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# Our new understanding of heart failure: The role of beta-blockers in treatment

## ABSTRACT

Beta-blockers, long considered contraindicated in heart failure, improve left ventricular function in this disease by improving the biology of cardiac myocytes. Whether they improve survival remains to be determined.

## KEY POINTS

Heart failure is a downward spiral, in which impaired ventricular dysfunction elicits a cascade of compensatory mechanisms, including activation of the sympathetic nervous system, the renin-angiotensin system, and a variety of neurohormones. These compensatory mechanisms improve cardiac function in the short term, but worsen it over the long term.

Inotropic agents and some vasodilators can accelerate the pathophysiologic process of heart failure.

Recent findings indicate that beta-blockers, used with angiotensin-converting enzyme inhibitors, blunt the damaging effects of these compensatory mechanisms, improving the biology of cardiac myocytes and preserving ventricular function.

Candidates for beta-blocker therapy should be in stable condition, in class II or III heart failure.

The initial dosage should be very low and increased gradually, with vigilance for signs of cardiac decompensation.

**F**OR A LONG TIME, cardiologists viewed chronic heart failure as essentially pump failure—a syndrome of abnormal hemodynamics and cardiac reserve resulting in shortness of breath, fatigue and inability to exercise. In line with this thinking, treatment emphasized drugs such as inotropes to improve contractility, and vasodilators and diuretics to reduce load,<sup>1</sup> all with the goal of improving resting hemodynamics and exercise tolerance. By pharmacologically manipulating these hemodynamic measures, we hoped to improve outcome.

In the short term, these drugs seemed to work.<sup>2–8</sup> For a time patients could walk farther and faster, and reported having a better quality of life. Unfortunately, in the long term, these same drugs did not improve patient survival and in some cases actually decreased the survival rate.<sup>9–13</sup> The reason for this lack of long-term improvement is that inotropes and vasodilators did not improve the underlying abnormal biologic processes that damage cardiac myocytes as heart failure progresses. In fact, inotropes actually exacerbate these processes.<sup>14</sup>

The understanding of heart failure began to change in the late 1980s, when researchers discovered that angiotensin-converting enzyme (ACE) inhibitors decrease preload and afterload, increase exercise tolerance, stop ventricular remodeling, and increase the survival rate in patients with heart failure.<sup>15–25</sup> The reason for these improvements, as we are now finding out, is that ACE inhibitors improve the underlying biological processes affecting the myocytes.

In the last few years, we have found that beta-blockers can also improve the biology of



the cardiac myocyte, especially when combined with an ACE inhibitor.<sup>14</sup> And in the next few years, we will discover whether the biological benefits of this therapy will translate into prolonged survival.

## ■ WHY HEART FAILURE PROGRESSES

Imagine a patient with asymptomatic heart failure and an ejection fraction of 40%. Four years later, his ejection fraction has decreased to 20%, and he is in class III heart failure on the New York Heart Association (NYHA) scale. Yet he suffered no event such as a myocardial infarction in the intervening years. What happened?

### Response to cardiac injury signals pathologic growth and remodeling

When a normal heart sustains an initial insult (due to a myocardial infarction, myocarditis, long-standing valvular heart disease or hypertension, or some unknown reason), the resulting left ventricular dysfunction activates several compensatory mechanisms<sup>14</sup>:

- Elevated preload stretches the myocytes, activating tissue-level factors such as angiotensin II<sup>26</sup> and atrial natriuretic factor.<sup>27</sup>
- Decreased blood flow in the aorta alters baroreceptor sensitivity, which de-inhibits the sympathetic nervous system, leading to prolonged sympathetic nervous system arousal.<sup>28</sup>
- The renin-angiotensin system and sympathetic nervous system cross-activate each other: release of angiotensin II stimulates presynaptic norepinephrine release,<sup>29,30</sup> and stimulation of beta-1 receptors in the kidney stimulates renin release<sup>31</sup>;
- Other neurohormones, including cytokines (tumor necrosis factor- $\alpha$ , interleukin-6),<sup>32,33</sup> endothelins,<sup>34-36</sup> and peptide growth factors<sup>37-39</sup> may also be activated by the failing heart.

Thus, in the short term, the sympathetic nervous system and the renin-angiotensin system compensate for a failing heart by constricting blood vessels to maintain blood pressure, increasing heart rate and contractility, and increasing preload to augment stroke volume by a Frank-Starling mechanism.<sup>14,40,41</sup>

Unfortunately, over the long term, all of these factors also act as growth signals to the failing heart, triggering a process of pathological growth and remodeling.<sup>14</sup>

### In response to growth signals, heart cells grow abnormally

The adult myocyte is terminally differentiated and so cannot enter the cell cycle and divide.<sup>42,43</sup> Thus, when it receives growth signals, it can only do one of two things: grow abnormally or die by apoptosis.<sup>14,42</sup>

Failing myocytes grow by constructing sarcomeres in series rather than in parallel.<sup>44,45</sup> Thus, they elongate, and as they do they change the size and shape of the left ventricle from small and elliptical to large and more spherical (FIGURE 1).<sup>46,47</sup>

### Failing hearts need more oxygen but get less, leading to ischemia

The change in ventricular geometry increases the stress on the ventricular wall.<sup>48</sup> In turn, the elevation in wall stress leads to an increase in heart rate by sympathetic nervous system stimulation, which in turn leads to an increase in myocardial oxygen consumption.<sup>49,50</sup>

The failing heart also needs more oxygen because the myocytes are becoming less efficient in their use of energy. When myocytes grow pathologically, their ratio of myofibrils to mitochondria increases.<sup>51</sup> In addition, sympathetic nervous system stimulation causes a shift from using carbohydrates (which are efficient fuels) to free fatty acids (which are less efficient).<sup>52</sup>

Another reason these myocytes are less efficient is that as they are stimulated to grow, yet are unable to produce new cells, their genetic coding to produce fetal-like proteins is turned back on. Thus, instead of producing adult forms of myosin (alpha isoforms) to contract and relax the heart muscle, they produce a slower, less-efficient form (beta isoforms).<sup>53</sup> They may also produce other fetal products such as atrial natriuretic peptide and skeletal alpha actin.<sup>26,27,54,55</sup> Experiments in animals suggest that these myocytes also down-regulate their production of calcium-controlling proteins such as sarcoplasmic reticulum calcium ATPase,<sup>55-57</sup> although this has not been definitively shown in humans.

**The sympathetic nervous system, renin, cytokines, and endothelins all promote abnormal cardiac remodeling**

All of these changes further impair ventricular function, leading to a vicious cycle of further neurohormonal activation. Yet, at the same time that the damaged heart needs more oxygen than before, it receives less, due to other processes that limit oxygen delivery to the myocytes. To begin, the large spherical heart is less efficient as a pump; therefore, the coronary perfusion pressure is lower. In addition, the ventricular diastolic pressure is higher. Both of these factors reduce the blood flow to the myocytes.<sup>58</sup>

On the cellular level, angiotensin II stimulates fibroblasts, resulting in an increase in interstitial fibrosis and a change in the skeletal structure of the heart.<sup>59,60</sup> This process increases the distance that oxygen must travel as it diffuses from the capillaries to the myocytes, reducing the amount of oxygen reaching the myocytes.<sup>61–63</sup>

The failing heart thus becomes energy-depleted and can become ischemic, especially in the subendocardium, leading to cell injury and necrosis. Cell necrosis also appears to occur as an end result of direct exposure to norepinephrine<sup>64</sup> and angiotensin II.<sup>65</sup> This process may lead to more myocardial dysfunction.

## ACE inhibitors plus beta-blockers reverse cardiac remodeling

### Apoptosis

Although myocytes can die by the ischemic process described above, they can also die by apoptosis, a noninflammatory process that has been shown to occur in humans with dilated cardiomyopathy. Apoptosis may be mediated by a variety of factors such as tumor necrosis factor, transforming growth factor-beta, binding of the Fas ligand to the Fas receptor, calcium overload, activation of tumor suppressor genes (such as p53), or an increase in free radicals and oxidants, all of which are increased in the failing heart.<sup>66</sup> The resulting progressive cell death may also lead to a vicious cycle of worsening ventricular function and further up-regulation of neurohormones.<sup>14</sup>

### INOTROPIC TREATMENT CAN ACCELERATE HEART FAILURE

Inotropic agents and some vasodilators can stimulate arrhythmias<sup>9,10,67</sup> and further neurohormonal activation<sup>68,69</sup> in patients with

heart failure. Their use may lead to better hemodynamic measures in the short term, but a greater chance of dying in the long term as they accelerate the pathophysiologic process of heart failure.

In contrast, ACE inhibitors and beta-blockers reduce these growth-stimulating signals to the heart,<sup>14</sup> blocking and even in some cases reversing pathological growth.<sup>14,21,22,70</sup> ACE inhibitors by themselves attenuate abnormal growth,<sup>14,21,22</sup> but do not reverse the process, in part because the sympathetic nervous system continues to be activated over time.<sup>71</sup> Consequently, ACE inhibitors have a modest effect on survival.

### BETA-BLOCKERS IMPROVE CARDIAC FUNCTION

More than 15 placebo-controlled studies involving more than 2,000 patients with chronic heart failure due to systolic dysfunction have examined the effect of beta-blockers on ventricular function.<sup>52,72–91</sup> Every study that lasted more than 1 month consistently showed that the left ventricular ejection fraction increases with beta-blocker therapy.

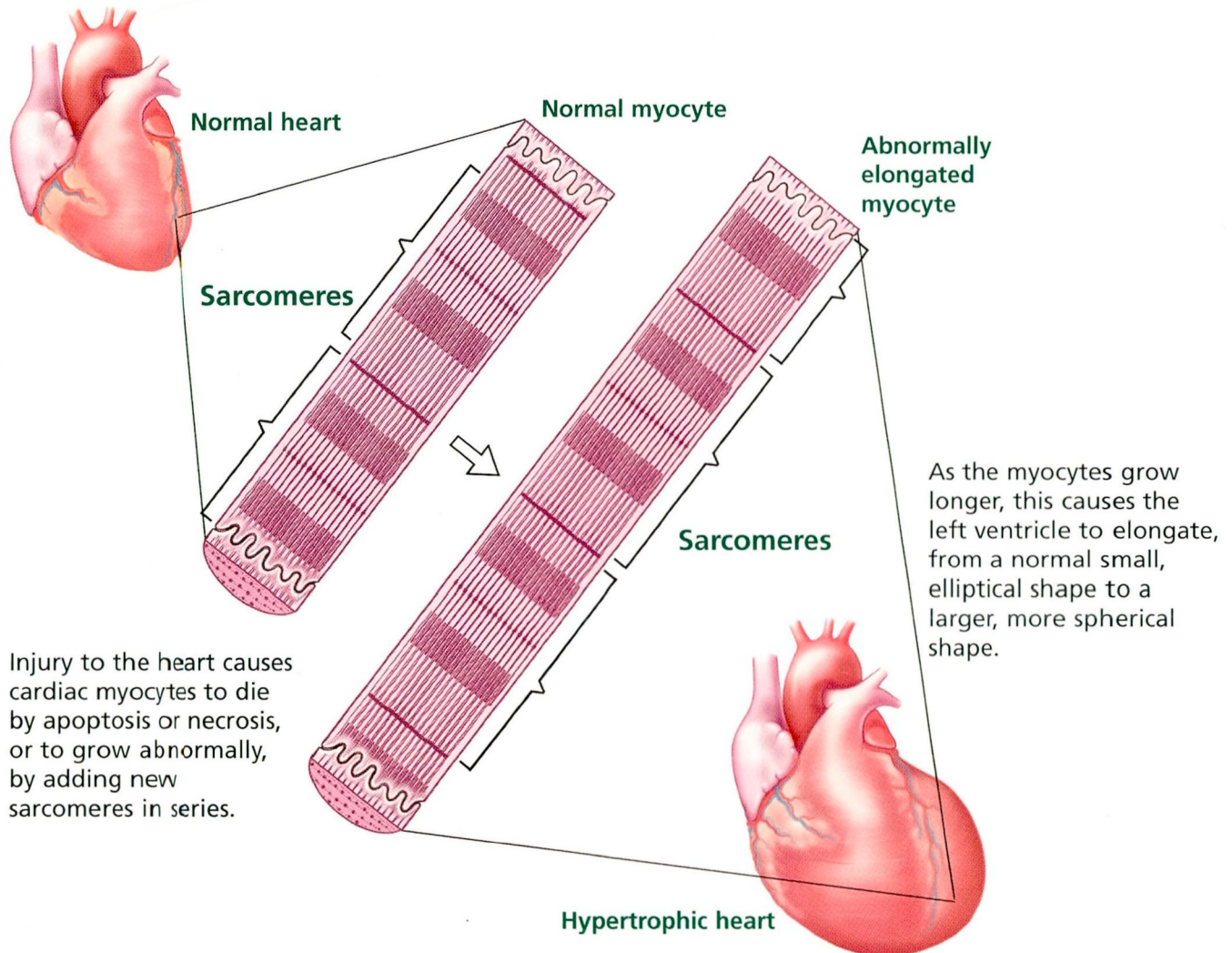
### Ventricular function is improved

Most important, three human studies<sup>52,82,92</sup> and one animal study,<sup>93</sup> using four different beta-blockers, showed that the improvement in ventricular function is due to increased systolic ventricular performance. Improved performance appears to be due to enhanced contractility.<sup>93</sup> Not only does ventricular function improve, but myocardial oxygen consumption—the cost of doing work—does not increase.<sup>52</sup> This means that this therapy improves the mechanical and energy efficiency of the heart.

The improvement in ventricular function appears to be due to a biological effect on the myocytes.<sup>14,94</sup> Evidence for this comes in part from an echocardiographic study showing that the left ventricular ejection fraction does not increase at all during the first month of beta-blocker therapy.<sup>70</sup> Rather, the improvement appears to occur between 1 and 3 months, suggesting a late biological effect. In addition, a recent study demonstrated that as left ventricular function improved, myocyte proteins



## ■ How an injury to the heart causes ventricular dysfunction



**FIGURE 1**

changed from slow beta-myosin heavy chains to the faster, adult alpha-myosin isoform.<sup>94</sup>

### **Pathologic ventricular remodeling is reversed**

Long-term echocardiographic studies have demonstrated that left ventricular mass and volume decrease in response to beta-blocker therapy, and the shape of the ventricle changes from spherical to elliptical.<sup>70,95</sup> This suggests that beta-blockers, when added to ACE inhibitors, may reverse the remodeling

of the failing ventricle, more evidence of a beneficial biological effect.

### **Exercise tolerance: mixed results**

Exercise tolerance increased with beta-blocker therapy in some studies,<sup>72,76,78–80,83–85</sup> but not in others.<sup>75,77,81,82,86–88</sup> Because beta-blockers block the normal increase in heart rate and contractility that occurs in response to exercise (and to norepinephrine spillover during exercise), it is difficult to demonstrate a normalized response to exercise with beta-

blockers on board. However, in placebo-controlled studies, patients taking beta-blockers generally felt better and were better able to perform their daily activities.

Exercise tolerance tends to improve slightly with selective second-generation agents such as metoprolol, atenolol, and bisoprolol, but not with nonselective third-generation agents such as bucindolol, labetalol, and carvedilol.<sup>96</sup> The reason may be that second-generation agents cause less adrenergic blockade, allowing some increase in heart rate and contractility with exercise.<sup>96</sup>

### ■ DO BETA-BLOCKERS REDUCE MORTALITY?

Information from two databases suggest (but do not prove) that beta-blockers will reduce mortality in heart failure.<sup>89,97</sup>

The CIBIS trial<sup>89</sup> examined the effect of bisoprolol on survival in patients with NYHA class III and IV heart failure. The mortality rate was 20% lower in the group receiving bisoprolol than in those receiving placebo, but this trend did not reach statistical significance because the trial was too small.

Four US trials<sup>97</sup> examined exercise capacity and progression of heart failure with the third-generation, nonselective agent carvedilol. These trials failed to demonstrate an improvement in exercise capacity,<sup>87,88</sup> but when the trials were put together and examined by a common data and safety monitoring board, a 65% reduction in all-cause mortality was observed.

The US trials were not designed to examine mortality, had an open-label period prior to randomization (which may have created a selection bias), were too short in follow-up, and had too few events to definitively state that carvedilol reduces mortality. However, the data are highly suggestive. In addition, all four trials together demonstrated a reduction in mortality and hospitalization, and each individual trial was consistent in the direction of these results.

Two carvedilol trials that had longer follow-up, the Mild Heart Failure trial from the US Program<sup>98</sup> and the Australia-New Zealand trial,<sup>86,99</sup> both demonstrated in patients with primarily NYHA class I and II heart failure that carvedilol reduced the combined end-

point of mortality and all-cause hospitalization.

Despite these results, the question of mortality remains unanswered. The US Carvedilol and Australia-New Zealand databases are not sufficient to definitively state that beta-blockade reduces mortality. These databases also do not allow a sufficiently long follow-up (ie, > 12 months) in NYHA class III and IV patients to understand the long-term effects in these patients. For that reason, several ongoing trials in the United States and Europe continue to randomize patients. The Beta-Blocker Evaluation of Survival Trial (BEST)<sup>100</sup> and COPERNICUS trial will randomize patients to the nonselective, third-generation agents bucindolol and carvedilol. The CIBIS II<sup>101</sup> and MERIT-HF trials have randomized patients to the beta-1 selective agents bisoprolol and metoprolol. The CIBIS-2 trial has been terminated early for a presumed mortality benefit, although the data have yet to be revealed.

Although third-generation nonselective agents such as bucindolol, carvedilol, and labetalol have more antiadrenergic properties than beta-1 selective agents such as metoprolol, it is unclear if they protect the heart from sudden death better. One head-to-head trial of carvedilol and metoprolol, the COMET trial, will help to answer this important question.

### ■ HOW TO USE BETA-BLOCKERS

Beta-blockers can be difficult to titrate in patients with heart failure, and this therapy should be administered only by persons trained and familiar with it. Moreover, I recommend the following cautions when starting therapy.<sup>96</sup>

**Beta-blockers are not rescue therapy.** Patients in an unstable condition should not be started on beta-blockers. In general, candidates should be stable outpatients with class II, III, or perhaps early class IV heart failure (although data on class IV usage are currently lacking). When the large mortality studies are completed, we hope we will have insight into when and whom to treat with these promising agents.

**Start low, go slow.** Initial doses must be extremely low, such as one 3.125-mg carvedilol tablet twice a day—or half a tablet

**Titration of beta-blockers may take months, especially in very ill patients**

if the patient is in class IV or has severe right-sided heart failure with jugular venous distention, ascites, and edema.

Thereafter, the patient should come back every week or 2 weeks, and the dose can be doubled at each visit, as tolerated, up to a target of 25 mg of carvedilol twice a day (if the patient weighs less than 85 kg) or 50 mg twice a day (if the patient weighs 85 kg or more). Titration may take months, especially in very ill patients. Patients should be told they should not expect to see any improvement for at least a month after the beta-blocker is started.

**Watch for decompensation.** Patients should weigh themselves every day and contact the physician immediately if they gain more than 2 or 3 pounds. Usually, such fluid retention responds to increasing the dosage of the diuretic or ACE inhibitor temporarily, but if it does not or if the patient seems about to go into cardiogenic shock, the beta-blocker should be reduced or stopped.

At each visit during titration, I also check the blood urea nitrogen level, because some patients with heart failure develop prerenal azotemia while taking beta-blockers.

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