Intrapericardial Therapy and Diagnosis

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Introduction

Until recently, intrapericardial therapy and diagnosis in the absence of cardiothoracic surgery was restricted to diseases of the pericardium, and required a pericardial effusion for safe access to the pericardial cavity. The normal pericardial space is small (and mostly a potential space), containing 15 to 35 mL of serous fluid; therefore, a relatively large pericardial effusion was a requisite for nonsurgical access [1•,2]. Moreover, both diagnostic and therapeutic procedures were necessarily restricted to diseases of the pericardium itself (Table 1).

Pericardial Access as a Therapeutic and Diagnostic Route

Recently, the possibility of pericardial access to diagnose and treat diseases of the myocardium, coronary vessels, and conducting system (including arrhythmias) has been made feasible not only in the few patients who have a sufficiently large pericardial effusion, but also in the noneffusive, “dry” pericardium [3••,4–8]. The latter—potentially in any patient with disease of cardiac structures, with or without pericardial disease—is possible both via a catheter passed through the right atrial appendage (so far only in experimental animals) [9], or a newly developed instrument, the PerDUCER (Comedicus, Central Heights, MN), which has the capability of entering the dry pericardium. The PerDUCER has provided safe and effective access to the pericardium in numerous animals, and an increasing number of human patients [2,3••].

Inherent Superiority of the Pericardial Route

Heretofore, most diseases have required oral or parenteral administration of therapeutic and diagnostic modalities that would reach particular tissues and organs through the bloodstream, always with the possibility of many unwanted systemic effects. These include toxicity, as well as dispersion and dilution of the administered agents, before reaching target tissues. The intrapericardial route for therapeutic and diagnostic modalities makes possible a direct attack on diseases of the coronary arteries and veins, autonomic nerves, conducting tissues, myocardium, and endocardium, as well as allowing direct diagnoses by obtaining tissue and performing electrophysiologic investigations [10••].

Experimental Results

In experimental animals, the normal pericardium has been safely penetrated with delivery of medicines specifically targeting selected structures, including the coronary arteries, cardiac sympathetic and parasympathetic nerves, and myocardium, and even penetration to the conducting tissues and endocardium [6,11,12]. Such intrapericardially delivered therapies have numerous advantages over systematically administered therapies, including 1) use of label-specific drugs to target specific cells, receptors, channels, and other structures; 2) inherent superiority over systemic and endoluminal therapy because of increased concentration at (or very near) the target tissue and, because it remains locally contained in the pericardial reservoirs, minimal to no systemic effects; and, 3) tissue specificity. A potential additional application is stimulation of the pericardial mesothelium itself, for increased production of many active substances.

Variety of Successful Agents

Antiarrhythmic therapy applied directly to the epicardium in experimental animals has included L-arginine, procainamide, and amiodarone; many of these have been in swine, which have cardiac and thoracic functional and anatomic
Targets (pericardial diseases)

<table>
<thead>
<tr>
<th>Type</th>
<th>Targets (pericardial diseases)</th>
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<tbody>
<tr>
<td>Fibrinolytic Streptokinase/strptodornase</td>
<td>Blood, hemopericardium</td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>Malignant tissue</td>
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<tr>
<td>Sclerotherapy</td>
<td>Persistent effusions</td>
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<tr>
<td>Corticosteroids</td>
<td>Inflammation: general, vasculitis, immunopathic</td>
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<tr>
<td>Antibiotics (generally unnecessary)</td>
<td>Specific infections</td>
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(Adapted from Spodick [20].)

(including coronary) similarities to human beings. It has successfully terminated both arrhythmias due to experimental acute myocardial infarction and other experimentally induced arrhythmias [6,11,12]. Gene therapy is a promising variant, with gene carriers targeting both the coronary vessels and the pericardial mesothelium. This includes methods using an antibody carrier, one head of which seeks specific tissues, and the other of which carries the antiarrhythmic agents [13,14••]. In damaged (ie, depolarized) cardiac cells, intrapericardial voltage-sensitive agents have an antiarrhythmic effect. Intrapericardial electrophysiologic methods include epicardial mapping and ablative therapy, with the potential for ablation of any epicardial arrhythmogenic zones [9,10].

Other examples of successful intrapericardial therapy include apoplipoprotein A-Milano, which has been shown to reach the intima and adventitia of coronary vessels. Infarct-avid agents have successfully decreased excessive intracellular calcium accumulations [15]. Successful angiogenesis has been accomplished with basic fibroblast growth factor (bFGF), which targets coronary vessels by increasing myocardial vascularity both in chronic ischemia and acute myocardial infarction [17–20]. Intrapericardial delivery of hypothermia-inducing agents has significantly reduced epicardial temperature, and with it various degrees of ischemia and ischemic myocardial damage produced experimentally. Nitric oxide donors and L-arginine (a nitric oxide precursor), delivered in concentrations that could be toxic if given systemically, have successfully reduced or prevented not only acute and chronic ischemia, but also the development of atherosclerotic lesions in the porcine overstretch model of experimental atherosclerosis. Like PGII2, they also antagonize platelet aggregation in the coronary vessels [7,8,11,12,15,18,19].

Stimulation of the Normal Pericardial Mesothelium

Normal pericardial tissue has a microphysiology that is ideal for stimulating the naturally produced metabolites of its mesothelium, including prostanooids such as prostacyclin E2, eicosanoids, and prostanoids, as well as enzymes like cyclooxygenase, lipoxygenase, and prostacyclin synthetase [1,20]. All of these metabolites, particularly the prostanoids, affect myocardial sympathetic neurotransmission, myocardial contractility, vasodilation, and inhibition of platelet aggregation, both in the pericardium and within the coronary vessels themselves (they may also affect reperfusion arrhythmias) [20].

Normal pericardial fluid is fundamentally a plasma ultrafiltrate, enriched by substances of mesothelial and myocardial origin, including products of myocardial and pericardial paracrine activities [20]. Selective stimulation of the pericardial microphysiology to utilize the abundant paracrine activity of the pericardial mesothelium has been accomplished in animals. Arachidonic acid applied (by superfusion) to the normal pericardial cavity stimulates excessive production of PGII2, with improvement in pericardial coronary blood flow and disaggregation of intracoronary platelet clumps [21,22]. Other paracrine products of the pericardial mesothelium, and of substances in the normal pericardial fluid that appear to derive from either the mesothelium or from myocardial sources, are potential targets for stimulation [20]. In contrast, pericardially derived endothelin is a potential target for suppression, because of its vasoconstrictive properties [23].

An important product of paracrine cardiac activity is FGF2, which is present with a decreasing concentration gradient from the myocardium to the serum (this supports the myocardium as a major source of FGF2 in pericardial fluid). Indeed, when present in large concentration, this substance is not a part of the usual plasma ultrafiltrate represented by pericardial fluid. Greater FGF2 concentration in pericardial fluid is also associated with lower osmolality and protein concentrations, a discovery that is further evidence that it is not actively concentrated from the serum, and is probably released into the pericardial fluid from the cardiac interstitium [22,24••,25]. Atrial natriuretic protein (ANP) is another example; it is produced in the heart and released with a higher pericardial fluid than serum concentration. It is a marker for cardiac hypertrophy, although ANP itself has no intrinsic hypertrophic effects, unlike FGF2, which seems to have a role in myocyte protein synthesis, and may normally help to regulate cardiac muscle mass [20,24•]. Indeed, serum has less of a trophic effect than pericardial fluid on adult myocytes, probably due to high concentrations of FGF2 in every patient studied, regardless of age, sex, or disease [25]. These significant physiologic and dysphysiologic responses can be further investigated by direct access to the heart within the normal pericardium.

The Pericardium as a Therapeutic Reservoir

Ultimately, the physical size of molecules, and long-acting formulations of agents delivered intrapericardially will