Suppression of Insulin-Induced Sympathetic Activation and Vasodilation by Dexamethasone in Humans

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Background. Physiological hyperinsulinemia in lean human subjects stimulates sympathetic nerve activity and blood flow in skeletal muscle, but the underlying mechanism is unknown. Potential mechanisms include central neural or peripheral actions of insulin. Glucocorticoids may potentially interfere with both such actions and thereby may attenuate sympathoexcitatory and vasodilatory effects of insulin in skeletal muscle.

Methods and Results. To determine whether insulin-induced sympathetic activation and vasodilation are attenuated by dexamethasone, we measured muscle sympathetic nerve activity and muscle blood flow during euglycemic hyperinsulinemia before and after short-term administration of this pharmacological agent. Insulin concentrations, which normally doubled sympathetic activity and markedly increased blood flow, had no such stimulatory effect after short-term dexamethasone administration. In contrast, responses to two noninsulin sympathetic stimuli, the Valsalva maneuver and immersion of the hand in ice water, and the vasodilatory response to calf vascular occlusion were not altered by dexamethasone.

Conclusions. These results demonstrate a dramatic impairment of insulin-induced sympathetic activation and vasodilation by dexamethasone in lean, healthy humans. This study suggests that dexamethasone administration to lean subjects may offer an experimental model to examine underlying mechanisms that regulate the interplay between cardiovascular, sympathetic, and metabolic effects of insulin. (Circulation 1993;88:388-394)

KEY WORDS • sympathetic nervous system • microneurography • neuropeptide Y • corticotropin releasing hormone

Insulin not only plays an important role in the regulation of intermediary metabolism but also has effects on the cardiovascular system. There is increasing evidence that in lean, healthy humans, acute elevation of insulin to high physiological concentrations stimulates both sympathetic activity and blood flow in skeletal muscle. In addition, recent observations in humans suggest that there may be a physiologically important interplay between the metabolic and vascular actions of insulin. Using the euglycemic clamp technique, it has been shown that insulin generates dose-dependent increases in muscle blood flow that are closely correlated with whole-body glucose uptake.

The mechanism by which insulin exerts its sympathoexcitatory and vasodilatory effects remains unknown. Potential mechanisms include peripheral and central neural actions of insulin. With regard to the latter, in experimental animals, there is compelling evidence that modulatory effects of insulin on food intake are centrally mediated. In addition, it has been shown in rats that glucocorticoids may impair the ability of insulin to regulate food intake by altering insulin-induced central neural peptide and neurotransmitter release. Interestingly, some of these peptides such as corticotropin releasing hormone (CRH) and neuropeptide Y (NPY) also have cardiovascular effects. Furthermore, their release can be modulated by dexamethasone. Alternatively, glucocorticoids, by inducing insulin resistance, also may interfere with peripheral sympathoexcitatory and vasodilatory actions of insulin. Thus, these observations raise the possibility that dexamethasone administration may attenuate the cardiovascular and sympathetic effects of insulin.

To test this possibility, we performed simultaneous microelectrode recordings of sympathetic nerve discharge to skeletal muscle and plethysmographic measurements of muscle blood flow during euglycemic hyperinsulinemia in lean, healthy humans both before and after dexamethasone administration.

Methods

Subjects
Six lean, healthy volunteers (weight, 65.3±4.5 kg; height, 169.5±3.1 cm; body mass index, 22.8±0.7 kg/m²; age, 29±4 years [mean±SEM]) were included in this study after providing informed written consent. All had
normal glucose tolerance, were taking no medications, and had no evidence of metabolic or cardiovascular disease. Tests were performed within an interval of 1 to 3 weeks. Before the second test, dexamethasone (2 mg/d divided into four doses) was administered for 48 hours. All tests were conducted in the morning after an overnight fast. Subjects were on a weight-maintaining diet containing at least 40% carbohydrates. The experimental protocol was approved by the Institutional Review Board on Human Investigation.

**General Procedures**

Studies were carried out with subjects in the supine position. Heart rate (ECG), respiratory excursions (pneumobelt), blood pressure (Finapres blood pressure monitor, Ohmeda, Englewood, Colo.),23 calf blood flow, and efferent muscle sympathetic nerve activity (MSNA) were recorded continuously on an electrostatic recorder and on a TEAC tape recorder (TEAC Tokyo). Respiratory excursions were monitored to detect inadvertent performance of a Valsalva maneuver or prolonged expiration, since these respiratory maneuvers can markedly stimulate sympathetic outflow.24 Intravenous catheters were inserted in a right and left antecubital vein, one for substrate infusion, the other for blood sampling.

**Recording of Sympathetic Nerve Activity**

Multiunit recordings of sympathetic nerve activity were obtained with unipolar tungsten microelectrodes inserted selectively into muscle nerve fascicles of the peroneal nerve posterior to the fibular head by the microneurographic technique of Vallbo et al.25 The neural signals were amplified (by 20 to 50×10^5), filtered (bandwidth, 700 to 2000 Hz), rectified, and integrated (time constant, 0.1 second) to obtain a mean voltage display of sympathetic activity. A recording of MSNA was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity that increased during the Valsalva maneuver but not during arousal stimuli such as loud noise. Sympathetic bursts were identified by inspection of the filtered and mean voltage neurograms. In a systematic evaluation by two of us (U.S., P.V.), of 21 recordings obtained during this and a related project11 project, the intraobserver (U.S., P.V.) coefficients of variation of the mean in identifying bursts averaged 2.9% (with a range of 0% to 10%) and 6.0% (with a range of 0% to 17%), respectively; the coefficient of variation of the mean exceeded 10% in only one recording. The interobserver coefficient of variation of the mean in identifying bursts on these 21 recordings was 8.7%, with a range of 0% to 21%; the coefficient of variation exceeded 15% in only two recordings. Nerve traffic was expressed both as bursts per minute, an index of the frequency of the activity, and as bursts per minute times mean burst amplitude, an index of integrated (total) activity.

**Calf Blood Flow**

Blood flow in the calf was measured with venous occlusion plethysmography, using mercury-in-silastic strain gauges.26 The calf was elevated 10 to 15 cm above the level of the right atrium to collapse the veins. The circulation to the foot was arrested by inflating a cuff around the ankles during blood flow determinations, which were performed at 15-second intervals for 5 minutes.

**Experimental Protocols**

**Protocol 1: Hyperinsulinemic euglycemic clamp.** After instrumentation and 1 hour of baseline measurements, all six subjects received a primed continuous infusion of insulin (Actrapid HM, Novo Industri S/A, Bagsvaerd, Denmark) at a rate of 6 pmol/kg per minute for 2 hours. Euglycemia was maintained by the determination of the plasma glucose concentration every 5 minutes and periodically adjusting a variable infusion of 20% dextrose.27 Hypokalemia was prevented by administration of KCl infused at a rate of 10 mEq/h. Sympathetic nerve activity and hemodynamic measurements were recorded for 5 out of every 15 minutes throughout the study. Blood samples were collected in the basal state and at timed intervals throughout the study for analysis of substrate and hormone concentrations.

**Protocol 2: Hyperinsulinemic euglycemic clamp after dexamethasone administration.** All six subjects repeated the same protocol as above after 48 hours of dexamethasone administration (2 mg/d divided in four doses), a maneuver designed to suppress CRH release.21 To control for potential effects of decreased muscle glucose uptake after dexamethasone administration28 on insulin-induced stimulation of MSNA and muscle blood flow, during the second hour of the test, exogenous glucose was infused at a rate matched to that of the corresponding control test period.

**Protocol 3: Noninsulin stimuli of sympathetic and vasodilator outflow.** We used baroreceptor deactivation evoked by the Valsalva maneuver,24 and stimulation of cutaneous afferents by 2-minute immersion of the hand in ice water29 (cold pressor test) as noninsulin stimuli of MSNA. Reactive hyperemia of the calf to 10 minutes of vascular occlusion was used as a noninsulin vasodilator stimulus.30 Responses to these interventions were examined immediately after termination of the insulin/glucose infusions.

**Analytical Methods**

Plasma glucose was determined in duplicate by the glucose oxidase method on a Beckman glucose analyzer (Beckman Instruments, Fullerton, Calif). Plasma insulin was measured by radioimmunoassay31 and catecholamines were measured by high performance liquid chromatography.32

**Data Analysis**

Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure. Vascular resistance in the calf was calculated as mean arterial pressure in millimeters of mercury divided by blood flow in milliliters per minute per 100 mL of tissue and expressed in units. The 5 minutes of data from intraneural recordings of MSNA, calf blood flow, blood pressure, and heart rate collected every 15 minutes were averaged to a single value. Whole-body glucose uptake was averaged for 30-minute periods. Glucose uptake was assumed to be equal to the amount of exogenous glucose infused. During the second hour of insulin/glucose infusion in protocol 2, this value was corrected for urinary losses and variations in glucose pool size, assuming a volume of distribution for glucose of 25% body weight. Statistical analysis was performed using ANOVA for repeated measures and paired t tests with the Bonferroni adjustment for multiple compari-
sons. A value of $P<.05$ was considered statistically significant. Data are given as mean±SEM.

**Results**

Resting values of MSNA, plasma noradrenaline, calf blood flow, calf vascular resistance, blood pressure, and plasma insulin were not altered by dexamethasone administration (Table). A 2-hour infusion of exogenous insulin, which elevated insulinemia to high physiological concentrations, increased MSNA by 15±2 bursts per minute and muscle blood flow by 0.6±0.16 mL/min per 100 mL (Figs 1 and 2 and Table). Both MSNA and calf blood flow had increased significantly 30 minutes after the start of insulin infusion. Since insulin infusion did not have any detectable effect on mean arterial pressure, these increases in calf blood flow resulted in significant ($P<.05$) decreases in calf vascular resistance by 11.6±5.2 U. The observed increases in sympathetic outflow to skeletal muscle were reflected by significant ($P<.05$) increases in plasma noradrenaline concentrations (Table).

In contrast, insulin infusion at the same rate, performed after 48 hours of dexamethasone administration, had no detectable effect on MSNA, calf blood flow, or calf vascular resistance, even though increases in insulinemia were comparable (Fig 1 and Table). Indeed, at the end of the second hour of infusion, plasma insulin concentrations tended to be higher (625±99 versus 411±41 pmol/L, $P=.09$) than those observed during the control experiments because glucose was infused at the same rate as during the control studies and led to hyperglycemia (8.2±0.2 mmol/L), which in turn stimulated endogenous insulin production. As for MSNA, insulin infusion after dexamethasone administration also did not have any detectable effect on plasma noradrenaline concentrations.

During both protocols, blood pressure remained unchanged. Heart rate increased significantly ($P<.05$) by 7±2 beats per minute when insulin was infused alone but did not change significantly when insulin was infused after dexamethasone administration (Table).

In protocol 1, plasma glucose was clamped at 5.4±0.1 mmol/L, with a coefficient of variation of 2.1%. In protocol 2, during the first hour of insulin/glucose infusion, glucose was clamped at 5.6±0.1 mmol/L, with a coefficient of variation of 3.9%; during the second hour, when glucose infusion rate was increased to match the rate observed in protocol 1, glycemia increased to 7.6±0.2 mmol/L at 90 minutes and then remained stable (8.1±0.2 and 8.2±0.2 mmol/L at 105 and 120 minutes, respectively).

Plasma potassium concentrations remained unchanged during both studies. At the end of the 2-hour insulin infusions, they were 3.6±0.1 and 3.3±0.1 mmol/L before and after dexamethasone administration, respectively ($P>.1$).

Before dexamethasone administration, values for glucose uptake during the four consecutive 30-minute periods of the clamp were 3.06±0.21, 6.06±0.59, 6.53±0.80, and 6.17±0.73 mg/kg per minute, respectively. After dexamethasone administration, values for glucose uptake during the corresponding time periods were 2.47±0.23, 2.94±0.28, 4.04±0.28, and 5.79±0.82 mg/kg per minute, respectively. Thus, dexamethasone significantly ($P<.05$) decreased the rate of exogenous glucose required to maintain euglycemia during the first hour of the clamp. However, during the second hour of the clamp performed after dexamethasone, when glucose infusion was matched to the rate observed during the control experiments, glucose uptake increased similarly as it did during the first hour of the studies performed before dexamethasone administration; during the last 30 minutes of insulin/glucose infusion, glucose uptake was not different before and after dexamethasone administration ($P>.1$).

Unlike insulin infusion, which had no effect on MSNA after dexamethasone administration, noninsulin stimuli to sympathetic outflow evoked comparably large increases in MSNA before and after dexamethasone administration. Peak sympathetic responses during a Valsalva maneuver were 59±2 bursts per minute before and 62±5 bursts per minute after dexamethasone. During a cold pressor test,29 peak MSNA responses were 41±4 bursts per minute and 42±9 bursts per minute, respectively.

Dexamethasone also did not alter vascular responses to a noninsulin vasodilator stimulus.30 Peak reactive hyperemia to 10 minutes of calf vascular occlusion was 21.8±2.4 mL/min per 100 mL before and 22.1±1.9 mL/min per 100 mL after dexamethasone administration.

**Discussion**

Even though there is abundant evidence in animals and humans that insulin stimulates both sympathetic efferent outflow and blood flow in skeletal muscle, the underlying mechanism has not been elucidated.5,6,8,10,12,13,15 The major new finding of this study is that in normal humans, plasma insulin levels within the physiological range that consistently elicited large increases in sympathetic outflow and blood flow in skeletal muscle had no such stimulatory effect after short-term dexamethasone administration. These findings provide evidence in humans that dexamethasone administration dramatically impairs the ability of insulin to stimulate sympathetic activity and blood flow in skeletal muscle, a major insulin-sensitive tissue.

This interpretation is predicated on the assumption that dexamethasone administration did not result in a nonspecific impairment of sympathetic or vasodilator responsiveness. This possibility is unlikely for several reasons. First, resting MSNA and calf blood flow were not altered by dexamethasone administration. Second, preservation of reflex sympathetic responses during a Valsalva maneuver24 and during immersion of the hand in ice water26 indicate that efferent sympathetic pathways were not altered by dexamethasone administration and could respond appropriately to baroreceptor deactivation and activation of cutaneous afferents. Third, dexamethasone also did not alter vascular responses to reactive hyperemia, indicating preservation of blood vessel responsiveness to this noninsulin vasodilator stimulus.27 Possible mechanisms by which dexamethasone may suppress insulin-induced sympathetic activation and vasodilation in skeletal muscle are peripheral or central neural actions.

Glucocorticoids induce a resistance to insulin-mediated glucose metabolism by impairing the ability of insulin to suppress hepatic glucose output28 and decreasing insulin-mediated glucose disposal.22 However, several lines of evidence suggest that the absence of an increase in MSNA and calf blood flow during insulin/glucose infusion after
Dexamethasone administration cannot be explained on the basis of resistance to insulin stimulation of glucose uptake alone. First, recent findings suggest that insulin-induced sympathetic activation and vasodilation are related to hyperinsulinemia per se rather than to total glucose metabolism or glucose oxidation. Second, in the present
studies performed without dexamethasone administration but was not associated with any significant increase in MSNA and calf blood flow. Conversely, in the absence of dexamethasone administration, insulin/glucose infusion at the rate used in the present experiments consistently has been found to evoke robust increases in MSNA and muscle blood flow within 60 minutes of the start of infusion.\textsuperscript{10,11,12} Thus, whereas the present findings suggest that it is unlikely that suppression of insulin-induced stimulation of MSNA and calf blood flow by dexamethasone is related to differences in glucose uptake alone, we cannot exclude the possibility that this agent may have altered a carbohydrate metabolism-related signal, which may trigger stimulation of muscle blood flow and sympathetic activity during euglycemic hyperinsulinemia.

An alternative peripheral mechanism is that dexamethasone may have inhibited insulin-induced vasodilation in skeletal muscle. Such vasodilation, for example, could be related to a direct vasodilator effect of insulin, as suggested by the observation of dose-dependent increases in forearm blood flow during local intra-arterial insulin infusion into human forearm tissue.\textsuperscript{33} Inhibition of vasodilation by dexamethasone may in turn have prevented slight decreases in arterial pressure and sinoaortic baroreflex-mediated increases in MSNA. In this regard, Anderson et al\textsuperscript{10} found a small but significant decrease in diastolic pressure during euglycemic hyperinsulinemia in humans that may have contributed to stimulation of sympathetic outflow in skeletal muscle. However, it is unlikely that baroreflex-mediated sympathetic stimulation is the sole mechanism that increases MSNA during insulin infusion in humans because in the present as well as in most other studies,\textsuperscript{12,13,34} blood pressure did not decrease during insulin/glucose infusion.

Although peripheral actions of dexamethasone may offer one potential explanation for the present findings, an alternative mechanism could be related to a central neural action of this agent. For example, in rats, central administration of CRH evokes sympathetic nerve\textsuperscript{19,35} and hindlimb blood flow\textsuperscript{20} responses that closely resemble the insulin-induced sympathoexcitatory and vasodilator responses\textsuperscript{10} in humans. Conversely, dexamethasone administration suppresses stress-induced sympathetic activation in experimental animals,\textsuperscript{38} presumably by acting on release of CRH\textsuperscript{21} or related central autonomic nervous system regulating peptides\textsuperscript{36} and, in the present study, insulin-induced stimulation of sympathetic and vasodilator outflow in humans. Alternatively, there is evidence in rats that glucocorticoids may induce a central resistance to the effects of insulin on food intake.\textsuperscript{16} In this animal model, the centrally mediated effects of insulin on food intake involve alteration of NPY availability.\textsuperscript{16} Preliminary evidence in rats suggests that dexamethasone suppresses the inhibitory effect of insulin on central NPY gene expression and release.\textsuperscript{33} Such inhibition of NPY release by insulin might result in sympathetic activation because in rodents, central administration of NPY has been shown to inhibit sympathetic outflow to brown fat and the heart.\textsuperscript{18,38} Thus, insulin-induced stimulatory effects on MSNA and muscle blood flow in humans could be centrally mediated and involve the release of specific neuropeptides. CRH and NPY are such candidate peptides.

Recent observations in humans could be consistent with the hypothesis that the sympathoexcitatory and vasodilatory effects of insulin may be centrally mediated. Lembo et

Fig 2. Plots show comparative effects of insulin infusion (6 pmol/kg per minute) in the same six subjects studied before (C--C) and after 48 hours of oral dexamethasone administration (---) on muscle sympathetic nerve activity (MSNA) and calf blood flow. Data represent mean±SEM. *P<0.05 vs insulin infusion before dexamethasone administration. Insulin infusion increased insulinemia similarly to high physiological levels before and after dexamethasone administration. This hyperinsulinemia evoked marked and roughly parallel increases in both MSNA and calf blood flow that were suppressed by short-term administration of dexamethasone.
Responses to 2 Hours of Insulin Infusion Performed Alone and After Administration of Dexamethasone for 48 Hours

<table>
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<th>Basal</th>
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<th>Basal</th>
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<td>activity units</td>
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<td>228±52</td>
<td>221±52§</td>
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<td>Calf vascular</td>
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<td>Mean arterial</td>
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<td>Heart rate (bpm)</td>
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<td>Insulin (pmol/mL)</td>
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<td>82±17</td>
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<td>5.6±0.1</td>
<td>8.2±0.2†§</td>
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<td>2.04±0.30*</td>
<td>1.78±0.24*</td>
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<td>1.11±0.13‡</td>
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<td>(nmol/L)</td>
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<td>355±45</td>
<td>352±44</td>
<td>237±28</td>
<td>259±15</td>
<td>249±14</td>
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Entries are mean±SEM for six subjects. Muscle sympathetic nerve activity (MSNA) given in units (bursts per minute·mean burst amplitude). bpm, Beats per minute.

*P<.05 vs corresponding basal period.
†P<.01 vs corresponding basal period.
‡P<.05 vs insulin infusion alone.
§P<.01 vs insulin infusion alone.

al compared effects of systemic versus local hyperinsulinemia on MSNA as determined by measurements of local norepinephrine spillover. They showed that insulin/glucose infusion at the rate used in the present studies is a potent stimulus to MSNA. In contrast, local hyperinsulinemia had no detectable sympathoexcitatory effects in these human subjects. Similarly, even though this issue is more controversial,33 several studies examining the effects of local intra-arterial insulin infusion on muscle blood flow found no vasodilatory effects.41,42 whereas in the present and other studies,10,11,15,41 systemic hyperinsulinemia consistently has been found to evoke large increases in muscle blood flow.

An important unresolved issue is whether, during euglycemic hyperinsulinemia, sympathetic activation and vasodilation in skeletal muscle are causally related. Although the present findings showing that dexamethasone abolishes both insulin-induced stimulation of MSNA and blood flow are consistent with such a concept, they do not show this conclusively. In humans, an earlier study suggested that insulin-induced stimulation of muscle blood flow may be sympathetically mediated because propranolol infusion attenuated forearm vasodilation evoked by intra-arterial insulin infusion.33 However, in this study, intra-arterial insulin infusion without concomitant glucose administration resulted in hypoglycemia and epinephrine release, which in turn may have caused β-adrenergically mediated vasodilation. Indeed, recent findings suggest that during euglycemic hyperinsulinemia, a situation in which epinephrine does not increase, propranolol infusion does not significantly attenuate stimulation of calf blood flow.41 Potential neural sympathetic vasodilator mechanisms that may mediate stimulation of calf blood flow during euglycemic hyperinsulinemia include cholinergic vasodilation42,43 and nonadrenergic-noncholinergic vasodilation.44 In this regard, preliminary findings from this laboratory suggest that stimulation of muscle blood flow during euglycemic hyperinsulinemia may not be mediated primarily by cholinergic mechanisms.41

Plethysmographic measurements of calf blood flow are a composite of both muscle and skin blood flow. However, it is unlikely that our results have been markedly influenced by changes in skin blood flow, since recent findings indicate that skin blood flow does not change during euglycemic hyperinsulinemia in humans.45 These data for skin blood flow are consistent with neurophysiological data demonstrating that, in contrast to MSNA, skin sympathetic nerve activity also does not change during hyperinsulinemia in humans.9,12

Dexamethasone administration in the present studies also attenuated the increase in heart rate evoked by euglycemic hyperinsulinemia. Such stimulation of heart rate has been thought to indicate cardiac sympathetic activation because it is abolished by propranolol administration.46 Thus, the present findings are consistent with the interpretation that dexamethasone may also attenuate cardiac sympathetic activation.

In summary, these findings indicate that in lean, healthy humans, dexamethasone administration dramatically impairs the ability of insulin to stimulate sympathetic activity and blood flow in skeletal muscle. Elucidating the exact underlying mechanism by which dexamethasone exerts its effects may be of potential importance, because recent evidence in humans suggests that impaired ability of insulin to stimulate muscle blood flow could contribute to insulin resistance.15 Thus, dexamethasone administration to lean subjects may offer an experimental model to study underlying mechanisms that regulate the interplay between cardiovascular, sympathetic, and metabolic effects of insulin.
Acknowledgments
This work was supported in part by grants from the Swiss National Science Foundation, the Emma Muschamp Foundation, Nestec SA, Vevey, Switzerland, the Jubilaeumsfond der Schweizerischen Chemiker, and the Max Clöetta Foundation. The authors are indebted to Dr. Kevin Acheson for his critical review of this work, to Marie A Blanc for secretarial assistance, and to Catherine Jan, Dorothy Pioud, and Eunika Rossi for technical assistance.

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_Circulation_. 1993;88:388-394
doi: 10.1161/01.CIR.88.2.388

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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