Editorial

Repolarization abnormalities in heart failure

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See article by Lacroix et al. [1] (pages 42–50) in this issue.

The paper by Lacroix et al., published in this issue of Cardiovascular Research, is of interest because it deals with the question of mechanisms underlying sudden arrhythmic death in patients with heart failure [1]. This is a problem of great clinical significance, because increasing numbers of patients are suffering from heart failure and are at risk of sudden cardiac death [2], especially at moderate degrees of failure [3].

Heart failure is extremely difficult to study experimentally, not only because it is difficult to define [4], but also because a single suitable experimental model is not available. Several models relevant for the study of arrhythmogenesis in heart failure exist [5–8], but since heart failure in man results from a plethora of conditions, none of these models can withstand criticism regarding its clinical significance. In addition, the development of experimental models is costly as it involves the study of animals over prolonged periods of time. Another complicating factor is that, if the model is truly representative, a high percentage of the animals will die suddenly before they can be studied.

In the majority of cases, sudden death in heart failure is caused by sustained ventricular tachyarrhythmias [9]. For the study of arrhythmogenic mechanisms, one should discriminate between the mechanism underlying the initiating beat (the ‘trigger’) and that of the continuation of the arrhythmia (‘the continuator’). Favourable pre-existing conditions (‘the substrate’) may facilitate the onset and maintenance of the arrhythmia. These three mechanisms may be altered by various modulating factors (e.g. circulating catecholamines, anti-arrhythmic drugs). The presence of a single of these four mechanisms is not sufficient for the onset of a sustained arrhythmia. The paper of Lacroix et al. deals with both a triggering mechanism and a substrate of arrhythmogenesis in heart failure: The hypotheses that inspired the investigation are that (1) the prolongation of the action potential duration known to exist in heart failure may trigger action potentials caused by early after depolarizations and (2) that the substrate for arrhythmogenesis is formed by heterogeneity in ventricular refractoriness. The latter hypothesis is based on the idea that heterogeneities in repolarization may cause unidirectional block, which is a pre-requisite for the initiation of a re-entrant arrhythmia [10,11]. Factors favouring continuation of a re-entrant arrhythmia are slow conduction and/or a short refractory period [10].

Lacroix et al. present a model of heart failure in a large mammal, the pig, where heart failure was induced by rapid pacing and which fulfils the criterion of a high loss of animals resulting from sudden death. They are to be praised for the comprehensive integrative approach of the hypotheses, with data on ion-channel function, epicardial strips of muscle, isolated perfused hearts, as well as on in vivo telemetric ECG recordings in the awake animals, and hemodynamic and echocardiographic documentation of heart failure.

For the main results of the study, the reader is referred to the paper itself, but some of the results presented by Lacroix et al. warrant comment because they may have led to underestimation of the effect of heart failure or deserve emphasis. One is the appropriateness of Bazett’s formula. With an absence of a significant difference in QT-interval, the authors have used Bazett correction of the QT-interval. It would probably have been sufficient to point out that the same QT-interval in the heart failure group occurred at a much (110 ms) shorter cycle length. Bazett’s correction is a way to normalize QT-intervals to a cycle length of 1000 ms in man. It assumes a restitution curve given by a simple formula. It is known, however, that the restitution curve is altered in heart failure [8], and the use of the same correction in the control animals and the failing animals (or...
during baseline and after pacing) probably underestimates this effect. Assessment of the restitution curve would demonstrate this.

A second point of consideration regards the heterogeneity in activation recovery interval (ARI). Lacroix et al. have compared the heterogeneity in ARIs at levels across the ventricular wall and report a decreased heterogeneity in its value relative to the mean. For the occurrence of unidirectional block, absolute differences in the timing of repolarization are important, because it defines a time window in which a premature activation may encounter refractory tissue. Interestingly, their data of the overall mean ARI indicate a significant larger variance in heart failure animals that is not evident from a layer by layer comparison. It can, however, not be excluded that this variance is caused by differences between animals.

A point deserving some emphasis is a negative result: the absence of an M-cell layer in these pigs, even when they are failing. In normal pigs, this point has been made earlier [12], but it has been argued that the remodeling induced by heart failure would reduce cellular coupling and expose intrinsic heterogeneities. Stankovicova et al., however, found M-cell like properties in isolated (thus completely uncoupled) porcine ventricular myocytes [13]. In intact diseased human hearts transmural gradients were not detected [14].

A recent paper by Watanabe et al. [8] addressed similar questions in pacing induced heart failure in dogs. They did find increased dispersion in repolarization and correlated this with inducibility of arrhythmias. Interestingly, they measured the restitution curves and describe a steeper slope of the restitution curves in failing than in normal animals, especially at the apex. This may play a role in the continuation of a re-entrant arrhythmia.

Inherent to the field of study, many questions still remain to be answered, some of which are: Does prolonged remodeling (as in human heart failure) expose more pronounced heterogeneity in repolarization than in the subacute model of heart failure used by Lacroix et al.? Does increased interstitial fibrosis or gap junctional redistribution unmask heterogeneities? What is the relation between altered tissue architecture and arrhythmogenesis in heart failure? What is the explanation for increased arrhythmogenesis in patients with moderate heart failure? What is the relation between these electrophysiological changes and the spontaneous occurrence of arrhythmias?

The paper by Lacroix et al. presents us with a multitude of relevant data regarding a large mammalian model of heart failure in which sudden death occurs. More of these, difficult, integrative studies are needed to solve this major healthcare problem.

References