Conclusions—Metoprolol treatment of rats with CHF results in an improved ability to excrete both short- and long-term decreases left ventricular mass, and reduces mortality. In the absence of an increase in plasma volume. In metoprolol administration lowered cardiac output and arterial pressure, and renal plasma flow, and long-term propranolol diuresis and natriuresis despite reductions in glomerular filtration rate and renal plasma flow, or renal vascular resistance. Similarly, no long-term metabolol treatment has been observed on sodium, potassium, or free water excretion, and there are no changes in body fluid composition or weight. However, there are few data on the effect of long-term metoprolol treatment (as monotherapy) on renal sodium handling in CHF.

The aim of the present study was to examine the effect of long-term metoprolol treatment on renal sodium handling in a model of experimental CHF in the rat.

Methods
Adult male Sprague-Dawley rats (weight, 275 to 325 g), allowed free access to normal sodium rat-pellet diet (Teklad: Na⁺ 172 mEq/kg, K⁺ 180 mEq/kg) and distilled water as drinking fluid, were used for all studies. All animal procedures were performed in compliance with the University of Iowa “Policies and Guidelines Concerning the Use of Animals in Research and Teaching” and the US Public Health Service Guide for the Care and Use of Laboratory Animals.

Congestive Heart Failure
A previously described technique involving ligation of the left coronary artery was used to produce chronic CHF. Rats were anesthetized with methohexital sodium (50 mg/kg IP); an oral endotracheal tube was inserted, and mechanical ventilation with room air was instituted. Via a left thoracotomy, the heart was exteriorized, and the left coronary artery was ligated between the pulmonary outflow tract and the left atrium. The heart was returned...
to its normal position, and the thorax was closed with removal of air. After recovery from anesthesia and removal from the ventilator, rats were returned to individual metabolism cages with free access to normal sodium rat-pellet diet and distilled water.

Between 27 and 29 days after coronary artery ligation, the rats were anesthetized with methohexital sodium (50 mg/kg IP), and via an abdominal incision, osmotic minipumps were inserted containing either metoprolol, sufficient to deliver 1.5 mg·kg⁻¹·h⁻¹, or vehicle (distilled water) for 4 weeks.

Groups of both metoprolol- and vehicle-treated rats were evaluated by 2 protocols.

**Short-Term Intravenous Isotonic Saline Load**

Between days 21 and 26 after osmotic minipump insertion (ie, between 48 and 55 days after coronary artery ligation), rats were anesthetized with methohexitol sodium 50 mg/kg IP and instrumented with right jugular vein and carotid arterial catheters, as well as a urinary bladder catheter. The rats were allowed to recover from anesthesia and returned to their home cages. Two days later, they were placed in individual restraining devices and received isotonic saline 0.05 mL/min IV. Sixty minutes later, consecutive 10-minute urine collections with continuous measurement of mean arterial pressure (MAP) and heart rate (HR) were begun. After 3 such collections, a 5% body weight isotonic saline load was administered intravenously over 30 minutes. The experimental urine collection period encompassed the 30 minutes during the administration of the load and the 90 minutes thereafter. At the end of the experiment, HR responses to isoproterenol 0.1 and 0.2 µg IV were determined. The rats were anesthetized with methohexital 25 mg/kg IV, and the right carotid artery catheter was advanced into the left ventricle for measurement of left ventricular end-diastolic pressure (LVEDP). An aortic blood sample was taken. The rats were killed by an overdose of intravenous methohexital. The pleural and abdominal cavities were examined for presence of hydrothorax and ascites. The hearts were excised, drained, and weighed.

Urinary sodium excretion rates were calculated for each of the 10-minute control and experimental urine collection periods.

**Long-Term Dietary Sodium Load**

On day 23 after osmotic minipump insertion (ie, between 50 and 52 days after coronary artery ligation), rats were placed on a low-sodium diet (sodium <0.002 mEq/g) and given distilled water as drinking fluid. The rats were placed in individual metabolic balance cages, and daily measurements of body weight, volume of drinking fluid consumed, urine volume, and urine sodium concentration were initiated. After 3 days of control measurements and while rats continued to consume a low-sodium diet, the drinking fluid was switched to 0.9% NaCl drinking fluid, and experimental measurements were continued for another 5 days. On the next day, rats were anesthetized with methohexital 50 mg/kg IP, and catheters were introduced into the right carotid artery and jugular vein. MAP and HR were recorded on a pen-writing recorder (Grass). Urine volume was measured gravimetrically, and urinary sodium concentration was measured with a flame photometer. Plasma concentrations of metoprolol were measured by gas chromatography with electron-capture detection. Statistical analysis was performed with ANOVA with repeated measures and Scheffe test for comparison among means in the short- and long-term sodium-loading experiments. The significance level was set at a value of P<0.05 (2-sided). All data in text, tables, and figures are presented as mean±SE.

**Results**

At autopsy, all rats had evidence of bilateral hydrothorax and ascites.

**Short-Term Intravenous Isotonic Saline Load**

As seen in Table 1, metoprolol CHF rats had lower levels of MAP and HR and reduced HR responses to isoproterenol than vehicle CHF rats. Body and heart weight, body/heart weight ratio, and LVEDP were similar between vehicle and metoprolol CHF rats.

<table>
<thead>
<tr>
<th>Vehicle (n=10)</th>
<th>Metoprolol (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>413±6</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>2.81±0.07</td>
</tr>
<tr>
<td>Heart/body weight, %</td>
<td>0.68±0.02</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>126±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>417±11</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>11.6±0.7</td>
</tr>
<tr>
<td>Plasma metoprolol, nmol/L</td>
<td>1±1</td>
</tr>
<tr>
<td>ΔHR to isoproterenol IV</td>
<td>0.1 µg</td>
</tr>
<tr>
<td></td>
<td>0.2 µg</td>
</tr>
<tr>
<td></td>
<td>0.1 µg</td>
</tr>
</tbody>
</table>

|                | 0.2 µg             | 61±7*           |

Data are mean±SE. *P<0.05 for metoprolol vs vehicle.

HR were recorded on a pen-writing recorder (Grass). Urine volume was measured gravimetrically, and urinary sodium concentration was measured with a flame photometer. Plasma concentrations of metoprolol were measured by gas chromatography with electron-capture detection.

HR remained significantly lower in metoprolol CHF rats than in vehicle-treated rats, whereas Uₘ,V was not different between the 2 groups.

The short-term intravenous isotonic saline load was administered during periods 4 through 6. Compared with the averages of their respective control phase (periods 1 through 3), HR was significantly decreased during periods 7 through 15 in vehicle CHF rats and was significantly increased during periods 5 to 7 in metoprolol CHF rats. Throughout, HR remained significantly lower in metoprolol CHF rats than in vehicle CHF rats. Compared with the averages of their respective control phase (periods 1 through 3), MAP was not significantly changed in either vehicle or metoprolol CHF rats. MAP was significantly lower in metoprolol CHF rats than in vehicle CHF rats during periods 1 through 4 and 12 through 15. Compared with the average of their respective control phase (periods 1 through 3), Uₘ,V was significantly increased within both vehicle and metoprolol CHF rats from period 4 to period 15. Uₘ,V was significantly greater in
metoprolol CHF rats than in vehicle CHF rats from period 6 to period 14. When the UNaV response was analyzed as area under the curve, the natriuretic response of metoprolol CHF rats was 54 ± 64% greater than that of vehicle CHF rats (P < 0.05). At the end of the experimental protocol, plasma metoprolol concentration was 161 nmol/L (range, 0 to 10 nmol/L; 1 value of 10, and other 9 were 0) in vehicle CHF rats and 236 ± 649 nmol/L (range, 17.7 to 869 nmol/L) in metoprolol CHF rats.

**Long-Term Dietary Sodium Load**

As seen in Table 2, metoprolol CHF rats had lower levels of MAP and HR and reduced HR responses to isoproterenol compared with vehicle CHF rats. Body and heart weight, body/heart weight ratio, and LVEDP were similar between vehicle and metoprolol CHF rats.

Cumulative sodium balance data are shown in Figure 2. During the period of low dietary sodium intake (days 2 to 0), urinary sodium excretion was greatly reduced in both vehicle and metoprolol CHF rats so that daily net sodium balance and cumulative sodium balance were very close to zero and not significantly different between vehicle and metoprolol CHF rats. After the institution of increased dietary sodium intake, cumulative sodium balance progressively increased over the ensuing 5 days in both vehicle and metoprolol CHF rats. Cumulative sodium balance was significantly less in metoprolol CHF rats than in vehicle CHF rats (P < 0.05). At the end of the experimental protocol, plasma metoprolol concentration was 0 nmol/L (all values were 0 nmol/L) in vehicle CHF rats and 253 ± 83 nmol/L (range, 42 to 869 nmol/L) in metoprolol CHF rats.

**Discussion**

The major finding of this study is that long-term metoprolol therapy significantly improves the ability of CHF rats to excrete both short- and long-term sodium loads. Measurement of LVEDP, heart weight, and body weight occurred at the end of the experiment in each protocol. By that time, 50 to 60 days had passed since coronary ligation, and the rats had been treated with metoprolol for 27 to 31 days. All rats showed increased heart/body weight ratio compared with normal values of 0.40% in sham or control rats in our laboratory.14,15,17 All rats had increased LVEDP compared with normal values of 3.0 mm Hg in sham or control rats in our laboratory.14,15,17 At autopsy, all rats had bilateral hydrothorax and ascites, which reflects their avid
renal sodium retention, as previously documented in balance studies.15 Thus, the CHF rats were characterized by edema formation, cardiac hypertrophy, and elevated cardiac filling pressure. We17 have previously demonstrated that these CHF rats have depressed cardiac index and an abnormal cardiac function curve wherein the low basal cardiac index fails to increase during volume expansion–induced increases in LVEDP.

Although long-term metoprolol treatment had no effect on cardiac hypertrophy (heart/body weight ratio) or LVEDP, it did decrease MAP and HR. Further evidence of the effectiveness of long-term metoprolol treatment was its ability to blunt isoproterenol-induced increases in HR. Plasma metoprolol concentrations averaged ≈250 nmol/L in metoprolol CHF rats and were undetectable in vehicle CHF rats.

In previous studies in rats, short-term administration of the nonselective β-adrenergic antagonist propranolol to SHR resulted in diuresis and natriuresis despite decreases in renal blood flow and glomerular filtration rate.5,6 However, diuretic and natriuretic responses to the short-term administration of the selective β1-adrenoceptor antagonist metoprolol to SHR were associated with increases in renal blood flow and glomerular filtration rate and decreases in arterial pressure and renal vascular resistance, ie, marked renal vasodilation.7

In the present study, metoprolol enhanced the natriuretic response to intravenous isotonic saline volume loading despite a reduction in arterial pressure. This suggests that the mechanisms contributing to the enhanced natriuretic response, whether related to improved intrarenal hemodynamics or decreased renal tubular sodium reabsorption, were sufficiently potent to overcome the antinatriuretic effect of the decrease in renal perfusion pressure.

Bauer and Reams11 have reviewed the studies in human subjects. In 6 studies comprising 79 patients with essential hypertension, long-term metoprolol therapy had small effects on glomerular filtration rate (−4%), effective renal plasma flow (−6%), and renal vascular resistance (2%). However, in 1 of the studies,20 although long-term metoprolol therapy (5 to 7 weeks) did not affect glomerular filtration rate or renal blood flow, normalization of arterial pressure was associated with an 11% decrease in renal vascular resistance (from 0.120±0.010 to 0.107±0.008 mm Hg · mL⁻¹ · min⁻¹ · 1.73 m⁻²) and an increase in absolute (from 133±13 to 211±21 mEq/24 hours) and fractional sodium excretion (0.69±0.06% to 1.00±0.10%). These results suggest that the increase in renal sodium excretion occurred in association with an autoregulatory adjustment in renal vascular resistance whereby renal blood flow remained constant in the face of decreasing renal perfusion pressure. Because an increase in sodium excretion occurred with a decrease in arterial pressure, a resetting of the pressure-natriuresis relationship occurred in association with the adjustments in intrarenal hemodynamics.

Some general mechanisms may be considered for the favorable effect metoprolol exerts on renal sodium handling. To the extent that this was associated with increments in renal blood flow and/or glomerular filtration rate, it may be more related to increased filtered sodium load or intrarenal hemodynamic changes. On the other hand, if this was achieved at unchanged or decreased renal blood flow or glomerular filtration rate, it may be more related to inhibition of renal tubular sodium reabsorption.

In CHF, the decrease in cardiac output is associated with decreases in renal perfusion pressure, renal fraction of cardiac output, renal blood flow (increased renal vascular resistance), and glomerular filtration rate. Commonly, renal blood flow is reduced to a greater extent than is glomerular filtration rate, resulting in an increase in filtration fraction. CHF is characterized by increased activity of both the renin-angiotensin system and the sympathetic nervous system, with specific increases in renal sympathetic nerve activity; these may contribute to the observed renal hemodynamic alterations. Metoprolol administration is known to decrease activity of the renin-angiotensin system21,22 and to decrease renal sympathetic nerve activity.23,24 The decrease in activity of the renin-angiotensin system occurs both by blockade of β1-adrenoceptors located on renin-secreting juxtaglomerular granular cells as well as by decreasing renal sympathetic nerve activity.21,22 Decreased activity of the renin-angiotensin system could improve renal sodium excretory ability in CHF both by decreasing angiotensin II–mediated renal tubular sodium reabsorption and by decreasing angiotensin II–mediated renal vasoconstriction, leading to increases in both renal blood flow and glomerular filtration rate.25 The decrease in renal sympathetic nerve activity would reduce the direct effect of enhancing renal tubular sodium reabsorption and reduce sympathetic nervous system–mediated renal vasoconstriction with a similarly favorable effect on renal blood flow and glomerular filtration rate.21,22 In the study referred to above,20 although urinary excretion of catecholamines and metabolites and plasma dopamine-β-hydroxylase activity (as indexes of overall activity of the sympathetic nervous system) were unchanged, the usual stimulatory effect of upright posture on plasma renin activity was abolished by long-term metoprolol treatment. To the extent that the favorable effect of metoprolol on cardiac performance would increase cardiac output or the renal fraction of cardiac output or otherwise favorably influence renal hemodynamics, such changes would also contribute to increased renal sodium excretory ability in CHF.7

It is of interest that the renal hemodynamic pattern in CHF, a reduction in renal blood flow with relative preservation of glomerular filtration rate, is similar to that in essential hypertension, a clinical disorder in which diuretic and natriuretic responses to metoprolol have been observed.20 Although there are abundant data on the cardiovascular effects of metoprolol in CHF, comprehensive information on the renal functional effects of long-term metoprolol monotherapy in patients with CHF is not available. It is possible that part of the overall beneficial effect of long-term metoprolol therapy in CHF occurs via improvements in both renal hemodynamics and renal sodium excretory capacity.

In summary, long-term metoprolol treatment improved the ability to excrete both short and long-term sodium loads in an experimental rat model of CHF. It is a testable hypothesis that long-term metoprolol treatment has similar beneficial effects on renal sodium handling in human subjects with CHF.
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