Tissue Doppler imaging for the pre-clinical diagnosis of cardiomyopathy

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This editorial refers to "Tissue Doppler imaging detects early asymptomatic myocardial abnormalities in a dog model of Duchenne's cardiomyopathy"† by V. Chetboul on page 1938

Duchenne muscular dystrophy is an important cause of cardiomyopathy in children and adolescents and is caused by mutations in the gene coding for the protein dystrophin [1]. Dystrophin participates in linking the sarcomere to the sarcolemma and extracellular matrix and plays a role in cell signalling [2]. The disease is characterised by skeletal and cardiac myopathies. Because it is inherited as an X-linked recessive disorder, males are the primarily affected gender, although female carriers can present with cardiac abnormalities later in life. Given the devastating and relentless progression once the disease is well established, early and accurate diagnosis of cardiac dysfunction is an important goal.

Animal models have proved useful in increasing our understanding of this and other cardiomyopathies. In this issue of the Journal, Chetboul et al. [3], using a natural canine model of the human disease: the golden retriever muscular dystrophy (GRMD) dog model, report on the application of tissue Doppler imaging (TDI) in the early diagnosis of cardiac dysfunction. In the GRMD dog model, fibrosis in the subepicardial region of the left ventricular free wall and myofibrillar loss are classic histopathological findings. Subsequently, the pathology extends to other segments including the septum and papillary muscles. Chetboul et al. [3] imaged the animals and acquired M-mode TD data from the posterior wall in short axis views. Despite similar heart rate and blood pressure, TD systolic and diastolic endocardial velocities and myocardial velocity gradient (MVG or strain rate) readily identified the afflicted animals from the control dogs at a time when left ventricular and left atrial dimensions, wall thickness, mitral inflow, and fractional shortening were indistinguishable between the two groups. The authors included myocardial biopsy as part of the study protocol and were able to show that interstitial collagen was slightly but significantly increased in the GRMD group of animals.

This important study [3] adds to the existing literature regarding the use of TDI in diagnosing patients with Duchenne and Becker muscular dystrophy [4], and provides a unique insight into the structural correlates of TD measurements in a clinically relevant animal model. While fibrosis and apoptosis may have contributed to the abnormal TD velocities and MVG, an average interstitial collagen density of 6.1 ± 0.3% and few apoptotic cells do not account for the majority of the profound changes in endocardial TD velocities (decrease of 35% and 56%, respectively, in systolic and diastolic velocities) and MVG (decrease of 72% and 79%, respectively, in systolic and diastolic gradients). It is most likely, at least at this early stage of the disease, that the primary defect in cardiac muscle [5] — because of dystrophin deficiency — is the major contributor to the segmental abnormality identified by TDI. Similar to the findings in this dog model, we recently reported, in a transgenic rabbit model of human hypertrophic cardiomyopathy, reduced myocardial systolic and diastolic TD velocities at a time concordant with the lower calcium sensitivity of myofibrillar ATPase activity [6], but preceding the activation of stress related signalling kinases and the development of hypertrophy and fibrosis. Therefore, it appears that the early reduction in myocardial function detected by TDI in these two distinct cardiomyopathic disorders, is primarily related to myocyte abnormalities rather than secondary interstitial changes and/or hypertrophy.
In the context of this report, it is important to comment on the advantages and limitations of TDI as well as its current and evolving clinical applications.

As for the advantages, TDI enjoys high feasibility, reproducibility (in experienced hands), less dependence on the quality of 2D images and for MVG (and strain) minimal effect of translation and tethering. These advantages contrast with the conventional 2D echocardiographic assessment of cardiac function, which can be hampered by poor acoustic windows and is heavily influenced by translation and tethering. However, there are a number of caveats that must be considered to achieve the most optimal results. These include TDI’s critical dependence on proper alignment of the ultrasound beam with the plane of cardiac motion, the need for a high frame rate (for MVG and strain imaging), and the lower specificity in older subjects where age and co-existing cardiac disorders (for example coronary artery disease) are important confounders that must be taken into consideration.

As for clinical applications, TDI has made several advances over the past few years. The field moved from validation studies to a number of clinical applications aimed at evaluation of myocardial function in several diseases including coronary artery disease, congenital heart disease, diabetes mellitus, hypertrophic, dilated, and restrictive cardiomyopathy, systemic hypertension, left and right ventricular diastolic dysfunction and estimation of filling pressures, transplant rejection, valvular heart disease and pericardial disorders. In addition, TDI techniques are proving highly valuable in identifying left ventricular dyssynchrony in patients with heart failure and can play the critical role of selecting the proper candidates for biventricular pacing.

However, regarding the use of TDI in the preclinical diagnosis of cardiomyopathy, a most important application remains to be tested — namely using TDI to inform timely clinical decisions of prevention or treatment. TDI, coupled with a sound clinical approach and effective therapeutic armamentarium, may offer patients a chance to receive early therapy aimed at halting or reversing the progression of cardiac phenotypes (for example ACE-inhibitors and b-blockers in the case of dystrophin-related cardiac disorders). This exciting and promising role of TDI awaits additional work but may prove to be one of its most rewarding applications.

References