Chronic Treatment with Carvedilol Improves Ca\(^{2+}\)-Dependent ATP Consumption in Triton X-Skinned Fiber Preparations of Human Myocardium


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ABSTRACT

Evidence is given that \(\beta\)-blocker treatment differentially influences gene expression and up-regulation of \(\beta_1\)-adrenoceptors in human myocardium. Here, we investigate whether long-term treatment with carvedilol or metoprolol may functionally alter myofibrillar function in end-stage human heart failure. Investigations were performed in Triton X (1%, 4°C, 20 h)-skinned fiber preparations of explanted hearts from patients undergoing heart transplantation due to idiopathic dilative cardiomyopathy. Five patients were not on \(\beta\)-adrenoceptor blocker treatment (DCM_NBB), and 5 patients received either carvedilol (DCM_CAR) or metoprolol (DCM_MET). Nonfailing (NF) donor hearts (\(n = 5\)), which could not be transplanted due to technical reasons, were investigated for comparison. Ca\(^{2+}\)–dependent tension (DT) development and actomyosin-ATPase activity (MYO) were measured and tension-dependent ATP consumption was calculated by the ratio of DT and MYO ("tension cost").

In addition, we measured the phosphorylation of troponin I (TNI) by back phosphorylation. Maximal DT and TNI phosphorylation were reduced, with myofibrillar Ca\(^{2+}\) sensitivity of DT and MYO as well as tension cost being increased in DCM_NBB compared with NF. Metoprolol treatment restored TNI phosphorylation, decreased Ca\(^{2+}\) sensitivity of tension development and of myosin-ATPase activity, but did not alter the tension-dependent ATP consumption. Carvedilol treatment improved maximal DT and significantly decreased tension-dependent ATP consumption without altering myofibrillar Ca\(^{2+}\) sensitivity. TNI dephosphorylation was increased in patients treated with carvedilol. In conclusion, chronic \(\beta\)-adrenoceptor blockade functionally alters myofibrillar function. The more economic cross-bridge cycling in patients under carvedilol treatment may provide an explanation for the efficacy of carvedilol in the treatment of chronic heart failure patients.

The results of a recent clinical trial suggest that carvedilol may be superior to metoprolol in the treatment of heart failure patients (Poole-Wilson et al., 2003). This result may be due to the fact that myocardial contractility is decreased less when carvedilol is used instead of metoprolol as shown by some clinical trials investigating smaller patient populations (Gilbert et al., 1996; Sanderson et al., 1999; Metra et al., 2000). The reasons for the minor cardiodepressant effects of carvedilol in comparison to metoprolol are unclear. It has been shown previously that treatment of heart failure patients with \(\beta\)-adrenoceptor blockers results in alterations of gene expression regarding myofibrillar proteins (Lowes et al., 2002). Thus, changes in the myofibrillar response to Ca\(^{2+}\) may be an explanation for the differences between the inotropic effects of \(\beta\)-adrenoceptor blockers. We have demonstrated previously that myofibrillar Ca\(^{2+}\) sensitivity of human myocardium is not altered acutely by carvedilol or metoprolol treatment under in vitro conditions (Bundkirchen et al., 2001); however, changes in myofibrillar Ca\(^{2+}\) responsiveness due to \(\beta\)-adrenoceptor blocker treatment may occur during chronic treatment. Therefore, we investigated Ca\(^{2+}\)-dependent tension and actomyosin-ATPase activity in

ABBREVIATIONS: DCM, dilative cardiomyopathy; NF, nonfailing; MET, metoprolol; CAR, carvedilol; NBB, non-\(\beta\)-adrenoceptor blocker treatment; pCa, −log [Ca].

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chemically skinned fiber preparations of left ventricular myocardium from patients who were on treatment with carvedilol (DCM_CAR) or metoprolol (DCM_MET). Left ventricular failing myocardium from patients who did not receive β-adrenoceptor blocker treatment (DCM_NBB) as well as nonfailing (NF) left ventricular myocardium was studied in comparison.

**Materials and Methods**

**Cardiac Tissue**. Failing left ventricular tissue was obtained during cardiac transplantation. Patients suffered from heart failure clinically classified as New York Heart Association class IV on the basis of clinical symptoms and signs as judged by the attending cardiologist shortly before operation. All patients gave written informed consent before surgery. Only male patients aged between 40 and 60 years were included for the present study. The treatment with carvedilol and metoprolol, respectively, had been administered for approximately 2 to 12 months. The patients’ characteristics are given in Table 1. Drugs used for general anesthesia were flunitrazepam and pancuronium bromide with isoflurane. Cardiac surgery was performed on cardiopulmonary bypass patients with cardioplegic arrest during hypothermia. The cardioplegic solution (a modified Bretschneider solution) contained 15 mM NaCl, 9 mM KCl, 4 mM MgCl2, 180 mM histidine, 2 mM tryptophan, 30 mM mannitol, and 1 mM potassium dihydrogen oxoglutarate.

Nonfailing human myocardium was obtained from donor hearts, which were rejected for further transplantation due to technical reasons. The mean age of the donor group was 50.6 ± 2.8 years. No cardiac catheterization had been performed in the organ donor group, but none of the donors had a history of heart disease and all had normal left ventricular function as measured by echocardiography. The study was approved by the local ethics committee.

**Chemically Skinned Left Ventricular Fibers**. Left ventricular muscle fibers were prepared with minor modifications as described previously (Brixius and Schwinger, 2000). In brief, frozen cardiac tissue had normal left ventricular function as measured by echocardiography and was successfully increased every 30 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979). Measurement of developed tension and myosin-ATPase activity started after 3 s. Free Ca2+ concentration was determined by calculating programs designed for experiments in skinned muscle cells (Fabioti and Fabioti, 1979).

**Immunocytochemistry and Measurement of Sarcomere Length**. Skinned fibers of human hearts, prepared as described above, were used for immunocytochemical labeling of the Z-lines by α-actinin staining. After three washes in 0.1 mM phosphate-buffered saline buffer, the skinned fiber preparations were incubated in a 1:800 dilution of mouse anti-rat α-actinin antibody for 1 h at room temperature, followed by treatment with a secondary biotinylated goat anti-mouse antibody (1:400) for 1 h and Cy3-labeled extravidin (1:600) for 1 h (Ji et al., 1999). Afterward, the skinned fibers were washed with 0.1 M Tris-buffered saline and stored at −20°C until the sarcomere length measurements.

The measurements of sarcomere length were performed using a Zeiss Axiovert 135 fluorescence microscope (Zeiss, Oberkochen, Germany), a Sony three chip camera, and computer-assisted imaging software (Optimas 6.01). For investigation of the sarcomere length, the skinned fibers were fixed at slack position in relaxation solution. The distance of 10 to 15 actin/Cy3-labeled Z-lines was measured at 10 different areas of each skinned fiber using a 40× Neofluar objective (Zeiss). The sarcomere length was calculated by dividing the measured distance by the number of spaces between labeled Z-lines. The mean of sarcomere length for each skinned fiber was calculated from all investigated areas. The experiments were performed as described previously (Brixius and Schwinger, 2000). Average sarcomere length was 1.95 ± 0.04 μm.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of patients with DCM</th>
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<td>No.</td>
<td>Group</td>
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<td>1</td>
<td>NBB</td>
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<td>2</td>
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<td>3</td>
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<td>14</td>
<td>CAR</td>
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<tr>
<td>15</td>
<td>CAR</td>
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EF, ejection fraction (%); LVDEP, left ventricular end-diastolic pressure (mm Hg); CI, cardiac index (l · min⁻¹ · m⁻²); NI, nitrates; Diu, diuretics; Gly, glycosides; ACE, angiotensin-converting enzyme inhibitors; AT1, AT2, antagonists.
5 mM histidine-HCl, 0.2 mM dithiothreitol, 25 mM NaF, 10 mM EDTA, 50 mM NaH2PO4, and 0.1 mM phenylmethylsulfonyl fluoride (pH 7.4). The homogenates were stored at −80°C. For back phosphorylation, 40 μg of protein (final verification by Bradford’s assay (Bradford, 1976)) were phosphorylated in a medium containing 40 mM histidine-HCl, 100 mM NaCl, 10 mM MgCl2, 15 mM NaF, 1 mM EDTA, 1% Triton X, 100 μg of BSA, and 0.5 U/ml catalytic subunit of protein kinase A in the presence of 50 μM [γ-32P]ATP (pH 6.8). The reaction was stopped after 10 min with ice-cold stop solution containing 50 mM HEPES, 0.5 mM ATP, and 15% trichloroacetic acid. After centrifugation (2000g, 20 min), the precipitate was directly processed for electrophoresis in sample buffer (50 mM H3PO4, 5 M EDTA, 1% mercaptoethanol, 2% SDS, 10% glycerol, and a trace of bromphenol blue as tracking dye, pH 6.8 adjusted with Tris), boiled at 95°C for 5 min, and subjected to a 7.5% urea/SDS-polyacrylamide gel electrophoresis as described previously (Swank and Munkres, 1971). Gels were stained with Coomassie blue and destained with methanol/acetic acid/water (3:1:6 v/v). As molecular mass marker, the kaleidoscope stained marker (with seven marker proteins) from Bio-Rad (Hercules, CA) was used. The gels were exposed to X-ray films. Autoradiography using X-OMAT film (Eastman Kodak, Rochester, NY) and intensifying screens permitted the detection of 32P-labeled proteins on the gels. Densitometric units of the signals were investigated by scanning the respective bands for troponin I of the whole autoradiogram. The band intensities were evaluated by densitometric scanning using a computerized imaging system. Previous measurements reveal evidence that the troponin I content is similar without nonfailing and DCM (nonischemic) failing hearts. Therefore, we assume that the protein content of our preparations reflects that of the myofibrillar proteins.

Materials. All chemicals were of analytical grade or the best grade commercially available. The 30% acrylamide/bisacrylamide and kaleidoscope stained marker were from Bio-Rad and γ-32P]ATP from ICN (Eschwege, Germany). All compounds were dissolved in twice-distilled water. Applied agents did not change the pH of the medium.

Statistics. All values are means ± S.E.M. unless otherwise noted. One-way ANOVA was used to test significance. p values of <0.05 were accepted as significant. pCa force as well as pCa actomyosin-ATPase activity (EC50 for Ca2+ estimation) and intensifying screens permitted the detection of 32P-labeled proteins on the gels. Densitometric units of the signals were investigated by scanning the respective bands for troponin I of the whole autoradiogram. The band intensities were evaluated by densitometric scanning using a computerized imaging system. Previous measurements reveal evidence that the troponin I content is similar without nonfailing and DCM (nonischemic) failing hearts. Therefore, we assume that the protein content of our preparations reflects that of the myofibrillar proteins.

Results

Nonfailing Versus Failing Myocardium in the Absence of β-Adrenoceptor Blocker Treatment. The present study investigated the influence of chronic β-adrenoceptor blocker treatment on myofibrillar function in human myocardium. Table 2 summarizes the results obtained in Triton X-skinned fiber preparations by simultaneous measurements of Ca2+-dependent force and actomyosin-ATPase activity in DCM_NBB in comparison to NF myocardium.

In DCM_NBB, maximal Ca2+-dependent tension was significantly decreased compared with NF. This was accompanied by a significant increase in Ca2+-sensitivity of tension and actomyosin-ATPase activity in DCM_NBB compared with NF. There was no difference in Ca2+-activated actomyosin-ATPase activity between the two groups.

Tension Development after Chronic Treatment with Carvedilol or Metoprolol. Figure 1 summarizes the results obtained for Ca2+-dependent tension development in human nonfailing and failing myocardium with and without β-blocker treatment. The depression of maximal Ca2+-dependent tension in DCM_NBB was not restored in patients chronically treated with metoprolol. However, metoprolol significantly shifted the Ca2+-concentration/tension relationship to the right (EC50 of Ca2+ tension DCM_MET, 0.60 ± 0.03); i.e., metoprolol decreased the Ca2+-sensitivity of human failing myocardium to values similar to those obtained in human nonfailing hearts (Table 2). In contrast to metoprolol, carvedilol significantly increased maximal Ca2+-dependent tension (although the tension development was not fully restored compared with human nonfailing myocardium), without altering the Ca2+-sensitivity of myofibrillar tension (EC50 of Ca2+ tension DCM_CAR, 0.52 ± 0.05). There were no significant alterations between the Hill coefficients of the four groups (nH of ATPase NF, 1.33 ± 0.06; DCM_CAR, 1.90 ± 0.04; DCM_NBB, 1.70 ± 0.06; DCM_MET, 2.20 ± 0.04). This means that after chronic treatment with carvedilol, the Ca2+-sensitivity of human failing myocardium is still significantly increased in failing compared with nonfailing hearts.

Actomyosin-ATPase Activity. In human heart failure, the ATP turnover is a critical point for the pathophysiology of the disease, because the ATP supply is hampered in the failing human myocardium. Both carvedilol and metoprolol decreased the maximal Ca2+-dependent actomyosin-ATPase activity (Fig. 2, left). In addition, metoprolol (EC50 of Ca2+ ATPase DCM_MET, 0.54 ± 0.03), but not carvedilol (EC50 of Ca2+ tension DCM_CAR, 0.44 ± 0.03), induced a rightward shift of the Ca2+-sensitivity of the actomyosin-ATPase activity (Fig. 2, right; Table 2). Hill coefficients of the Ca2+ /actomyosin-ATPase activity were similar for all four groups (nH of ATPase NF, 1.33 ± 0.06; DCM_NBB, 1.37 ± 0.04; DCM_MET, 1.34 ± 0.06; DCM_CAR: nH, 1.40 ± 0.04).

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NF (n = 5 Men)</th>
<th>DCM_NBB (n = 5 Men)</th>
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<tr>
<td>Tension</td>
<td></td>
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<tr>
<td>Maximum (mN/mm²)</td>
<td>21.4 ± 1.9</td>
<td>13.7 ± 1.5 *</td>
</tr>
<tr>
<td>EC50 Ca²⁺ (μM)</td>
<td>0.71 ± 0.07</td>
<td>0.43 ± 0.04 *</td>
</tr>
<tr>
<td>Actomyosin-ATPase activity</td>
<td></td>
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<tr>
<td>Maximum (μM ADP%/s)</td>
<td>40.2 ± 2.2</td>
<td>45.4 ± 1.6 *</td>
</tr>
<tr>
<td>EC50 Ca²⁺ (μM)</td>
<td>0.64 ± 0.04</td>
<td>0.38 ± 0.02 *</td>
</tr>
<tr>
<td>Tension-dependent ATP consumption</td>
<td>α (μM ADP·s⁻¹/(mm²·mmN⁻¹))</td>
<td>1.79 ± 0.03</td>
</tr>
</tbody>
</table>

α, slope of the myosin-ATPase/tension relationship; EC50 Ca²⁺, Ca²⁺ concentration at which a 50% increase of tension or myosin-ATPase activity was achieved. * p < 0.05 vs. NF.
Tension-Dependent Myofibrillar ATP Consumption and β-Adrenoceptor Blocker Treatment. The tension-dependent ATP consumption was evaluated by the ratio of Ca^{2+}-dependent tension and suprabasal actomyosin-ATPase activity for the very steep part of the Ca^{2+}/tension, namely, actomyosin-ATPase relationship. A linear line fit was done for all data points obtained in the different groups. Figure 3 shows the results. Metoprolol treatment did not significantly alter the tension-dependent ATP consumption in human failing myocardium. In contrast, carvedilol completely restored the increased tension-dependent ATP consumption. The tension-dependent ATP consumption of Triton X-skinned fiber preparations obtained from human failing myocardium of patients who had undergone chronic treatment with carvedilol was similar to that of human nonfailing myocardium.

Troponin I Phosphorylation. It has been shown that the increased myofibrillar Ca^{2+} sensitivity of human failing myocardium may be due to alterations in the phosphorylation of contractile proteins, e.g., troponin I (van der Velden et al., 2003a,b). Therefore, we investigated the phosphorylation status of troponin I using the back phosphorylation technique. Figure 4 presents the original blots as well as the summarized data. Although the phosphorylation varied within the different samples of one group, back phosphorylation of troponin I was significantly increased in myocardium of heart failure patients who had not been treated with β-adrenoceptor blockers compared with nonfailing myocardium, which indicates a higher phosphorylation status in nonfailing myocardium. Although chronic treatment with metoprolol reversed this situation in DCM, the dephosphorylation of troponin I was further decreased in human failing myocardium in hearts of patients chronically treated with carvedilol.

Discussion

The present study investigated Ca^{2+}-dependent tension and myosin-ATPase activity in patients suffering from di-
increased Ca$^{2+}$ renoceptor treatment differentially influences myofibrillar
significantly increased maximal Ca$^{2+}$ (Omerovic et al., 2003). Indicating that the increased Ca$^{2+}$
different groups (Wolff et al., 1996; van der Velden et al.,
and have also been confirmed in single-cell preparations by
Carvedilol did not alter myofibrillar Ca$^{2+}$ has been described for metoprolol (Omerovic et al., 2003).
may be the consequence of the 
 phosphorylation of troponin I, which
because of an increased phosphorylation of troponin I, which
explained cardiomyopathy who had been treated without a 
$\beta$-adrenoceptor blocker or who had received chronic treatment
with carvedilol or metoprolol. Evidence is provided that $\beta$-adrenoceptor
treatment differentially influences myofibrillar function. Chronic treatment with metoprolol restores the
increased Ca$^{2+}$ sensitivity of the myofilaments at least partly
because of an increased phosphorylation of troponin I, which
may be the consequence of the $\beta$-adrenergic remodeling, as
has been described for metoprolol (Omerovic et al., 2003).
Carvedilol did not alter myofibrillar Ca$^{2+}$ sensitivity but
significantly increased maximal Ca$^{2+}$-dependent tension
development by simultaneously decreasing the Ca$^{2+}$-dependent
ATP consumption. The more economic cross-bridge
cycling in patients under carvedilol treatment may be one
explanation for the efficacy of carvedilol in the treatment of
chronic heart failure patients.

Alterations of Myofibrillar Function in Human Failing Myocardium. In the present study it was shown that
myofibrillar Ca$^{2+}$ sensitivity of myofibrillar function is
significantly increased in heart failure patients without $\beta$-adrenoceptor blocker treatment. These findings are in agreement
with previous results from our group (Brixius et al., 2002)
and have also been confirmed in single-cell preparations by
different groups (Wolff et al., 1996; van der Velden et al.,
2003b) indicating that the increased Ca$^{2+}$ sensitivity is a
phenomenon that can be attributed to alterations on the
cardiomyocyte itself and is not solely due to alterations of the
extracellular matrix, which have been described in human
heart failure (for review, see Jane-Lise et al., 2000). However,
the results of the present study are in contrast to a study on
right ventricular myocardium of human failing hearts (Hajjar et al., 1992), indicating that regional differences exist in
heart muscle regarding myofibrillar function. Only recently,
regional differences have been described for human
right atrial and left ventricular myocardium (Narolska et al.,
2005). In addition, the present findings are in contrast to

Although the $\beta$-blockers metoprolol and carvedilol have
been shown to be beneficial for heart failure patients and to
significantly prolong the survival of these patients to a similar
extent (for review, see Domanski et al., 2003), the
pharmacodynamic profile of the two drugs is different. Thus,
carvedilol but not metoprolol is a scavenger of radicals and
thus unfolds antioxidant properties that may significantly
contribute to its beneficial effects in heart failure (Flesch et
al., 1999; Arumanayagam et al., 2001; Nakamura et al.,
2002). As shown previously, chronic treatment with metoprolol reversed the hyperphosphorylation of the ryanodine re-
ceptor and restored the stoichiometry of the ryanodine recep-
tor macromolecular complex (Reiken et al., 2003). The
present study shows that metoprolol treatment also restores
the functional integrity of the myofibrillar system, because
metoprolol treatment improved the phosphorylation of tropo-
nin I, and this improvement was paralleled by a decrease in
myofibrillar Ca$^{2+}$ sensitivity. Although these alterations
may be advantages for the diastolic cardiac function and may
prevent cardiac Ca$^{2+}$ overload, metoprolol did not alter the
myofibrillar ATP consumption and thus did not improve
myofibrillar economy, at least under the in vitro system of
skinned fiber preparations.

In contrast, carvedilol significantly reduced tension-depend-
ent ATP consumption. This may be of especial advantage in
a situation of ATP deprivation, as has been described in
failing myocardium (Hearse, 1979). In addition, carvedilol
treatment increased maximal Ca$^{2+}$-dependent tension
development. These effects of carvedilol may be the result of its
antioxidant effects (Flesch et al., 1999; Arumanayagam et al.,
2001; Nakamura et al., 2002). An alternative explanation
may be an altered expression of myofibrillar proteins under
chronic treatment with carvedilol. Thus, it has been shown in
previous studies that carvedilol treatment results in an up-
regulation of the $\alpha$-myosin heavy chain mRNA and a down-
regulation of the $\beta$-myosin heavy chain mRNA (Lowes et al.,
2002). However, whether these alterations also occur on the
protein level has to be investigated in further studies. As
shown in this study, carvedilol did not alter the increased
myofibrillar Ca$^{2+}$ sensitivity and even increased the dephos-
phorylation of the troponin I protein. A very effective sup-
pression of the $\beta$-adrenergic system by carvedilol has been
described previously, and this $\beta$-adrenergic suppression may
also have been present after the carvedilol treatment was
stopped (Maack et al., 2000).

Limitations of the Present Study. In contrast to our
previous studies, we observed a significant decrease in maxi-
mal Ca$^{2+}$-activated force in human failing myocardium. One
difference between our present study and the previous studi-
ies is that for the present study, the myocardial samples had
been frozen and were thawed for the preparation of skinned
fibers. The freezing and thawing treatment of the fibers may
have altered myofibrillar function. Nevertheless, functional
data obtained in the present samples are in the range of

Fig. 4. Influence of NF, DCM_NBB, DCM_MET, and DCM_CAR on
troponin I phosphorylation status assessed via back phosphorylation
technique. Top, original gels from NF, DCM_NBB, DCM_MET, and
DCM_CAR. Bottom, densitometric analysis of the bands (+, $p < 0.05$
versus NF; #, $p < 0.05$ versus DCM_NBB). Note that a low back phos-
phorylation signal indicates a high phosphorylation status.
those obtained in fresh preparations (Schwinger et al., 1994). In addition, by using this method, we were able to perform investigations in a very clearly defined patient collective (all males, aged between 40 and 60 years). The reason for the alterations in the maximal tension development by different treatment of the fibers has to be investigated in further studies.

A further limitation of the study is the high variability inherent to studies in humans. However, to avoid this issue, we have selected patients from a group of more than 200 heart transplantations with definite criteria. The groups we investigated consisted only of male patients between the ages of 40 and 60 years, who were on a definite pharmacological treatment (i.e., either no β-blocker, carvedilol, or metoprolol). Thus, although the groups are very small, they are very homogenous regarding the patients included.

In conclusion, a more detailed understanding of the molecular consequences of β-blockers may be of importance for a differential therapy of heart failure patients. Thus, in a situation of increased β-adrenergic suppression induced by carvedilol, it may be contraindicated to treat the patients with Ca2+-dependent positive inotropics, e.g., digitalis, because the risk for Ca2+ overload of the cardiomyocytes may be increased. Furthermore, additional treatment with a Ca2+-sensing levesimendan may be unfavorable in addition to carvedilol, because the myofibrillar Ca2+-sensitivity may be increased to such an extent that diastolic dysfunction may result. A recent clinical trial has demonstrated that levesimendan as well as carvedilol improves cardiac function. Thus, further studies are needed to more clearly define the pharmaco-molecular mechanisms underlying β-blocker treatment.

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References


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