SCIENTIFIC LETTER

Cardiac tissue velocities and strain rate in the early detection of myocardial dysfunction of asymptomatic boys with Duchenne's muscular dystrophy: relationship to clinical outcome

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Duchenne's muscular dystrophy (DMD) is one of the most common neuromuscular disorders. Boys with DMD lose independent ambulation by the age of 12 and die of respiratory failure or cardiomyopathy in their late teens or early 20s.¹

Histological changes in the heart include fibrosis, degeneration and fatty infiltration starting from the left ventricular posterior wall, which is a specific finding for DMD.² The posterior wall can be more sensitive in identifying impaired myocardial function.

Recent consensus guidelines on the early cardiac follow up and for the treatment of asymptomatic dysfunction have been proposed.³ An unresolved issue is, however, the timing of introducing treatment. Some authors have proposed that, in view of the almost invariable development of dilated cardiomyopathy (DCM), treatment should be started even in the absence of echocardiographic signs of dysfunction. It is therefore important to be able to identify early changes that precede DCM.³

We hypothesised that strain rate (SR) can identify early myocardial dysfunction in young asymptomatic boys with DMD without conventional echocardiographic signs of DCM. We related SR to the development of cardiomyopathy over a three-year follow up.

METHODS

Fifty six consecutive asymptomatic boys with DMD (mean age 8.8 (2.85) years) were enrolled. Diagnosis was confirmed by DNA analysis, unequivocal findings in muscle biopsy, or positive family history. The patients were not taking any cardiac drugs and had normal ECGs and routine echocardiograms (fractional shortening > 29%). Twenty two healthy volunteers (mean age 9 (SD 2.96) years) were recruited from the children's outpatient department.

We used the HDI 5000 (Phillips Medical Systems) machine equipped with a P4-2 transducer for conventional and tissue Doppler imaging echocardiographic studies. The conventional study included two dimensional and Doppler blood flow velocity measurements according to standard clinical protocol. From parasternal long axis projections the colour M mode tissue Doppler imaging of the posterior wall of the left ventricle was obtained. Derived tissue velocities (TV) were analysed with dedicated research software (HDI-lab, V.1.91d, Phillips Medical Systems). The multipoint algorithm was used to trace the endocardial and epicardial borders. To reduce the random noise component of the acquired data, we defined a 0.6 mm sample volume at the subendocardium (a) and subepicardium (b).

Radial SR was defined as the difference of the instantaneous velocities (V) between the two points a and b along the

ultrasound beam, divided by their distance (d) at the time of measurement⁴ ($SR = (V_a - V_b)/d$).

We used the velocity gradients in time described in previous studies⁵ to estimate the radial SR in peak systole (SRs), in early diastole (SRed) and in late diastole (SRld). The mean TV from all points from subendocardium to subepicardium were also calculated in peak systole (TVs), early diastole (TVed) and late diastole (TVld). Corrected time to onset of relaxation (TRc) was defined as the time from the beginning of the R wave of the ECG to the transition where the SR crosses the zero line from positive to negative polarity.

Interobserver reliability was tested in 45 randomly selected cases. To test intraobserver reliability, one of the two observers re-evaluated the same 45 cases after one week. A good reproducibility of sampled data of SR, TV and TRc (< 3.5% changes for each variable) was obtained.

Patients were followed up for three years with regular clinical outpatient appointments and six-monthly conventional echocardiograms. The end point was an abnormal fractional shortening (< 29%).

Data were analysed with the SPSS package (SPSS, Chicago, Illinois, USA). Intraobserver and interobserver variabilities for SR, TV and TRc were estimated by means of absolute differences between observations. Continuous variables between groups were compared by t test for normally distributed values, as assessed by the Kolmogorov–Smirnov test. For the non-parametric statistics, we used the Mann–Whitney U test. Correlations were assessed by the Pearson's test. The least significant difference pairwise multiple comparison test was also used. Data are presented as mean (SD).

RESULTS

Clinical characteristics and two dimensional and Doppler data did not differ between boys with DMD and controls. Tissue Doppler imaging values in boys with DMD were lower for TVs (26.8 (5.9) v 33.4 (11.4) mm/s, $p < 0.002$) and TVed (−44.7 (11.3) v −60.4 (11.9) mm/s, $p < 0.000$), and SRs (1.7 (0.7) v 2.8 (0.8) 1/s, $p < 0.000$) and SRed (−5.1 (2) v −9 (2) 1/s, $p < 0.000$) than controls, while TRc was longer (38.3 (4.1) v 36.4 (3.7) ms, $p < 0.02$). Multivariate analysis for heart rate, TVs, TVed, TVld, SRs, SRed, SRld and TRc differed significantly between boys with DMD and controls.

Abbreviations: DCM, dilated cardiomyopathy; DMD, Duchenne's muscular dystrophy; SR, strain rate; SRed, strain rate in early diastole; SRld, strain rate in late diastole; SRs, strain rate in peak systole; TRc, corrected time to onset of relaxation; TV, tissue velocities; TVed, tissue velocities in early diastole; TVld, tissue velocities in late diastole; TVs, tissue velocities in peak systole

On univariate analysis, there were differences in heart rate, TVs, TVed, SRs, SRed and TRc.

Thirty three of the 48 (69%) boys with DMD completed a three-year follow up (mean 40 (4) months). Seven boys (mean age 16.5 years) had deteriorated left ventricular function with fractional shortening < 29%.

SRs, SRed and SRld predicted the adverse outcome with 63.64% accuracy and TVs, TVed and TVld with 54.55% accuracy. The combination of SRed and TRc produced the highest accuracy (84.85%) of all combinations to correctly predict the poor outcome. Figure 1 (right panel) shows the predictive boundary between good and poor outcomes in terms of deterioration of cardiac function.

DISCUSSION

In this study we have confirmed our original hypothesis that SR and TV may be used to identify early myocardial dysfunction in asymptomatic boys with DMD. We showed that SRs, SRed and TRc are sensitive markers for early diagnosis of myocardial dysfunction. Lastly, SR appeared to

be of prognostic significance in predicting adverse outcomes in these young patients. DCM is the most common type of cardiac involvement in DMD, affecting up to 90% of boys older than 18 years. It is considered the second most common determinant of disease survival, causing 20% of deaths. The incidence rises steadily with age.¹

Measurements were made at the posterior wall, which is most often affected in DMD. The mechanisms underlying the lower SR values and the prolonged TRc are uncertain but possible explanations are delayed local activation, a conduction delay or a mechanical phenomenon caused by the fibrous and fatty tissue replacement of myocardial muscular fibres.

Children with diagnosed DMD are followed up echocardiographically according to guidelines.³ Patients in our study population had normal fractional shortening and good overall systolic function but, over the period of follow up, seven developed myocardial dysfunction and three died. Current recommendations state that, if ventricular dysfunction is detected by ECG or conventional echocardiography,

Figure 1 Prediction of outcome according to strain rate in early diastole (SRed) and corrected time to onset of relaxation (ms) (TRc). (Top left) Receiver operating characteristic (ROC) curve with accuracy of 84.85% for SRed and TRc, which was the higher from all other combinations. (Top right) Predictive boundary between good and poor outcomes according to SRed and TRc. The patients in the red area are very likely to develop dilated cardiomyopathy. In contrast, patients in the green area will have a milder cardiac involvement. (Bottom panels) Two examples of colour M mode recording of a patient with Duchenne's muscular dystrophy (DMD) with a poor outcome (A) and a healthy volunteer (B) (adapted to match in heart rate). We can appreciate a difference in colour in the upsloping systolic part (brighter red) and downsloping diastolic component (brighter blue).

early treatment with angiotensin converting enzyme inhibitors, β blockers, or both should be instituted. SRed and TRc can be used to classify boys with DMD as being at high or low risk. Selectively instituting early treatment and potentially slowing down the progress to DCM may be possible. SR may be used in future longitudinal studies assessing the beneficial effect of treatment of asymptomatic boys with DMD.

Tissue Doppler imaging echocardiography may be angle dependant. Chest deformity and the tachycardia made acquisition difficult. The high signal to noise ratio may be the greatest limitation of the technique with the current technology.

In this study we showed that SR and TV are significantly lower in asymptomatic boys with DMD, when conventional echocardiography failed to show any abnormality. Myocardial function in these patients appears to be impaired from a very young age. SR and TV can be reliably used to identify early myocardial dysfunction and predict an adverse outcome. These conclusions need further validation on independent datasets and larger population samples.

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IMAGES IN CARDIOLOGY

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Atrial myocarditis: a possible cause of idiopathic enlargement of bilateral atria

In March 1997, a 72 year old woman with a cardiothoracic ratio of 90% on chest x ray was admitted to our hospital with a haemorrhagic gastric ulcer. However, at that time, she had no cardiac symptoms. Epstein's anomaly was excluded and no other congenital or acquired cardiac abnormality without atrial fibrillation and tricuspid regurgitation was detected. We then made the diagnosis of idiopathic dilatation of the bilateral atria. In October 2003, she came back to our hospital because of congestive heart failure with progressing mitral regurgitation. The echocardiogram revealed notably

enlarged atria (right atrium 115.0×73.7 mm in diameter; left atrium 102.0×53.5 mm in diameter) (panel A). However, no dilation of the ventricles was observed and systolic function was normal. Since bilateral heart failure was resistant to conventional treatment, she received surgical reduction of both atria and tricuspid and mitral valvular annuloplasty was performed because no organic valvular degeneration was confirmed in the operation. Microscopic examination revealed persistent myocarditis with severe scarring (panel B). The major histocompatibility complex (MHC) class

I antigens, which are required for the action of direct cytotoxic T cells, were found to be expressed on the myocytes and over expressed in the interstitial spaces (panel C). MHC class II antigens were also over-expressed in the interstitium. This case suggests that this congenital benign anomaly might be contributed to by atrial persistent myocarditis. This unique condition should be reinvestigated using up-to-date diagnostic tools.

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