**Inotropic Effects of Endothelin-1**

**Interaction With Molsidomine and With BQ 610**

Martin E. Beyer, Günther Slesak, Tobias Hövelborn, Silke Kazmaier, Stefan Nerz, Hans Martin Hoffmeister

**Abstract**—In vivo studies could not detect a positive inotropy of endothelin (ET)-1 as described in in vitro experiments. ET-induced direct positive inotropy, which seems to be mediated by ETA receptors, may be antagonized in vivo by an indirect cardiodepressive effect owing to an ET-induced coronary vasoconstriction via ETB receptors. This study compares the effects of a dose of 1 nmol/kg ET-1 alone on myocardial contractility and myocardial energy metabolism with the effects of 1 nmol/kg ET-1 after pretreatment with 5 mg/kg molsidomine or with 100 μg/kg of the ETB receptor antagonist BQ 610. We investigated the effects of ET-1 versus saline controls in open-chest rats. In addition to measurements in the intact circulation, myocardial function was examined by isovolumic registrations independent of peripheral vascular effects. We also studied the effect of ET-1 on myocardial high-energy phosphates. Pretreatment with molsidomine and BQ 610 attenuated the ET-induced reduction of cardiac output (ET-1: −62%; molsidomine+ET-1: −47%; BQ 610+ET-1: −27% different from controls). After a transient initial vasodilation, ET-1 raised total peripheral resistance (ET-1: +190%; molsidomine+ET-1: +171%; BQ 610+ET-1: +89%). BQ 610 was more effective in preventing ET-induced vasoconstriction. The increase of isovolumic peak first derivative of left ventricular pressure (ET-1: −2%; molsidomine+ET-1: +16%; BQ 610+ET-1: +19%) after pretreatment with molsidomine or BQ 610 indicates that these drugs unmask the positive inotropy of ET-1. ET-induced myocardial ischemia was abolished by molsidomine and BQ 610. Pretreatment with molsidomine or blockade of ETB receptors by BQ 610 can unmask the positive inotropy of ET-1 by preventing ET-induced myocardial ischemia. The positive inotropic effect of ET-1 seems to be mediated by ETA receptors. (Hypertension. 1999;33:145-152.)

**Key Words:** endothelin • BQ 610 • molsidomine • contractility • phosphates, high-energy • rats

The peptide endothelin (ET)-1 is the most potent vasoconstrictor known to date, and it is involved in the development of several diseases. Increased ET plasma concentrations have been reported in patients with angina, myocardial infarction, or heart failure. Drugs that antagonize or block the effects of ET-1 may consequently be of importance in the treatment of these diseases. Two different ET receptors have been characterized (the ETA and the ETB). Many selective and nonselective ET receptor antagonists have been synthesized. Nevertheless, until now it has been unclear whether selective or nonselective ET receptor antagonists should be used in therapy.

In addition to its important vascular effects, several experiments with isolated cardiac tissues demonstrated a positive inotropic effect of ET-1. In isolated hearts and in vivo studies, ET-1 showed a controversial effect on myocardial contractility. In a previous in vivo study with rats, we could not detect the described positive inotropy of ET-1. We supposed that the potent vasoconstrictive effect of ET-1 might cause myocardial ischemia with consequent cardiodepression, thereby masking the described direct positive inotropic effect of ET-1 in vivo. Our hypothesis was confirmed by the fact that the combination of ET-1 with high doses of the potent vasodilator adenosine unmasked in the same animal model the positive inotropy of ET-1 in vivo.

Activation of ETA receptors by the selective ETB agonist IRL 1620 also produced positive inotropy in our in vivo model.

The present study examined the hemodynamic and inotropic effects of ET-1 under different conditions in the previously described open-chest animal model. In addition to measurements in the intact circulation, this model also permits isovolumic measurements to determine direct myocardial effects that are independent of peripheral vascular effects but dependent on myocardial perfusion. In the first part of the study we investigated whether a clinically used vasodilator could unmask the “beneficial” positive inotropic effect of ET-1. Therefore, the effect of ET-1 was studied after pretreatment with the nitric oxide (NO) donor molsidomine, which is used clinically for treatment of myocardial ischemia. The second part of the study examined the effect of ET-1 after selective blockade of the ETA receptors by the ETB receptor antagonist BQ 610. Additionally, the effect of...
ET-1 on coronary flow and on myocardial energy metabolism under different conditions was investigated by colored microsphere technique and by determination of the myocardial high-energy phosphates.

**Methods**

**Hemodynamic Measurements**

Animal experiments for this study were performed according to national regulations on the use of laboratory animals. The protocol was approved by the local committee on ethics in animal research.

The study was performed on 4-month-old normotensive male Wistar rats (n = 123; weight, 350 to 450 g). The procedure of the experiments has been described in detail previously. In addition to hemodynamic measurements in the intact circulation, isovolumic measurements were performed to determine isovolumic left ventricular systolic pressure (peak LVSP) and peak first derivative of left ventricular end-diastolic pressure were determined.

Figure 1. Registration of an isovolumic measurement by cross-clamping the ascending aorta. AoP indicates aortic pressure; AF, aortic flow; a LVP, amplified left ventricular pressure; and LVP, left ventricular pressure. *Beat with maximal isovolumic LVSP (peak LVSP); from this beat peak dP/dt max and peak left ventricular end-diastolic pressure were determined.

ET-1 on coronary flow and on myocardial energy metabolism with molsidomine. Therefore, 5 mg/kg molsidomine (Hoechst) was dissolved in a final volume of 1 mL NaCl solution and was infused over a period of 7 minutes. The dose of molsidomine was selected according a previous in vivo study in rats. Ten minutes after termination of molsidomine infusion, preinfusion control data were recorded, and 3 minutes later the ET-1 (n = 10) or NaCl infusions (n = 11) were started. To test the effect of ET-1 on ET A receptors, 2 other groups (ET-1: n = 10; NaCl: n = 10) were pretreated with the selective ET A receptor antagonist BQ 610. A dose of 100 µg/kg BQ 610 (Phoenix Pharmaceuticals) dissolved in 4% dimethyl sulfoxide solution was infused during 7 minutes. The following procedure was the same as after pretreatment with molsidomine. To evaluate whether the ET effects after BQ 610 infusion are mediated by ET A receptors, in addition to ET A blockade by BQ 610, 5 animals underwent an ET B blockade by infusion of 0.5 µmol/kg IV of the selective ET B antagonist BQ 788 (Phoenix Pharmaceuticals) before ET-1 infusion was started.

**Coronary Flow**

Coronary flow cannot be measured directly in the in vivo model that we used. Thus, the effect of ET-1 (without or with pretreatment with molsidomine or BQ 610) on myocardial perfusion was determined in further experiments by a colored microsphere technique. In addition to the hemodynamic measurements, the effects of ET-1 on myocardial high-energy metabolism under different conditions were studied. The animals of this examination underwent the same procedure described for the hemodynamic experiments.

**Myocardial High-Energy Phosphates**

In addition to the hemodynamic measurements, the effects of ET-1 on myocardial high-energy metabolism under different conditions were studied. The animals of this examination underwent the same procedure described for the hemodynamic experiments.

Myocardial ATP, ADP, AMP, and creatine phosphate were determined by bioluminescence (for details, see Reference 18). The energy charge according to Atkinson was calculated as an index of myocardial energy metabolism, as follows: Energy Charge = [ATP + (ADP/2)]/[ATP + ADP + AMP].

**Statistical Analysis**

All data are expressed as mean ± SEM. Hemodynamic data were normalized to the individual preinfusion control data (100% at the beginning of the ET or NaCl infusion). Statistical analyses were performed at the end of infusion and 5 and 15 minutes after termination of infusion. We compared normalized data from each of the 3 ET groups with the respective control group using a 2-tailed version of the Student’s t test modified according to the Bonferroni-Holm correction for multiple comparisons. Additionally, the effect of ET-1 without pretreatment was compared with the effect of ET-1 after pretreatment with molsidomine or with BQ 610 by ANOVA followed by Dunnett’s test and the Bonferroni-Holm correction. (No significant difference between the control group without pretreatment and the control groups with pretreatment was detectable with this test.) This test was also used to compare the data of the coronary
TABLE 1. Hemodynamic Measurements in Intact Circulation and Isovolumic Registrations at Beginning of Infusion of 1 mL NaCl or 1 nmol/kg ET-1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No Pretreatment</th>
<th>5 mg/kg Molsidomine</th>
<th>100 μg/kg BQ 610</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NaCl</td>
<td>ET-1</td>
<td>NaCl</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td>120.4±6.3</td>
<td>132.6±6.0</td>
<td>104.4±3.4</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>3.1±0.3</td>
<td>3.7±0.4</td>
<td>3.0±0.3</td>
</tr>
<tr>
<td>AoP&lt;sub&gt;a&lt;/sub&gt;, mm Hg</td>
<td>45.0±3.3</td>
<td>49.6±5.3</td>
<td>41.6±2.2</td>
</tr>
<tr>
<td>AoP&lt;sub&gt;r&lt;/sub&gt;, mm Hg</td>
<td>59.7±3.9</td>
<td>63.0±4.9</td>
<td>54.6±2.3</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s</td>
<td>5939±321</td>
<td>6905±588</td>
<td>5065±195</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>242.6±7.1</td>
<td>276.1±7.8</td>
<td>258.1±13.5</td>
</tr>
<tr>
<td>LVEDV, μL</td>
<td>292.5±11.7</td>
<td>285.5±9.4</td>
<td>261.0±14.0</td>
</tr>
<tr>
<td>SV, μL</td>
<td>205.7±26.9</td>
<td>213.5±21.1</td>
<td>133.0±10.5</td>
</tr>
<tr>
<td>TPR, mm Hg · min · kg/mL</td>
<td>1.4±0.1</td>
<td>1.2±0.1</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td>Peak LVSP, mm Hg</td>
<td>263.5±6.5</td>
<td>283.4±6.4</td>
<td>261.9±3.7</td>
</tr>
<tr>
<td>Peak dP/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s</td>
<td>9890±312</td>
<td>10 932±440</td>
<td>9912±326</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. LVEDP indicates left ventricular end-diastolic pressure; AoP<sub>a</sub>, diastolic aortic pressure; AoP<sub>r</sub>, mean aortic pressure; HR, heart rate; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; TPR, total peripheral resistance; and peak LVSP and peak dP/dt<sub>max</sub> data derived from isovolumic maximum beat.

Results

**Hemodynamic and Inotropic Effects of Molsidomine**

Molsidomine caused a slight fall of blood pressure: mean aortic pressure was reduced ≈9.6% at the beginning of NaCl infusion and ≈11.2% at the beginning of ET-1 infusion. Heart rate and cardiac output were not affected by molsidomine. Total peripheral resistance was reduced by molsidomine (NaCl group, −7.5%; ET group, −6.0%). The data of the isovolumic measurements were not changed by molsidomine (peak LVSP: NaCl group, −3.4%; ET group, −2.6%; peak dP/dt<sub>max</sub>: NaCl group, −1.2%; ET group, +0.5%).

**Hemodynamic and Inotropic Effects of BQ 610**

BQ 610 caused a slight decrease of blood pressure (mean aortic pressure: NaCl group, −4.9%; ET group, −5.8%). Although heart rate was not influenced by BQ 610, cardiac output was slightly increased (NaCl group, +7.1%; ET group, +7.0%) associated with a reduction of total peripheral resistance (NaCl group, −9.3%; ET group, −2.6%) by BQ 610. The isovolumic maxima were not affected by BQ 610 (peak LVSP: NaCl group, −0.3%; ET group, 1.2%; peak dP/dt<sub>max</sub>: NaCl group, +5.8%; ET group, +1.2%).

**Hemodynamic Effects of ET-1**

The hemodynamic and inotropic effects of molsidomine and BQ 610 are excluded in the following section because the data were normalized to the individual preinfusion control data at the beginning of the ET or NaCl infusion (for absolute values, see Table 1). At that time a steady state after molsidomine or BQ 610 infusion was obtained.

The results of the hemodynamic measurements in the intact circulation are shown in Table 2. ET-1 caused a transient decrease followed by a sustained increase of LVSP. This biphasic blood pressure response was even more pronounced for mean and diastolic aortic pressure, reflecting the peripheral vascular effects of ET-1. Pretreatment with molsidomine or BQ 610 had no effect on the ET-induced biphasic blood pressure response. The ET-induced initial fall of blood pressure was abolished after additional blockade of the ETA receptors by BQ 788.

A dose of ET-1 alone had no chronotropic effect. In the molsidomine and the BQ 610 groups, ET-1 caused an increase of the heart rate of ≈10% after termination of infusion. In both of these groups the positive chronotropic effect of ET-1 was identical.

ET-1 caused a significant fall of stroke volume (5 minutes after infusion: 45.5±4.7% versus 102.8±3.4%; P<0.001). An identical effect was seen after pretreatment with molsidomine (5 minutes after infusion: 46.8±4.2% versus 98.4±2.2%; P<0.001). Blockade of the ETA receptors by BQ 610 prevented in part the ET-induced fall of stroke volume (5 minutes after infusion: 70.5±3.3% versus 101.8±2.4%; P<0.001).

Because of the effects on stroke volume and heart rate, ET-1 caused a significant reduction of cardiac output (Figure 2A). Molsidomine influenced this effect of ET-1 only to some degree (Figure 2B), whereas pretreatment with BQ 610 reduced the ET-induced effect on cardiac output by ≈50% (Figure 2C). Comparable effects can be shown for the ejection fraction (Table 2).

After an initial vasodilation (maximum in the second minute of infusion), ET-1 caused a tremendous increase of the calculated total peripheral resistance (Figure 3A). Pretreatment with molsidomine had no effect on the initial vasodilation, but the following increase of total peripheral resistance was less pronounced (Figure 3B). Blockade of the ETA receptors by BQ 610 clearly diminished the ET-induced increase of total peripheral resistance (Figure 3C).
Peripheral resistance in the second minute of ET infusion: prevented the initial vasodilative effect of ET-1 (total 3C). Additional ET_a blockade by BQ 788 completely prevented the initial vasodilative effect of ET-1 (total peripheral resistance in the second minute of ET infusion: 107.3±4.1%).

**Inotropic Effects of ET-1**

The effect of ET-1 on the isovolumic peak dP/dt_max as a function of left ventricular end-diastolic volume 5 minutes after termination of infusion is shown in Figure 4. Although
a dose of ET-1 alone had no effect on peak dP/dt max (Figure 4A), pretreatment with molsidomine (Figure 4B) or BQ 610 (Figure 4C) caused a significant increase of peak dP/dt max by ET-1. This effect was more pronounced after blockade of the ETA receptors by BQ 610. The preload values from which the isovolumic maximal beats were obtained tended to a lower range. Peak LVSP also was significantly increased by ET-1 after molsidomine or BQ 610 infusion (Figure 5, Table 2). The increase of both indices of myocardial contractility reached a maximum 5 minutes after termination of ET infusion. Pretreatment with the ETB antagonist BQ 788 in addition to the ETA receptor blockade by BQ 610 significantly attenuated the inotropic response to ET-1 (5 minutes after termination of ET-infusion: peak LVSP, 101.1 ± 4.1, P<0.001 versus ET-1 after BQ 610; peak dP/dt max, 91.4 ± 6.7, P<0.01 versus ET-1 after BQ 610), and both indices of myocardial contractility were no longer significantly different from those of the control group.

Myocardial High-Energy Phosphates
A dose of ET-1 alone caused a significant reduction of myocardial ATP content (3.35 ± 0.10 versus 4.44 ± 0.23 μmol/g wet weight; P<0.01) with an insignificant increase of ADP and AMP levels. Myocardial creatine phosphate content was also significantly reduced by ET-1 (4.66 ± 0.27 versus 7.73 ± 0.61 μmol/g wet weight; P<0.01). Pretreatment with molsidomine tended to abolish the ET-induced effects on myocardial high-energy phosphates. In comparison with the control group, the ADP and AMP levels were still increased, but the ATP level (4.18 ± 0.29 μmol/g wet weight) was no longer reduced significantly; creatine phosphate levels did not differ...
from those of control (8.73 ± 1.05 μmol/g wet weight). After blockade of the ET₄ receptors by BQ 610, the effects of ET-1 on myocardial high-energy phosphates were completely abolished (ATP, 4.51 ± 0.19 μmol/g wet weight; creatine phosphate, 7.60 ± 0.62 μmol/g wet weight).

The calculated energy charge as an indicator of myocardial energy level (Figure 5) shows that a dose of ET-1 alone caused a significant decrease. This ET-induced decrease was antagonized in part by molsidomine and was even completely abolished by blockade of the ET₄ receptors by BQ 610.

**Coronary Flow**

Figure 5 shows the results of the coronary perfusion measurements 5 minutes after termination of infusion. In parallel to the changes of the energy charge, the coronary flow was significantly reduced by a dose of ET-1 alone by about 50%. The ET-induced reduction of coronary perfusion was slightly reduced after pretreatment with molsidomine and was even less pronounced after ET₄ receptor blockade by BQ 610.

**Discussion**

The effects of ET-1 on ventricular function have been controversial: in vitro experiments in animals and in human cardiac tissues showed a positive inotropic effect of ET-1, while experiments with isolated hearts or in vivo experiments could not detect such a positive inotropy, or even described a cardiodepressive effect of ET-1. Our previous in vivo experiments on rats also could not detect an ET-induced effect on myocardial contractility. We supposed that the described direct positive inotropy of ET-1 was counterbalanced in our experiments by a cardiodepressive effect as a result of a coronary constrictive effect of ET-1 with consecutive myocardial ischemia. Indeed, the administered dose of ET-1 caused myocardial ischemia, and pretreatment with the vasodilator adenosine unmasked the positive inotropy of ET-1 by preventing myocardial ischemia. To unmask the positive inotropy of ET-1, rather high doses of adenosine were necessary, which themselves have impressive hemodynamic effects.

ET-1 acts via ET₄ and ET₆ receptors, and ET-induced vasoconstriction seems to be mediated mainly by ET₄ receptors. In additional experiments with the selective ET₆ agonist IRL 1620, we demonstrated that the ET₆ receptor might provide evidence for ET-induced positive inotropy. The present study examined whether the NO donor molsidomine, used clinically as a coronary dilating drug, might unmask the positive inotropy of ET-1 by attenuating ET-induced myocardial ischemia without affecting the hemodynamics as adenosine does. Furthermore, we tested how effectively selective blockade of ET₄ receptors by BQ 610 is able to prevent ET-induced myocardial ischemia with subsequent depression of ventricular function.

In rats, ET-1 produces a biphasic blood pressure response, reflecting its vasoactive effects. ET₄ receptors on endothelial cells mediate ET-induced vasorelaxation by activating NO synthase to produce NO via increased endothelial [Ca²⁺]. Our findings support the hypothesis that ET-induced vasorelaxation is mediated by ET₆ receptors because the initial fall of total peripheral resistance was still present after ET₄ receptor blockade by BQ 610 but was completely abolished after additional ET₆ receptor blockade by BQ 788. The vasorelaxatory effect of molsidomine was mediated by its active metabolite 3-morpholino-sydnonimine (SIN-1), which releases NO. The ET-induced initial vasoconstriction via endogenous NO was not abolished in our experiments after pretreatment with molsidomine. This is in accordance with a previous study in which the endothelium-dependent relaxation of human coronary arteries was not influenced by exposure to SIN-1. In contrast to minor effects of molsidomine on ET-induced increase of total peripheral resistance, the blockade of ET₄ receptors significantly reduced the vasoconstrictive effect of ET-1. It is known that ET-induced vasoconstriction in rats is mainly mediated by ET₄ receptors and that the blockade of ET₄ receptors reduces the vasoconstrictive effect of ET-1. In our experiments the vasoconstrictive effect of ET-1 was not completely prevented by BQ 610. This can be explained (in part or totally) by the fact that the activation of ET₆ receptors also causes vasoconstriction. Although our dosage of BQ 610 was high compared with other studies and the blocking effect of BQ 610 seems to be much more potent than that of the frequently used selective ET₄ antagonist BQ 123, we cannot exclude that there still were some ET₄-mediated effects in our experiments after pretreatment with BQ 610.

While in vitro studies describe a positive chronotropic effect of ET-1, in vivo studies cannot demonstrate an ET-induced increase of heart rate. Mir et al suggest that a hypoxia-induced bradycardia antagonizes the direct positive chronotropic effect of ET-1. The positive chronotropic effect of ET-1 in our experiment after pretreatment with molsidomine or BQ 610 provides evidence for this hypothesis. The positive chronotropic effect of ET-1 after ET₄ receptor blockade clarifies that the ET₆ receptor is involved in the chronotropic effect of ET-1. This is in accordance with previous studies describing a positive chronotropic effect of ET₆ agonists.

The reduction of cardiac output and ejection fraction by ET-1 was the consequence of an increased afterload because the cardiodepressive effects of ET-1 were not detectable in our experiments. Pretreatment with BQ 610 in particular diminished the ET-induced reduction of cardiac output.

ET-1 has a considerable effect on afterload. Thus, the measurement of myocardial contractility independent of changes in peripheral perfusion is important. The procedure of determining isovolumic measurements by cross-clamping the ascending aorta fulfills this criterion: the determined peak LVSP and the corresponding peak dP/dtₘₐₓ are indices of myocardial contractility independent of peripheral vascular effects but dependent on coronary perfusion. Whereas the results of isovolumic measurements after a dose of ET-1 alone do not indicate a positive inotropic effect, pretreatment with molsidomine reveals the positive inotropic effect of ET-1. The same effect has been seen after pretreatment with adenosine: adenosine prevents ET-induced myocardial ischemia by vasodilating effects and consequently unMASKS the direct positive inotropic effect of ET-1 in vivo. Although molsidomine (in contrast to adenosine) can antagonize the peripheral vascular effects of ET-1 only to some
degree, the increase of the indices of myocardial contractility is significant. Additionally, the determination of coronary flow and of myocardial high-energy phosphates elucidates that molsidomine effectively prevents ET-induced myocardial ischemia. Molsidomine mainly dilates the coronary arteries and reduces the preload of the heart because of its venodilating effect. There is only a minor effect of molsidomine on peripheral resistance. In our experiments molsidomine prevented in part the vasoconstrictive effects of ET-1 on the coronary arteries. Pretreatment with BQ 610 also unmasked the positive inotropy of ET-1. The effects of ET-1 in combination with BQ 610 on total peripheral resistance, coronary flow, and myocardial high-energy phosphates show that the vasoconstrictive effects of ET-1 with consecutive myocardial ischemia are mainly mediated by ET<sub>A</sub> receptors. The positive inotropic effect of ET-1 was still present after administration of BQ 610 but was completely abolished after additional ET<sub>B</sub> blockade by BQ 788. In the same experimental model, an equipotent dose of the selective ET<sub>B</sub> agonist IRL 1620 caused a positive inotropic effect identical to that of ET-1 after pretreatment with BQ 610. The present results confirm our assumption that the positive inotropic effect of ET-1 is mediated in rats mainly (or totally) by ET<sub>B</sub> receptors. This is in accordance with other experimental studies that describe the significance of the ET<sub>B</sub> receptor for myocardial inotropy.

In summary, our study verifies that the lack of positive inotropy of ET-1 in vivo is the result of ET-induced myocardial ischemia due to the coronary constrictive effect of the peptide with a resultant indirect cardiodepressive effect of ET-1. Whereas vasoconstriction is mainly mediated by ET<sub>A</sub> receptors, the direct positive inotropy of ET-1 is mediated by ET<sub>B</sub> receptors. The NO donor molsidomine reveals the positive inotropy of ET-1. This may be relevant in the future in terms of drug therapy. Molsidomine is used clinically to treat patients with angina pectoris. Increased ET levels can be detectable in these patients. On the other hand, these patients often suffer from heart failure, and they may profit from the ability of molsidomine to unmask the positive inotropic effect of endogenous ET-1. BQ 610 can also reveal the positive inotropy of ET-1. In the future, ET receptor antagonists may also be used for therapy. Further studies must examine whether selective ET<sub>A</sub> receptor antagonists or nonselective ET receptor antagonists should be used for therapy.

**Acknowledgment**

This study was supported in part by a grant from the University of Tübingen (fortüne 348).

**References**


Inotropic Effects of Endothelin-1: Interaction With Molsidomine and With BQ 610
Martin E. Beyer, Günther Slesak, Tobias Hövelborn, Silke Kazmaier, Stefan Nerz and Hans Martin Hoffmeister

Hypertension. 1999;33:145-152
doi: 10.1161/01.HYP.33.1.145

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/33/1/145

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/