Venous Hemodynamics May Enhance Collateral Perfusion and the Fibrinolytic Milieu in Paradoxical Embolism

To the Editor:

Paradoxical embolism via right-to-left shunts (RLS) has rapidly evolved into an area of intense research in stroke and migraine. Increasing attention focuses on distinguishing anatomic features of a patent foramen ovale (PFO) visualized by transesophageal echocardiography (TEE) from functional aspects (ie, shunts) that allow clots to pass from venous to arterial circuits, thereby circumnavigating typical filtration in the lungs. TEE and transcranial Doppler (TCD) microbubble injection techniques may detect shunting at rest or with Valsalva maneuver to accentuate venous pressures, yet thromboemboli are rarely noted. Intense speculation, however, has centered on clot composition and potential response to fibrinolytics despite that only a few dozen clots causing strokes in humans have ever been analyzed. Kimura et al provide fascinating data demonstrating a link between RLS and dramatic response to fibrinolytics in acute stroke (OR, 5.9; 95% CI, 1.3 to 27.3; \( P = 0.022 \)), yet a type III error may have implicated clot composition when venous hemodynamics were the actual underlying mechanism.\(^1\)

Hemodynamics and thromboemboli are inextricably linked. Stasis or local hemodynamic conditions may shape clot formation and architecture, turbulent or laminar flow influence the trajectory, and downstream resistance may largely determine the site of embolic occlusion. Vigorous collateral perfusion enhances clearance or washout of emboli due to only minimal downstream resistance and collaterals bolster both spontaneous and therapeutic thrombolysis.\(^2\) Collaterals also augment thrombolytic exposure to the distal clot. Emboli, clot composition, and thrombolytic response must therefore be considered in the context of hemodynamics. Furthermore, the overwhelming focus on arteries and thrombotic occlusions in acute ischemic stroke has largely ignored the pivotal role of venous hemodynamics on the microcirculation and cerebral perfusion.\(^1\)

Kimura et al elegantly document how the presence of RLS may affect the site of embolic occlusion, the fibrinolytic milieu, and vascular elements that enhance clearance (Figure).\(^1\) No venous thromboses were noted, TEE characterization of PFO was not provided, and no clots were analyzed. TCD evidence of RLS demonstrated elevated systemic venous pressures. Although more shunts may have been detected if Valsalva was routine, spontaneous shunts reflect relatively higher venous pressures at the time of insonation. Such elevation in venous pressures is directly transmitted to the cerebral venous circulation due to absence of valves, extensive anastomoses and unique capacity for bidirectional flow (A in the Figure) that allow for maximal oxygen and nutrient exchange. Venous engorgement may radically augment cerebral blood volume (CBV), offset collapse of the cerebral veins due to low perfusion hyperemia in acute ischemic stroke, and mitigate potentially devastating effects of cerebral venous steal that cause infarct growth.\(^3\) Such favorable venous hemodynamics manifest by RLS may underlie the fact that no cases of internal carotid artery (ICA) occlusion were noted in RLS cases compared with 11 in cases without shunting (0% versus 35.5%, \( P = 0.004 \)). As emboli traversed the terminal ICA junction, preserved downstream resistance may have allowed distal propagation (B in the Figure) in cases with shunting. This “cerebral afterload” effect enhancing blood flow in the brain may parallel cardiac preload. Diminished CBV in cases without

![Figure. Schematic diagram of venous hemodynamics with bidirectional flow (A) and engorgement leading to distal emboli propagation (B), increased collateral delivery of lytics (C), and improved perfusion due to reduced venous collapse (D).](http://stroke.ahajournals.org/)

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shunting may have led to more proximal occlusion. Disproportionately lower CBV may also result in lower baseline DWI-ASPECTS scores. These more proximally situated clots may have been exposed to less fibrinolytic agent due to less extensive collaterals that typically provide lytic exposure to the distal clot (C in the Figure). Although post-thrombolysis recanalization data were not provided, dramatic improvement likely reflected restored arterial patency and tissue reperfusion. Cases with shunting and associated dramatic improvement may have had higher recanalization rates due to enhanced collateral perfusion (D in the Figure) or CBV, driven by venous phenomena.

Venous hemodynamics, not necessarily clot composition, may have yielded the striking association of RLS with dramatic improvement. The complex function of the cerebral venous circulation, simultaneously incorporating distinct functional regions akin to pulmonary West zones, must be considered in future studies of acute ischemic stroke. Many collateral therapeutic strategies including external counterpulsation, aortic manipulation, volume repletion, pressor therapy and head positioning may exploit such venous hemodynamics.4,5

Disclosures
None.

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