International Journal of Cardiology 286 (2019) 81–82

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Altered mechano-electrical coupling: An underappreciated factor in sympathetically mediated torsades de pointes in the long QT_1 syndrome

Richard L. Verrier

Harvard Medical School, Beth Israel Deaconess Medical Center, Division of Cardiovascular Medicine, 99 Brookline Avenue, RN-301, Boston, MA 02215-3908, USA

ARTICLE INFO

Article history:
Received 27 February 2019
Accepted 1 March 2019
Available online 4 March 2019

A paradigm shift in conceptualization of pathophysiologic mechanisms responsible for sympathetically mediated torsades de pointes (TdP) in the long QT_1 (LQT_1) syndrome surfaced in the early 1990s. In their thought-provoking editorial, "Long QT Syndrome, a Purely Electrical Disease? Not Any More," De Ferrari and Schwartz [1] discussed emerging evidence [2,3] supporting mechano-electrical interactions as an underappreciated factor underlying arrhythmogenesis in this syndrome. A critical piece of evidence cited was the observation that abnormalities in left ventricular contraction occurred in 23 of a series of 42 patients with the long QT syndrome (LQTS) [2]. Specifically, they found evidence of a slow contraction phase before relaxation, which was manifest either as a plateau or double peak in T-wave morphology. Interestingly, calcium channel blockade by intravenous verapamil administration normalized abnormal electrocardiographic patterns also including a double peak in T-wave morphology in LQTS patients [4]. Thus, the principle of mechano-electrical coupling in electrocardiographic patterns in LQTS was implicated. This pioneering observation [2] was subsequently further supported in elegant echocardiographic studies showing dispersion in regional wall-motion abnormalities in patients with LQTS [5].

A valuable tool that has advanced our understanding of the role of mechano-electrical coupling in the proarrhythmic consequences of LQTS is referred to as the electromechanical window (EMW) [6]. The EMW is based on a simple concept and equation:

EMW = duration of mechanical systole–duration of electrical systole

Under normal conditions, the duration of mechanical systole is longer than the period of electrical systole, so that EMW is positive. During abnormal conditions such as drug-induced or congenital LQTS, electrical systole outlasts mechanical systole, and EMW becomes negative. This property can be measured either experimentally or clinically using transthoracic echocardiograms to assess duration of mechanical contraction and ECGs to determine the duration of the QT interval. The experimental approach is illustrated in Fig. 1 (lower panels) of the current study by ter Bekke et al. [7], showing the time-interval between the end of the T-wave in lead II and the 90% recovery value of left ventricular pressure recording in intact anesthetized canines. At baseline, the EMW was positive (151 ms) but became negative (−40 ms) during left stellate ganglion stimulation (LSGS) and was associated with a junctional tachycardia with intervening ventricular extrasystoles.

EMW has clinical translational value as this property can be accurately measured noninvasively in human subjects by combining QT interval measurements with continuous wave echocardiography. Ter Bekke, Volders, et al. [8] showed that EMW can be calculated by subtracting the QT interval from the Q-wave onset to aortic valve closure interval. Using this methodology, the authors demonstrated that patients with a positive genotype for LQTS exhibit EMW negativity, which is enhanced in individuals with documented arrhythmic events.

In their current study, ter Bekke et al. [7] conducted an elegant series of experiments in anesthetized dogs in which they compared the arrhythmogenic effects of LSGS and right stellate ganglion stimulation (RSGS) with and without infusion of a selective inhibitor of the slow component of the delayed rectifier potassium current, the KCNQ1/I_{Ks} blocker HMR1556. The basic rationale was to simulate excess prolongation of the QT interval as occurs in LQTS and to determine whether during LSGS or RSGS would predispose to greater risk for TdP. The proposed hypothesis was that altered mechano-electrical coupling as evaluated by EMW would exaggerate regional dispersion of refractoriness and thereby facilitate ventricular arrhythmias. The study employed state-of-the-art recording techniques involving high-resolution left ventricular solid-state micromanometers and monophasic action potential catheters. The main findings were that triggered early afterdepolarizations and EMW negativity but no ventricular tachyarrhythmias occurred in response to I_{Ks} blockade alone to prolong the QTc interval. However, when LSGS was superimposed, EMW negativity was significantly enhanced and precipitated TdP within 30 s in 5 of 9 dogs. TdP deteriorated into ventricular fibrillation (VF) in 4 of the 5 animals. Interestingly, the preceding extrasystoles originated mostly from the outflow tract region, consistent with clinical observations in LQTS. RSGS did not precipitate TdP or VF. Based on these observations, the authors concluded that in

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.01.098.
E-mail address: rverrier@bidmc.harvard.edu.

https://doi.org/10.1016/j.ijcard.2019.03.004

their model of drug-induced LQT_1, LSGS was highly arrhythmogenic, leading to TdP and VF when repolarization was prolonged only when the EMW became significantly negative. In the authors' view, the main factor underlying arrhythmogenesis was disruption of mechano-electrical coupling and the attendant exacerbation of nonuniformities in repolarization.

An additional important insight was complex involvement of vagal tone rebound that led to marked slowing with prolonged RR intervals predisposing to ventricular escape beats, further setting the stage for enhanced dispersion of repolarization and arrhythmogenesis. These findings appear consistent with the concept of "autonomic conflict" [9], which through complex interactions disrupts beat-to-beat variability and presumably disrupted intracellular calcium cycling, which can result in excess cytosolic calcium, thereby predisposing to triggered arrhythmias.

As with any innovative study, questions arise regarding potential limitations and logical next steps. A basic inference of the current study is that the heightened arrhythmogenicity of a negative EMW leads to an exaggeration of regional dispersion of refractoriness. While this is a reasonable assumption, it was not tested in the current investigation. A number of new, robust methods for assessing interlead heterogeneity of repolarization have shown clinical promise in terms of sudden cardiac death risk assessment [10] and could be applied in follow-up studies. Thus, the authors could test the exact relationship between the degree of EMW negativity and the precise magnitude of heterogeneity enhancement that may be specifically related to alterations in mechano-electrical coupling.

Another important question is the extent to which the current findings in the experimental model of drug-induced QT prolongation apply to individuals with the congenital LQT_1 syndrome. Fortunately, as discussed above, techniques are currently available in which noninvasive echocardiography can be employed to assess EMW. This appears to be a logical next step to examine the transferability of the main concepts elucidated in the present study to the clinical condition. Also, it will be interesting to determine precisely how these new insights implicating mechano-electrical factors help to advance therapy in LQTS.

The authors are to be commended on this illuminating investigation of mechanisms underlying arrhythmogenesis in the LQT_1 syndrome, which will no doubt stimulate further study to reduce the toll of premature deaths associated with the scourge of this condition.

Disclosure

The author reports no relationships that could be construed as a conflict of interest.

References

[1] G.M. De Ferrari, P.J. Schwartz, Long QT syndrome, a purely electrical disease? Not anymore, Eur. Heart J. 30 (2009) 253–255.
[2] F. Nador, G. Beria, G.M. De Ferrari, et al., Unsuspected echocardiographic abnormality in the long QT syndrome. Diagnostic, prognostic, and pathogenetic implications, Circulation 84 (1991) 1530–1542.
[3] K.H. Haugaa, T. Edvardsen, T.P. Leren, J.M. Gran, O.A. Smiseth, J.P. Amlie, Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high risk individuals with long QT syndrome, Eur. Heart J. 30 (2009) 330–337.
[4] G.M. De Ferrari, F. Nador, G. Beria, S. Sala, A. Lotto, P.J. Schwartz, Effect of calcium channel block on the wall motion abnormality of the idiopathic long QT syndrome, Circulation 89 (1994) 2126–2132.
[5] K. Nakayama, H. Yamanari, F. Otsuka, et al., Dispersion of regional wall motion abnormality in patients with long QT syndrome, Heart 80 (1998) 245–250.
[6] H.J. Van der Linde, B. Van Deuren, Y. Somers, B. Loenders, R. Towart, D.J. Gallacher, The electro-mechanical window: a risk marker for torsade de pointes in a canine model of drug induced arrhythmias, Br. J. Pharmacol. 161 (2010) 1444–1454.
[7] ter Bekke RMA, Moers AME, de Jong MMJ, et al. Proarrhythmic proclivity of left-stellate ganglion stimulation in a canine model of drug-induced long-QT syndrome type 1. Int. J. Cardiol. https://doi.org/10.1016/j.ijcard.2019.01.098
[8] R.M. Ter Bekke, K.H. Haugaa, A. van den Wijngaard, et al., Electromechanical window negativity in genotyped long-QT syndrome patients: relation to arrhythmia risk, Eur. Heart J. 36 (2015) 179–186.
[9] J. Winter, M. Tipton, M.J. Shattock, Autonomic conflict exacerbates long QT associated ventricular arrhythmia, J. Mol. Cell. Cardiol. 116 (2018) 145–154.
[10] R.L. Verrier, H.V. Huikuri, Tracking interlead heterogeneity of R- and T-wave morphology to disclose latent risk for sudden cardiac death, Heart Rhythm. 14 (2017) 1466–1475.