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 133Xe 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 transplantation,⁶ it is reasonable to assume that CBF alterations may occur in patients with CHF. However, the effect of severe CHF on CBF has only been incompletely investigated in humans. In this study we compared CBF values in patients with severe CHF with those of an age-matched control group; the effect of heart transplantation on cerebral hemodynamics was also investigated.

Subjects and Methods

Patients

Twelve patients (11 men; mean±SEM age, 51.9±4.9 years) with severe heart failure due to either dilated cardiomyopathy (n=9) or ischemic heart disease (n=3) were included in the study. All patients were in New York Heart Association (NYHA) functional class III/IV and had been evaluated for cardiac transplantation. Five of the CHF patients underwent a cardiac transplantation within the following 6 months. Twelve age-matched healthy volunteers (11 men; mean±SEM age, 47.4±2.1 years) were included as normal controls. Baseline demographics are shown in the Table. None of the subjects had diabetes, epilepsy, hypertension, or liver, lung, or brain disease. CHF patients using nitrates had this treatment suspended 24 hours before and during the investigation. None of the control subjects had...
ACE, angiotensin-converting enzyme.

Cardiac output corrected for body surface (normal range, 2.5–4.0 L/min); and CVP, central venous pressure (normal range, 1–6 mm Hg); cardiac index, 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 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 a function of time. Radioactivity of 133 Xe in the brain was measured after the subject had been in a supine position for at least 10 minutes.

Blood pressure was measured with a fully automated monitor (OMRON M4) on the patient’s left upper arm.

Statistical Analysis

Values in the 2 study groups (CHF and controls) were compared by Student’s t test for unpaired observations. Pretransplantation and posttransplantation values were compared by paired Student’s t test. Results are expressed as mean±SEM, and P<0.05 is considered significant.

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 before and 1 month after transplantation, but again the change did not reach statistical significance (Figure 2a). In the small number of patients on the same side of each patient throughout the study period. The position of the probes was secured by a rubber headband. MCAV was measured after the subjects had been in a supine position for at least 10 minutes.

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,11,12 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,13 the converse phenomenon is likely to happen in chronic hypotension. A leftward shift has previously been demonstrated after chronic cerebral hypotension14 and after ACE inhibitor administration.15 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.16

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,17 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,4 whereas acutely bled animals without heart failure preserve a normal2 or only slightly reduced CBF in the absence of profound hypotension. Human data are limited and conflicting,5,18 but in general CBF has been considered normal even in patients with moderate to severe heart failure.18 More recent data suggest that MCAV decreases with diminished cardiac output.19 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 output20 or cerebral vasospasm.21,22

On the basis of responses to hypercapnia, data from Georgiadis et al23 recently suggested that the cerebral arterial dilatory capacity becomes nearly exhausted in patients with severe CHF. The low CBF in this study is compatible with this suggestion. In moderately hypertensive animals, in which CBF is still normal because of arteriolar vasodilation, sympathetic stimulation significantly reduces CBF.11,24 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 arterial 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,25 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.25 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,6 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.

Acknowledgments

This study was supported by the Danish Heart Foundation, the Sophus Jacobsen and Astrid Jacobsens Foundation, the Beckett Foundation, the King Christian X Foundation, and the Leo Foundation. We would like to express our gratitude to laboratory technician Glenna Skouboe and the nursing staff of the unit of heart transplantation.

References

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

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

*Stroke*. 2001;32:2530-2533
doi: 10.1161/hs1101.098360

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/11/2530