scatter.\textsuperscript{33} Diastolic relaxation, as measured by reduced early diastolic tissue velocities may also be impaired in response to exercise in these patients, consistent with the notion that it is the fixed diastolic capacity of the systemic and pulmonary ventricles, rather than contractile or chronotropic insufficiency, that is responsible for the inability of the systemic RV to augment stroke volume in response to exercise or dobutamine stimulation.\textsuperscript{33,34}

The increased susceptibility of the systemic right ventricle to dysfunction has also been demonstrated in patients with ccTGA where tissue displacement as well as strain and strain rate were reduced in these individuals when compared with normal controls.\textsuperscript{35} Use of the newer methods may be helpful in quantifying RV dysfunction and identifying those patients with progressive disease where early therapy might influence the outcome.

Use of new techniques in hypoplastic left heart syndrome

The techniques reviewed in this paper are attractive for assessment of ventricular function in CHD with a functionally single ventricle, especially HLHS, due to their independence from morphological configuration, the ability to study both RV and LV function and the ability for serial examination. It is therefore surprising that there is a relative paucity of literature addressing the use of these techniques in HLHS. Frommelt \textit{et al.}\textsuperscript{36} used a large number of echocardiographic indices of systolic and diastolic function in children with HLHS in order to assess if there is an advantage in terms of ventricular function to placement of an RV to PA conduit vs. a systemic-pulmonary shunt at stage 1 palliative surgery (SP1). In this comprehensive study, tissue Doppler imaging at the lateral mitral annulus was used to derive systolic and diastolic velocities as well as isovolumic relaxation time, isovolumic contraction time, ejection time, and tricuspid closure time (defined as the time interval from cessation of diastolic annular motion to initiation of diastolic annular motion). The authors derive these measures from TDI rather than Doppler flow, a method which has been used previously, but merits additional validation with reference methods. While no significant difference in peak diastolic velocities or isovolumic relaxation or contraction was found between the groups at any stage, there was a trend towards decreasing E\textsubscript{0} velocities over time after staged palliation that reached statistical significance only in the BT shunt group when comparing pre-S1P with post-bidirectional Glenn procedure (SP2) values. Perhaps of greater significance is the finding of a progressive decrease in systolic annular velocities after S1P in both groups that persisted through the bidirectional Glenn procedure (S2P). As there is a subset of patients with HLHS that develop RV failure and are at risk of increased morbidity and mortality,\textsuperscript{37} this result is important and may suggest the need for particular attention to improved preservation of peri-operative myocardial function in the first months of life in this group of patients. Benefits of a BTS vs. an RV-PA conduit as part of S1P in terms of RV function has also been shown by Hughes \textit{et al.},\textsuperscript{38} albeit in a small cohort. Both peak systolic strain rate ($-1.24 \pm 0.19$ vs. $-0.91 \pm 0.21$, $P = 0.048$) and peak systolic strain were decreased in the BTS shunt group when compared with the RV-PA conduit group ($-17.8 \pm 1.8$ vs. $-13.4 \pm 2.0\%$, $P = 0.01$); although these were not as striking as the difference in RV fractional area change ($56 \pm 6\%$ for the RV-PA conduit group vs. $25 \pm 6\%$ for the BTS group, $P < 0.01$), a result not entirely accounted for by potential differences in loading conditions.
Use of new techniques in other lesions

Mertens et al.\textsuperscript{39} described the serial evolution of LV and RV strains in an infant after repair of anomalous coronary artery from the pulmonary artery. Although this study reports on a single patient, it is important none-the-less in demonstrating the utility of strain and strain rate in the serial assessment of ventricular function, something which few studies have done to date. In this infant, both longitudinal and radial LV deformations were reduced pre-operatively. Following re-implantation of the anomalous coronary, these improved over the first 10 months post-operatively, with radial function improving earlier and more completely than longitudinal function (Figure 6). RV strain was normal before surgery and was not significantly changed following coronary re-implantation. In a study from the same group, it was shown that despite normalization of radial function after coronary re-implantation in ALCAPA patients, longitudinal myocardial function remained abnormal during long-term follow-up.\textsuperscript{40} This might be related to subendocardial fibroelastosis which is commonly associated with this condition and reflects irreversible myocardial damage (Figure 7A and B).

Use of velocities, strain, and strain rate for assessment of myocardial wall motion abnormalities in congenital heart disease

Tissue velocities derived from tissue Doppler imaging as well as strain have been useful to demonstrate wall motion abnormalities that seem to be relatively common in certain types of CHD. Pulsed tissue Doppler has been used to demonstrate RV wall motion abnormalities in the sub-pulmonary RV after repair of TOF and in the systemic RV after atrial switch procedures for transposition of the great arteries.\textsuperscript{25,33,41} Others have used tissue Doppler imaging derived strain in patients after repair of TOF to demonstrate LV intraventricular delay between the lateral wall and septum, associated with decreased global LV function as measured by the myocardial performance index.\textsuperscript{42} These studies highlight the importance of electromechanical abnormalities in the late pathophysiology of TOF and it is well known that a prolonged QRS is a marker for arrhythmia and the risk of sudden death.\textsuperscript{43} RV mechanical dyssynchrony has also been demonstrated in children with hypoplastic left heart syndrome using tissue Doppler imaging as well as strain derived from vector velocity imaging (which uses tissue tracking of 2-D images),\textsuperscript{44} and this may be an important contributor to the ventricular dysfunction that some of these patients develop. Wall motion abnormalities have also been studied after surgery for CHD in the context of biventricular pacing. Using strain imaging, wall motion abnormalities have been shown both in the early post-operative period,\textsuperscript{45} as well as in the
longer-term, in the setting of failure of the systemic RV. These wall motion abnormalities as well as ventricular function improved with resynchronization by pacing.

**Problems with use of the newer techniques**

Problems that remain with the use of these techniques include difficulties in technical acquisition which affects data quality and interpretation, large inter and intra observer variability, large scatter and variation when compared with reference methods, conflicting data regarding load dependency of the various indices, standardization of what should be measured (regional vs. global function, how many myocardial segments and which ones should be measured), which method should be used in routine practice (velocities, strain, strain rate, a combination of these), standardization within the method (e.g. peak vs. mean velocities, colour vs. pulsed Doppler, TDI vs. 2D speckle derived strain, radial vs. longitudinal vs. circumferential strain vs. a combination of these), potential differences between data on 20 April 2018
obtained from the use of systems from different commercial vendors and long post-acquisition processing times. Also, an echo study that incorporates these techniques can yield a plethora of data points that need to be processed in the framework of busy clinical practice and synthesized into a coherent picture that is readily understood by the clinician and surgeon who may not be familiar with these methods. Standardized reporting also remains a challenge.

Summary

The use of newer techniques to assess ventricular function, including tissue velocities, strain, and strain rate, show great potential in the assessment of CHD. Their high temporal resolution, relative independence from volume loading in the clinical setting, as compared with shortening indices, ease of acquisition and the potential for serial evaluation are all benefits. However, it is now time to establish their utility for clinical decision making and prognostication. This will require larger prospective studies as well as an effort to standardize routine measurements, address the problems listed above, confirm normal reference values, and incorporate these methods into the realities of routine clinical practice.

Conflict of interest: none declared.

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