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Effects of Chronic Beta-Receptor Blocker Treatment on Cardiac High-Energy Phosphate Metabolism in Heart Failure

S. Neubauer

In heart failure, chronic therapy with beta-receptor blocking agents improves cardiac performance and prolongs survival, but the exact mechanisms whereby these compounds exert such beneficial effects remain unclear. One hypothesis is that beta-blockers improve the energetic balance of the heart and act, at least in part, by preserving high-energy phosphate metabolism. In experimental heart failure caused by chronic coronary ligation in the rat, the beta-blocker bisoprolol significantly improves cardiac function in parallel to preservation of phosphocreatine stores and intracellular ATP transfer rates, suggesting improved cardiac energetics as one mechanism of action. Clinical evidence on energetic effects of beta-blockers is still only anecdotal. We showed in four patients with dilated cardiomyopathy that the phosphocreatine/ATP ratio, measured by ^{31}P -MR spectroscopy, increases during chronic metoprolol therapy. Currently, a larger systematic placebo-controlled clinical trial of the functional and energetic effects of bisoprolol in dilated cardiomyopathy, followed sequentially by MR imaging and spectroscopy, is underway, which, when completed, should reveal whether beta-blockers in fact preserve high-energy phosphate metabolism in human heart failure. *J Clin Basic Cardiol 2000; 3: 119–22.*

Key words: beta-blocker, energy metabolism, ATP, remodeling

The prognosis of patients with heart failure remains poor, although chronic treatment with β -receptor blockers [1–3] reduces mortality. The mechanisms of the protective effects of β -receptor blockers are only partially understood and are, without doubt, complex and multifactorial. An attractive hypothesis is that in the failing heart, high-energy phosphate metabolism is deranged [4–6], and that the beneficial functional effects of β -receptor blockers are accompanied and possibly accounted for by preservation of high-energy phosphate metabolism. Unfortunately, apart from earlier indirect evidence showing that lactate production is reverted to lactate extraction after beta-blocker therapy in heart failure [7], until recently, no studies were available that examine the potential beneficial effects of beta-blockers on cardiac high-energy phosphate metabolism in heart failure. This is in contrast to work on angiotensin-converting enzyme inhibitors, where a number of experimental studies have shown that these compounds preserve cardiac energy metabolism as part of their beneficial action [8–10]. In the past several years, we have completed both extensive experimental [11, 12] and initial clinical [13] studies that define such effects of chronic beta-blocker treatment in heart failure.

Experimental studies

For our experimental studies, we employed the clinically most relevant heart failure model, that of chronic myocardial infarction following coronary ligation in the rat, as described in detail elsewhere [14, 15]. In this model, left coronary artery ligation (myocardial infarction = MI) or sham operation is achieved under ether anaesthesia. We tested the effects of the beta 1-selective blocker bisoprolol in comparison to a well-defined compound that has been shown to be protective in this model, the ACE inhibitor captopril. Rats were assigned to one of six groups: untreated sham (sham, $n = 9$), untreated MI (MI, $n = 8$), bisoprolol-treated sham (sham + biso, $n = 13$), bisoprolol-treated MI (MI + biso, $n = 6$), captopril-treated sham (sham + capto, $n = 11$) and captopril-treated MI (MI + capto, $n = 6$). After surgery,

bisoprolol-treated groups received 60 mg/kg/day bisoprolol. Captopril was added to the drinking water at 2 g/l. These concentrations were chosen since they were shown to exert a small but significant haemodynamic effect (10 % reduction of blood pressure (captopril) or heart rate (bisoprolol)) [11, 16].

Eight weeks after left coronary artery ligation, hearts were isolated and perfused in the Langendorff mode. Performance was measured with a left ventricular balloon, and Frank-Starling curves were obtained by stepwise increases of the balloon volume. ^{31}P -MR spectroscopy of perfused hearts at 7 Tesla was used to measure the high-energy phosphate compounds ATP, phosphocreatine (PCr) and inorganic phosphate (Pi). The free cytosolic ADP concentration was calculated by using [ATP], [PCr] and $[\text{H}^+]$ measured in the intact beating heart by ^{31}P -MR spectroscopy and total creatine measured chemically in right ventricular homogenates, and the free energy change of ATP hydrolysis (ΔG) was calculated as described elsewhere [11, 12].

Intracellular ATP transfer (creatine kinase reaction velocity) was quantified by ^{31}P -MR magnetization transfer measurements as previously described [5, 17]. Total creatine was determined by HPLC, creatine kinase total and isoenzyme activity by spectrophotometry and gel electrophoresis [11]. Infarct size was determined histologically after formalin fixation [12], and groups were matched for similar infarct sizes ($\sim 40\%$), a requirement for meaningful comparisons of treatment effects.

With bisoprolol treatment, the increase in left ventricular weight that occurs in infarcted hearts was no longer significant (Table 1). Infarction led to an increase in right ventricular weights which was prevented by both bisoprolol and captopril. Thus, both bisoprolol and captopril prevented post-MI cardiac hypertrophy. The table also shows that maximum left ventricular developed pressure, a preload-independent index of contractility, was reduced in infarcted hearts, and this decrease was prevented by bisoprolol, but only partially by captopril. Thus, chronic beta-receptor blockade also counteracted the development of chronic left ventricular dysfunction.

Table 1. Ventricular weights, functional and metabolic measurements

	Sham	MI	Sham + biso	MI + biso	sham + capto	MI + capto
LV weight [g]	1.09 ± 0.06	1.44 ± 0.07*	1.11 ± 0.07	1.32 ± 0.08	0.88 ± 0.03†	1.13 ± 0.06*
RV weight [g]	0.26 ± 0.02	0.38 ± 0.03*	0.28 ± 0.02	0.28 ± 0.02	0.25 ± 0.02	0.23 ± 0.01†
LVDP _{max} [mmHg]	185 ± 11	133 ± 9*	239 ± 12†	223 ± 14†	214 ± 11	160 ± 10
PCr [mM]	13.5 ± 0.7	10.6 ± 0.6*	13.4 ± 0.8	13.0 ± 0.9	14.1 ± 0.4	12.9 ± 0.8
ADP [μM]	77.4 ± 11.8	91.0 ± 5.4	111.2 ± 9.2	107.9 ± 26.7	73.8 ± 12.1	86.4 ± 12.0
ΔG [kJ/mol]	-61.2 ± 1.7	-59.0 ± 0.5	-58.7 ± 0.7	-58.9 ± 1.0	-60.2 ± 0.6	-60.0 ± 0.8
% mito-CK	31 ± 1	24 ± 2*	30 ± 1	29 ± 1	29 ± 1	30 ± 1
% MB-CK	14 ± 1	19 ± 2*	12 ± 1	13 ± 1†	14 ± 1	15 ± 1

Left ventricular weight (LV weight); right ventricular weight (RV weight), maximum left ventricular developed pressure (LVDP_{max}); phospho-creatine (PCr); ADP; free energy change (ΔG); creatine kinase %mito-, %MB-isoenzyme content. * p < 0.007 sham versus MI, † p < 0.007 bisoprolol- or captopril-treated versus untreated

Representative ³¹P-MR spectra from the various groups of hearts are shown in Figure 1. ATP and inorganic phosphate levels were similar among groups, but there was a significant reduction of the PCr resonance in untreated chronically infarcted hearts (10.6 ± 0.6 vs 13.5 ± 0.7 mM in untreated sham-operated hearts, p < 0.007). With bisoprolol-treatment, PCr remained almost unchanged during development of heart failure, while captopril partially prevented the reduction of PCr. There was no effect of treatment on ³¹P-metabolites in the sham-operated groups. Free cytosolic ADP concentrations were, on average, 89 ± 5 μM, and ΔG values were -59.5 ± 0.4 kJ/mol, with no significant differences among groups under baseline contractility conditions studied here. Figure 2 shows that creatine kinase reaction velocity was reduced in all infarcted hearts, but significantly less so in hearts treated with either bisoprolol or captopril. Thus, energy reserve via creatine kinase remained at higher levels when infarcted hearts were treated with either the beta-blocker bisoprolol or the ACE inhibitor captopril. The table also summarizes some of the results of enzyme analysis (for a detailed analysis, see [11, 12]). Creatine kinase isoenzyme distribution showed the changes characteristic of failing myocardium: A decrease of mito-CK activities and an increase of fetal B-containing isoenzymes. Treatment with bisoprolol or captopril completely prevented all changes in creatine kinase isoenzyme activities after MI, both in absolute (not shown) and relative terms.

In these experimental studies, we systematically analyzed the effects of beta-receptor blockers in comparison to ACE inhibitors on the various components of cardiac energy metabolism in the post-myocardial infarction rat model: Unequivocally, we demonstrate that the beneficial functional effects of both bisoprolol and captopril treatment are accompanied by beneficial effects on cardiac energy metabolism: Increased PCr content and creatine kinase reaction velocity; increased mitochondrial creatine kinase activities; and prevention of the fetal reprogramming with relative increase of the B-containing creatine kinase isoenzymes. It is likely that beta-receptor blockers, as well as ACE inhibitors, exert their beneficial effects mainly by chronically reducing the energetic needs of the heart, via reduction of heart rate and pre- and afterload, respectively. In addition, it is possible that these agents interfere more directly with energy metabolism, one potential site of action being the sarcolemmal creatine transporter [18].

The question is whether the observed beneficial effects on cardiac energy metabolism are causally related to the improvement of left ventricular function and geometry, or whether they merely are epiphenomena of the treatment with these compounds. The presently available data do not provide a final answer, but allow us to speculate: In principle, energy metabolism could limit performance in heart failure by three distinct mechanisms: (1) a reduction of ATP

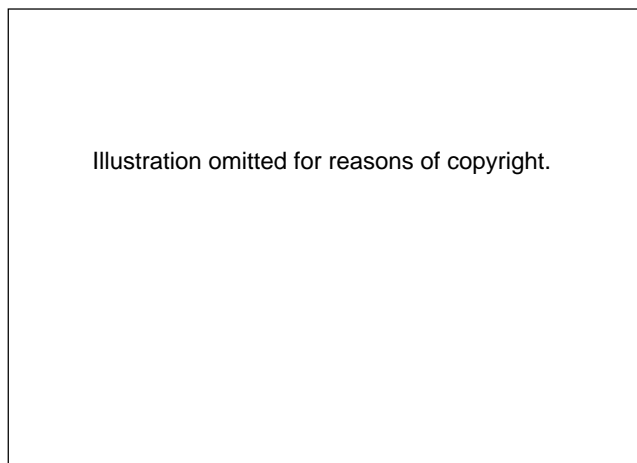


Figure 1. Typical ³¹P-MR spectra of sham operated and infarcted rat hearts, untreated or treated with bisoprolol or captopril. Preservation of the phosphocreatine resonance by bisoprolol in heart failure is evident. The area under each resonance is proportional to the respective metabolite content. From reference [12], printed with permission from the American Physiological Society.



Figure 2. Mean creatine kinase reaction velocity (ATP transfer rates) of sham operated and infarcted rat hearts, untreated or treated with bisoprolol or captopril. Preservation of ATP turnover rates by both captopril and bisoprolol. * p < 0.007 sham versus MI; † p < 0.007 bisoprolol- or captopril-treated versus untreated. From reference [12], printed with permission from the American Physiological Society.

content, (2) decrease of ATP transfer and thus, ATP availability at the myofibrils, and (3) a reduction of the free energy change of ATP hydrolysis. Since steady state ATP levels are unchanged in our model of heart failure, simply a preservation of ATP levels can be ruled out as a mechanism. In contrast, ATP transfer rates are reduced substantially in post-myocardial infarction rat hearts, and this reduction is almost completely prevented by bisoprolol and, to a lesser extent, by captopril. Thus, maintenance of ATP transfer, ie, energy reserve via creatine kinase, may be involved in the protective effect of beta-receptor blockers and ACE inhibitors. Finally, ΔG values remained unchanged for the baseline performance conditions studied here. However, Tian et al. [19] have demonstrated that hearts with a compromised creatine kinase system show reduced contractile reserve. It is, thus, conceivable that the effects of reduced creatine kinase flux and inability to maintain high ΔG combine to limit the contractile reserve of the failing heart during inotropic stimulation, and beta-receptor blockers may be able to maintain energy metabolism under these conditions. Therefore, these results do not prove a causal relation between the observed beneficial functional and energetic effects, but the findings are consistent with the view that preservation of energy metabolism explains, at least in part, the favourable effects of beta-receptor blockers and ACE inhibitors in chronic heart failure.

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Figure 3. ^{31}P -MR spectra of a patient with dilated cardiomyopathy before (upper panel) and 3 months after treatment with digitalis, diuretics, ACE inhibitors and β -blockers (lower panel). As the clinical status was improved from NYHA class III to II, the PCr/ATP ratio was increased. PDE = phosphodiesterases, 2/3 DPG = 2/3 diphosphoglycerate. From reference [13], printed with permission from the American Heart Association.

Clinical studies

^{31}P -MR spectroscopy is the only technique which allows the non-invasive determination of cardiac high-energy phosphate metabolism in the human heart [20, 21]. However, while experimentally, comparison with a ^{31}P -concentration standard or wet chemical analysis makes absolute quantification of high-energy phosphates straightforward, clinically, until recently, one had to resort to calculating the phosphocreatine/ATP ratio as an indirect measure of the energetic state of the heart. We and others have shown that in heart failure due to dilated cardiomyopathy, this ratio is significantly reduced [6, 13]. The only evidence on the chronic effects of beta-receptor blocker treatment in human heart failure comes from our previous work, where we studied six patients with dilated cardiomyopathy before and after 3 months of medical therapy leading to clinical recompensation, and four out of these six patients were treated with the betablocker metoprolol (50 mg/day). Figure 3 shows typical ^{31}P -spectra, Figure 4 phosphocreatine/ATP ratios during treatment, which increased significantly from 1.51 to 2.15 [13]. While this is no more than anecdotal evidence, this finding shows that with ^{31}P -MR spectroscopy, one can follow the energetic response of the human heart to chronic drug treatment. This is a critical ability, since all energetically favourable forms of heart failure treatment have so far ultimately proved beneficial while all energy-costly forms (with the possible exception of digitalis) have proven detrimental. More recently, we developed the tools to not only determine phosphocreatine/ATP ratios in the human heart but also absolute concentrations of high-energy phosphates using " ^{31}P -SLOOP-MR spectroscopy" [22]. With this method, we can now non-invasively determine myocardial ATP and phosphocreatine contents in mmol/kg; our initial experience indicates that ATP levels are decreased by about 20 % in heart failure, suggesting that the phosphocreatine/ATP

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Figure 4. PCr/ATP ratios before and after 12 ± 6 weeks of drug therapy in 6 patients with DCM. There was a significant increase of PCr/ATP from 1.51 ± 0.32 to 2.15 ± 0.27 (* $p < 0.01$). From reference [13], printed with permission from the American Heart Association.

ratio underestimates true alterations of high-energy phosphates that occur in heart failure. We currently are performing a placebo-controlled trial in patients with dilated cardiomyopathy, where we follow the functional effects of chronic bisoprolol treatment in comparison to placebo using MR imaging and the energetic effects (ie, ATP, phosphocreatine levels and their ratio) using MR spectroscopy. When this study is completed, it will answer the question whether in human heart failure, chronic beta-blocker treatment preserves cardiac high-energy phosphate metabolism. If so, this would also further fuel the search for treatment strategies that specifically improve high-energy phosphate metabolism, and one most likely target for such an approach is the myocardial creatine transporter [23].

Conclusion

Beta-receptor blockers improve both cardiac performance and prognosis in chronic heart failure. Experimental studies have shown that these effects are accompanied by beneficial actions on cardiac high-energy phosphate metabolism, where the beta-blocker bisoprolol preserved both steady-state and dynamic (turnover rates) levels of high-energy phosphates. This is most likely one facet of beta-blocker effects that contributes to their protective action in heart failure. Clinical evidence on the energetic effects of beta-blockers in heart failure is sporadic, but metoprolol can improve the myocardial phosphocreatine/ATP ratio of the failing human heart. The results of a larger systematic placebo-controlled trial of the energetic effects of bisoprolol in dilated cardiomyopathy should become available within the next two years.

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