Brain natriuretic peptide: is it a predictor of cardiomyopathy in cirrhosis?

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ABSTRACT

Subtle cardiac abnormalities have been described in patients with cirrhosis. Natriuretic peptide hormones have been reported to be sensitive markers of early cardiac disease. We postulate that plasma levels of N-terminal pro-atrial natriuretic peptide and brain natriuretic peptide could be used as markers of cardiac dysfunction in cirrhosis. The aim of the study was to evaluate the levels of N-terminal pro-atrial natriuretic peptide and brain natriuretic peptide and their relationship with cardiac structure and function in patients with cirrhosis. The study population comprised 36 patients with cirrhosis of mixed aetiologies, but with no cardiac symptoms; 19 of the patients had ascites and 17 did not. The subjects underwent (i) trans-thoracic two-dimensional echocardiography, and (ii) radionuclide angiography for measurements of cardiac structural parameters, diastolic and systolic function. Levels of N-terminal pro-atrial natriuretic peptide and brain natriuretic peptide were also measured. The results were compared with those from eight age- and sex-matched healthy volunteers. Compared with the controls, the baseline mean ejection fraction was increased significantly in both patient groups (P < 0.02), together with prolonged deceleration times (P = 0.03), left atrial enlargement (P = 0.03) and interventricular septal thickening (P = 0.02), findings that are compatible with diastolic dysfunction. Levels of N-terminal pro-atrial natriuretic peptide and brain natriuretic peptide were significantly higher in all patients with cirrhosis with ascites (P = 0.01 and P = 0.05 respectively), but in only some of the pre-ascitic cirrhotic patients, compared with controls. All high levels of brain natriuretic peptide were correlated significantly with septal thickness (P < 0.01), left ventricular diameter at the end of diastole (P = 0.02) and deceleration time (P < 0.01). We conclude that elevated levels of brain natriuretic peptide may prove to be useful as a marker for screening patients with cirrhosis for the presence of cirrhotic cardiomyopathy, and thereby identifying such patients for further investigations.

INTRODUCTION

Cardiovascular haemodynamic abnormalities have been known for the past 50 years to be associated with cirrhosis [1]. Cirrhotic patients have a hyperdynamic circulation, which is manifested primarily as high cardiac output, decreased systemic vascular resistance and widespread arterial vasodilatation [1]. More recently, both cardiac structural and functional abnormalities have also been described in patients with cirrhosis [2,3]. These include increased thickness of the left ventricle [2–4], associated with diastolic dysfunction, and systolic incompetence.

Key words: cardiomyopathy, cirrhosis, natriuretic peptides.
Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; E/A ratio, ratio between early maximal ventricular filling velocity (E velocity) and late diastolic or atrial velocity (A velocity); NT-ANP, N-terminal ANP.
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(the finding of a normal to increased baseline ejection fraction that does not respond normally to physiological challenges such as exercise), especially under conditions of stress [5–7]. The constellation of abnormalities has been termed cirrhotic cardiomyopathy. However, cirrhotic cardiomyopathy is not a well-recognized condition. It is often confused with alcoholic cardiomyopathy. Furthermore, even when the changes associated with cirrhotic cardiomyopathy are detected, they are often dismissed because overt cardiac failure is uncommon in cirrhosis. However, the occasional report of unexpected deaths due to heart failure following liver transplantation [8], transjugular intrahepatic portosystemic stent shunt insertion [9] and surgical portocaval shunts [10] in cirrhotic patients would suggest that cirrhotic cardiomyopathy may have clinical relevance in the management of these patients. Furthermore cirrhotic cardiomyopathy may be aggravated by sodium retention in cirrhosis, with increases in total and central blood volumes. Therefore early detection and intervention may prove beneficial for these patients.

A clinical diagnosis of cirrhotic cardiomyopathy is often not made, since the signs of cardiac dysfunction are subtle, and may be masked in cirrhotic patients by sodium retention. Features of cirrhotic cardiomyopathy can be detected by either two-dimensional Doppler echocardiography or radionuclide ventriculography. More recently, natriuretic peptide hormones such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have been reported to be sensitive and useful markers for early-stage heart disease [11–13], and have provided an opportunity for early diagnosis of cardiac dysfunction and intervention in other conditions such as ischaemic heart disease and hypertension. ANP levels have long been known to be elevated in cirrhosis [14–16]. These have always been regarded as markers of volume overload rather than markers of cardiac dysfunction in cirrhosis. However, N-terminal ANP (NT-ANP), a cleavage product of pro-ANP, has been associated with left ventricular dysfunction [11,17]. Its levels have not been reported in cirrhosis. BNP levels have been found to be elevated in decompensated cirrhosis [18], but levels in compensated cirrhosis are more controversial, having been found to be either normal or increased [18,19]. The significance of this finding has never been determined. Therefore the aim of the present study was to clarify further the status of the natriuretic peptides as markers of cardiac dysfunction in cirrhosis. In particular, this study aimed at answering the following questions: (i) do plasma levels of natriuretic peptides provide any information about abnormal cardiac function in cirrhosis?; (ii) is there an association between the plasma levels of natriuretic peptides and systolic and diastolic dysfunction?; and (iii) can plasma natriuretic peptides be used to identify early cirrhotic cardiomyopathy?

MATERIALS AND METHODS

Ethical approval for the study was granted by the Ethics Committee of the Toronto General Hospital, University Health Network. All control subjects and cirrhotic patients gave informed consent for the study.

Patients

A study population of 36 patients (34 males, two females), with biopsy-proven cirrhosis, were recruited from the General Hepatology and Pre-Transplant Clinics of the Toronto General Hospital. Of these, 17 patients had no history of ascites or diuretic use. The absence of ascites was confirmed by ultrasound before enrolment. These patients were therefore termed pre-ascitic cirrhotic patients. The remaining 19 patients had obvious ascites clinically, and this was confirmed on ultrasound. Nine pre-ascitic and 12 ascitic patients had alcoholic cirrhosis, but had been abstinent from alcohol for at least 6 months before enrolment. This was documented by questionnaires completed by the patient and his family during repeated clinic visits and by near-normal serum γ-glutamyltransferase levels. Cirrhosis was related to hepatitis C infection in nine patients and to hepatitis B infection in another two. Two patients had cryptogenic cirrhosis, while the remaining two patients had autoimmune hepatitis and drug-induced cirrhosis as a result of flutamide use respectively. All were ambulatory patients who had been stable and free of gastrointestinal bleeding in the previous 3 months. A negative history with regard to hypertension and cardiac and pulmonary disease, a normal clinical examination by a cardiologist, and normal ECG, chest X-ray, spirometry and oximetry were mandatory for inclusion in the study. In addition, all cirrhotic patients had to have normal blood pressure readings on at least two separate occasions before enrolment. A group of eight age- and sex-matched healthy individuals with no history of cardiac or pulmonary disease, a normal clinical examination by a cardiologist, and normal ECG, chest X-ray, spirometry and oximetry were controls. The demographics of all study subjects, and baseline parameters including the Pugh score in all cirrhotic patients, are given in Table 1.

Study design

The study was performed with the control subjects and pre-ascitic cirrhotic patients consuming a metabolic diet containing 200 mmol of sodium and 1.5 litres of fluid per day for 7 days. This sodium intake was chosen because the associated volume expansion has been shown to increase the subtle cardiac dysfunction in some pre-ascitic cirrhotic patients [2]. Furthermore, both control subjects and pre-ascitic cirrhotic patients have been shown to achieve a steady state after consuming this diet for 7 days [20]; this would ensure that a change in volume status was not introduced as a confounding factor in these two groups. In contrast, ascitic cirrhotic patients
Table 1 Baseline demographics of the control subjects and patients with cirrhosis

Significance of differences: *P < 0.05, **P < 0.01 compared with controls; †P < 0.05 compared with pre-ascitic cirrhotic patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Pre-ascitics</th>
<th>Ascitics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48 ± 3</td>
<td>50 ± 2</td>
<td>52 ± 2</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>6/2</td>
<td>17/0</td>
<td>17/2</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>133 ± 3</td>
<td>136 ± 3</td>
<td>121 ± 4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.04 ± 0.02</td>
<td>1.37 ± 0.05**</td>
<td>1.68 ± 0.10**</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>46 ± 1</td>
<td>39 ± 1</td>
<td>32 ± 2</td>
</tr>
<tr>
<td>Bilirubin (μmol/l)</td>
<td>12 ± 3</td>
<td>28 ± 3</td>
<td>40 ± 7**</td>
</tr>
<tr>
<td>Pugh score</td>
<td>–</td>
<td>5.9 ± 0.3</td>
<td>10.0 ± 0.4†</td>
</tr>
<tr>
<td>Aetiology of cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Drug-induced</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>–</td>
<td>1</td>
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</table>

retain sodium avidly even on a low sodium intake; therefore these patients were placed on a diet containing 20 mmol of sodium and 1.0 litre of fluid per day for 7 days. Day 1 of the study was the first day of the diet. All medications that could potentially affect cardiac function or volume status, such as β-blockers and diuretics, were withheld from day 1. None of the ascitic patients received a paracentesis for 2 weeks prior to the study.

All study subjects underwent (i) trans-thoracic echocardiography to assess cardiac structure and diastolic function; (ii) a radionuclide angiography to assess cardiac chamber volumes and ejection fraction, and (iii) blood sampling for measurements of NT-ANP and BNP after having been in a supine posture for at least 2 h.

Protocol

On day 8 of each study group’s respective diet, all subjects underwent a trans-thoracic echocardiographic examination to assess left ventricular systolic and diastolic chamber dimensions, interventricular septal thickness and left ventricular relative wall thickness [21]. Diastolic function was assessed by measuring the E/A ratio (where the E velocity is the early maximal ventricular filling velocity, and the A velocity is the late diastolic or atrial velocity), an assessment of the degree of impairment of diastolic relaxation, as well as the isovolumic relaxation time (the period of time from the closure of the aortic valve to the opening of the mitral valve) and the deceleration time (the time period during which the ventricle inflow decelerates to a complete stop). An increase in the isovolumic ventricular relaxation time and the deceleration time, and a decreased E/A ratio, suggest abnormal left ventricular diastolic filling [3,4], or abnormal left ventricular relaxation.

On day 9 of the study, 3 h after their usual breakfast, all subjects underwent a supine radionuclide angiography study for measurements of cardiac chamber volumes and ejection fraction, a measure of systolic function. The best septal view was used to determine the end-systolic and end-diastolic volumes using the modified Links method [22].

After completion of cardiac measurements on day 9, all study subjects, while remaining supine, had blood samples drawn into pre-chilled tubes containing EDTA and aprotinin for measurements of NT-ANP and BNP. Blood samples were centrifuged immediately at 4 °C at 3000 rev./min for 10 min before the plasma was frozen at −70 °C until analysis. Blood samples were also drawn for complete blood count, prothrombin time and liver function tests for calculation of the Child–Pugh score [23].

Procedures

Echocardiography

A comprehensive trans-thoracic echocardiographic examination was performed using commercially available cardiac ultrasound machines (Hewlett Packard, Andover, MA, U.S.A.). Patients were placed in the left lateral decubitus position, and standard parasternal, apical and subternal views were obtained. Pulsed and colour flow Doppler techniques were used to interrogate the isovolumic relaxation and deceleration times. All images were then recorded on VHS tapes for off-line analysis.

Radionuclide angiography

A detailed description of the technique of cardiac chamber volume measurements using radionuclide angiography can be found in [24]. Briefly, red blood cells were labelled using [99mTc]pertechnetate. The cardiac volumes were measured based on regional activity corrected for attenuation. The ejection fraction and cardiac volumes were analysed using semi-automated software. Quality assurance studies in our Nuclear Cardiology Laboratory have established the standard error of the estimate of left ventricular ejection fraction calculation to be less than 2% using the semi-automated technique. The standard error of the estimate of ventricular volume calculation is less than 5 ml [25].

Laboratory analysis

A complete blood count, assessment of prothrombin time and liver function tests were performed using standard laboratory automated techniques. Plasma concentrations of NT-ANP and BNP were measured by
Table 2 Baseline haemodynamics and cardiac structure and function for control subjects and patients with cirrhosis

Significance of differences: * P < 0.05 compared with controls; † P < 0.05 compared with pre-ascitic cirrhotic patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Pre-ascitics</th>
<th>Ascitics</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 ± 5</td>
<td>71 ± 2</td>
<td>71 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>91 ± 5</td>
<td>90 ± 2</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>58.9 ± 1.6</td>
<td>64.7 ± 2.6*</td>
<td>64.1 ± 1.6*</td>
</tr>
<tr>
<td>End-diastolic volume (ml)</td>
<td>106 ± 14</td>
<td>112 ± 11</td>
<td>108 ± 8</td>
</tr>
<tr>
<td>End-systolic volume (ml)</td>
<td>43 ± 6</td>
<td>46 ± 5</td>
<td>38 ± 4</td>
</tr>
<tr>
<td>Left atrial size (mm)</td>
<td>39.5 ± 2.6</td>
<td>43.3 ± 1.6*</td>
<td>42.0 ± 1.3*</td>
</tr>
<tr>
<td>Left ventricular diameter at end-diastole (mm)</td>
<td>48.8 ± 1.7</td>
<td>50.4 ± 1.2</td>
<td>44.6 ± 1.28†</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.40 ± 0.20</td>
<td>1.19 ± 0.10</td>
<td>1.18 ± 0.07</td>
</tr>
<tr>
<td>Isovolumic relaxation time (ms)</td>
<td>78.9 ± 4.8</td>
<td>89.8 ± 2.7*</td>
<td>92.7 ± 3.8*</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>196 ± 13</td>
<td>227 ± 11</td>
<td>250 ± 14</td>
</tr>
<tr>
<td>Interventricular septal thickness (mm)</td>
<td>9.1 ± 0.5</td>
<td>10.6 ± 0.3*</td>
<td>10.9 ± 0.3*</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>8.9 ± 0.6</td>
<td>9.8 ± 0.3</td>
<td>9.4 ± 0.3</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>146 ± 12</td>
<td>175 ± 10</td>
<td>195 ± 13</td>
</tr>
</tbody>
</table>

RESULTS

Cardiac structural parameters

Both the pre-ascitic and ascitic cirrhotic patients had significantly increased interventricular septal thickness compared with the control subjects (P = 0.017). Left ventricular posterior wall thickness, as well as left ventricular mass, were increased in both groups of cirrhotic patients compared with the controls; however, the differences were not statistically significant (P > 0.05) (Table 2). Left atrial size in both the cirrhotic groups was significantly increased compared with that in the controls (P = 0.03).

Systolic and diastolic function

No wall motion or valvular abnormalities were noted during the echocardiological examination for both the controls and the cirrhotic patients. The radionuclide angiography ejection fraction was significantly higher in both groups of cirrhotic patients compared with the controls (Table 2). Neither the end-diastolic nor the end-systolic volume was significantly different in the cirrhotic patients compared with the controls (P > 0.05). The ascitic, but not the pre-ascitic, cirrhotic patients had a significantly smaller left ventricular diameter at the end of diastole compared with the controls (P = 0.03) (Table 2).

The E/A ratio, a measure of the degree of impairment of diastolic relaxation, was reduced in the cirrhotic patients compared with the control subjects, but the difference was not statistically significant. However, the isovolumic relaxation time was significantly prolonged in both the pre-ascitic (P = 0.05) and the ascitic (P = 0.04)

Statistical analysis

All results were expressed as mean ± S.E.M. For each parameter, the differences between the three study groups were assessed by ANOVA. Correlation analysis was used to determine the relationships between the cardiac parameters and natriuretic peptide levels. A P value of < 0.05 was considered to be statistically significant.
Brain natriuretic peptide in cirrhosis

Figure 1 NT-ANP and BNP levels in control subjects and in pre-ascitic and ascitic cirrhotic patients

Pre-ascitic (L), pre-ascitic patients with low natriuretic peptide levels; pre-ascitic (H), pre-ascitic patients with high natriuretic peptide levels. Significance of differences: *P < 0.05 compared with controls, #P < 0.05 compared with pre-ascitic (L).

Natriuretic peptide levels

NT-ANP levels were similar in the controls and the pre-ascitic cirrhotic patients (Figure 1). In contrast, the ascitic cirrhotic patients had significantly higher NT-ANP levels (P = 0.01). Likewise, BNP levels were similar in the controls and the pre-ascitic cirrhotic patients, but the ascitic cirrhotic patients had significantly higher levels compared with the controls (P = 0.05) (Figure 1).

When the individual results for NT-ANP and BNP levels were analysed in the pre-ascitic group, a subgroup of 10 of the 17 patients were found to have higher natriuretic peptide levels than the mean of the control group; only six of these 10 patients with higher natriuretic peptide levels had alcohol as the aetiology of their cirrhosis. When the pre-ascitic cirrhotic group was separated into subgroups with high and low levels of natriuretic peptides, the levels in the former group were significantly increased compared with those in the control group (P = 0.02 for NT-ANP; P < 0.01 for BNP) (Figure 1). However, there was no statistically significant difference in any of the cardiac parameters between the subgroups with high and low hormone levels.

When the natriuretic peptide hormone levels of the high pre-ascitic cirrhotic subgroup and the ascitic cirrhotic patients were combined and correlated with parameters of cardiac structure and function, BNP showed a significant correlation with septal thickness (P < 0.01), left ventricular diameter at end-diastole (P = 0.05).
The fact that elevated levels of BNP can identify asymptomatic patients with diastolic dysfunction in the absence of systolic abnormalities has made it a useful screening tool for the detection of cardiac dysfunction.

Our cirrhotic patients with ascites indeed had elevated levels of both NT-ANP and BNP, suggesting the presence of cardiac dysfunction. This was despite a normal clinical cardiological examination, ECG and chest X-ray. It is interesting to note that the pre-ascitic cirrhotic patients as a group did not show any evidence of elevated natriuretic peptide hormone levels, despite the fact that the echocardiographic and radionuclide findings suggested the presence of structural and functional abnormalities. However, careful analysis of the individual patients revealed that some, but not all, pre-ascitic patients had elevated natriuretic peptide hormone levels. This may explain the controversy in the literature with regard to BNP levels in pre-ascitic cirrhotic patients [18,19], as only some, but not all, pre-ascitic cirrhotic patients have cirrhotic cardiomyopathy. This is analogous with a previous finding that, while many pre-ascitic cirrhotic patients showed an increase in systolic pressure with an increase in cardiac volume following sodium loading, some such patients actually showed an inverse pressure/volume relationship, i.e. increased volume resulted in a decrease rather than an increase in systolic pressure [2]. These combined results suggest that only some, but not all, pre-ascitic cirrhotic patients have evidence of cardiac dysfunction. Alcohol does not appear to be a contributory factor to the development of cirrhotic cardiomyopathy, as only some of the patients with cardiac dysfunction had alcohol as the aetiology of their cirrhosis. Furthermore, the ventricles are dilated with systolic dysfunction in alcoholic cardiomyopathy, in contrast with the ventricular hypertrophy with diastolic dysfunction observed in cirrhosis.

Volume overload leading to activation of neurohormones, including noradrenaline [34], angiotensin and aldosterone [35,36], has been implicated in cardiac hypertrophy and fibrosis, resulting in structural remodelling with increased collagen accumulation in the interstitium, which greatly increases myocardial stiffness. The increased left ventricular wall tension in turn activates the release of BNP, and to a lesser extent ANP. Both ANP and BNP have potent natriuretic, diuretic and vasodilatory properties. Their presence may be regarded as counter-regulatory to the actions of the sympathetic and renin–angiotensin–aldosterone systems. Therefore both ANP and BNP represent an in-built mechanism to counteract the development of heart failure, while at the same time providing a marker for the early detection of cardiac dysfunction.

The fact that there was a significant correlation between the elevated BNP levels, but not NT-ANP levels (when including pre-ascitic and ascitic patients), and
interventricular septal thickness and deceleration time suggests that BNP is a better marker than NT-ANP of diastolic function in cirrhosis. Elevated BNP levels have been shown to accurately reflect isolated diastolic dysfunction in the absence of systolic failure [37] with a sensitivity of 85% and a specificity of 74% [32]. The fact that elevated BNP levels were also correlated with the left ventricular diameter at end-diastole suggests that increased intraventricular volume also contributed to BNP secretion. The combined effects of a thicker left ventricle together with increased intraventricular volume would result in a higher left ventricular end-diastolic pressure, leading to increased ventricular wall stress, thereby stimulating BNP secretion. The presence of a large left atrium compared with the controls suggests that the diastolic dysfunction was associated with increased atrial pressure, thereby accounting to some extent for the raised NT-ANP levels.

Although Doppler indices of diastolic filling have been validated by catheterization assessment, other factors, such as preload, afterload, left ventricular function, arrhythmias and the presence of mitral valve disease, may confound these Doppler indices [38]. In the present study we have minimized the influence of these confounding physiological factors, as our patients were in normal sinus rhythm, had preserved left ventricular systolic function and did not have valvular abnormalities. In addition, preload was kept constant, as patients were not taking diuretics and their salt and water intake was kept constant during the study period. The effect of age was minimized, as the mean ages of the three study groups were similar. As the Doppler parameters were obtained at rest, we are not able to comment on the effect of exercise on diastolic filling.

Thus we have shown that abnormal plasma levels of BNP do provide information about abnormal cardiac function in patients with cirrhosis, and that elevated levels of BNP correlate best with diastolic dysfunction in these patients. Because cardiac dysfunction is largely asymptomatic in cirrhosis, clinical assessment is not always reliable, and since investigations such as echocardiography and radionuclide angiography are time-consuming and costly as screening procedures, BNP would result in a higher left ventricular end-diastolic pressure, leading to increased ventricular wall stress, thereby stimulating BNP secretion. The presence of a large left atrium compared with the controls suggests that the diastolic dysfunction was associated with increased atrial pressure, thereby accounting to some extent for the raised NT-ANP levels.

In conclusion, the present study demonstrates that, in patients with cirrhosis, natriuretic peptide levels were increased in those patients with cardiac dysfunction, and that BNP levels were related to interventricular septal thickness and impairment of diastolic function. BNP shows promise as a screening test for the need for further cardiac investigations [34], and may eventually prove to be a marker of successful therapeutic intervention in cirrhosis.

ACKNOWLEDGMENTS

We thank Dr Gordon Moe of St Michael’s Hospital, Toronto, for performing the NT-ANP and BNP assays, Jim Graba for performing the echocardiological examinations, Yasmin Alidina for performing the radionuclide angiography studies, and Shona Mackenzie for her nursing support. P. L. is The Heart and Stroke Polo Chair Professor in Cardiovascular Research, University of Toronto, Canada.

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Received 7 June 2001; accepted 1 August 2001