Vox clamantis in deserto. We spoke but nobody was listening: echocardiography can help risk stratification of the long-QT syndrome

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This editorial refers to ‘Electromechanical window negativity in genotyped long-QT syndrome patients: relationship to arrhythmia risk’, by R.M.A. ter Bekk et al., on page 179

Over 20 years ago we reported for the first time the presence of mechanical abnormalities in the contraction pattern of patients with the long QT syndrome (LQTS), showing the presence both of rapid early contraction and of an extended ‘plateau’ phase clearly visible at M-mode Doppler before rapid relaxation.1 These abnormalities were almost absent in controls and more prevalent among symptomatic than asymptomatic patients (77% vs. 19%, relative risk (RR) 2.75), suggesting their potential value for diagnosis and risk stratification of LQTS patients. This report and our subsequent evidence that these abnormalities were abolished by calcium blockers2 and could be the mechanical counterparts of early afterdepolarizations (EADs), thus being markers of arrhythmic propensity, were received with scepticism and essentially ignored. Eventually, an abnormal contraction pattern was confirmed by others, mostly using tissue Doppler imaging3–5 thus ending the era in which LQTS was considered a pure electrical disease.6

Once set in motion, the ball keeps rolling. Now ter Bekk et al.7 describe the presence of a negative ‘electromechanical window’ (EMW) in LQTS patients and report a strong association between a markedly negative value and arrhythmic events. One strength lies in the size of the population, almost 250 genotype-positive LQTS patients and 74 controls, much larger than previous studies.1–5 This allowed a reliable estimate of the sensitivity and specificity of the echocardiographic indexes and the execution of multivariable analyses. Adding EMW to QTc resulted in a significant improvement in the identification of symptomatic patients; EMW but not QTc was an independent predictor of arrhythmic events. This finding is in agreement with the demonstration by Haugaa et al.8 that echocardiographic contraction duration identified symptomatic patients with better sensitivity and specificity compared with QTc (79% and 74% vs. 70% and 50%, respectively), and with our original indication that echocardiography was superior to ECG.1

The choice of the best mechanical index would be facilitated if we had a good understanding of the pathophysiology underlying the contraction and relaxation abnormalities present in LQTS patients. This is one weakness of the present study by ter Bekk et al. which suggests that LQTS patients may have enhanced lusitropy as a consequence of heterogeneous sympathetic activation.7 As a matter of fact, this is unlikely because LQTS patients actually show abnormally impaired echocardiography can provide valuable information, and within a few minutes.

Importantly, the almost 100 patients with arrhythmic events allowed a reliable estimate of the sensitivity and specificity of the echocardiographic indexes and the execution of multivariable analyses. Adding EMW to QTc resulted in a significant improvement in the identification of symptomatic patients; EMW but not QTc was an independent predictor of arrhythmic events. This finding is in agreement with the demonstration by Haugaa et al.8 that echocardiographic contraction duration identified symptomatic patients with better sensitivity and specificity compared with QTc (79% and 74% vs. 70% and 50%, respectively), and with our original indication that echocardiography was superior to ECG.1

The time has come to start using echocardiographic indexes in addition to QTc in the risk stratification of patients with LQTS. It is unclear, however, which parameter performs best and, in this regard, neither the study by Haugaa et al.8 nor that by ter Bekk et al. is very helpful because the authors did not compare their index, EMW, with those previously described.1–5 The use of EMW was suggested as a risk marker for Torsades des Pointes (TdP) in experimental studies,8,9 but its superiority to QTc has been questioned.10

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Ranolazine, a late INa blocker, shortened QTc by 4.6% from 558 ± 55 ms to 532 ± 46 ms, and by a significant 13% a previously prolonged isovolumic relaxation time of 125 ± 27 ms in 12 patients with LQT311, the LQTS subtype caused by enhanced late INa

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A delay in left ventricular (LV) relaxation was also shown in an animal model of LQT2. Post-systolic shortening and a significant biventricular diastolic dysfunction were found in LQT3 patients, suggesting that the diastolic dysfunction could be secondary either to systolic dysfunction, i.e. post-systolic shortening encroaching on diastole, or to deranged calcium homeostasis.

Actually, the two mechanisms are not mutually exclusive. Our initial hypothesis that in patients with a ‘double peak’ morphology the second shortening could have been the mechanical equivalent of an EAD appeared to be confirmed by the subsequent demonstration that i.v. verapamil normalized the contraction pattern by abolishing both ‘plateau-like’ and ‘double peak’ morphologies. By focusing on the calcium transients linked to EADs in isolated cardiomyocytes, we then showed that phase 2 EADs caused a marked secondary calcium rise (with accompanying contraction) by occurring at a time when [Ca]i is decreasing but not back to baseline (Figure 1A). Our combined studies supported the hypothesis of a mechanical counterpart of subthreshold EADs and, more broadly, our interpretation that the contraction/relaxation abnormality was a consequence of altered calcium handling. A pivotal role for abnormal calcium handling was also suggested by Guns et al., who advocated the necessity of a negative EMW to allow the occurrence of TdP. Notably, they found aftercontractions in the left ventricular pressure (LVP) signal. Indeed, EADs cause both a significant QT interval prolongation and secondary pressure rises in LVP, which are, however, unable to delay aortic valve closure (Figure 1B). The ensuing QT prolongation with unmodified systolic time produces a negative EMW. Even in the absence of EADs, increased calcium influx because of prolonged action potential duration (APD) may alter the late contraction pattern and impair diastole, but this will probably be highly correlated with the QT interval, thus not providing additional prognostic value. Notably, even in the absence of EADs, an inhomogeneity in the end of contraction among different areas of the ventricle may exist (such as a transmural inhomogeneity, caused by markedly different APDs), causing the abnormal contraction pattern. Since the developed tension would be insufficient to maintain aortic valve opening, this phenomenon may explain the presence of myocardial contraction after aortic valve closure.

What often escapes clinical cardiologists is the fact that these non-homogeneous contractions and aftercontractions alter the geometry of the beating heart and activate the sensory endings of cardiac sympathetic mechanoreceptors, thus eliciting an excitatory sympathetic reflex. This leads to the arrhythmogenic localized release of norepinephrine which further increases the heterogeneity of ventricular repolarization, already present in LQTS, thus favouring re-entry. This sequence of events also helps in understanding the antifibrillatory efficacy of left cardiac sympathetic denervation for LQTS and other cardiovascular diseases associated with risk for sudden cardiac death.

In conclusion, the well-conceived report by ter Bekk et al. further demonstrates the critical role that echocardiography deserves in the clinical evaluation and management of LQTS patients and highlights how mechanical abnormalities can significantly contribute to risk stratification because they appear linked to the mechanisms underlying TdP and can themselves trigger arrhythmogenic...
sympathetic activation. What remains to be defined, after proper comparison and prospective validation in an appropriately sized population, is which of the various echocardiographic parameters can represent the best marker of arrhythmic risk.

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References