Transition to Collateral Flow After Arterial Occlusion Predisposes to Cerebral Venous Steal

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Background and Purpose—Stroke-related tissue pressure increase in the core and penumbra determines regional cerebral perfusion pressure (rCPP) defined as a difference between local inflow pressure and venous or tissue pressure, whichever is higher. We previously showed that venous pressure reduction below the pressure in the core causes blood flow diversion–cerebral venous steal. Now we investigated how transition to collateral circulation after complete arterial occlusion affects rCPP distribution.

Methods—We modified parallel Starling resistor model to simulate transition to collateral inflow after complete main stem occlusion. We decreased venous pressure from the arterial pressure to zero and investigated how arterial and venous pressure elevation augments rCPP.

Results—When core pressure exceeded venous, rCPP=inflow pressure in the core. Venous pressure decrease from arterial pressure to pressure in the core caused smaller inflow pressure to drop augmenting rCPP. Further drop of venous pressure decreased rCPP in the core but augmented rCPP in penumbra. After transition to collateral circulation, lowering venous pressure below pressure in the penumbra further decreased rCPP and collaterals themselves became a pathway for steal. Venous pressure level at which rCPP in the core becomes zero we termed the “point of no reflow.” Transition from direct to collateral circulation resulted in decreased inflow pressure, decreased rCPP, and a shift of point of no reflow to higher venous loading values. Arterial pressure augmentation increased rCPP, but only after venous pressure exceeded point of no reflow.

Conclusions—In the presence of tissue pressure gradients, transition to collateral flow predisposes to venous steal (collateral failure), which may be reversed by venous pressure augmentation. (Stroke. 2012;43:575-579.)

Key Words: collaterals | hemodynamics | ischemia zero flow | no reflow | perfusion pressure | stroke | venous

Extensive efforts have been devoted to understanding the basis of collateral failure after acute ischemic stroke. Collaterals should intuitively counteract the effects of cerebral arterial occlusion if they function properly, yet after ischemic stroke, there is a tendency for collateral failure. Collateral circulation may be defined as the blood flow that is supplied through secondary channels after arterial obstruction in a principal channel supplying downstream reaches of the brain. This article investigated the basis of collateral failure by investigating how continuation of flow in the nonobstructed, parallel venous outflow pathways leads to a drop in the collateral perfusion pressure and, at the extreme manifesting as the phenomenon of no reflow when inflow pressure becomes equal to the external tissue pressure (zero flow pressure). Through our analysis we demonstrate that transition to collateral flow after arterial occlusion does not necessarily re-establish flow but, on the contrary, predisposes to venous pressure-dependent flow diversion, known as cerebral venous steal, with collaterals themselves often serving as the pathways for steal.

Methods

We modified 2 parallel Starling resistors with a common inflow model (Pranevicius, 2002) to simulate progression of partial inflow occlusion to the complete inflow occlusion with residual collateral flow (Figure 1). The ischemic region was represented by 2 Starling resistors (Rcore and Rpen with external pressures Pcore and Ppen) and common inflow pressure (Pi). Loading was defined by arterial pressure and venous pressure. The model assumed that regional cerebral blood flow is determined by the regional cerebral perfusion pressure (rCPP), defined as a Starling resistor: rCPPcore=0 if Pcore>Pi; rCPPcore=Pcore-Pi if Pcore<Pi>Pi-Ppen if Ppen=venous pressure. Equations defining rCPP are presented in the Appendix (online-only, http://stroke.ahajournals.org).

All resistors in the series were described by the equivalent lumped resistor that already considers the effect of various sources of resistance including precapillary factors.
The model describes steady-state rCPP distribution. The model assumes exhausted autoregulation as would be expected immediately after complete arterial occlusion and intraluminal pressure drop with transitioning to collateral inflow. Residual autoregulation, if present, would compensate for the reduced rCPP but autoregulation rarely, if ever, is present in the area of ischemia.

In the situation of complete inflow occlusion (Figure 1B), all flow to the ischemic region comes through collateral connections (Rcol) from the unaffected parallel vascular network–collateral source. Collateral pressure at the takeoff is Pcol and inflow pressure in the ischemic region at the distal end of collateral connection is Pi. Part of the collateral source before collateral connection takeoff has resistance, Rpre, and part after takeoff, Rpost. We compared rCPPcore and rCPPpen at the time venous pressure was decreased from arterial pressure to 0 in the event of complete and partial inflow obstruction.

Complete diversion of flow resulting in rCPPcore/Pcore we defined as the point of no reflow. External pressure Pcore at the point of no reflow is the minimal Pcore required to completely stop flow at the core. Venous pressure at the point of no reflow is the minimal venous pressure required to re-establish flow stopped by a given external pressure, Pcore.

### Results

Transition to the collateral circulation decreases inflow pressure Pi due to additional pressure drop at the collateral source (arterial pressure-Pcol; Figure 2). Regional cerebral perfusion pressure of the ischemic core and penumbra is determined by the inflow pressure less venous pressure or tissue pressure, whichever is higher (Figure 3). When venous pressure drops below the pressure level of the core (Pcore), rCPPcore decreases, yet at the same time, rCPPpen increases (venous steal). Transition to collateral inflow decreases inflow pressure Pi and shifts the point of no reflow to the lower venous pressure values (Figure 3). Additionally, when venous pressure drops below the pressure within the penumbra or Ppen, collaterals serve as a pathway for venous steal; whereas if inflow were to remain direct, rCPP would remain the same.

Alternatively, if venous pressure is raised from zero to Ppen, the outflow pressure is not affected, whereas at same time inflow, pressure increases, but only when inflow is supplied by the collateral connection (Figure 3). Figure 4 shows the combined effects of both arterial and venous pressure on rCPP; in the presence of the cerebral venous steal, both venous and arterial pressures can augment rCPP, yet the venous augmentation effect is an order of magnitude higher.
Figure 5 shows that moving the collateral takeoff position from arterial to venous end decreases inflow pressure and rCPP, which is partially reversed by increased venous pressure. Figure 6 shows that increasing collateral resistance decreases rCPP in the core, which is further compromised by even a relatively small tissue pressure increase. Increasing venous pressure largely reverses this steal.

**Discussion**

A 2-parallel Starling resistor model may be used to explain the evolution of hemodynamic events in the brain after acute ischemic stroke. Our simulations revealed that under conditions of local tissue pressure increases due to early ischemic infarction apparent as cytotoxic edema, a steal-like phenomenon can be triggered immediately after stroke. The degree of steal is higher if there is a persistent tissue pressure gradient between the ischemic core and the penumbra, and even higher if the blood flow supply comes solely from the collaterals, which typically have higher resistance to flow. These events provide a logical explanation for collateral failure after stroke onset.3

However, once the stroke is established, steal phenomenon may become beneficial, maintaining perifocal flow. Even with current stroke therapies, no reflow after revascularization remains problematic. Recanalization without effective reperfusion is an enigma and is considered to be a principal reason for failure of reperfusion strategies. Reperfusion is often incomplete after reopening the occluded arterial lumen.4 This condition has been termed “no reflow” phenomenon and describes failure of microvasculature perfusion after blood flow is restored in the principal arteries. The no reflow phenomenon was first observed in the rabbit brain after the transient interruption of cerebral blood flow,4 but since then, it has been viewed as the primary culprit for reperfusion failures in stroke. Explanations for this phenomenon have been numerous: blockage of the vascular lumen by platelets and red cell aggregates5; change in blood viscosity6; local intravascular coagulation; and direct
capillary compression from edematous endothelial and glial cells.7 Similarly, an alternative pattern of postischemic circulatory disturbance was discovered in which an initial increase in cerebral blood flow, “reactive hyperemia,” is followed by a reduction in flow, “delayed hypoperfusion.” This secondary hypoperfusion has been demonstrated in the isolated canine brain8 following global cerebral ischemia in the cat,9 dog,10 monkey11 and rat,12 yet up to this day, these explanations have failed to find their way into routine clinical practice and management of patients with stroke.

Recanalization without reperfusion in stroke remains an influential and recognized challenge in routine clinical practice, yet strict definitions of such revascularization results are often variable unless documented in systematic prospective studies. Detailed imaging protocols with noninvasive and conventional angiography measures have previously noted discordance between recanalization and reperfusion.13 Distinguishing no reflow from other causes of neurological worsening requires detailed imaging. No reflow is suspected in cases when clinical improvement is lacking despite blood flow restoration in the major arteries. One study noted the lack of such improvement in one third of stroke victims with early recanalization, whereas four fifths of these nonresponders had persistent severe neurological deficits at 24 hours after stroke.14

The model simulates platelet aggregation as inflow occlusion and/or collateral connection resistance increases. Mechanical compression of the capillary bed is simulated using a Starling resistor with external pressure $P_{\text{core}}$. Increased inflow resistance and focal compression creates conditions for venous steal and rCPP drops to zero even if arterial pressure remains higher than focal tissue pressure. Our analyses provide compelling evidence that implicates the transition to collateral circulation after ischemic stroke as a trigger for cerebral venous steal and consequentially, to collateral failure, evolution of ischemia, and no reflow phenomena. We applied a “global Starling resistor” equation used to define cerebral perfusion pressure: central perfusion pressure

$$\frac{P_a}{P_{\text{core}}} = \frac{P_{\text{col}}}{P_{\text{col}}}$$

Figure 5. Variable collateral takeoff. If collateral connection is moved from the arterial to venous end at collateral source ($R_{\text{pre}}$ increases from 0% to 100%), that drops collateral inflow pressure $P_{\text{col}}$ from $P_a$ to $P_v$. Venous pressure drop from $P_v = P_{\text{pre}}$ to $P_v' = 0$ causes $P_{\text{col}}$ to drop to $P_{\text{col}}'$ and $P_i$ to $P_i'$, reducing rCPP. Decreasing venous pressure only at the collateral source causes collateral “steal,” whereas reducing it at the penumbra adds core steal. Residual rCPP becomes zero at PONR. $P_{\text{pre}}$, for illustrative purposes was chosen to be 20% of $P_a$. $P_{\text{col}}$ indicates arterial pressure; $P_v$, venous pressure; $P_i$, inflow pressure; rCPP, regional cerebral perfusion pressure; PONR, point of no reflow.

Figure 6. Effect of collateral resistance on rCPP. Collateral resistance $R_{\text{coll}}$ is expressed as percentage of total resistance in the ischemic region. As $R_{\text{col}}$ increases to 100%, rCPP drops to zero. When core tissue pressure is 10% of rCPP drops to zero at lower collateral resistances (63%). Increase of $P_v$ from 0 to $P_{\text{pre}}$ recruits most of the rCPP drop. $R_{\text{pre}}$ was chosen to be 50% of collateral source resistance. rCPP indicates regional cerebral perfusion pressure; $P_v$, venous pressure.
sure > central venous pressure) for the purposes to study regional cerebral blood flow, when tissue pressure is locally increased. The diversion of blood flow occurs under these conditions, but it can be reversed by the elevation of venous pressure.2

The core-to-penumbra steal phenomenon may help preserve penumbra’s flow in case of established stroke, whereas during stroke progression, it may expand the core; additionally, it is important to keep in mind that our model simulated rCPP, not regional cerebral blood flow distribution. Regional cerebral blood flow distribution was implicitly assumed to follow rCPP distribution but in this model, it was not studied explicitly because that would require knowledge of the absolute resistor values.

Striking experimental findings indicate a close relationship between collateral flow and systemic venous pressures. Most of these findings were obtained from the experiments in cats, when immediately after middle cerebral artery occlusion, pial artery pressure dropped from 56.2±1.6 to 7.8±0.4 mm Hg and exhibited respiratory pressure variations, passively after rCPP.17 These findings were obtained from the experiments in cats, because that would require knowledge of the absolute resistor distribution but in this model, it was not studied explicitly because that would require knowledge of the absolute resistor values.

Through our analyses we were able to show that arterial pressure augmentation increases collateral flow, but only if venous pressure exceeds the critical zero flow threshold, point of no reflow. The point of no reflow defines the very essence of complete flow diversion: arterial pressure augmentation has no effect on ischemic flow if venous pressure < point of no reflow. Augmentation of venous pressure to the level of point of no reflow increases inflow pressure into ischemic core and re-establishes flow at the point when inflow pressure exceeds external tissue pressure.

Although the models presented in this article are deductive in nature, meaning that the conclusions should be correct, if the assumptions are correct, the model assumptions are very intuitive, that rCPP is determined by the local tissue pressure and that rCPP is determined by the local tissue pressure and that regional cerebral blood flow passively follows rCPP when autoregulation is exhausted. Both these assumptions have to be verified experimentally. Future studies using imaging and supportive translational research paradigms will facilitate our growing understanding of such complex phenomena in acute ischemic stroke. Limitations of our analyses also included the fact that we only considered steady state, without any reference to the transitional states, and that we did not incorporate 3-dimensional geometry of the realistic cerebrovascular tree.

Future research efforts should incorporate 3-dimensional cerebral blood flow models, incorporating the principles outlined in this article by adding additional Starling resistors in both parallel and serial arrangements. Such consideration will allow virtual manipulation of CBV—cerebral blood flow distribution and correlation of this distribution with imaging that may provide a framework not only for explanation of evolution of hemodynamic events after ischemic stroke due to vascular occlusion, but also to disclose novel therapeutic strategies.

Conclusions
A schematic physiological framework for hemodynamics after onset of ischemic stroke, incorporating seemingly unrelated phenomena such as no reflow, postischemic luxury perfusion, collateral failure, and brain edema may expand current clinical strategies. Consideration of established cerebral blood flow physiology, in terms of cerebral vessel configuration, inflow/outflow pressures, and cerebrovascular supply predisposes to cerebral venous steal.

Disclosures
None.

References
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### Appendix

List of definitions and abbreviations

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<th><strong>Collateral source</strong></th>
<th>Parallel vascular network which provides <em>collateral connection</em> to the ischemic area.</th>
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<tr>
<td><strong>R&lt;sub&gt;source&lt;/sub&gt;</strong></td>
<td>Resistance of collateral source</td>
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<td><strong>P&lt;sub&gt;col&lt;/sub&gt;, R&lt;sub&gt;col&lt;/sub&gt;</strong></td>
<td>Inflow pressure and resistance of the <em>collateral connection</em></td>
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<td><strong>R&lt;sub&gt;pre&lt;/sub&gt;, R&lt;sub&gt;post&lt;/sub&gt;</strong></td>
<td>Resistance proximal to the takeoff of collateral connection.</td>
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<td><strong>Pa</strong></td>
<td>Arterial pressure</td>
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<td><strong>Pv</strong></td>
<td>Venous pressure</td>
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<tr>
<td><strong>R&lt;sub&gt;i&lt;/sub&gt;</strong></td>
<td>Inflow resistance in the partial occlusion model or collateral resistance in collateral inflow model</td>
</tr>
<tr>
<td><strong>Pi</strong></td>
<td>Inflow pressure of the ischemic region distal to R&lt;sub&gt;i&lt;/sub&gt; or R&lt;sub&gt;col&lt;/sub&gt;.</td>
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<tr>
<td><strong>R&lt;sub&gt;pen&lt;/sub&gt;, P&lt;sub&gt;pen&lt;/sub&gt;</strong></td>
<td>Resistance and tissue pressure in the penumbra.</td>
</tr>
<tr>
<td><strong>R&lt;sub&gt;core&lt;/sub&gt;, P&lt;sub&gt;core&lt;/sub&gt;</strong></td>
<td>Resistance and tissue pressure in the core.</td>
</tr>
<tr>
<td><strong>No reflow</strong></td>
<td>Cessation of flow when P&lt;sub&gt;core&lt;/sub&gt;(\geq)Pi; rCPP&lt;sub&gt;core&lt;/sub&gt;=0.</td>
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<tr>
<td><strong>PONR= (P&lt;sub&gt;core&lt;/sub&gt;, Pv, Pa)</strong></td>
<td>Point of no reflow- values of P&lt;sub&gt;core&lt;/sub&gt;, Pv and Pa at which rCPP&lt;sub&gt;core&lt;/sub&gt; becomes zero.</td>
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For residual direct inflow pressure Pi calculation was described earlier \(^2\).
After transition to the collateral inflow Pi is calculated for decreasing venous pressure Pv:

For $Pi > P_v > P_{core}$ and $Pi > P_v > P_{pen}$:

$$Pi_{33} = \frac{(Pa \cdot R_{post} + P_v \cdot R_{pre} \cdot R_{post} / R_{core} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{pen} + P_v \cdot R_{pre} + P_v \cdot R_{source} \cdot R_{post} / R_{source} \cdot R_{pre} \cdot R_{post} / R_{pen})}{(R_{source} \cdot R_{post} / R_{core} + R_{source} \cdot R_{pre} \cdot R_{post} / R_{pen})}$$

For $Pi > P_{core} > P_v$ and $Pi > P_v > P_{pen}$:

$$Pi_{23} = \frac{(Pa \cdot R_{post} + P_v \cdot R_{pre} \cdot R_{post} / R_{core} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{pen} + P_v \cdot R_{pre} + P_{core} \cdot R_{source} \cdot R_{post} / R_{source} \cdot R_{pre} \cdot R_{post} / R_{pen})}{(R_{source} \cdot R_{pre} / R_{core} + R_{source} \cdot R_{pre} / R_{pen})}$$

For $Pi > P_{core} > P_v$ and $Pi > P_{pen} > P_v$:

$$Pi_{22} = \frac{(Pa \cdot R_{post} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{core} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{pen} + P_v \cdot R_{pre} + P_{core} \cdot R_{source} \cdot R_{post} / R_{source} \cdot R_{pre} \cdot R_{post} / R_{pen})}{(R_{source} \cdot R_{pre} / R_{core} + R_{source} \cdot R_{pre} / R_{pen})}$$

For $Pi < P_{core} > P_v$ and $Pi > P_v > P_{pen}$:

$$Pi_{13} = \frac{(Pa \cdot R_{post} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{core} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{pen} + P_v \cdot R_{pre} + P_{core} \cdot R_{source} \cdot R_{post} / R_{source} \cdot R_{pre} \cdot R_{post} / R_{pen})}{(R_{source} \cdot R_{pre} / R_{core} + R_{source} \cdot R_{pre} / R_{pen})}$$

For $Pi < P_{core} > P_v$ and $Pi > P_{pen} > P_v$:

$$Pi_{12} = \frac{(Pa \cdot R_{post} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{core} + P_{core} \cdot R_{pre} \cdot R_{post} / R_{pen} + P_v \cdot R_{pre} + P_{core} \cdot R_{source} \cdot R_{post} / R_{source} \cdot R_{pre} \cdot R_{post} / R_{pen})}{(R_{source} \cdot R_{pre} / R_{core} + R_{source} \cdot R_{pre} / R_{pen})}$$

For $Pi < P_{core} > P_v$ and $Pi < P_{pen} > P_v$:

$$Pi_{11} = (Pa - P_v) / (R_{post} + R_{pre}) \cdot R_{post} + P_v$$