Editorial

Cellular Basis for Therapeutic Choices in Heart Failure

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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) dilatation.1 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.2 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)4 and CHARM-Added (all participants already treated with an ACEi; 55% were also being treated with β-blockers and 17% with spironolactone).5 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).

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It is not surprising that patients who were not already receiving an ACEi responded positively to the added ARB.4 Therefore, the most interesting components of the combination data came from the CHARM-Added study,5 in which a clear-cut response to the added ARB was noted in patients who were already receiving a β-blocker or the recommended dose of an ACEi (see Figure 3 in the original article). No information was provided in that study or in the combined analysis, however, on the response in patients who were receiving both a β-blocker and full-dose ACEi. Even if all of the patients who received the β-blocker in CHARM-Added also received full-dose ACEi, this number represents only 483 of the 1276 patients treated by candesartan in CHARM-Added, meaning that by current standards (not the same as those when the trial began) the majority were undertreated when the study started. For example, only 17% of the CHARM-Added participants received spironolactone. In the Young et al study, only 472 participants received spironolactone and only 39 of 2289 candesartan-treated patients received ACEi plus β-blocker plus spironolactone.

Good trials often give rise to questions that cannot be answered readily. As already argued, the reanalysis of CHARM by Young et al does not necessarily establish that the added ARB provided any benefit to patients already “fully treated” with the currently recommended mortality-reducing triple therapy (ACEi, β-blockade, and aldosterone blockade). It is also not known whether the benefits of candesartan are drug-specific, especially bearing in mind contradictions from the Valsartan Heart Failure Trial (Val-HeFT)2 and the Valsartan in Acute Myocardial Infarction (VALIANT) studies,6 or whether candesartan might relate to ARBs as a class. The study by Young et al also does not clarify whether to add candesartan or aldosterone blockade to patients who are already receiving dual lifelong therapy (ACEi and β-blockade). In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) study,7 the aldosterone blocker eplerenone was added to the treatment regimen of postinfarct patients (mean ejection fraction of 33%), the vast majority of whom were already being treated with an ACEi or ARB and a β-blocker. Total mortality was reduced by 15% (CI 0.75 to 0.96), which is not much different from the 12% reduction from added candesartan in the study by Young et al.3 Hyperkalemia, a potentially life-threatening complication, increased in both trials,5,7 meaning that previous renal function and serum potassium must be carefully studied before adding the aldosterone blocker or candesartan in the appropriate doses, with careful follow-up.8 In the absence of any comparative trial data, the decision whether to add aldosterone blockade or candesartan after ACEi and β-blockade might be determined by clinical features, the former being preferred if residual edema is observed. In reality, the traditional order of therapy—ACEi before β-blocker and both before aldosterone blockade—largely developed from the sequence in which large persuasive clinical studies were reported. This order should be reexamined, with present experimental knowledge being taken into account.

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

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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 paths. 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 paths 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 reticulum (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-endoplasmic reticulum calcium-uptake pump (SERCA) and, more specifically, the cardiac isoform SERCA2a. In β-blockaded 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)-1 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 β-blockade. It is logical to assume that, with the adrenergic response being such 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. 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.

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, is that there exists a metabolic vicious circle. In the vicious circle, sustained adrenergic activation increases the circulating levels of free fatty acids that in turn promote the activity of uncoupling proteins in the heart, thereby stealing oxygen from glucose and wasting it. As Taegtmeyer offers, “The opportunities for regeneration of normal cardiac myocyte function through metabolic interventions seem unlimited,” but these opportunities could well start with direct lessening fatty acid metabolism and increase the metabolic cost of glucose.

References

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