EDITORIAL COMMENT

Patients With Heart Failure With Reduced Ejection Fraction Have Exaggerated Reductions in Cerebral Blood Flow During Upright Posture*

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Cognitive dysfunction (CD) is a major and often underappreciated complication among patients with heart failure (HF). Memory and attention deficits are the most common manifestations, with a prevalence of 30% to 80% depending on patient age (1). However, up to 25% of patients with HF may have moderate to severe impairments in cognition, which increase the risk of medication nonadherence and HF hospitalizations, physical disability, and mortality (2). Although the association between HF and CD is based on multiple shared risk factors such as hypertension (3), atherosclerosis (4), and diabetes mellitus (5), cerebral hypoperfusion in its own right has been advanced as a primary contributor to CD (6). Indeed, hypoperfusive lesions have been observed in the form of white matter hyperintensities (7) and, in the Framingham Heart Study, cardiac index (CI) was positively related to total brain volume and information-processing speed (8).

In this regard, patients with heart failure with a reduced ejection fraction (HFrEF) represent a substrate of subjects at particularly increased risk for CD due to the combination of a low output state and multiple comorbidities. Furthermore, the majority of activities of daily living occur in an upright posture, which might lead to further reductions in cerebral perfusion due to a gravitational displacement of blood below the brain on both the arterial and venous sides of the circulation. In healthy young adults, upright positioning (without muscle tensing) reduces cardiac output (Qc) by ~2 l/min, with concomitant reductions in mean arterial pressure (MAP) at the level of the middle cerebral artery by ~10 mm Hg and cerebral oxygenation by ~7% (9). In addition, reductions in cerebral blood flow (CBF) have previously been shown to impair attention tasks (10). In this issue of *JACC: Heart Failure,* Fraser et al. (11) hypothesized that patients with HFrEF would be more susceptible than healthy control subjects to cerebral hypoperfusion during postural change from supine to upright due to a lower resting Qc. To test this

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hypothesis, 22 HFrEF patients (mean left ventricular ejection fraction, 33 ± 11%) and 22 age- and sex-matched healthy control subjects underwent hemodynamic assessment during a transition from supine to an upright, seated position. Supine CI, estimated from pulse contour analysis (12), was lower among HFrEF patients compared with the healthy control subjects (3.2 ± 1.5 l/min/m² vs. 5.2 ± 1.3 l/min/m²; p < 0.05). Supine CBF, estimated by using a Doppler ultrasound of the right and left internal carotid arteries (ICAs), was also lower in HFrEF patients than in the control subjects. Among HFrEF subjects, upright positioning led to a 12% and 15% reduction in CI and CBF, respectively. Among the control subjects, heart rate increased and, as a result, CI was minimally affected (although, as noted earlier, this finding is unusual in the literature using other techniques to assess CI); CBF was also

FIGURE 1 Hypothetical Autoregulatory Curves Demonstrating a Reduction in CBF Among HFrEF Patients When Transitioning From Supine to Upright
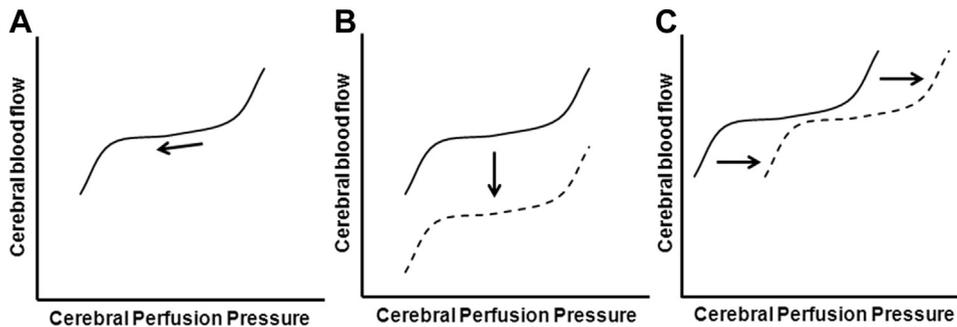
(A) No change has occurred, and subjects are operating at the lower end of a normal curve. Alternatively, sympathetic activation resulting from the reduction in cardiac output could cause either a **(B)** downward or **(C)** rightward shift in the autoregulatory curve by an increase in cerebrovascular resistance, with the end result being a reduction in cerebral blood flow (CBF). HFrEF = heart failure with a reduced ejection fraction.

preserved. Among the overall cohort (HFrEF patients plus control subjects), there was a nonlinear relationship between supine CI and the change in CBF from the supine to upright position, such that subjects with the lowest resting CI had the greatest decrement in CBF. Fraser et al. interpret their data to suggest a "threshold effect" of CI on CBF, such that subjects with a resting CI of <3 l/min/m² had greater reductions in CBF than subjects whose resting CI was >3 l/min/m² (Figure 3 in their article [11]). However, it should be noted that this relationship was driven almost entirely by 2 subjects with extremely low Qc, both of whom had large decreases in CBF. Thus, it is unclear whether a true "threshold" actually exists.

These results support the hypothesis of Fraser et al. (11) and suggest that HFrEF patients experience greater reductions in CBF during upright positioning as a result of a lower resting Qc. However, when interpreting these results and considering their implications, potential limitations associated with Qc and CBF quantification must be acknowledged. Qc was determined according to the Modelflow algorithm (12) from arterial pressure waveforms collected by using a Finometer Pro (Finapress Medical Systems, Arnhem, the Netherlands). Briefly, this noninvasive algorithm estimates Qc from arterial blood pressure waveforms by using a 3-element Windkessel model of aortic input impedance (aortic characteristic impedance, arterial compliance, and systemic vascular resistance) and requires multiple assumptions about intrinsic arterial function to estimate stroke volume and thereby cardiac output. The strength of the model lies in its ability to track relative changes in cardiac output that occur (e.g., during changes in posture) (13). The model is less reliable for determination of absolute values of Qc and has never been considered to be a suitable replacement for other methods considered the gold standard for Qc determination (14). The assumptions that underlie the method may have important systematic differences between patients and control subjects due to intrinsic vascular disease or even medication use. Second, CBF was estimated in the supine position by using Doppler ultrasound of the right and left ICAs to determine time-averaged mean velocity and diameter of the vessel. CBF was then calculated as: mean flow velocity $\times \pi(\text{diameter}/2)^2$. Because supine CBF was similar between the right and left ICA, only the right ICA was assessed during upright positioning. It is also noteworthy that the posterior circulation (Doppler ultrasound of the vertebral arteries) was not assessed in either the supine or upright position (15). Thus, the CBF values reported are only an estimation of total flow to the brain.

Fraser et al. (11) have shown that CBF was decreased in HFrEF patients during the upright position. The question is why did this occur? Is cerebral autoregulation impaired in these patients? A recent study by our group found that at least after Qc has been restored in HFrEF patients by use of a left ventricular assist device, cerebral autoregulation is well preserved (16). How, then, does Qc influence CBF? Obviously, cerebral perfusion pressure

(MAP – intracranial pressure) is a major determinant of CBF. However, there was no difference in arterial perfusion pressure between patients and control subjects during upright posture. The authors do not discuss the importance of cerebral outflow resistance, although this neglected concept may actually underpin at least some of their differences between groups. For example, many of the HFrEF patients were categorized as New York Heart Association class III, and these patients almost certainly had elevated venous pressures in the supine position, and likely in the upright position as well. Because Qc by itself has no intrinsic influence on CBF except as it determines arterial pressure, it is possible that the low CI in the HFrEF patients is a surrogate for elevated cerebral venous pressures and increased outflow resistance.

It is also important to note that MAP was not assessed at the level of the ICA or corrected for the hydrostatic gradient, which is proportional to the product of the sine of the tilt angle and distance from the heart to the ICA. Therefore, while sitting upright, blood pressure at the head is several millimeters of mercury lower than at the level of the heart. Thus, cerebral inflow pressure in the upright position is less than the inflow pressure in the supine position. Because height and MAP between control subjects and HFrEF patients were similar, this effect is likely to be modest in the present experiment (11). However, HFrEF patients had a greater reduction in CI from supine to upright than control subjects (-12% vs. -0.44%; p = 0.065), which would promote sympathoexcitation through a baroreceptor-mediated pathway with an increase in cerebrovascular resistance. The subsequent reduction in CBF indicates that these patients are either operating at the lower end of the autoregulatory curve (**Figure 1**) or that a downward (17,18) or rightward (19) shift has occurred.

An equally important difference between groups is the effect of medications. As expected, these patients (11) were on evidence-based treatments for heart failure, including beta-blockers, angiotensin-converting enzyme inhibitors, diuretics, and aldosterone antagonists. All of these medications influence vascular resistance, blood volume distribution, and hemodynamics during changes in posture, and these medications certainly contributed to the difference in outcome between groups. Perhaps a better control population would have been patients with hypertension being managed with a similar constellation of therapies but without HF. We hope that future studies from this excellent research team will include such control groups.

Fraser et al. (11) hypothesized that exaggerated reductions in CBF may contribute to the CD observed in patients with HFrEF, an argument that has been previously advanced. For example, Zuccala et al. (20) reported that cognitive performance declines sharply among HFrEF patients at a left ventricular ejection fraction cutoff of 30%, and CD is related to stroke volume and CI in these patients (21). In the present study, HFrEF subjects had lower scores on the Montreal Cognitive Assessment compared with the healthy control subjects. Placed in the context of other existing data, there is a strong argument to be made that cerebral hypoperfusion contributes to CD, particularly because it has been shown that cognitive performance improves after restoration of Qc with insertion of a left ventricular assist device (22).

In addition, gait speed was lower in the HFrEF subjects than in the healthy control subjects in the study of Frazer et al. (11). However, it is difficult to attribute this finding solely to a lower supine CI, because it has been shown that flow to the cerebellar vermis increases from supine to standing (23) and, as previously noted, posterior flow was not assessed in the present study. Gait speed is likely a multifactorial process and related to age, comorbidities, frailty, and medication effects. Although it is reasonable to hypothesize that hypoperfusion contributes to impaired gait speed, further investigation is necessary before firm conclusions can be made.

Fraser et al. (11) are to be congratulated for advancing the field. Their study has shown that HFrEF patients experience exaggerated reductions in CBF while in the upright position, as a result of reductions in Qc, elevated venous pressures, and possibly a downward or rightward shift in the autoregulatory curve. This study sets the stage for additional investigations into dynamic cerebral autoregulation among patients with HFrEF and also whether any interventions, such as exercise (24), or strategies to reduce venous outflow resistance (e.g., nitrates) could improve cognition in these patients.

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REFERENCES

1. Bennett SJ, Sauve MJ. Cognitive deficits in patients with heart failure: a review of the literature. J Cardiovasc Nurs 2003;18:219–42.

2. Heckman GA, Patterson CJ, Demars C, St. Onge J, Turpie ID, McKelvie RS. Heart failure and cognitive impairment: challenges and opportunities. Clin Interv Aging 2007;2:209–18.

3. Lis CG, Gaviria M. Vascular dementia, hypertension, and the brain. Neurol Res 1997;19: 471–80.

4. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rottderdam Study. BMJ 1997;308:1604–8.

5. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology 1999;53:1937–42.

6. Roman GC. Brain hypoperfusion: a critical factor in vascular dementia. Neurol Res 2004;26:454–8.

7. Jefferson AL, Tate DF, Poppas A, et al. Lower cardiac output is associated with greater white matter hyperintensities in older adults with cardiovascular disease. J Am Geriatr Soc 2007;55: 1044–8.

8. Jefferson AL, Himali JJ, Beiser AS, et al. Cardiac index is associated with brain aging: the Framingham Heart Study. Circulation 2010;122:690–7.

9. van Lieshout JJ, Pott F, Madsen PL, van Goudoever J, Secher NH. Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. Stroke 2001; 32:1546–51.

10. Marshall RS, Lazar RM, Pile-Spellman J, et al. Recovery of brain function during induced cerebral hypoperfusion. Brain 2001;124:1208–17.

11. Fraser KS, Heckman GA, McKelvie RS, et al. Cerebral hypoperfusion is exaggerated with an upright posture in heart failure: impact of depressed cardiac output. J Am Coll Cardiol HF 2015;3:168–75.

12. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 1993;74:2566–73.

13. Jellema WT, Imholz BP, Oosting H, Wesseling KH, van Lieshout JJ. Estimation of beat-to-beat changes in stroke volume from arterial pressure: a comparison of two pressure wave analysis techniques during head-up tilt testing in young, healthy men. Clin Auton Res 1999;9: 185–92.

14. Fu Q, Verheyden B, Wieling W, Levine BD. Cardiac output and sympathetic vasoconstrictor responses during upright tilt to presyncope in healthy humans. J Physiol 2012;590:1839–48.

15. Schoning M, Walter J, Scheel P. Estimation of cerebral blood flow through color duplex sonography of the carotid and vertebral arteries in healthy adults. Stroke 1994;25:17–22.

16. Cornwell WK 3rd, Tarumi T, Aengevaeren VL, et al. Effect of pulsatile and nonpulsatile flow on cerebral perfusion in patients with left ventricular assist devices. J Heart Lung Transplant 2014;33: 1295–303.

17. Guo H, Tierney N, Schaller F, Raven PB, Smith SA, Shi X. Cerebral autoregulation is preserved during orthostatic stress superimposed with systemic hypotension. J Appl Physiol 2006; 100:1785–92.

18. Bondar RL, Kassam MS, Stein F, Dunphy PT, Fortney S, Riedesel ML. Simultaneous cerebrovascular and cardiovascular responses during presyncope. Stroke 1995;26:1794–800.

19. Levine BD, Giller CA, Lane LD, Buckey JC, Blomqvist CG. Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. Circulation 1994;90:298–306.

20. Zuccala G, Cattel C, Menes-Gravina E, Di Niro MG, Cocchi A, Bernabei R. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. J Neurol Neurosurg Psychiatry 1997;63:509–12.

21. Bornstein RA, Starling RC, Myerowitz PD, Haas GJ. Neuropsychological function in patients with end-stage heart failure before and after cardiac transplantation. Acta Neurol Scand 1995;91: 260–5.

22. Petrucci RJ, Rogers JG, Blue L, et al. Neurocognitive function in destination therapy patients receiving continuous-flow vs pulsatile-flow left ventricular assist device support. J Heart Lung Transplant 2012;31:27–36.

23. Ouchi Y, Okada H, Yoshikawa E, Futatsubashi M, Nobezawa S. Absolute changes in regional cerebral blood flow in association with upright posture in humans: an orthostatic PET study. J Nuclear Med 2001;42: 707–12.

24. Garcia S, Alosco ML, Spitznagel MB, et al. Cardiovascular fitness associated with cognitive performance in heart failure patients enrolled in cardiac rehabilitation. BMC Cardiovasc Disord 2013;13:29.

KEY WORDS cerebral blood flow, cognitive dysfunction, heart failure with reduced ejection fraction