Repolarization abnormalities and arrhythmogenesis in hypertrophic myocardium

Luigi De Ambroggi, Pietro Francia, Guido De Ambroggi

Department of Cardiology, IRCCS Policlinico San Donato, University of Milan, Italy

ABSTRACT

Left ventricular hypertrophy (LVH) is accompanied by specific changes of the cellular electrophysiology, which are potentially arrhythmogenic, mainly prolongation of action potential duration due to down-regulation of several K channels. Moreover, transmural dispersion of repolarization due to presence of cell types with different repolarization properties within the ventricular wall plays an essential role in the development of transmural functional reentry responsible for the maintenance of ventricular tachycardia (VT), once it has been initiated. Experimental evidence has been provided that phase 2 early afterdepolarizations (EAD) can be generated from hypertrophied left ventricular wall in the absence of action potential duration (APD) prolonging agents. Phase 2 EADs could be associated with malignant "R on T" extrasystoles, initiating polymorphic VT. Unfortunately, the abnormalities of ventricular repolarization are not always revealed on surface electrocardiogram (ECG) and when present they have a low predictive power for occurrence of life-threatening arrhythmias and sudden cardiac death. In order to reveal signs of repolarization heterogeneities not apparent from 12-lead ECG analysis, we studied body surface potential maps in a group of patients with LVH due to valvular aortic stenosis. The similarity index was significantly lower and the late repolarization deviation index was significantly higher in patients than in normal subjects. These findings suggested a higher than normal degree of heterogeneities of repolarization in LVH patients, not detected by the usual ECG analysis.*(Anadolu Kardiyol Derg 2007: 7 Suppl 1; 71-2)*

Key words: left ventricular hypertrophy, cardiac arrhythmias, ventricular repolarization

Introduction

Left ventricular hypertrophy (LVH) is associated with increased risk of malignant arrhythmias and is recognized as an independent risk factor for sudden cardiac death (SCD) (1, 2). It has been reported that a large proportion of deaths occurring in patients with LVH is sudden and that most deaths are likely due to a polymorphic ventricular tachycardia (VT) rapidly evolving to ventricular fibrillation (VF) (3, 4).

Experimental studies

The increase vulnerability to ventricular arrhythmias appears to be a consequence of repolarization related arrhythmogenesis. In fact, LVH is accompanied by specific changes in the electrophysiology of the ventricle at the cell and tissue levels (4, 5), which are potentially arrhythmogenic.

The main electrophysiological characteristic of cardiac hypertrophy, observed in isolated ventricular tissues, is the prolongation of action potential duration (APD) due to down-regulation of several K channels responsible for repolarization. The hypothesis that polymorphic VT in patients with LVH may share similar mechanisms to that observed in patients with QT prolongation has been postulated (3). As in long QT syndrome, focal activities originated from endocardium or subendocardium contribute importantly to the initiation of polymorphic VT (6). On the other hand, transmural functional reentry is believed to be responsible for the maintenance of VT once it has been initiated. Transmural dispersion of repolarization (TDR) due to the existence of cell types with different repolarization properties within ventricular wall plays an essential role in the development of such a transmural circus movement. Multiple ionic and cellular alterations in LVH may exert different influences on TDR.

With the use of arterially perfused left ventricular wedge preparation isolated from LVH rabbits (renovascular hypertension model), Yan et al. (7) demonstrated that preferential prolongation of APD in subendocardium and endocardium was associated with a marked increase in TDR, that was particularly striking at lower pacing rates. Moreover, they provide a direct evidence from intracellular recordings that phase 2 early afterdepolarizations (EAD) can be generated from hypertrophied LV wall in the absence of APD prolonging agents. Phase 2 EADs could be associated with malignant "R on T" extrasystoles on the ECG.

All these electrophysiological alterations play an important role in the development of polymorphic VT in the setting of LVH.

Clinical studies

Unfortunately, the abnormalities of ventricular repolarization are not always revealed on surface electrocardiogram (ECG) and, when present, they have a low predictive power for occurrence of life-threatening arrhythmias and SCD.

Address for Correspondence: Prof. L. De Ambroggi, IRCCS, Policlinico San Donato 20097 San Donato Milanese, Italy
Phone/Fax: +39.02.52774520 E-mail: luigi.deambroggi@unimi.it

Dispersion of QT interval was studied as an index of repolarization heterogeneity in hypertensive men. Perkiomaki et al (8) reported that QT and QT apex dispersions were significantly higher in patients with than without LVH.

Other ECG indices of repolarization heterogeneity were studied in small groups of patients. Yi et al (9) assessed the complexity of T wave using principal component analysis (PCA) in patients with hypertrophic cardiomyopathy (HCM). The PCA ratio was significantly greater in HCM patients than in normal control subjects. Moreover, increased PCA ratio was associated with a history of syncope, but was similar in patients with and without non-sustained VT on Holter recording.

Recently, Schillaci et al (10) in a large population of patients with uncomplicated hypertension found that a prolonged QTc was associated with a nearly 2-fold increase in risk of cardiovascular death.

In order to reveal signs of repolarization heterogeneities not apparent from 12-lead ECG analysis, we studied body surface potential maps (BSPM) in a group of patients with LVH due to valvular aortic stenosis (11). Body surface potential maps were recorded from 62 chest leads in 16 patients with LVH and in 35 normal subjects. By applying principal component analysis of the ST-T waves, we computed the similarity index. The value of the similarity index is inversely proportional to the variability of T wave morphologies and a low value is considered a marker of repolarization heterogeneity (12). Similarity index was significantly lower in LVH patients than in normal subjects both in 62 leads (0.73±0.067 vs 0.77±0.044, p=0.03) and in 12 unipolar leads (V1-V8, V3R, VR, VL, VF) extracted from the map (0.77±0.075 vs 0.81±0.045, p=0.03). Moreover, we computed the "late repolarization deviation index", which quantifies the instantaneous variations of surface potential distribution from peak to end of the T wave. This index was significantly higher in the LVH patients than in controls (in 62 leads: 0.07±0.05 vs 0.028±0.016, p=0.005; in 12 leads: 0.064±0.052 vs 0.024±0.020, p=0.008). Therefore, the values of similarity index and of late repolarization deviation index found in LVH patients suggest a higher than normal degree of heterogeneities of repolarization, not detected by the usual ECG analysis. The two indices could be proposed as markers of repolarization heterogeneity, and thus as candidate markers of vulnerability to arrhythmias in left ventricular hypertrophy. However, further studies in a larger population of LVH patients with and without occurrence of ventricular arrhythmias are warranted.

References

1. Levy D, Anderson KM, Savage DD, Balkus SA, Kannel WB, Castelli WP. Risk of ventricular arrhythmias in left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol 1987; 60: 560-5.
2. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol 1998; 32: 1454-9.
3. Marban E. Heart failure. The electrophysiologic connection. J Cardiovasc Electrophysiol 1999; 10: 1425-8.
4. Tomaselli GF, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res 1999; 42: 270-83.
5. Cooklin M, Wallis WR, Sheridan DJ, Fry CH. Changes in cell-to-cell electrical coupling associated with left ventricular hypertrophy. Circ Res 1997; 80: 765-71.
6. El-Sherif N, Chinushi M, Caref EB, Restivo M. Electrophysiological mechanism of the characteristic electrocardiographic morphology of torsade de pointes tachyarrhythmias in the long QT syndrome: detailed analysis of ventricular tridimensional activation patterns. Circulation 1997; 96: 4392-99.
7. Yan GX, Rials SJ, Wu Y, Liu T, Xu X, Marinchak RA, et al. Ventricular hypertrophy amplifies transmural repolarization dispersion and induces early afterdepolarization. Am J Physiol Heart Circ Physiol 2001; 281: H1968-75.
8. Perkiomaki JS, Ikaheimo MJ, Pikkujamsa SM, Rantala A, Lilja M, Kesaniemi YA, et al. Dispersion of the QT interval and autonomic modulation of heart rate in hypertensive men with and without left ventricular hypertrophy. Hypertension 1996; 28: 16-21.
9. Yi G, Elliott P, Sharma S, Guo X, McKenna WJ, Malik M. T wave complexity in patients with hypertrophic cardiomyopathy. Pacing Clin Electrophysiol 1998; 21: 2382-6.
10. Schillaci G, Pirro M, Ronti T, Gemelli F, Pucci G, Innocente S, et al. Prognostic impact of prolonged ventricular repolarization in hypertension. Arch Intern Med 2006; 166: 909-13.
11. Corlan AD, De Ambroggi L. New quantitative methods of ventricular repolarization analysis in patients with left ventricular hypertrophy. Ital Heart J 2000; 1: 542-8.
12. De Ambroggi L, Negroni MS, Monza E, Bertoni T, Schwartz PJ. Dispersion of ventricular repolarization in the long QT syndrome. Am J Cardiol 1991; 68: 614-20.