Microphysiology of the Pericardium in Relation to Intrapericardial Therapeutics and Diagnostics

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Summary: Intrapericardial delivery of therapeutic agents for pericardial diseases has long been available in the presence of excess pericardial fluid. Most patients with myocardial and coronary disease have no such excess so that their direct treatment requires pericardial access, for which a new instrument has succeeded in animals with induced infarctions, coronary lesions and arrhythmias. Nitric oxide (NO) donors, calcium-avid drugs, antibodies, angiogenic agents (pharmacologic coronary bypass), and hypothermic solutions have been instilled intrapericardially, and even iontophoresis has been used; gene therapy is also promising. Intrinsic pericardiogenic substances may potentially be stimulated for comparable purposes.

Key words: pericardial microphysiology, intrapericardial therapy, coronary disease, myocardial disease, arrhythmias

Intrapericardial Therapy for Pericardial Disease

Nonsurgical intrapericardial therapy has a long history. However, it has been restricted to patients with sufficient fluid in the pericardium (pericardial effusions of sufficient size) for a needle or catheter to be placed safely, and it has been for specific treatment of the causes of such effusions.1 For example, patients with recurrent uremic pericarditis or connective tissue disease, particularly lupus erythematosus, with life-threatening effusions can be treated with corticosteroid agents. Antineoplastic agents have been used for malignancies. With hemopericardium, streptokinase has recently been successful in preventing fibrous organization and adhesions (and subsequent constriction). Similarly, with pyopericardium, streptodornase has been added to streptokinase to destroy the components of pus. Until recently, sclerosants have been used for stubbornly recurrent effusions, particularly in malignancies, but it has been found that leaving a drainage tube in place sufficiently long would adequately sclerose the layers of the pericardium to check further effusion.1

Intrapericardial Therapy for Diseases of the Heart and Coronary Arteries

The prospect of intrapericardial therapy for heart disease targets a rich spectrum of abnormalities, most often with a normal pericardium. Success in animals indicates that appropriate instrumentation is vitally necessary to enter the normal pericardium, which would have only 15–35 ml of fluid, making an extremely thin layer and therefore bringing the pericardium much closer to the heart than with any effusion. It is evident that the direct targeting of the myocardium and the coronary arteries could have advantages in terms of local drug concentration and the prevention or minimization of systemic effects of any therapeutic agent. Animal studies have shown that several agents deposited intrapericardially have a concentration gradient decreasing from the epicardium to the endocardium but that certain antiarrhythmics can penetrate myocardial infarcts.

Experimental Results

Nitric oxide (NO) donors have been used successfully intrapericardially at high concentrations—which, via the venous system, could be detrimental. Willerson et al.2 demonstrated that nitroprusside protects against platelet aggregation in animals with experimental coronary endothelial injury. March utilized NO to significantly decrease coronary wall thickening and lumen narrowing in the porcine over-stretch model of mural response to coronary injury.3

In searching for superior management of dangerous arrhythmias, Zipes and colleagues4 investigated voltage-sensitive chemicals to target depolarized cells in the damaged myocardium and calcium-avid drugs that seek increased intracellular calcium. Antibody techniques were also investigated such that one “head” of an antibody seeks myosin of damaged cells with the other “head” attached to an antiarrhythmic agent. They showed that amiodarone migrates transmurally with significant electrophysiologic effects and appears to suppress induced atrial fibrillation. They also noted that L-arginine decreases the shortening of the tissue effective refractory period and the severity of ventricular arrhythmias (probably due to cardiac NO production).5

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Avitall et al., using the very old technique of iontophoresis via an epicardial patch electrode, achieved high drug concentrations transmurally with penetration of infarcted myocardium. Iontophoresis achieved more rapid suppression of ventricular tachycardia than the usual mechanism for intrapericardial agents—passive diffusion—and also more rapid suppression than intravenous drug.

Uchida et al.8 achieved a kind of pharmacologic coronary bypass therapy by angiogenic therapy of acute myocardial infarction. Basic fibroblast growth factor (bFGF) given intrapericardially increased the vascularity of the heart in comparison with control animals. There was a greater effect subepicardially (as expected) with angiogenesis and consequent myocardial salvage. In the future, this technique promises treatment for angina as well as infarction.

Dave et al. used the PerDUCER (Comedicus, Inc., Columbia Heights, Minnesota) device to introduce a hypothermic solution during experimental acute myocardial infarction.8 Hypothermic pericardial perfusion reduced the myocardial temperature and reduced infarct necrosis and infarct size by 50%. (This could also become an adjunct to thrombolysis and to minimally invasive cardiac surgery.)

Landau et al.9 reported angiogenic therapy of chronic myocardial ischemia, using a rabbit model with A-II induced left ventricular hypertrophy. They gave bFGF intrapericardially and noted marked angiogenesis versus controls, with the effect particularly marked subepicardially. March,10 with molecular vectors, utilized intrapericardial gene delivery for perivascular and epivascular therapy to achieve transduction of epicardial and parietal pericardial mesothelium. In both swine and dogs, there were no ill effects.

In conclusion, intrapericardially targeted drug therapy and hypothermic superfusion has the advantages of (1) site specificity, (2) superiority to systemic therapy due to increased local concentration and decreased to absent systemic toxicity, and (3) delivery of label-specific therapeutic agents to target cells, receptors, channels, and other structures.

**Intrinsic Pericardial Microphysiology: A Further Target**

The rich microphysiology of the pericardium makes it a natural target for investigation of intrapericardial therapy. Microphysiology includes pericardial servomechanisms due to neuroreceptors in the epicardium and the fibrosa, and sympathetic efferents, as well as mechanoreceptors sensitive to changes in ventricular stretch, determined by volume and transmural pressure.

Some of these, along with phrenic afferents, appear to monitor beat-to-beat changes in cardiac volume, while mechanoreceptors with unmyelinated fibers signal myocardial tension and reflexly match contraction strength with peripheral resistance (for example, with exercise). Chemoreceptors sensitive to substances in the pericardial fluid require further exploration.

The pericardial mesothelium has active metabolic activity including metabolism of cyclooxygenase, prostacyclin synthetase, and lipoxygenase. Prostaglandin E2, eicosanoids, and large amounts of prostacyclin (PGI2) are continually released by the mesothelium, especially from the visceral layer into the pericardial cavity. In response to stretch, increased myocardial work and loading, and hypoxia, prostanooids can alter pericardial sympathetic neurotransmission and myocardial contractility and may modulate the caliber and tone of the underlying coronary vessels (i.e., directly via vasodilation by prostaglandin and indirectly by opposing coronary spasm).11 A potentially adverse metabolic activity is production of endothelin with a higher pericardial fluid concentration than in all mammalian biologic fluids tested; in congestive heart failure, its concentration is inversely related to the New York Heart Association class. This requires further elucidation, but endothelin is a vasoconstrictor and theoretically may have to be neutralized under certain circumstances.

**Conclusion**

The experimentally demonstrated and great number of potential avenues for further experimentation in most forms of heart and pericardial disease make the capability to do effective intrapericardial therapy and diagnosis extremely promising. Further investigation, particularly in humans, is urgent.

**References**