Editorial

Cellular Basis for Therapeutic Choices in Heart Failure

Lionel H. Opie, MD

Stop it at the start; it’s late for medicine to be prepared when disease has grown strong through long delays. —Ovid, Remedia Amoris

A crucial experimental study in 1985 showed that the angiotensin-converting enzyme inhibitor (ACEi) captopril did more than reduce the after- and preload on the heart in failure; captopril also improved remodeling by lessening the degree of left ventricular (LV) dilation. A series of powerful clinical studies starting in 1987 established the crucial role of ACE inhibition in severe heart failure such that it almost became unethical to test other modalities of heart failure therapies except as add-on therapies. Thus, it was difficult to know whether the advent of the angiotensin II subtype I receptor blockers (ARBs) brought improvement beyond those of standard ACEi therapy. The most practical approach was to add an ARB such as valsartan to the therapeutic regimen of patients, 86% of whom were already receiving an ACEi. In the small non-ACEi group, valsartan appeared to be even more effective, but the limited size of the group made it difficult to be sure. Furthermore, the addition of valsartan to the small number of patients already being treated with ACEi and β-blockade appeared to be harmful. These defects have been remedied by another ARB, candesartan, which was evaluated in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) series of studies. The study by Young et al³ represents the effects of candesartan versus placebo given to a prespecified subgroup of patients with heart failure and a low ejection fraction (≤40%). They combined data from the CHARM-Alternative (participants who could not tolerate ACEi) and CHARM-Added (all participants already treated with an ACEi; 55% were also being treated with β-blockers and 17% with spironolactone). Whereas in the original 2 separate CHARM trials mortality was not reduced by added candesartan, the combined study of Young et al on almost double the number of patients showed a small but significant all-cause mortality reduction with a hazard ratio of 0.88 (CI 0.79 to 0.98).

See p 2618

It is not surprising that patients who were not already receiving an ACEi responded positively to the added ARB. Therefore, the most interesting components of the combina-

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Hatter Institute for Cardiology Research, University of Cape Town, Cape Town, South Africa.

Correspondence to Dr Lionel H. Opie, Hatter Institute for Cardiology Research, Chris Barnard Building, Cape Heart Center Faculty of Health Sciences, University of Cape Town, 7925 Observatory, Cape Town, South Africa. E-mail opie@capechoet.uct.ac.za

(Circulation 2004;110:2559-2561.)

© 2004 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000146803.14063.F7

2559
Hyperadrenergic Signaling in Heart Failure

Despite the downregulation of the myocardial β-adrenergic receptor, heart failure can be viewed as a hyperadrenergic state for several reasons. First, β-adrenergic activation is an early and constant event in heart failure in that plasma norepinephrine rises consistently even in untreated heart failure, whereas plasma renin only rises consistently in response to diuretic therapy. Second, in response to exercise, much more marked episodic elevations in plasma norepinephrine occur in heart failure than in healthy hearts, raising the possibility that excess stimulation even of down-regulated receptors could activate intracellular regulatory pathways. Third, basic studies show that in heart failure models responses to β-adrenergic surges with increased ventricular L-type calcium current and cytosolic calcium transients still occur, translating into episodic enhanced contractile activity of failing isolated trabeculae. Limitation of such calcium surges may well explain the capacity of β-blockers to reduce calcium-mediated ventricular arrhythmias that may underlie sudden death in heart failure. These diverse responses could best be explained by excess activation of intracellular β-adrenergic-mediated pathways such as those involving cAMP and protein kinase A (PKA).

Hyperadrenergic circulating catecholamine patterns should be reflected in PKA-induced hyperphosphorylation of intracellular targets, including the internal tail of the β-receptor, thereby leading to receptor desensitization. The current focus is on the ryanodine receptor RyR, which governs the release of calcium from the sarcoplasmic reticular (SR) in response to calcium entry via the L-channel. The hypothesis is that excess PKA-mediated stimulation of the ryanodine receptor results in the depletion of the stabilizing protein (FKBP12.6) so that RyR leaks and malfunctions. In studies on transplanted human hearts, previous β-blockade restored the RyR function, phosphorylation, and levels of the binding proteins toward reference, with improved myocardial compliance and response to isoproterenol. These studies do not explain why the ARB valsartan can restore the function of the ryanodine receptor and normalize the calcium leak from the SR without improving resting cardiac function.

The abnormalities of intracellular cardiac calcium kinetics in heart failure could equally well lie in defective uptake of calcium into the SR by the sarcoplasmic-endoisoplasmic reticulum calcium-uptake pump (SERCA) and, more specifically, the cardiac isoform SERCA2a. In β-blocked patients who are being prepared for organ transplant, the SERCA protein and the calcium transients increase through still-unknown mechanisms, thus helping to explain increased contraction. Other possible mechanisms for the benefit of β-blockade are receptor resensitization, decreased calcium-dependent apoptosis, and a major metabolic effect with increased efficiency of work.

Angiotensin II Signaling in Ventricular Remodeling

Angiotensin II receptor stimulation leads to both growth and apoptosis. Angiotensin II is rapidly released from myocardial cells in response to stretch. Angiotensin II stimulation of the angiotensin II-subtype I (AT)-I receptor leads to the path that activates the mitogen-activated protein kinase group of enzymes, which contains components that promote both growth (eg, extracellular signal-regulated kinase or ERK1/2 and p38-β) and apoptosis (such as c-Jun amino-terminal kinase or JNK and p38-α).

Angiotensin II also stimulates the formation of extracellular collagen. Several profibrotic messengers appear to be involved, including transforming growth factor-β1. Once collagen is formed, deterioration from the collagen-bound hypertrophied LV to the dilated LV depends on the breakup of collagen crosslinks, an event that is mediated by matrix metalloproteinases. What activates these enzymes? Besides mechanical factors, the renin-angiotensin system promotes the activity of matrix metalloproteinases, thereby increasing ventricular dilation (Figure). Collectively, these studies and others demonstrate the crucial role of angiotensin II in cardiac remodeling and explain why the ARB losartan was better able than the β-blocker atenolol to decrease myocardial collagen in people with LV hypertrophy.

Aldosterone and Myocardial Fibrosis

The link between renin-angiotensin activation and hyperaldosteronism is long established. Recently, the emphasis has been on locally produced aldosterone that can greatly exceed circulating concentrations. Aldosterone can induce myocardial fibrosis even in the absence of renin-angiotensin activation. Angiotensin II stimulates the synthesis and release of aldosterone from the heart so that both ACEI and ARBs can prevent or ameliorate aldosterone-induced myocardial fibrosis. Some patient data suggest that the benefit of aldosterone blockade may in part be linked to decreased tissue collagen.
Where to Start: β-Blockers, ACEi/ARBs, or Aldosterone Blockers?

The mechanism of protection of β-blockers, ACEi/ARBs, or aldosterone blockers cannot be fully separated because of interlinking signal systems and postreceptor cross-talk, yet each modality has one major effect, namely improved calcium kinetics and cardiac output with β-blockers, decreased adverse remodeling with the ACEi/ARBs, and decreased myocardial fibrosis with the aldosterone blockers. A daring clinical trial would be to pit each of these modalities against the other two in a large multicenter heart failure study. After all, we need to “stop it at the start.” My bet would be on a large multicenter heart failure study. After all, we need to “stop it at the start.” My bet would be on an early event in heart failure, β-blockade should be given earlier and not only added to a preexisting therapy with an ACEi or ARB.27 Indeed, a recent South African study argued for β-blockade even before ACEi in NYHA class II and III patients who are already being treated with diuretics and digoxin.28

Where to Go: Somewhere New?

Perhaps an even more daring trial would be to take a metabolic look at heart failure. The Cape Town hypothesis, based on the novel data of Clarke’s group at Oxford,29 is that there exists a metabolic vicious circle. In the vicious circle, sustained adrenergic activation increases the circulating levels of free fatty acids in the heart, thereby stealing oxygen from glucose and wasting it.30 As Taegtmeyer offers, “The opportunities for regeneration of normal cardiac myocyte function through metabolic interventions seem unlimited,”51 but these opportunities could well start with major clinical trials on agents such as glucagon-like peptide, trimetazidine, and ranolazine, all of which either directly or indirectly lessen fatty acid metabolism and increase the metabolism of glucose.

References

Cellular Basis for Therapeutic Choices in Heart Failure
Lionel H. Opie

Circulation. 2004;110:2559-2561
doi: 10.1161/01.CIR.0000146803.14063.F7
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/17/2559

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/