Editorial

Mechano-electrical feedback

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See article by Nanthakumar et al. [6] (pages 303–309) in this issue.

1. Introduction

During the last two decades, there has been growing interest in the effect that mechanical heart disorders have on the heart’s electrophysiological properties. It has been shown in numerous animal experiments that myocardial stretch produced by volume or pressure overload or direct distension of a muscle strip leads to significant electrophysiological changes [1,2]. This interaction, which has been termed mechano-electrical feedback (MEF), is a concept that undoubtedly has evolved into an accepted mechanism today. MEF describes electrophysiological changes caused by changes in myocardial segment length. These changes most notably include: (1) a shortening of the action potential duration (APD), (2) a decrease in the resting diastolic potential, (3) a decrease in the maximum systolic action potential amplitude, (4) development of early afterdepolarizations, (5) ectopic beats originating from afterdepolarization in myocardium sustaining the greatest stretch (reaching threshold for depolarization first), (6) and other contour changes of the cardiac action potential. Most prior studies on MEF have examined the effect of increases in mechanical load (stretch) on the cardiac action potential duration and configuration while fewer studies have investigated the effect of ventricular unloading. In most studies, the monophasic action potential (MAP) recording method was used to evaluate alterations in local action potential characteristics subsequent to changes in myocardial loading or segment length. Also, in the majority of these studies, MEF has been measured under conditions of excessive, unphysiologic loading or stretch of myocardium in experimental animals. Human studies addressing MEF also have focussed on unphysiological conditions, such as compression/decompression of the left ventricle during cardiopulmonary bypass surgery [3], transient aortic occlusions [4] or aortic balloon angioplasty [5].

To date, direct evidence for mechano-electrical feedback in the human heart under conditions that may mimic real-life clinical or physiological scenarios, has been scarce. In that regard, the study by Nanthakumar et al. [6] in this issue of the journal is a welcome addition. The authors used a novel and noninvasive approach for estimating changes in ventricular repolarization during the physiological maneuvers of Valsalva and tilt-table testing. A previously implanted stimulus to T wave (Stim-T) sensing pacemaker was used to assess repolarization intervals in the apical region of the right ventricle. They were able to discern a minor lengthening of RV apical repolarization when RV volume was changed by Valsalva and head-up tilt testing. Even after blockade of autonomic reflexes by the combined administration of atropin and propanolol and keeping heart rate constant by external transthoracic pacing, these changes, while miniscule, remained statistically significant. This observation lends further credence to the existence of MEF in the human heart. Even more so as it was obtained by noninvasive methods (lest the fact that it required prior pacemaker implantation) and relied on a sensor which differed from the MAP technique normally used to ascertain such repolarization effects. These observations do not, however, provide added insight into potential arrhythmic mechanisms of MEF in humans. It is noteworthy that the authors did not make such claim.

1.1. Minimal changes in repolarization

The degree of changes in repolarization observed in the study by Nanthakumar et al. [6] was extremely small. It amounted to 1.1±0.7% of baseline, which translates into roughly 4 ms shortening from the baseline duration of 370 ms. One needs to wonder if there is any scientific or
clinical relevance attached to such observations. Extrapolating to a different field, we usually don’t get intrigued by a 1% drop in blood pressure or hematocrit. In most experimental studies and some human studies, APD shortening of greater than 10 ms were measured. One can think of several reasons why the changes in local repolarization during the study in the study by Nanthakumar et al. [6] were so miniscule and differed from previous reports on MEF.

1. The method of measuring repolarization changes by an implanted pacemaker lead may have underestimated the maximum amount of repolarization shortening which may occur at levels other than the one sensed by the stim-T wave. The stim-T wave sensing method applied in this study determines the repolarization at a single moment of repolarization which, depending on the slope of local repolarization (slope of phase 3 of the action potential), may not pinpoint the maximal degree of APD shortening at another level. Although the authors have previously ‘validated’ the stim-T wave sensing technique against recordings from an adjacent monophasic action potential (MAP) catheter, this does not ensure validation of other repolarization levels being reciprocated by their technique. Similar to ERP determinations at a single stimulus strength, only a singular repolarization level will be disclosed.

2. A bipolar pacemaker lead was used. It is a matter of debate if bipolar leads are able to discern local repolarization changes with accuracy [7]. Validation of such measurements against MAP measurements may fall short of validating local repolarization changes when only interventions which alter repolarization characteristics in the entire ventricle are used as was reported in the authors’ earlier study (referenced in their article in this journal). In other words, changes of heart rate or administration of action potential prolonging drugs will alter both MAP duration and stim-T intervals and will provide for highly significant correlation statistics. They do not, however, prove that stim-T intervals discern changes in local repolarization.

3. Measurements were done from an endocardial pacemaker lead which was anchored chronically in the RV apex endocardium. This region is likely to undergo less segment length changes than the RV free wall. The echocardiographic diameter assessments were made across the midsection of the RV. The extent to which the apical region participates in these length changes is unknown but probably less than the free wall, due to the law of Laplace and the fact that the RV apex is less likely to ‘collapse’ than the anatomically less restricted free wall of the RV. Often, permanent pacemaker lead tips are anchored so far apical that they in fact rest on septal myocardium, considered to be a part of the LV anatomical structure.

4. Perhaps most important, only decreases in volume and pressure were administered to the RV. Most prior studies applied increases in volume or pressure and often by excessive amounts. Under those experimental conditions, a pronounced shortening of repolarization was reported. Myocardial segment length reductions may not occur during pressure or volume deflations in the RV because even under physiological conditions, RV endsystolic and diastolic pressure is near zero and the RV wall already is close to the septum or even resting on it, and further collapse of the intramyocardial segment length may not occur. Again, the RV apex may be even more ‘immune’ to such RV volume changes. Electrophysiological interrogation by the pacemaker lead was done at the apex while echocardiographic measurements were done elsewhere, so there is little reason for a close correlation.

5. It cannot be excluded that decreases below physiological volume or pressure levels do not cause any changes at all or only minimal ones, because the channel-based MEF mechanisms have already reached their physiological minimum.

2. Previous observations

Effects on left ventricular repolarization by Valsalva maneuvers has previously been studied by Taggart et al. [8] using endocardial MAP recordings. Their study group included patients with post-infarct states and ventricular wall motion abnormalities. Despite this more invasive method and interrogation of left ventricular endocardium, the repolarization changes during the phase of decompression of the ventricles was reported as only slightly larger than in the present study. Constant rate pacing was not applied. Some patients were on beta-blockers but did not have significantly different results from those who were not.

The majority of prior studies concerned with MEF did not use decompression of the ventricular myocardium but rather an increase in intraventricular pressure or volume. These studies generally used unphysiologically high pressure or volume increases to investigate the effects of MEF. Increases in volume (or stretch) affects the action potential in quite different ways, depending on the timing of stretch in correspondence to the action potential phase. This was studied comprehensively by Zabel et al. [9] who used abrupt and short lasting, as well as sustained, volume pulses to interrogate the susceptibility of the cardiac action potential to stretch at different times of the cardiac cycle. Stretch pulses applied during early systole (coinciding with phase 2 of the AP) caused a dip in the AP plateau (i.e. a repolarizing effect for the duration of the stretch). Stretch pulses applied during later phases of phase 2 and early stages of phase 3 still accelerated repolarization. Pulses applied at mid phase 3 did not have any measurable effect on repolarization. (This is quite intriguing because during this time systolic pressure reaches its maximum, and the cells’ electrophysiological ‘immunity’ for stretch at this time is a powerful mechanism to protect against peak wall stress). Pulses applied during late systole (final repolarization phase and early diastole) resulted in action potential
prolongation, sometimes due to development of EADs. These experimental findings were further corroborated by a computer model which had added to the Oxford Heart system the characteristics of stretch-activated channels (SAC) with a reversal potential of 30 mV inside-out [9].

These data help explain previous observations which showed that myocardial stretch leads to action potential shortening predominantly at the plateau and early phase 3 level but to little changes or lengthening of the action potential during the terminal repolarization phase. Lengthening, when it occurs, is usually due to the manifestations to early afterdepolarizations. (It needs to be emphasized that these ‘afterdepolarizations’ are stretch-induced and stretch-controlled depolarizations, and are not to be equated with classical EADs which are triggered by the preceding action potential).

2.1. Clinical relevance of MEF

The clinical relevance of MEF under physiological changes in ventricular loading has not yet been established (including the present article in this journal). However, there is ample room for speculating on its significance under pathophysiological conditions during which more excessive length changes may occur. Pathophysiological conditions can be divided into two scenarios, an ‘active’ and a ‘passive’ one. The first includes conditions during which an abnormally high MEF force is expressed against otherwise normal (at least initially) myocardium. This scenario includes ventricular outflow tract obstruction and arterial hypertension, sudden intraventricular volume shifts, congestive heart failure, and similar conditions which elevate intraventricular pressure or volume and are likely to place abnormal strain on the ventricular wall. The second, ‘passive’, scenario occurs when there is an increased myocardial susceptibility to MEF. This includes regional myocardial ischemia (with weaker myocardial segment elastance during systole), post-infarction stunning, or border zones of a post-infarction scar or ventricular aneurysm.

2.2. How does MEF relate to arrhythmogenesis?

There is little doubt that under excessive loading conditions MEF can play a role in arrhythmogenesis. MEF may act as a trigger for ectopic depolarizations when stretch-induced depolarizations of a particular region reaches threshold. This has been demonstrated in dogs during sudden clamping of the ascending aorta which resulted in massive intraventricular pressure increases, early afterdepolarizations, and ectopic beats [10,11]. In isolated rabbit hearts, shortening of refractory periods (which usually accompanies shortening of repolarization) has been shown to correlate with an increased propensity for atrial fibrillation [12]. A canine study showed that atrial pressure or volume increase can lead to increased dispersion of atrial refractory periods, which also appeared to predispose to atrial fibrillation [13].

2.3. The ionic mechanism

The ionic mechanism underlying stretch-induced changes in electrophysiological properties of the myocardium is only partially understood. The existence of stretch-activated channels (SAC) has been proven for many tissue types. In myocardium, SAC are activated only during unphysiological degrees of stretch and probably play no role in causing the small repolarization changes shown in the study by Nanthakumar et al. [6]. SAC blocking agents, such as gadolinium [14] or the more specific Grammostola spatulata toxin, can reverse the effects of stretch on arrhythmogenesis in both ventricle and atria. For modest volume changes, as in this journal’s study, it is plausible that a simple decrease and increase in intracellular calcium concentration may have changed the duration of repolarization, essentially as part of and an electrophysiological manifestation of the Frank–Starling mechanism. Inotropic interventions, whether by loading or pharmacological agents, also generally affect the duration of the cardiac action potential in parallel to the changes in contractility [15]. Such changes in inotropy, if any, are probably very minor during Valsalva maneuvers, and therefore would lead to only minimal changes in repolarization.

In summary, while MEF plays an important role in global or regional pathophysiological increases in myocardial loading, there is no evidence to date (including the study by Nanthakumar et al. [6]) that it has clinical significance under physiological conditions.

References

[7] Franz MR. Current status of monophasic action potential recording: