Comparison of Neuroendocrine Activation in Patients With Left Ventricular Dysfunction With and Without Congestive Heart Failure

A Substudy of the Studies of Left Ventricular Dysfunction (SOLVD)

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Neuroendocrine activation is known to occur in patients with congestive heart failure, but there is uncertainty as to whether this occurs before or after the presence of overt symptoms. In the Studies of Left Ventricular Dysfunction (SOLVD), a multicenter study of patients with ejection fractions of 35% or less, we compared baseline plasma norepinephrine, plasma renin activity, plasma atrial natriuretic factor, and plasma arginine vasopressin in 56 control subjects, 151 patients with left ventricular dysfunction (no overt heart failure), and 81 patients with overt heart failure before randomization. Median values for plasma norepinephrine \( (p=0.0001) \), plasma atrial natriuretic factor \( (p<0.0001) \), plasma arginine vasopressin \( (p=0.006) \), and plasma renin activity \( (p=0.03) \) were significantly higher in patients with left ventricular dysfunction than in normal control subjects. Neuroendocrine values were highest in patients with overt heart failure. Plasma renin activity was normal in patients with left ventricular dysfunction without heart failure who were not receiving diuretics and was significantly increased \( (p<0.05) \) in patients on diuretic therapy. We conclude that neuroendocrine activation occurs in patients with left ventricular dysfunction and no heart failure. Neuroendocrine activation is further increased as overt heart failure ensues and diuretics are added to therapy. \( (Circulation \ 1990;82:1724–1729) \)

Congestive heart failure is a complex clinical syndrome with varying pathophysiology and clinical expression. It is well known that overt heart failure is characterized by activation of several neuroendocrine systems.\(^1\) Plasma norepinephrine (PNE)\(^2\) and plasma atrial natriuretic factor (ANF)\(^3\) are increased and known to be prognostic factors in patients with heart failure. Activation of the renin-angiotensin system is common in patients with advanced heart failure. Angiotensin converting enzyme inhibitor therapy improves survival in patients with advanced heart failure,\(^4\) suggesting that the renin-angiotensin system plays an important role in the pathogenesis of symptomatic heart failure. It has been unclear, however, whether neuroendocrine activation occurs in response to the clinical features of heart failure or in patients with asymptomatic left ventricular dysfunction. The identification of very early neuroendocrine activation has important therapeutic implications because early introduction of treatment designed to block certain neuroendocrine activation may prevent progression of ventricular dilatation\(^5\,6\) and may prevent development of clinical heart failure. Studies in animals have demonstrated that converting enzyme inhibitor therapy introduced early in the course of left ventricular dysfunction may prevent progressive neuroendocrine activation\(^7\) and left ventricular remodeling\(^8\) and improve survival.\(^9\)

The first purpose of our study was to determine if patients with left ventricular dysfunction who were asymptomatic or only mildly symptomatic (no overt heart failure) have neuroendocrine activation. Sec-
ond, we compared neuroendocrine levels in patients with left ventricular dysfunction with values in patients with overt congestive heart failure.

Methods

Study Design

The Studies of Left Ventricular Dysfunction (SOLVD) is a multicenter study encompassing two trials. First, the prevention trial is designed to test the hypothesis that enalapril, a converting enzyme inhibitor, will prevent the development of clinical heart failure and reduce mortality in patients with left ventricular dysfunction (ejection fraction, \( \leq 35\% \)) who do not yet require digitalis or diuretics for control of signs or symptoms of congestion (prevention group). Patients in the prevention group may receive diuretics for the treatment of hypertension and digitalis for control of ventricular heart rate in atrial fibrillation. The treatment trial is designed to test the hypothesis that enalapril will reduce mortality in patients with left ventricular dysfunction (ejection fraction, \( \leq 35\% \)) and symptomatic heart failure requiring therapy with digitalis, diuretics, and/or nonconverting enzyme inhibitor vasodilators (treatment group). Both trials contain a placebo control group. It was decided in advance to measure PNE, plasma renin activity (PRA), plasma ANF, and plasma arginine vasopressin (AVP) in a subset of at least 200 patients before their randomization to placebo or enalapril in both the prevention and treatment trials of SOLVD and to compare these values with those from a group of control subjects without cardiovascular disease. Collaboration was invited from all 23 participating SOLVD centers, and 17 centers agreed to collaborate (see "Appendix").

Patient Selection

Patients were selected for SOLVD if they were not receiving angiotensin converting enzyme inhibitors and had a left ventricular ejection fraction of 35% or less by radionuclide ventriculography, contrast ventriculography, or two-dimensional echocardiography within the previous 3 months. Patients were excluded if they had acute myocardial infarction within 30 days, valvular or outflow tract obstruction requiring surgery, constrictive pericarditis, complex congenital heart disease, planned cardiac surgery, advanced pulmonary disease or cor pulmonale, uncontrolled hypertension (>140/95 mm Hg), significant liver disease, or other life-threatening disorders. Data collection for the neuroendocrine substudy began in 1987 and continued until November 1988. All consecutive patients who were willing to participate were enrolled.

One-hundred fifty-one patients recruited for the prevention group had neurohormones measured (Table 1). Average age was 59±11 (±SD) years and ranged from 21 to 79 years. Twenty percent of patients were taking diuretics for hypertension, and 13% were taking digitalis for control of arrhythmias, usually atrial fibrillation. Men composed 87% of the group. Underlying ischemic heart disease was present in 82%. Average left ventricular ejection fraction in the prevention group was 29±5%.

Eighty-one patients recruited for the treatment group of SOLVD had neurohormones measured before randomization. Average age was 63±9 years and ranged from 34 to 79 years. Mean ejection fraction was 26±6%. Diuretics and digitalis were being used by 89% and 59%, respectively. Underlying ischemic heart disease was present in 85% of patients. Men composed 79% of the group. The subset of patients participating in the neuroendocrine substudy is broadly comparable to the larger group of patients entering SOLVD, except for a somewhat higher rate of coronary artery disease and lower use of digitalis in the treatment group of substudy patients.

Fifty-six control subjects were also studied. Control subjects were recruited by each clinic and were eligible if there were no historical or physical findings of heart disease or hypertension. Friends and relatives of patients frequently participated as control subjects if they were clinically free of heart disease or hypertension. None was taking medications known to influence neurohormones. Men composed 70% of the control group. The average age was 56±12 years and ranged from 37 to 80 years.

The protocol was approved by the local hospital review boards. All control subjects and patients provided written informed consent to participate in the study.

Neuroendocrine Measurements

An intravenous cannula (short 18- or 20-gauge plastic catheter connected to a three-way stopcock) was inserted. The catheter was filled with dilute heparinized saline, and samples were obtained after 30 minutes of supine rest. After we aspirated and discarded the catheter dead space, blood was withdrawn into a plastic syringe. Five milliliters were

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>n</td>
<td>56</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.4±11.6</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>70</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>29±5</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>82</td>
</tr>
<tr>
<td>Diuretic use (%)</td>
<td>20</td>
</tr>
<tr>
<td>Digitalis use (%)</td>
<td>13</td>
</tr>
<tr>
<td>Serum sodium (meq/l)</td>
<td>140±2.5</td>
</tr>
<tr>
<td>Serum potassium (meq/l)</td>
<td>4.3±0.6</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg%)</td>
<td>17.3±5.0</td>
</tr>
<tr>
<td>Serum creatinine (mg%)</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42.5±4.1</td>
</tr>
</tbody>
</table>
placed into a prechilled tube containing reduced glutathione and calcium chelator EGTA preservative for PNE analysis. The sample was centrifuged within 1 hour at 4°C at 2,500 rpm for 12 minutes. Plasma was then transferred to a polypropylene tube and stored at −20°C or colder temperature. Five milliliters for PRA analysis were placed into an evacuated tube containing liquid potassium and EGTA. The tube was inverted several times and centrifuged within 1 hour of collection at 4°C at 2,500 rpm for 12 minutes. Plasma AVP and ANF samples were placed in evacuated, prechilled EGTA tubes. Centrifuge, transfer, and storage were similar to those for PNE and PRA. Collection of blood samples occurred between approximately 8:00 AM and 5:00 PM.

Samples were shipped on dry ice for analysis to the SOLVD Neuroendocrine Core Laboratory at the University of Texas at Galveston.

Neuroendocrine Assays

PNE levels were measured by a radioenzymatic method using the enzyme catechol-α-methyl transferase.10 PRA was measured using the modified radioimmunoassay technique of Sealey and Laragh.11 Plasma AVP and ANF were measured by a simplified radioimmunoassay using commercially available antibodies.12 All samples were analyzed without knowledge of the patient’s clinical condition.

Sensitivity and Reproducibility of Assays

The radioenzymatic assay for PNE has a sensitivity of 1 pg/ml, which yields a sample-to-blank radioactivity count ratio of more than 2. In addition, the interassay coefficient of variation is 6.1% (calculated from 20 different assays done consecutively on 20 different days). The radioimmunoassay for PRA is dependent on the sensitivity of the antibody used in the assay, which can reliably detect 2 pg angiotensin I (sample-to-blank ratio, 2). This assay can detect very low PRA (0.1 ng/ml/hr). The interassay coefficient of variation for PRA is 13.6% The radioimmunoassay for ANF has a sensitivity of 2 pg/ml, and the sensitivity for AVP is 0.22 pg/ml. The interassay coefficients of variation for ANF and AVP are 13.7% and 11.6%, respectively.

Additionally, previously assayed test samples of PNE were mailed from the core laboratory to the clinics where they were stored and then returned and reanalyzed to assess the stability of the samples during transportation. There was no significant difference in the PNE values (278±28 versus 269±32 pg/ml, p=NS) in 123 samples studied in this fashion.

Statistics

Although mean values are presented, neuroendocrine data are also expressed in median values and their interquartile intervals (25% and 75% percentile) because the values were not normally distributed. The Wilcoxon rank-sum test was used to make comparisons between any two groups, and the Kruskal-Wallis test was used to compare the data for all three groups.

Results

Detailed history and physical examination indicated that the majority (>80%) of the patients in the prevention group had no signs or symptoms of heart failure. On the contrary, the majority (>90%) of the patients in the treatment group had signs and symptoms of heart failure. Ischemic heart disease was the dominant etiology in both groups. There was no significant difference between the prevention and treatment groups regarding the time from acute myocardial infarction to randomization. The overall results of the baseline neuroendocrine values for the three groups are shown in Table 2 and Figure 1. Both mean and median values, as well as overall significance, are shown in Table 2. Also shown is the interquartile range (25% to 75%). The median PNE was 317 pg/ml (242–450 pg/ml) in the control group compared with 422 pg/ml (312–566 pg/ml) in the prevention group and 507 pg/ml (368–644 pg/ml) in the treatment group. The median PRA was 0.60 ng/ml/hr (0.3–0.9 ng/ml/hr) in the control group compared with 0.7 ng/ml/hr (0.3–1.6 ng/ml/hr) in the prevention group and 1.4 ng/ml/hr (0.5–3.8 ng/ml/hr) in the treatment group. The median ANF level was 48 pg/ml (31–65 pg/ml) in the control group compared with 103 pg/ml (69–139 pg/ml) in the prevention group and 146 pg/ml (91–203 pg/ml) in the treatment group. The median plasma AVP was 1.8 pg/ml (1.4–2.3 pg/ml) in the control group compared with 2.2 pg/ml (1.7–3.0 pg/ml) in the prevention group and 3.0 pg/ml (2.3–4.4 pg/ml) in the treatment group.

The median values in the prevention group are all significantly greater than those in the control group, and the values in the treatment group are all significantly greater than those in the prevention group (Figure 1). However, PRA was only marginally increased in the prevention group compared with control subjects (p=0.03); this could be accounted for by the fact that 20% of these patients were taking diuretics for hypertension. The data were therefore reanalyzed according to diuretic use. The values for PNE, ANF, and AVP were still significantly elevated in both prevention and treatment groups. However, PRA was not significantly elevated in prevention patients not on diuretics (Table 3). This implies that virtually all of the increase in PRA is accounted for by diuretic use. The median value for PRA, with or without diuretic therapy, is within the normal range in the prevention group. The patients in the treatment group who are not on diuretics also have a normal PRA, but the number of such patients is very small (n=9).

Discussion

This study demonstrates that patients with a left ventricular ejection fraction of 35% or less who have been judged by their physician to not need treatment
TABLE 2. Mean and Median Neuroendocrine Levels in Prevention Patients, Treatment Patients, and Control Subjects

<table>
<thead>
<tr>
<th>Neuroendocrine measurement</th>
<th>Trial</th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>Interquartile range (25% to 75%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNE (pg/ml)</td>
<td>Control</td>
<td>54</td>
<td>346</td>
<td>317</td>
<td>242–450</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Prevention</td>
<td>151</td>
<td>468</td>
<td>422</td>
<td>312–566</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>81</td>
<td>576</td>
<td>507</td>
<td>368–644</td>
<td></td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>Control</td>
<td>56</td>
<td>0.7</td>
<td>0.6</td>
<td>0.3–0.9</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Prevention</td>
<td>151</td>
<td>1.4</td>
<td>0.7</td>
<td>0.3–1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>80</td>
<td>2.6</td>
<td>1.4</td>
<td>0.5–3.8</td>
<td></td>
</tr>
<tr>
<td>AVP (pg/ml)</td>
<td>Control</td>
<td>54</td>
<td>2.0</td>
<td>1.8</td>
<td>1.4–2.3</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Prevention</td>
<td>147</td>
<td>2.6</td>
<td>2.2</td>
<td>1.7–3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>80</td>
<td>3.5</td>
<td>3.0</td>
<td>2.3–4.4</td>
<td></td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>Control</td>
<td>54</td>
<td>51.4</td>
<td>48.3</td>
<td>31–65</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Prevention</td>
<td>147</td>
<td>117.3</td>
<td>102.8</td>
<td>69–139</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>80</td>
<td>154.9</td>
<td>145.7</td>
<td>91–203</td>
<td></td>
</tr>
</tbody>
</table>

PNE, plasma norepinephrine; PRA, plasma renin activity; AVP, arginine vasopressin; ANF, atrial natriuretic factor.

We have shown that neuroendocrine activation occurs at a symptomless or mildly symptomatic stage of left ventricular dysfunction and therefore is not likely to be a simple consequence of worsening congestion. Our data suggest that there is additional progressive neuroendocrine activation as patients progress from early asymptomatic or mildly symptomatic left ventricular dysfunction to symptomatic heart failure. Similar findings have been observed in the pacing animal model of heart failure. Although patients in both the prevention and treatment groups have left ventricular dysfunction, the left ventricular ejection fraction in the sample from the treatment group (25±6%) was significantly lower than that for the prevention group (29±5%).

FIGURE 1. Bar graphs of incremental and significant increase in plasma norepinephrine, plasma renin activity, plasma arginine vasopressin (AVP), and plasma atrial natriuretic factor (ANF) in control subjects, prevention patients, and treatment patients. Treatment values are higher than control values for each neurohormone. Median values and interquartile ranges, 25% to 75%.

with digitalis, diuretics, or vasodilators for signs and symptoms of heart failure have neuroendocrine activation. There is a highly significant increase in the median values for PNE, plasma ANF, and plasma AVP compared with those for control subjects. The median value for PRA is only marginally increased in this group of patients and is probably due to diuretic therapy. There is an additional significant increment in PNE, PRA, ANF, and AVP in patients with overt signs and symptoms of congestive heart failure compared with patients with left ventricular dysfunction in the prevention group. The above trends were observed for all neurohor- mones other than PRA when analyses were confined to those not on diuretics.
TABLE 3. Plasma Neuroendocrine Levels in Prevention Patients, Treatment Patients, and Control Subjects

<table>
<thead>
<tr>
<th>Neurohumoral measurement</th>
<th>Median and interquartile ranges</th>
<th>Prevention patients</th>
<th>Treatment patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>No diuretics</td>
<td>On diuretics</td>
</tr>
<tr>
<td>PNE (pg/ml)</td>
<td>316.5 (242–450)</td>
<td>422.0 (309–548)</td>
<td>416.5 (341–625.8)</td>
</tr>
<tr>
<td>(n=54)</td>
<td>(n=121)</td>
<td>(n=30)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0.6 (0.3–0.9)</td>
<td>0.7 (0.3–1.5)</td>
<td>1.0 (0.5–2.4)</td>
</tr>
<tr>
<td>(n=56)</td>
<td>(n=121)</td>
<td>(n=30)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>AVP (pg/ml)</td>
<td>1.8 (1.4–2.3)</td>
<td>2.3 (1.7–3.0)</td>
<td>2.2 (1.7–2.8)</td>
</tr>
<tr>
<td>(n=54)</td>
<td>(n=117)</td>
<td>(n=30)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td>48.3 (30.6–64.8)</td>
<td>102.8 (68.5–133.3)</td>
<td>103.9 (73.6–180.2)</td>
</tr>
<tr>
<td>(n=54)</td>
<td>(n=117)</td>
<td>(n=30)</td>
<td>(n=9)</td>
</tr>
</tbody>
</table>

PNE, plasma norepinephrine; PRA, plasma renin activity; AVP, plasma arginine vasopressin; ANF, plasma atrial natriuretic factor.

Comparisons of PNE, AVP, and ANF between controls and prevention patients not on diuretics are significant at \( p=0.0002 \), \( p=0.007 \), and \( p=0.0001 \), respectively. PRA levels are not significantly different between the two groups. The addition of diuretics is associated with a marked increase in PRA.

Control subjects versus prevention patients on no diuretics: PNE, \( p=0.0002 \); PRA, \( p=0.1 \); AVP, \( p=0.007 \); ANF, \( p=0.0001 \).

Prevention patients on no diuretics versus prevention patients on diuretics: PNE, \( p=0.6 \); PRA, \( p=0.02 \); AVP, \( p=0.9 \); ANF, \( p=0.6 \).

Prevention patients on diuretics versus treatment patients on diuretics: PNE, \( p=0.3 \); PRA, \( p=0.3 \); AVP, \( p=0.005 \); ANF, \( p=0.04 \).

Treatment patients on diuretics versus treatment patients on no diuretics: PNE, \( p=0.4 \); PRA, \( p=0.05 \); AVP, \( p=0.4 \); ANF, \( p=0.3 \).

This small difference was not unexpected, as the treatment group members had symptomatic heart failure and were probably more advanced in the natural course of their disease. The treatment group was also older (62.7 years) than the prevention group (59.2 years), which was in turn older than the control group (56.4 years). Despite these differences, the patient groups were similar for other variables, including a preponderance of men, a high prevalence of ischemic heart disease, and electrolytes, hemato-crit, serum creatinine, and blood urea nitrogen levels. Reanalysis of the data after stratifying for the small differences in age and ejection fraction did not alter the results.

PRA was normal among those patients not on diuretics in both the prevention and treatment trials. It is therefore likely that activation of the circulating renin-angiotensin system in patients with left ventricular dysfunction as well as in those with symptomatic heart failure is a phenomenon that is in part related to diuretic use. Diuretics and sodium-restrictive diets are well known to increase PRA in patients with heart failure. It is possible that the tissue-bound renin-angiotensin system is active in patients with asymptomatic or mildly symptomatic left ventricular dysfunction despite only marginal increases in circulating renin activity, but we have no data on tissue-bound angiotensin activity.

There are several other important limitations of this study. These patients were not followed sequentially but rather represent two distinct groups studied at different points in their natural histories. Direct proof of incremental neuroendocrine activation would require follow-up and sequential measurements in patients from the asymptomatic stage to the overt symptomatic heart failure stage. Such studies are currently being carried out. It is also likely that there is some overlap in the prevention and treatment groups. Although both groups had definite left ventricular dysfunction, the use of digitalis and diuretics to treat symptoms of congestion was based on clinician judgment. It is possible that a few patients in the prevention group had mild heart failure not detected clinically and that some patients in the overtly symptomatic group did not have heart failure. Although this overlap in clinical spectrum might tend to decrease any real differences between the prevention and treatment patients, detailed history and physical examination revealed none of the symptoms or signs of heart failure in the majority (>80%) of the patients in the prevention group. The majority of patients in the treatment group (>90%) had these signs and symptoms. The neuroendocrine values were essentially unchanged when accounting for these factors.

The main findings of this study are that both vasoconstrictor and vasodilator systems are activated in the very early stages of left ventricular dysfunction before the onset of overtly symptomatic congestive heart failure. The implications of these observations are currently speculative but may offer a rationale for the very early introduction of therapy designed to alter neuroendocrine activation before the onset of overt symptoms of congestive heart failure. However, the lack of an observed increase in circulating PRA in patients with left ventricular dysfunction suggests that sympathetic nervous system activation and release of ANF and AVP may precede activation of the renin-angiotensin system.

Summary

We have demonstrated in a large group of patients with left ventricular dysfunction that there is activation of the sympathetic nervous system, as measured by PNE, as well as the release of AVP and ANF. Circulating renin activity is within normal limits. Patients requiring therapy for symptomatic congestive heart failure have evidence of even greater
neuroendocrine activation, with significant increases in PNE, plasma AVP, and plasma ANF. Neuroendo-
crine activation appears to precede overtly symptomatic heart failure and may therefore contribute to its development.

Appendix
The following individuals (listed by centers) contributed importantly to the conduct of the study.

University of Michigan, Ann Arbor. Principal Investigator, J. Nicklas; L. Quain.

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Harvard University/West Roxbury Veterans Affairs Medical Center, Boston. Principal Investigator, K.M. McIntyre; P.A. Woods.

Mont Godinne Hospital, Belgium. B. Marchandise, E. Schroeder, C. Libois.

Buffalo University, Buffalo, N.Y. Principal Investigator, R.M. Kohn; L.D. Banks, J.A. Celano.

University of Illinois, Chicago. Principal Investigator, J.G. Shanes; J. Ghalu, B.J. Dierenfeldt.


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Study Chairman. B. Pitt, University of Michigan, Ann Arbor.

Project Office (SOLVD). Clinical Trials Branch, National Heart, Lung, and Blood Institute, National Institutes of Health. Project Officer, S. Yusuf; J. Probstfield.

Acknowledgments
The secretarial assistance of Mrs. Sandy Thiesse and the statistical programming of George D. Williams are greatly appreciated. There were many members of the SOLVD group who contributed importantly by drawing blood samples and participating during discussions of the project, and their help is gratefully acknowledged.

References

Key Words: congestive heart failure • neuroendocrine • hormones • left ventricular dysfunction • clinical trials
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Circulation. 1990;82:1724-1729
doi: 10.1161/01.CIR.82.5.1724

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