Cerebral Blood Flow in Patients With Chronic Heart Failure Before and After Heart Transplantation

Nicolai Gruhn, MD; Fin S. Larsen, PhD; Søren Boesgaard, PhD; Gitte M. Knudsen, PhD; Svend A. Mortensen, PhD; Gerda Thomsen; Jan Aldershvile, PhD

Background and Purpose—Arterial blood pressure and cardiac output are often reduced in patients with chronic heart failure (CHF). Counterregulatory mechanisms with increased neurohormonal activation and changes in the distribution of cardiac output are assumed to secure vital organ perfusion. However, clinical examination of patients with CHF frequently reveals neurological symptoms with dizziness and memory problems, suggesting altered brain perfusion. In this study we determined whether cerebral blood flow (CBF) is reduced in patients with New York Heart Association (NYHA) functional class III and IV (n=12) compared with healthy control subjects (n=12). Furthermore, we examined whether heart transplantation (n=5) could restore CBF.

Methods—CBF was estimated by single-photon emission computed tomography and $^{133}$Xe as tracer, and middle cerebral artery velocity was measured by transcranial Doppler ultrasound.

Results—In the CHF patients, CBF was 36±1 mL/min per 100 g, corresponding to a 31% reduction compared with the control group (52±5 mL/min per 100 g) (P<0.05). After heart transplantation, CBF increased from 35±3 mL/min per 100 g before transplantation to 50±3 mL/min per 100 g within the first postoperative month (P<0.05).

Conclusions—We conclude that CBF is substantially, but reversibly, reduced in patients with NYHA class III/IV heart failure. This phenomenon suggests that redistribution of cardiac output inadequately secures brain perfusion in patients with severe CHF. (Stroke. 2001;32:2530-2533.)

Key Words: cerebral blood flow ■ heart ■ heart failure ■ heart transplantation

Normal resting cerebral blood flow (CBF) is approximately 50 mL/min per 100 g, and it is kept constant within a wide range (60 to 150 mm Hg) of mean arterial blood pressure (MAP).1 The brain is especially sensitive to circulatory changes that reduce oxygen and glucose delivery and is critically dependent on an adequate distribution of cardiac output and an accurate regulation of CBF. In the absence of profound hypotension, an acute lowering of cardiac output in experimental animals is associated with normal or only slightly reduced CBF values.2 Likewise, patients with heart failure are generally considered to have normal CBF because of the redistribution of blood flow toward the heart and brain and away from the skeletal muscles and cutaneous, splanchnic, and renal vascular beds.3 Other findings, however, do not uniformly support this generalization. Despite compensatory changes, chronic low cardiac output is associated with a 25% reduction in CBF in cardiomyopathic rabbits.4 In humans, CBF may be slightly reduced,5 and cognitive impairment with lethargy, confusion, memory problems, and dizziness may increase morbidity in patients with severe chronic heart failure (CHF). Since these neuropsychological problems are relieved by heart transplan-
Hemodynamic Measurements

CBF was measured with a brain-dedicated single-photon emission CT scanner with the use of the $^{133}$Xe inhalation technique (Tomomatic 564, Medimatic Inc).

$^{133}$Xe is rapidly washed out from the brain, permitting sequential measurements within short time intervals. $^{133}$Xe was inhaled for 1.5 minutes from a 4-L bag filled with atmospheric air and oxygen with a $^{133}$Xe concentration of 740 MBq/L. The energy window was set at 66 to 142 keV. A collimated NaI crystal, recording radioactivity as an estimate of the arterial input curve to the brain, was placed over the apex of the right lung. Cerebral activity was recorded for 270 s.

The regional distribution of CBF was not changed (Figure 1a). The regional distribution of CBF was not changed (Figure 2a). Although a trend toward decreased MCAV was seen in CHF patients, these changes did not reach statistical significance because of a rather large variability (CHF, 36 ± 6 cm/s; control, 49 ± 9 cm/s; $P > 0.05$) (Figure 2a).

CBF values before and 1 month after transplantation were 35 ± 3 and 50 ± 3 mL/min per 100 g, respectively ($P < 0.05$) (Figure 1b). Thus, CBF normalizes rapidly after heart transplantation (Figure 1b). MCAV values were increased after transplantation, but again the change did not reach statistical significance (Figure 2b). In the small number of patients

<table>
<thead>
<tr>
<th>Baseline Characteristics of the CHF Group, Control Group, and Subgroup of Cardiac Transplanted Patients</th>
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<tbody>
<tr>
<td>CHF $(n=12)$</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
</tr>
<tr>
<td>NYHA class III</td>
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<tr>
<td>NYHA class IV</td>
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<tr>
<td>LVEF, %</td>
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<td>CVP, mm Hg</td>
</tr>
<tr>
<td>Cardiac index</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
</tr>
<tr>
<td>CBF, mL/min · 100 g</td>
</tr>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Loop diuretics</td>
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<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Nitrates</td>
</tr>
</tbody>
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LVEF indicates left ventricular ejection fraction (normal range, 58–75%); CVP, central venous pressure (normal range, 1–6 mm Hg); cardiac index, cardiac output corrected for body surface (normal range, 2.5–4.0 L/min); and ACE, angiotensin-converting enzyme.

*As estimated from history and clinical examination.

any cardiovascular diseases. All study subjects gave informed consent. The study was approved by the local ethical committee (protocol No. KF 01-256/98) and followed the principles of the Helsinki Declaration.

Study Design

Supine resting arterial blood pressure, heart rate, CBF, and middle cerebral artery blood flow velocity (MCAV) were measured in all CHF patients and healthy volunteers. In the 5 transplanted CHF patients, measurements were repeated 1 (n=5) and 6 months (n=3) after the transplantation.

Results

CBF and MCAV

Resting CBF was 36 ± 1 mL/min per 100 g in the 12 CHF patients, corresponding to a 31% reduction compared with the control group (52 ± 5 mL/min per 100 g) ($P < 0.05$) (Figure 1a). The regional distribution of CBF was not changed ($P > 0.05$). Although a trend toward decreased MCAV was seen in CHF patients, these changes did not reach statistical significance because of a rather large variability (CHF, 36 ± 8 cm/s; control, 49 ± 9 cm/s; $P > 0.05$) (Figure 1b).

CBF values before and 1 month after transplantation were 35 ± 3 and 50 ± 3 mL/min per 100 g, respectively ($P < 0.05$) (Figure 1b). Thus, CBF normalizes rapidly after heart transplantation (Figure 1b). MCAV values were increased after transplantation, but again the change did not reach statistical significance (Figure 2b). In the small number of patients

Figure 1. a, CBF in patients with CHF (right; n=12) and an age-matched control group (left; n=12). *$P < 0.05$ compared with control. b, CBF in 5 patients with CHF before (left) and 1 month after (right) heart transplantation (n=5). *$P < 0.05$ compared with pretransplantation.

Figure 2. a, MCAV in patients with CHF (right; n=12) and an age-matched control group (left; n=12). b, MCAV in 5 patients with CHF before (left) and 1 month after (right) heart transplantation (n=5).
Blood Pressure and Carbon Dioxide

Resting MAP was significantly lower in the CHF group (76±5 mm Hg) than in the 12 controls (95±3 mm Hg). MAP pressure was significantly increased after transplantation (before transplantation, 76±5 mm Hg; after transplantation, 93±7 mm Hg; n=5) and did not differ from MAP in the healthy volunteers. CHF patients had slightly lower end-expiratory CO2 concentrations than their control group (4.6±0.2 versus 5.2±0.1 kPa; P<0.05).

Discussion

We have found that CBF is reduced by approximately 30% in patients with severe CHF compared with a healthy age-matched control group. This finding is further substantiated by a significant increase in CBF among patients undergoing heart transplantation and by qualitatively similar changes in MCAV.

Autoregulation of flow ensures that flow through an organ or a vascular bed is maintained fairly constant despite changes in MAP. Under normal circumstances, CBF starts to drop when MAP decreases to approximately 80% of baseline MAP values (usually approximately 60 mm Hg), which is somewhat lower than the average baseline MAP of 76 mm Hg found in the CHF patients in this study. It is unknown whether the cerebral autoregulation is preserved in patients with CHF. Theoretically, CHF-induced activation of physiological neurohormonal counterregulatory mechanisms, such as the sympathetic nervous system and the renin-angiotensin system, may result in a rightward shift of the lower limit of autoregulation, whereby a decrease in CBF may result from the low MAP values found in the CHF patients. On the other hand, since adaptive mechanisms for rightward shift of the lower limit of autoregulation are known to occur in arterial hypertension, the converse phenomenon is likely to happen in chronic hypotension. A leftward shift has previously been demonstrated after chronic cerebral hypotension and after ACE inhibitor administration. However, future studies are needed to address whether the limits of cerebral autoregulation are affected by the presence of CHF.

CHF patients had slightly lower end-expiratory CO2 concentrations than their control group. Even if one assumes normal cerebrovascular CO2 reactivity, this reduction in PCO2 would only be responsible for approximately 18% of the observed CBF decrease. Furthermore, since hypocapnia is a well-known chronic phenomenon in many CHF patients, and since a cerebral hemodynamic adaptation takes place in response to prolonged reduction in CO2, the influence of the present difference in end-expiratory CO2 on CBF is questionable.

In moderate heart failure, a normal resting cardiac output rises insufficiently during exercise, while in more severe heart failure cardiac output is already reduced at rest. In this latter condition, it has generally been accepted that blood flow is redistributed in favor of the brain and heart to preserve blood flow to these organs. However, patients with severe CHF show a paradoxical baroreceptor-mediated peripheral vasodilation in the upright position, which may counteract blood flow distribution to the brain and direct blood flow away from the cerebral circulation. In fact, chronic low cardiac output is associated with a reduction in CBF in cardiomyopathic rabbits, whereas acutely bled animals without heart failure preserve a normal or only slightly reduced CBF in the absence of profound hypotension. Human data are limited and conflicting. More recent data suggest that MCAV decreases with diminished cardiac output. A trend was also observed in the present study (CHF group versus control group). Furthermore, other reports suggest that it is the augmentation of cardiac output, rather than raised arterial blood pressure, that increases CBF in conditions characterized by low cardiac output or cerebral vasospasm.

On the basis of responses to hypercapnia, data from Georgiadis et al recently suggested that the cerebral arteriolar dilatory capacity becomes nearly exhausted in patients with severe CHF. The low CBF in this study is compatible with this suggestion. In moderately hypotensive animals, in which CBF is still normal because of arteriolar vasodilation, sympathetic stimulation significantly reduces CBF. Exaggerated activity of the sympathetic and the renin-angiotensin systems is a central neurohormonal response to maintain cardiac output and central hemodynamic integrity during the development of CHF. Consequently, one may speculate that in patients with severe CHF, the overall combination of reduced MAP and increased neurohormonal activity cannot be compensated for by cerebral arteriolar autoregulated vasodilation and/or by systemic mechanisms available for blood flow redistribution. In this respect it is of interest that the angiotensin-converting enzyme inhibitor captopril has been shown to augment CBF in patients with CHF, while no study to our knowledge has evaluated the effect of, for example, beta-adrenergic inhibition on CBF in patients with CHF.

In normal subjects, an acute 30% lowering of CBF is associated with mild symptoms of cerebral hypoperfusion, and mental confusion occurs at 50% to 60% of normal CBF levels. It is therefore likely that neurological/mental symptoms associated with CHF are caused by either chronic or intermittent episodes of cerebral hypoperfusion. Recent data suggest that mental symptoms are potentially reversible after heart transplantation, which restores central hemodynamics (eg, MAP and cardiac output) and normalizes the neurohormonal drive seen before transplantation. We did not perform neuropsychological tests, but the finding that the 30% reduction in CBF in patients awaiting heart transplantation was normalized within 1 month after the operation may provide a physiological explanation for the reported neuropsychological effects of transplantation.

During calculations of CBF, we assumed that the xenon transit time from the lungs to the brain in CHF patients is similar to the transit time in healthy subjects. A substantially increased uncorrected pulmonary transit time will yield a somewhat decreased CBF, which theoretically then could explain part of the reduced CBF in our CHF patients. Data on this issue are limited, but CHF patients with cardiac index of...
2.8±0.2 L/min per square meter have been shown to have a normal pulmonary transit time, and only patients with a cardiac index of 1.9 have a transit time twice as high. In our study, since cardiac index was 2.5±0.2 in the CHF group, changes (if present) in transit time in this group are likely to induce only minor alterations in measured CBF values. This is substantiated by the finding that calculations based on transit times twice normal values still produced a CBF that was significantly reduced in patients with CHF.

In conclusion, we find that CBF is reduced by approximately 30% in patients with severe CHF (NYHA class III and IV) and that CBF normalizes after cardiac transplantation. This is the first study to show that CBF is reversibly reduced in patients with NYHA class III/IV heart failure. This phenomenon may contribute to the neurological symptoms often experienced by patients with CHF.

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References
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