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, ie, 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, and 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, ie, 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 (ie, 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.
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


10. Rahimtoola SH. As a perspective on the three large multicenter randomized 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.


Key Words: ischemic heart disease • hibernating myocardium • arrhythmias • sudden cardiac death • remodeling
Myocardial Hibernation: A Double-Edged Sword
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