Published in final edited form as:

Neurocrit Care. 2018 April ; 28(2): 257–258. doi:10.1007/s12028-018-0517-9.

Letter to the Editor

Rajat Dhar¹

¹Department of Neurology, Washington University in St. Louis School of Medicine

Engquist et al. evaluated the effect of HHH-therapy on global and regional cortical CBF, measured using Xenon CT in twenty SAH patients [1]. They studied those with severe SAH and DCI who were sedated and ventilated and employed a HHH protocol comprising predominantly volume expansion (dextran and albumin) without a significant component of induced hypertension. In fact, mean arterial pressure (MAP) was no higher during HHH-therapy than at the time of the baseline study. In contrast, hematocrit was significantly reduced (from 36.4 to 31.7%). They acknowledge limitations of their methodology: for example, since the two studies were approximately two days apart, the causal relationship between HHH-therapy and CBF changes cannot be precisely confirmed. Nonetheless, from their findings they draw two main conclusions: that their modified version of HHH-therapy (essentially hypervolemic hemodilution without induced hypertension) improves cerebral perfusion and that volume expansion is likely responsible for this proposed benefit.

I would like to propose two caveats to their conclusions: firstly that it is more likely that hemodilution and not simply hypervolemia (i.e. volume expansion at stable hematocrit) was the primary driver of their observed effect and that secondly, the net benefits of the improvement in CBF may at least partially be attenuated by the detrimental effects of hemodilution on oxygen delivery. A prior randomized study demonstrated that hypervolemia alone does not improve CBF either over time or in comparison to normovolemic controls [2]. In contrast, it is well established that hemodilution can effect changes in CBF; for example, Ekelund demonstrated that isovolemic hemodilution in SAH patients (from a hematocrit of 36 to 28%, a larger but not dissimilar reduction to that observed in this study) increased CBF by 12% and that this was cerebrovascular response was not altered by induction of hypervolemia [3]. More importantly, the reduction in hematocrit and resultant impairment of arterial oxygen carrying capacity in the cerebral blood offset any benefit on net cerebral oxygen delivery in that study. Therefore, some caution should be employed in interpreting hypervolemic hemodilution as potentially beneficial for SAH patients with DCI without concomitant evaluation of its cumulative effects on oxygen transport and ischemia (for example, assessed by gold-standard measures such as oxygen extraction fraction [OEF] using positron emission tomography imaging). In fact, our recent studies have suggested that although transfusion of red blood cells (essentially hemoconcentration) may impair CBF in some SAH patients, the increase in hematocrit actually improves overall oxygen delivery and reduces OEF [4]. In studies of cerebrovascular hemodynamics, oxygen delivery is likely more relevant to cerebral oxidative metabolism than CBF alone and we suggest that CBF

Send correspondence to: Rajat Dhar, MD, Department of Neurology (Division of Neurocritical Care), Washington University in St. Louis School of Medicine, 660 S Euclid Avenue, Campus Box 8111, Saint Louis, MO 63110, (314) 362-2999, dharr@wustl.edu.

should not be used as an isolated biomarker of beneficial response, especially when evaluating studies that alter hematocrit.

We do agree with the authors that induced hypertension is of uncertain value (at least in terms of improving CBF) in patients with DCI after SAH. A recent study that we performed demonstrated that raising MAP by over twenty percent using vasopressors resulted in little-to-no improvement in global or regional CBF in SAH patients [5]. We have also noted a number of complications from high-dose vasopressor therapy for DCI, including a series of cases of posterior reversible encephalopathy syndrome [6]. For this reason, we believe that further physiologic and clinical studies of the efficacy and safety of HHH-therapy are very much still needed and applaud the authors for adding their study to our knowledge.

References

1. Engquist H, Rostami E, Ronne-Engstrom E, Nilsson P, Lewen A, Enblad P. Effect of HHH-Therapy on Regional CBF after Severe Subarachnoid Hemorrhage Studied by Bedside Xenon-Enhanced CT. *Neurocrit Care*. 2017 Oct 5. doi:10/1007/s12028-107-0439-y.
2. Lennihan L, Mayer Sa, Fink ME, et al. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage : a randomized controlled trial. *Stroke*. 2000; 31:383–91. [PubMed: 10657410]
3. Ekelund A, Reinstrup P, Ryding E, et al. Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. *Acta neurochirurgica*. 2002; 144:703–12. [PubMed: 12181704]
4. Dhar R, Zazulia AR, Derdeyn CP, Diringner MN. RBC Transfusion Improves Cerebral Oxygen Delivery in Subarachnoid Hemorrhage. *Crit Care Med*. 2017; 45:653–59. [PubMed: 28169942]
5. Diringner MN, Dhar R, Scalfani M, et al. Effect of High-Dose Simvastatin on Cerebral Blood Flow and Static Autoregulation in Subarachnoid Hemorrhage. *Neurocrit Care*. 2016; 25:56–63. [PubMed: 26721259]
6. Dhar R, Dacey R, Human T, Zipfel G. Unilateral posterior reversible encephalopathy syndrome with hypertensive therapy of contralateral vasospasm: case report. *Neurosurgery*. 2011; 69:E1176–81. e81. [PubMed: 21971491]