Myocardial Hibernation
A Double-Edged Sword
Gerd Heusch, Karin R. Sipido

Ischemic heart disease remains a leading cause of morbidity and mortality. The survival after acute ischemic events has improved substantially in recent years, but new syndromes have emerged. Cardiac remodeling following a large myocardial infarction, with dilatation of the left ventricle, has deleterious hemodynamic consequences and is a major cause of chronic heart failure. The increased incidence of potentially lethal arrhythmias is related to the presence of scar tissue but also to altered properties of the surviving myocardium, as characterized in experimental studies. Myocytes in the remote myocardium are hypertrophied, and the contraction of isolated cells is reduced. This is related to a reduction in Ca\(^{2+}\) transient amplitude and slower Ca\(^{2+}\) removal. The changes in electrogenic Ca\(^{2+}\) transport via the Na/Ca exchanger also contribute to the electrical remodeling. Indeed, the action potential profile is altered and its duration is increased because of reduced density of K\(^{+}\) currents and the changes in Ca\(^{2+}\)-dependent ionic currents, and these changes are variable throughout the remaining myocardium. This remodeling process results in an increased susceptibility for arrhythmias with the myocardium as the substrate on which specific events trigger arrhythmias.

In contrast to the extensive characterization of cellular remodeling following myocardial infarction, much less information is available on the changes in hibernating myocardium, i.e., myocardium with reduced baseline blood flow and contractile dysfunction, which retains viability and recovers on revascularization. (This is the classical definition of hibernation, but others have viewed hibernation as a manifestation of repetitive stunning.) Nevertheless, the importance of this syndrome for clinical management is increasingly recognized, more specifically the need for its diagnostic recognition and therapy by timely revascularization. This is supported by the recent meta-analysis in patients with chronic coronary artery disease and left ventricular dysfunction: in patients with evidence of myocardial viability, revascularization decreased mortality (relative to medical therapy) from 16% to 3.2% during a 25±10 month follow-up interval, whereas in patients without viability, mortality was intermediate, and neither revascularization nor medical therapy was superior in terms of mortality (7.7% versus 6.2%). Excess death in the population with hibernating myocardium is, to a large extent, sudden presumed arrhythmic death. This is also underscored by the results of the Multicenter Automatic Defibrillator Implantation Trial II demonstrating the increased survival with implantation of an automatic defibrillator in patients with ischemic cardiomyopathy and by similar data from the Sudden Cardiac Death in Heart Failure Trial study recently reported at the meeting of the American College of Cardiology (available at www.acc.org). The mechanisms underlying hibernation have been studied in animal models, but so far, the presence of arrhythmias has not received much attention. In this issue of Circulation Research, Canty et al report on the increased incidence and characteristics of sudden cardiac death (SCD) in a retrospective analysis of their established model of repetitive stunning and hibernation in pigs. Although primarily descriptive, the study offers a first glimpse into mechanisms of arrhythmias, (i.e., the substrate and potential triggers; Figure).

Hibernating Myocardium as an Arrhythmogenic Substrate
Pathophysiological hibernating myocardium as viable myocardium in the face of a chronic coronary stenosis and chronic blood flow reduction, almost by definition, entails both adaptive features and the potential for further deterioration. The adaptation is characterized by an early biochemical mechanism that preserves the myocardial energetic state through reduced contractile function and a more delayed upregulation of survival genes. The morphology of chronic hibernation is also characterized by signs of adaptation (i.e., dedifferentiation secondary to contractile unloading) and of degeneration with replacement fibrosis. Presumably, the presence of small islands of nonconducting or poorly conducting tissue, be it degenerative or necrotic, can form a pathway for re-entry.

Canty et al attribute the arrhythmogenic substrate to cellular remodeling and the inhomogeneity of sympathetic innervation. The latter has been documented in this model of hibernating myocardium, but the former is less well documented. Structural changes with hypertrophy and glycogen loading with myolysis in a subpopulation of cells have been described, as well as downregulation of Ca\(^{2+}\)-handling proteins, but functional data at the cellular level are lacking. In a slightly different pig model of hibernating myocardium induced by 4 weeks of critical stenosis on the circumflex...
Elements of the arrhythmogenic substrate and triggers for arrhythmia in hibernating myocardium. See text for references.

artery, Bito et al recently characterized the properties of isolated myocytes. Ventricular cells were hypertrophied, had reduced contractions, and altered Ca$^{2+}$ handling. A prolongation of the action potential was a striking feature. This indicates that the viable myocytes in the hibernating area may be part of the arrhythmogenic substrate, contributing to increased heterogeneity of the myocardium, and being potentially more prone to early afterdepolarizations. The underlying changes in ion channels are still under investigation, but preliminary data include a reduction in Na$^+$ channel density, which can also affect conduction. Human hibernating myocardium is characterized by inhomogeneous expression of connexin 43, and this may also contribute to alterations in electrical impulse propagation and re-entry, as could differences in action potential restitution properties.

In their study, Canty et al carefully compared the available data on global ventricular function, coronary flow, and presence of myocardial infarction in animals with SCD and non-SCD animals. They conclude that the SCD animals did not differ significantly from the non-SCD animals, which suggests that the substrate is present in all animals but that arrhythmias were triggered by specific events in the SCD group. Although this seems reasonable, there is one important parameter that was significantly different, namely the fractional shortening. Although not detailed in the article, this measurement was presumably taken in a view that included the hibernating segment. Independently, it may indicate that the SCD animals have actually slightly better-compensated function. This could correspond to the observation that in the human heart failure population, SCD is relatively more common in the subgroup with relatively less compromised ventricular function. The mechanisms of arrhythmias in compensated hypertrophy may be specific to this condition.

The Trigger for Arrhythmias in Hibernating Myocardium

Several events could trigger arrhythmias in a vulnerable substrate, and some of the most obvious ones in the current setting are ischemia and increased adrenergic drive.

Increased sympathetic drive is evident in SCD animals from the sinus tachycardia of (on average) 220 bpm preceding ventricular fibrillation when monitored. Yet the authors dismiss adrenergically induced subendocardial ischemia as a major component, referring to a study that did not demonstrate ischemia in this setting. However, in this study, the heart rate did not exceed 130 bpm. Clearly, the much stronger sympathetic activation, which is evident from a heart rate of 220 versus 130 bpm, could still induce substantial ischemia, not only by $\beta$-adrenergic mechanisms and increased demand but also (at least in patients) by $\alpha$-adrenergic mechanisms and decreased supply. Even without inducing ischemia, increased adrenergic stimulation is a well known trigger of afterdepolarizations and associated arrhythmias. It is unclear whether the observed peak in the diurnal variation coincided with feeding time, a well known cause for excitement and adrenergic stimulation. The inhomogeneity of innervation may further exacerbate the effects of increased adrenergic drive.

Acute myocardial infarction was dismissed by the authors, but this may not be quite conclusive (as discussed later).

Another potential trigger is inflammation. Increased expression of inflammatory mediators such as tumor necrosis factor-$\alpha$, inducible nitric oxide synthase, and cyclooxygenase has been reported in human hibernating myocardium and needs to be studied in the experimental model.

Finally, and this may also relate to ischemia and inflammation, the potential for coronary microembolization from the coronary stenosis must be considered, because coronary microembolization in the absence of a major thrombotic occlusion has been identified as a mechanism of sudden death in patients with coronary artery disease. Stretch as a triggering event is unlikely because left ventricular end diastolic pressure was significantly lower in SCD animals than in those that survived.

Caveats

Canty et al report a retrospective analysis of a decade of work in their established pig model of myocardial stunning and hibernation. Although the number of animals subjected to a Kaplan-Meier analysis is truly impressive ($n=426$), only 34 to 97 animals at best, compared with 6 sham animals were studied after >3 months and are likely to fulfill the criteria of hibernation defined in this model. Indeed, according to the prior characterization, within 3 months following instrumentation, a significant stenosis had developed, but with a normal resting blood flow, leading to repetitive ischemia with subsequent stunning rather than hibernation; more than half of the reported SCD occurred in this initial period. In only 7 SCD animals were the functional criteria of hibernation actually verified and was a reduced resting blood flow documented; only 3 of these 7 animals relate to the 10 animals for which ventricular fibrillation and its prodromal rhythm was monitored. Histological analysis is available for only 4 SCD animals, whereas in the remaining 28 animals, only 2–3-5-triphenyl tetrazolium chloride (TTC) staining was used to examine the presence of infarction. Yet, importantly, in the absence of reperfusion, the lack of TTC-negative necrosis does not rule out (micro) infarction. Also, without reperfusion, histology does not identify acute myocardial infarction, and conversely, the small infarcts detected must have been at least several hours old before the animals died. These critical comments on the small sample size and heterogeneous character of the database and on the methodological limitation of the morphological data are not meant to detract from its value but must be kept in mind when
extrapolating to patients with hibernating myocardium and their risk of SCD.

Conclusions
This is the first study to report on an increased incidence of sudden death in an experimental model of chronic coronary stenosis. Despite the limitations inherent to a retrospective study, the data indicate that the hibernating myocardium is a potentially arrhythmogenic substrate and further underscore the need to improve treatment and management of chronic ischemia. To achieve this will require further insights into the underlying mechanisms.

References

Key Words: ischemic heart disease • hibernating myocardium • arrhythmias • sudden cardiac death • remodeling
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