Chronic Exercise Reduces Sympathetic Nerve Activity in Rabbits With Pacing-Induced Heart Failure
A Role for Angiotensin II

Jun-Li Liu, PhD; Scott Irvine, BS; Ian A. Reid, PhD; Kaushik P. Patel, PhD; Irving H. Zucker, PhD

Background—Chronic exercise (EX) improves the quality of life and increases the survival of patients with chronic heart failure (CHF). Because sympathetic nerve activity is elevated in the CHF state, it is possible that EX is beneficial in this disease due to a decrease in sympathetic outflow.

Methods and Results—We evaluated arterial baroreflex function and resting renal sympathetic nerve activity (RSNA) in EX normal and CHF rabbits before and after angiotensin II type 1 (AT₁) receptor blockade. Four groups of rabbits were studied: a normal non-EX group, a normal EX group, a CHF non-EX group, and a CHF EX group. EX lowered resting RSNA in rabbits with CHF but not in normal rabbits. In addition, EX increased arterial baroreflex sensitivity in the CHF group (heart rate slope: CHF 1.7±0.3 bpm/mm Hg, EX CHF 4.9±0.3 bpm/mm Hg; P<0.01; RSNA slope: CHF 2.2±0.2%max/mm Hg, EX CHF 5.7±0.4%max/mm Hg; P<0.01. AT₁ receptor blockade enhanced baroreflex sensitivity in the non-EX CHF rabbits but had no effect in EX CHF rabbits. Concomitant with this effect, EX lowered the elevated plasma angiotensin II concentration in the CHF group. A significant positive correlation was observed between sympathetic nerve activity and plasma angiotensin II.

Conclusions—These data strongly suggest that EX reduces the sympathoexcitatory state in the setting of CHF. Enhanced arterial baroreflex sensitivity may contribute to this reduction. In addition, EX lowers plasma angiotensin II concentration in CHF. These data further suggest that the lowering of angiotensin II may contribute to the decrease in sympathetic nerve activity after EX in the CHF state. (Circulation. 2000;102:1854-1862.)

Key Words: exercise ■ angiotensin ■ heart failure ■ nervous system, sympathetic

It is now well accepted that neurohumoral excitation is one of the primary and most reproducible sequelae of the chronic heart failure (CHF) syndrome.1 Excessive sympathetic activation not only exacerbates the heart failure state but also is prognostic of death and complications.2 Although the mechanisms for sympathoexcitation are not completely understood, therapeutic targeting of the sympathetic nervous system has proved to be beneficial for patients with CHF.3

Chronic exercise (EX) has recently been used as a therapeutic regimen in the CHF state.4,5 Patients engaged in an EX protocol have been shown to demonstrate improved EX tolerance and an enhanced quality of life and survival.6 In addition, EX by patients with CHF improves sympathovagal balance, thereby fostering a reduction in cardiac work.7 In the normal state, EX increases cardiac vagal tone and reduces sympathetic outflow at rest.8,9 On the other hand, arterial baroreflex sensitivity has been reported to be reduced,10 increased,11 or unchanged12 in subjects after a course of EX.

An important concern in this area relates to whether EX reduces sympathetic outflow in the CHF state. If so, what are the mechanisms? Is this effect simply due to an improvement in cardiac status, or is there a central effect that is called into play by EX?

Angiotensin II (Ang II) may also play a role in this regard. For instance, Stebbins and Bonigut13 demonstrated that the spinal administration of losartan attenuated the hemodynamic response to muscle contraction in anesthetized cats. In patients with CHF, EX plus lisinopril produced the most significant improvements in symptoms compared with lisinopril alone or EX alone.14 In normal subjects as well as in patients with ischemic heart disease, EX produced a small decrease in plasma renin activity, but more important, it produced a negative correlation between plasma renin activity and EX capacity.15

The aims of the present study were to (1) determine the effects of EX on directly recorded sympathetic nerve activity and baroreflex function in a conscious rabbit model of pacing-induced heart failure and (2) evaluate the effect of alterations in Ang II on sympathetic nerve activity and baroreflex function in conscious rabbits with CHF that were EX trained.
Methods

Experiments were carried out on 26 male New Zealand White rabbits that weighed between 2.5 and 3.5 kg. All experiments were reviewed and approved by the University of Nebraska Medical Center Institutional Animal Care and Use Committee. All experiments conformed to the guidelines for care and use of laboratory animals of the American Physiological Society and the National Institutes of Health.

Surgical Instrumentation

Rabbits were instrumented as described earlier. In brief, with sterile technique, a left thoracotomy was performed through the fourth intercostal space. After the pericardium was opened, a pair of 2-mm piezoelectric crystals (Sonometerics, Inc) were sutured across the left ventricle from anterior to posterior near the base of the ventricle. A platinum wire pacing electrode of our design was secured to the apical surface of the left ventricle. All wires were tunneled beneath the skin and exited in the midscapular area. The animals were treated with antibiotics (Baytril 2.3 mg/kg IM BID for 3 postoperative days) and allowed to recover for 2 weeks before being used in any experiment.

Induction of Heart Failure

After recovery from surgery, the heart failure groups were paced at rates of 320 to 340 bpm with a small lightweight pacing unit of our design. The pacing rate was then adjusted and monitored with the cardiac dimension tracings. In general, each rabbit was paced at 320 bpm for the first week to determine whether it would tolerate this protocol. After the first week, the pacing rate was increased to 340 bpm and left at this rate for the remainder of the protocol. The rabbits were continually paced for ~4 weeks (EX and non-EX groups), at which time a second operation was performed to implant the renal nerve recording electrodes and vascular catheters. Recordings of cardiac dimension and heart rate (HR) were made twice per week to monitor the degree of cardiac dilation during the pacing protocol. The rabbits were placed into a Plexiglas box that limited movement, and the pacemaker was turned off for 30 minutes before any data were recorded.

Renal Sympathetic Nerve and Arterial Pressure Recording

The renal sympathetic nerve recording electrodes were implanted as we described previously. In brief, pacing was temporarily halted during the surgery and was reinstated after recovery from anesthesia. Teflon-coated (except at the distal 1 to 2 mm) wire electrodes were wrapped around 1 or 2 renal sympathetic nerves that ran along the renal artery. A ground electrode was secured to the nearby muscle or perirenal fat. The entire electrode assembly was then covered with a silicone gel (Wacker Sil-Gel, 401 A and B). The electrode wires were then tunneled beneath the skin and exited in the midscapular area. Experiments were carried out 3 to 5 days after renal nerve electrode implantation.

A Tygon catheter was implanted into the left carotid artery and jugular vein to record arterial and central venous pressures (ABP and

### Table 1. Baseline MAP, HR, CVP, and Cardiac Diameters in Normal, CHF, EX-Normal, and EX-CHF Rabbits

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP, mm Hg</th>
<th>HR, bpm</th>
<th>CVP, mm Hg</th>
<th>ESD, mm</th>
<th>EDD, mm</th>
<th>−dD/dt\text{max}, mm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>79±1</td>
<td>236±5</td>
<td>0.9±0.4</td>
<td>21.4±0.8</td>
<td>23.5±0.9</td>
<td>−16.8±3.9</td>
</tr>
<tr>
<td>CHF</td>
<td>75±2</td>
<td>267±6*</td>
<td>6.3±0.5*</td>
<td>23.5±0.7</td>
<td>24.5±0.7</td>
<td>−9.5±2.9*</td>
</tr>
<tr>
<td>EX-Normal</td>
<td>79±1</td>
<td>220±6†</td>
<td>0.1±0.1†</td>
<td>20.9±0.8</td>
<td>22.9±0.9</td>
<td>−20.4±1.8</td>
</tr>
<tr>
<td>EX-CHF</td>
<td>76±1</td>
<td>232±2†</td>
<td>5.5±0.3*</td>
<td>23.6±1.5</td>
<td>25.1±1.6*</td>
<td>−12.1±1.7</td>
</tr>
</tbody>
</table>

ESD indicates end-systolic diameter; EDD, end-diastolic diameter.

*P<0.01 vs normal group.
†P<0.01 vs CHF group.
Figure 2. Baseline RSNA expressed as a percent of maximum nerve activity in each group of rabbits. Animals with CHF had significantly higher RSNA compared with normal (EX-Normal) rabbits or EX CHF rabbits. *P<0.01.

CVP, respectively) and to administer drugs during the experiment. Catheters were filled with heparin (1000 U/mL) and sealed until the day of the experiment.

EX Training Protocol
Rabbits were trained to run on a motor-driven EX wheel of our design. The rabbits were acclimated to the wheel before the initial surgery. The rate was gradually increased to 15 to 18 m/min. After recovery from surgery, rabbits were exercised for a total of 40 minutes per day for 6 days per week. A warm-up period of 5 minutes at 5 m/min was followed by peak EX for 30 minutes. This was followed by a cool-down period of an additional 5 minutes at 5 m/min.

Experimental Protocol
On the day of the experiment, the rabbit was placed in the Plexiglas box, and the pacemaker was turned off for 30 minutes. Baseline recordings of renal sympathetic nerve activity (RSNA), ABP, CVP, and HR were taken for several minutes. Maximal RSNA was determined in each rabbit by observing its response to (1) a puff of cigarette smoke blown into the nose17 and (2) a intravenous bolus injection of sodium nitroprusside (SNP; 100 g/kg), which lowered ABP to between 45 and 50 mm Hg.

Arterial baroreflex control of HR and RSNA was determined with the response of these parameters to an injection of SNP (100 g/kg) and phenylephrine (30 g/kg), respectively. The logistic regression curve as described previously19 was fit to the data points with the following equation:

\[ \text{Slope} = \frac{(A \times B \times \exp[B(MAP - C)])}{\left(1 + \exp[B(MAP - C)]\right)^2} \]

The mean value of each curve parameter was used to derive a composite curve for each group of rabbits before and after each intervention.

Data Analysis

RSNA Determination
All parameters were recorded with a MacLaboratory data acquisition and analysis system (model 85). Hemodynamic parameters were digitized at 100 samples/s. RSNA was digitized at 200 samples/s and preamplified with a Grass P15 preamplifier with the bandwidth set between 3 Hz and 1 KHz. The raw nerve activity was rectified and integrated. In addition, the frequency of nerve activity was determined by setting a cursor above the noise level so that all spikes that crossed the cursor were counted. Both frequency and integrated nerve activity were recorded continuously along with the raw nerve activity. The baseline and baroreflex data were expressed as a percent of maximum activity. Because the maximum activity was similar with the puff of smoke or SNP, we elected to use the response to SNP to determine maximum activity in this study.

Cardiac Dimensions
Left ventricular external dimensions were recorded with a Triton Electronics sonomicrometer. End-diastolic, end-systolic, and mean diameters were recorded with the MacLaboratory system. The maximum velocity of shortening (dD/dt; mm/s) was computed. The average of 5 consecutive beats were determined when the rabbit was standing quietly in the box.

Arterial Baroreflex
Arterial baroreflex curves were constructed as we described previously.19 In brief, several points for HR and RSNA were taken during the fall or increase in ABP after the administration of SNP and phenylephrine, respectively. The logistic regression curve as described by Kent et al20 was fit to the data points with the following equation:

\[ \text{HR or RSNA} = \frac{A}{1 + \exp[B(MAP - C)]} + D \]

where A is HR or RSNA range, B is the slope coefficient, C is the pressure at the midpoint of the range (BP_{50}), and D is minimum HR or RSNA. The peak slope (or maximum gain) was determined by taking the first derivative of the baroreflex curve described by equation 1. The first derivative is described by equation 2.

\[ \text{Slope} = \frac{(A \times B \times \exp[B(MAP - C)])}{\left(1 + \exp[B(MAP - C)]\right)^2} \]

The mean value of each curve parameter was used to derive a composite curve for each group of rabbits before and after each intervention.

Statistical Analysis
Data are expressed as the mean± SEM. The differences between groups were determined with a 1-way ANOVA with the Newman-
Table 2. Logistic Parameters of Baroreflex Curves in Normal, CHF, and EX-Trained Rabbits

<table>
<thead>
<tr>
<th>Group</th>
<th>HR Range, bpm</th>
<th>Min HR, bpm</th>
<th>BP_{50}, mm Hg</th>
<th>Peak Slope, bpm/mm Hg</th>
<th>RSNA Range, % μmax</th>
<th>Minimum RSNA, % μmax</th>
<th>BP_{50}, mm Hg</th>
<th>Peak Slope, % μmax/mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>253±20</td>
<td>115±12</td>
<td>75±3</td>
<td>5.6±0.6</td>
<td>99±2</td>
<td>2.0±0.8</td>
<td>72±2</td>
<td>5.7±0.5</td>
</tr>
<tr>
<td>CHF</td>
<td>129±35*</td>
<td>217±9*</td>
<td>73±4</td>
<td>1.7±0.3*</td>
<td>91±13</td>
<td>4.4±1.8</td>
<td>76±3</td>
<td>2.2±0.2*</td>
</tr>
<tr>
<td>EX-Normal</td>
<td>270±23†</td>
<td>105±5†</td>
<td>75±3</td>
<td>5.8±0.2†</td>
<td>99±2</td>
<td>0.6±0.4</td>
<td>71±1</td>
<td>6.1±0.6†</td>
</tr>
<tr>
<td>EX-CHF</td>
<td>263±37†</td>
<td>153±19†</td>
<td>71±4</td>
<td>4.9±0.3†</td>
<td>99±2</td>
<td>1.5±0.4</td>
<td>72±1</td>
<td>5.7±0.4†</td>
</tr>
</tbody>
</table>

*P<0.01 vs normal group.
†P<0.01 vs CHF group.

Figure 4. Arterial baroreflex curves for control of HR and RSNA in normal rabbits that were either non-EX (left) or EX (right) before and after AT_{1} receptor blockade with L-158,809.
TABLE 3. Baseline Hemodynamics and RSNA Before and After Administration of L-158,809 to Exercise-Trained and Nontrained Rabbits

<table>
<thead>
<tr>
<th></th>
<th>MAP, mm Hg</th>
<th>HR, bpm</th>
<th>RSNA, % max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>L-158,809</td>
<td>Control</td>
</tr>
<tr>
<td>Normal</td>
<td>79.4±1.3</td>
<td>77.3±0.3</td>
<td>236±5</td>
</tr>
<tr>
<td>CHF</td>
<td>75.3±1.9</td>
<td>71.5±1.5</td>
<td>267±8*</td>
</tr>
<tr>
<td>EX-Normal</td>
<td>78.8±1.4</td>
<td>77.1±2.4</td>
<td>220±7†</td>
</tr>
<tr>
<td>EX-CHF</td>
<td>75.6±1.3</td>
<td>75.0±1.8</td>
<td>232±2†</td>
</tr>
</tbody>
</table>

*P<0.01 vs normal group.
†P<0.01 vs CHF group.

Figure 5. Arterial baroreflex curves for control of HR and RSNA in CHF rabbits that were either non-EX (left) or EX (right) before and after AT₁ receptor blockade with L-158,809. *Significantly different from before L-158,809.
Keuls test used for post hoc analysis. A P value of <0.05 was considered statistically significant.

Results

Resting Hemodynamics in Normal, CHF, and EX-Trained Rabbits
Table 1 shows the values for mean arterial pressure (MAP), HR, CVP, and cardiac dimensions in conscious rabbits from the 4 groups studied. The CHF rabbits that were not EX trained exhibited a significantly higher HR and CVP than normal untrained rabbits. The EX normal rabbits exhibited a significantly lower HR than the untrained normal group and the untrained CHF group. There was no difference in CVP between the EX normal rabbits and the untrained normal rabbits. Finally, the EX CHF rabbits exhibited a significantly lower HR than the nontrained CHF rabbits. The CVP of the EX CHF rabbits was similar to that of the nontrained CHF rabbits.

The mean data for cardiac dimensions and $-d/dt_{max}$ are also shown in Table 1. CHF rabbits exhibited increased end-diastolic, end-systolic, and mean diameter compared with normal rabbits. $-d/dt_{max}$ was significantly reduced in CHF rabbits. These reductions did not differ between trained and untrained rabbits. There were no significant differences in trained versus nontrained rabbits in either group. Therefore, although EX lowered resting HR, it did not improve apparent cardiac function.

Resting RSNA in EX-Trained and Nontrained Rabbits
Figure 1 is an original recording of RSNA, MAP, and HR in an EX-trained and a untrained rabbit with pacing-induced CHF. The frequency of sympathetic bursts in the baseline state appears to be greater in the non-EX rabbit (left) than in the EX rabbit (right). The mean data for baseline RSNA (expressed as a percent of maximum nerve activity) are shown in Figure 2. As can be seen, animals with CHF that were not EX trained demonstrated a significantly higher RSNA than the normal untrained rabbits. RSNA was lowered in EX CHF rabbits, so there was no difference between EX CHF rabbits and EX normal rabbits or non-EX normal rabbits. RSNA from EX CHF rabbits was significantly lower than that of nontrained CHF rabbits. There was no significant difference in RSNA between normal nontrained rabbits and normal EX rabbits.

Arterial Baroreflex Control of HR and RSNA in EX-Trained Rabbits
Composite arterial baroreflex curves for the control of HR and RSNA in the 4 groups of rabbits are shown in Figure 3. As can be seen, rabbits with CHF exhibited a depressed baroreflex control of HR. This depression was due primarily to a reduction in the minimum HR achieved during increases in ABP. EX had little effect on the baroreflex control of HR in normal rabbits. In CHF rabbits, EX normalized baroreflex control of HR by increasing the peak slope and reducing the minimum HR.

For the baroreflex control of RSNA, EX normalized the sensitivity without significantly changing the minimum or maximum points. The baroreflex control of RSNA was depressed in nontrained CHF rabbits compared with either normal nontrained or EX normal or EX CHF rabbits. The mean curve parameters for the baroreflex control of HR and RSNA are presented in Table 2. The most prominent change occurred in the peak slope for both HR and RSNA, which was normalized by EX in CHF rabbits.

Role of Ang II on RSNA and Baroreflex Function in EX-Trained Rabbits
Plasma Ang II was measured in rabbits from the 4 groups. In 15 rabbits, plasma was taken to measure Ang II at the same time as we measured resting RSNA and baroreflex function. Plasma Ang II in normal rabbits was $12.8 \pm 2.0 \text{ pg/mL}$. Non-EX rabbits with CHF had a significantly higher Ang II level ($48.7 \pm 7.9, P < 0.01$) than either non-EX normal rabbits or EX normal rabbits ($11.4 \pm 2.8$). In addition, EX CHF rabbits exhibited a plasma Ang II concentration ($18.1 \pm 3.4$) that was significantly lower ($P < 0.01$) than that of nontrained CHF rabbits and not different from that of either EX normal rabbits or non-EX normal rabbits.

Effects of Ang II Receptor Blockade on Baroreflex Function in EX-Trained Normal and CHF Rabbits
The blockade of AT$_1$ receptors with L-158,809 had no effect on ABP, HR, or any baroreflex parameter in normal EX or nontrained rabbits. In addition, this agent did not lower resting RSNA in CHF rabbits (Figure 4, Table 3). On the other hand, L-158,809 significantly enhanced baroreflex reflex sensitivity for both HR and RSNA in normal rabbits.

Relationship Between Plasma Ang II and RSNA
In 15 rabbits from the various groups, plasma Ang II concentration was measured at the same time as baseline RSNA and baroreflex function were monitored. There was a clear positive relationship between Ang II and baseline RSNA ($P < 0.001$; Figure 6). In addition, a significant inverse relationship was observed between baroreflex sensitivity (slope) and plasma Ang II in these animals. Because normal rabbits and EX rabbits all had low levels of Ang II, they are grouped toward the left of these relationships (closed symbols). The 5 CHF animals in which these measurements were obtained at the same time are spread out toward the high end of Ang II concentrations in Figure 6 (open symbols).

Discussion

The data presented in the present study are the first, to our knowledge, to show a significant beneficial effect of EX on RSNA in an experimental model of CHF. In addition, these data strongly suggest that there may be a relationship among EX, RSNA, baroreflex function, and Ang II. This discussion focuses on (1) the effects of EX on sympathetic nerve activity in CHF, (2) the effects of EX on arterial baroreflex function, and (3) the role of Ang II in the modulation of both resting RSNA and baroreflex function in the setting of CHF.
EX Training and Sympathetic Nerve Activity

Because sympathoexcitation is a consistent finding in CHF and because it has been shown that plasma norepinephrine correlates with directly recorded RSNA, a comprehensive understanding of the mechanisms responsible for increased central sympathetic outflow is important. Furthermore, because it has been shown that a clear relationship exists between plasma norepinephrine and the severity of CHF, as well as long-term survival, the data presented in this study have important clinical implications and assist in understanding rational therapy, especially as far as Ang II blockade is concerned.

It was recently shown that animals with CHF experience significant benefits with EX in the response to endothelium-dependent vasodilators. Although the mechanism of enhanced endurance in these patients may be due in part to metabolic changes in skeletal muscle, there also may be changes in muscle and multiple organ blood flow due to reduced Ang II levels or sympathetic nerve activity. EX has been shown to have several important effects on autonomic outflow. First, EX results in an increase in HR variability. Studies with power spectral analysis have confirmed an increase in the high-frequency spectral component of HR variability after EX in the normal state and in the CHF state. Second, EX in patients with CHF increases endurance and quality of life and, most important, survival. The role played by changes in sympathetic outflow induced by EX remain unclear. Even though we measured only RSNA, we believe the decrease in activity represents global changes in sympathetic outflow. We base this on the fact that a close correlation was observed between RSNA and renal venous norepinephrine concentration. In addition, changes in sympathetic outflow to different vascular beds are directionally similar.

Sinoway et al showed that forearm training reduced the muscle sympathetic nerve response to handgrip EX. This effect was thought to be due to a reduction in the metabolic stimulation of muscle afferents in response to training and not due to a change in central command. Conceivably, it is possible that EX conditioning reduces input from ergoceptors or metaboceptors in skeletal muscle, thereby reducing sympathetic outflow in CHF.

EX Training and Arterial Baroreflex Function in CHF

Studies in humans and animals have shown increases, decreases, or no change in baroreflex sensitivity after various EX regimens. In the present study and in the study by Somers et al, baroreflex sensitivity was enhanced in 2 pathological states: hypertension and CHF. The differences between enhancement of baroreflex function in CHF and either no change or a decrease in baroreflex sensitivity in normal animals and in patients is not clear but may be due to differences in the level of EX or to changes in the neurohumoral environment after EX. The enhancement of baroreflex function by EX occurred only in rabbits with CHF, which exhibited depressed baroreflex function. This observation suggests that regardless of the mediator of the depressed baroreflex is, it is activated only in the CHF state.

Role of Ang II

We chose to investigate Ang II to be a likely candidate for the mediator of the depressed baroreflex in CHF for several reasons. First, literature has accrued that clearly shows an inhibitory effect of Ang II on baroreflex function. Second, the renin–Ang II system is activated in CHF. Increases in plasma Ang II are often seen in
severe (New York Heart Association functional classes III and IV) CHF\textsuperscript{32} and late in the pacing model of CHF.\textsuperscript{33} Tissue Ang II has also been shown to be increased in CHF.\textsuperscript{31,33,34} Last, we recently showed that the blockade of AT\(_1\) receptors was necessary to observe a sympathoinhibitory response after the administration of an NO donor in conscious rabbits with pacing-induced CHF.\textsuperscript{16} It is possible that EX upregulates NO synthesis, which is sympathoinhibitory.

Although the data presented here do not differentiate between a primary effect of Ang II on lowering sympathetic nerve activity in EX CHF rabbits and a secondary effect of RSNA lowering on plasma Ang II, they are consistent with there being some role of Ang II in baroreflex function and sympathetic nerve activity. It is of interest that AT\(_1\) receptor blockade did not lower resting RSNA (Table 4). If Ang II is responsible for the sympathoexcitation in the CHF state, one would have expected this to occur. The reason for this paradox is not clear. We administered L-158,809 as a bolus injection, which acutely blocked AT\(_1\) receptors. On the other hand, plasma Ang II was necessary to observe a sympathoinhibitory response after the administration of an NO donor in conscious rabbits with pacing-induced CHF.\textsuperscript{16} It is possible that EX upregulates NO synthesis, which is sympathoinhibitory.

The authors are indebted to the expert technical assistance of Johnnie F. Hackley and Pamela Curry.

**Acknowledgments**

This study was supported in part by NIH grants HL-R37-HL-38690 and PO1-HL-62222. Dr Liu was supported in part by a predoctoral fellowship from the American Heart Association, Nebraska Affiliate. The authors are indebted to the expert technical assistance of Johnnie F. Hackley and Pamela Curry.

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Circulation. 2000;102:1854-1862
doi: 10.1161/01.CIR.102.15.1854

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