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Mechanisms underlying heart failure

Mark E. Anderson

Carver College of Medicine, University of Iowa, Cardiovascular Research Center, 200 Hawkins Drive, Rm 315 GH, Iowa City, IA 52242-1081, United States

Mark E. Anderson: mark-e-anderson@uiowa.edu

Heart failure is a syndrome with high mortality and morbidity where cardiac function is inadequate to meet metabolic needs of the body. Heart failure is now one of the greatest public health problems for the developed world. Approximately 500,000 new patients are diagnosed with heart failure in the United States each year. On the one hand, heart failure therapies have been tremendously successful. In particular, β adrenergic receptor antagonist drugs (β blockers) and drugs targeting the renin–angiotensin–aldosterone signaling cascade have improved myocardial function, reduced sudden cardiac death from arrhythmias and ameliorated suffering and repeat hospitalizations for patients afflicted by heart failure. These drugs are by and large well tolerated and inexpensive. β Blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists all address the problem of excessively activated neurohumoral signaling that promotes heart failure from a wide variety of causes, including myocardial infarction. Unfortunately, some patients are intolerant of some or all of these medications and heart failure in many patients eventually progresses to a point where these agents are inadequate. Thus, developing new and improved therapies for heart failure is a major public health goal.

In comparison to the remarkable successes of neurohumoral antagonist therapies, the next generation of effective heart failure treatments has been a long time coming. In brief, the interregnum between the neurohumoral antagonist agent epoch and the apparent renaissance described in this focus issue of *Drug Discovery Today* occurred because positive inotropic drugs are largely ineffective and because developing new treatments is very expensive. Positive inotropic drugs are designed to improve myocardial function, particularly in patients with systolic heart failure where therapy with neurohumoral antagonists is inadequate for controlling symptoms. Positive inotropic drugs are necessary in acute decompensated heart failure, as adjunctive agents during cardiac arrest and for recovery from cardiac surgery. However, chronic therapy with positive inotropic agents has been disappointing. By and large, the epoch of positive inotropic agents, represents a sort of wilderness phase where trial after trial with each new agent produced disappointing but expensive negative results. In retrospect, the failure of early positive inotropic therapies to improve myocardial function and prolong life appears to have been partly foreseeable. After all, many positive inotropic drugs were designed to activate elements of the β adrenergic receptor signaling pathway, the target of the β adrenergic receptor antagonists that are now a mainstay for treating heart failure. However, before the long-term deleterious effects of chronic activation of the β adrenergic receptor pathway was appreciated, there was a widely held view that β adrenergic receptor pathway antagonist drugs were contraindicated in heart failure patients. Newer information and improved understanding of the β adrenergic receptor signaling pathway suggest that more refined medications, targeting specific receptor and phosphodiesterase isoforms may produce previously elusive results: to bolster myocardial performance without increasing myocardial death, disordered myocardial cell membrane excitability and arrhythmic sudden death. The failure of positive inotropic agents provided instructive information about signaling in myocardium that has partially informed the development of more recent therapies. In my view, the central issue for why ‘broad

spectrum' inotropic agents are unsuccessful in prolonging life is they promote intracellular Ca^{2+} dysregulation in myocardium.

As a background to the exciting emergent heart failure therapies that are the topic of this special issue, I would like to consider a general framework for contemplating heart failure as a disease syndrome. Heart failure has a variety of risk factors, including prior myocardial infarction, hypertrophy and a family history of heart failure (i.e. an underlying genetic defect). These risk factors represent threats to the health of myocardium. The predominant form of heart failure occurs due to systolic (inotropic) defects, but there is a growing recognition that defective relaxation (lusitropy) also contributes to heart failure. In some cases defects in lusitropy occur in the setting of preserved systolic function. Thus, most forms of heart failure occur because the myocardium itself is sick. Of the patients with heart failure who die, approximately half die suddenly from cardiac arrhythmias, while the other half perish more slowly from defective myocardial performance. The stability of this balance between electrical and mechanical death suggests a fundamental connection between these activities in myocardium and in heart failure. This connection between the electrical and mechanical activities is central to understanding heart failure from a basic and from a translational perspective. The myocardium is built around a connection between electrical and mechanical coupling (so-called excitation–contraction coupling, ECC) and the protein constituents, signaling chemicals and cellular ultrastructure that are required for healthy ECC are extraordinarily complex. Disturbances in any of the ECC components have the potential to contribute to reduced mechanical performance and an increase in the probability of arrhythmias. In addition to ECC, information, in the form of intracellular Ca^{2+} , from contraction is telegraphed in reverse to affect cell membrane potential. Thus, each heartbeat involves a bi-directional exchange of information between the electrically active cell membrane and the cytoplasmic constituents that drive the energetically active processes of contraction and relaxation. Defects in forward (ECC) and reverse coupling of cytoplasmic and cell membrane events probably underlie the twin phenotypes of congestive heart failure and arrhythmic sudden death.

Each myocardial cell contraction is initiated by a highly orchestrated cell membrane electrical event or action potential. The action potential in myocardium is remarkably long, in comparison to other electrically excitable tissues such as neurons, to grade the entry of Ca^{2+} through voltage-gated (activated) Ca^{2+} channel proteins in the cell membrane. The length of the myocardial action potential is a vulnerable element that can lead to the initiation of arrhythmias, particularly in injured or failing myocardium. Ca^{2+} crosses the cell membrane and enters the cytoplasm where it triggers regenerative release of Ca^{2+} from intracellular (sarcoplasmic reticulum, SR) stores. The Ca^{2+} released into the cytoplasm from the SR envelopes the myofilaments to drive contraction and is actively taken back up into the SR to promote relaxation. In addition SR Ca^{2+} feeds back to Ca^{2+} regulated conductances on the cell membrane (i.e. ion channels and exchangers), communicates with Ca^{2+} in the nuclear envelope to modulate Ca^{2+} -dependent transcription and with Ca^{2+} in mitochondria to affect metabolism and activate cell death programs. It is clear that Ca^{2+} is a central messenger for communicating contraction and relaxation, and that loss of normal Ca^{2+} homeostasis is a crucial step for promoting defective mechanical performance and electrical instability in heart failure. My view is that the coupling of mechanical and electrical events in heart failure, and the balance between congestive and sudden death in heart failure patients, are natural consequences of the ECC mechanism in myocardium. Through the lens of ECC it is possible to consider the failure of positive inotropic agents activating the β adrenergic receptor pathway as preordained because of their propensity to stress ECC components and lead to disturbed intracellular Ca^{2+} homeostasis.

Clearly, multiple known and unknown cellular signals participate in heart failure. And the complexity of these systems is both an obstacle and opportunity to developing new therapies with improved focus and efficacy, but reduced side effects. Thus, new heart failure therapies will need to reprogram sick and injured myocardium to improve contraction and relaxation without promoting arrhythmias or disadvantaging metabolism or activating death pathways. Future therapies in heart failure will need to address replacing dead (or terminally dysfunctional) myocardium and reconfiguring scar. The compilation of articles in this issue of Drug Discovery provides a cutting edge view of current concepts for repairing sick and replacing dead myocardium. These articles come from leading groups, each of which has made important contributions toward the discovery of new biological mechanisms and development of novel therapies for heart failure. The Koch laboratory has been a leader in understanding the regulation of the β adrenergic receptor pathway and here provides an overview work on G protein receptor kinases (GRKs). Multiple protein kinases have emerged as candidates for therapy in heart failure. The theme of targeting protein kinases for inhibition as a heart failure therapy is explicitly explored in three articles in this issue. The p38 mitogen-activated protein (MAP) kinase is a focus of the Force laboratory, Protein kinase C (PCK) is a focus of the Mochley-Rosen laboratory and calmodulin kinase II (CaMKII) is a focus of my laboratory and is discussed here in collaboration with Dr Howard Schulman, who discovered CaMKII during his postdoctoral studies with Paul Greengard. Proof-of-concept mitochondrial targeted therapies have recently emerged as an area of intense interest and the Mochley-Rosen laboratory provided a second article highlighting the basis for mitochondrial active therapies for heart failure. The Marks laboratory developed the concept that 'leaky' ryanodine receptors contribute to heart failure and arrhythmias, and here provide an exciting description of new drugs that can reduce ryanodine receptor leak and improve myocardial function. During the interregnum of drug therapies, device-based therapies have contributed to new concepts in heart failure. One of these, cardiac resynchronization therapy (CRT) is discussed by the Kass laboratory, which has made exciting discoveries that suggest the apparent mechanical benefits of CRT emerge, at least in part, but the surprising ability of successful CRT to reprogram sick cellular signaling pathways. The Hajjar laboratory has led the field in developing tools for increasing the uptake of cytoplasmic Ca^{2+} into the SR, using virally mediated over-expression of a Ca^{2+} ATPase with reduced expression in heart failure. His translational studies have recently moved from animals into patients. The Wu laboratory focuses on stem cells as a potential replacement therapy for dead or terminally dysfunctional myocardium, and here provides an overview of progress and challenges in this rapidly moving field. Diabetes is perhaps the most rapidly growing disease with the ability to contribute to heart failure, but the direct impact of diabetes on myocardium is relatively understudied. An article from the Hill laboratory provides a framework for considering the maladaptive signaling consequences of diabetes on myocardium. I hope that you enjoy reading these articles.

With best wishes,

Mark Anderson

Biography

Mark Anderson is the Head of the Department of Internal Medicine at the University of Iowa. He is a clinical cardiac electrophysiologist who has worked on basic signaling mechanisms promoting arrhythmias and heart failure. He grew up in Rochester, Minnesota, graduated from Macalester College, and obtained PhD and MD degrees at the University of Minnesota, working under Drs I.J. Fox and Sue Donaldson. He completed Internal Medicine, Cardiovascular Medicine and Clinical Cardiac Electrophysiology fellowships at Stanford University. Since fellowship he has focused on the role of CaMKII as a

proarrhythmic and procardiomyopathic signal. He began working with Howard Schulman during fellowship and is a co-founder of Allosteros, a biotech aiming to produce enzyme antagonist drugs for cardiovascular indications.