Time window for recanalization in basilar artery occlusion
Speculative synthesis

ABSTRACT
Basilar artery occlusion (BAO) is one of the most devastating forms of stroke and few patients have good outcomes without recanalization. Most centers apply recanalization therapies for BAO up to 12–24 hours after symptom onset, which is a substantially longer time window than the 4.5 hours used in anterior circulation stroke. In this speculative synthesis, we discuss recent advances in BAO treatment in order to understand why and under which circumstances longer symptom duration might not necrotize the brainstem and turn therapeutic attempts futile. We raise the possibility that distinct features of the posterior circulation, e.g., highly developed, persistent collateral arterial network, reverse filling of the distal basilar artery, and delicate plasma flow sided the clot, might sustain brittle patency of brainstem perforators in the face of stepwise growth of the thrombus. Meanwhile, the tissue clock characterizing the rapid necrosis of a typical anterior circulation penumbra will not start. During this perilous time period, recanalization at any point would salvage the brainstem from eventual necrosis caused by imminent reinforcement and further building up of the clot. Neurology® 2015;85:1806-1815

GLOSSARY
AICA = anterior inferior cerebellar artery; BA = basilar artery; BAO = basilar artery occlusion; BASICS = Basilar Artery International Cooperation Study; CTA = CT angiography; DWI = diffusion-weighted imaging; IAT = intra-arterial thrombolysis; ICA = internal carotid artery; IVT = IV thrombolysis; MCA = middle cerebral artery; MRA = magnetic resonance angiography; mRS = modified Rankin Scale; OTT = onset-to-treatment time; pc-ASPECTS = posterior circulation Alberta Stroke Program Early CT Score; PCA = posterior cerebral artery; PCom = posterior communicating artery; PICA = posterior inferior cerebellar artery; PWI = perfusion-weighted imaging; RCT = randomized controlled trial; SCA = superior cerebellar artery; sICH = symptomatic intracerebral hemorrhage; TOF = time-of-flight; VA = vertebral artery.

Basilar artery occlusion (BAO) is associated with high mortality (85%–95%) if recanalization does not occur. Evidence of the relative efficacies of different therapy protocols of IV thrombolysis (IVT) or intra-arterial thrombolysis (IAT) or mechanical endovascular treatment is based on retrospective or prospective patient cohorts, since there is only one randomized controlled trial (RCT) with 16 patients. In a systematic analysis comparing the outcomes after variable protocols to achieve recanalization in BAO, there was only negligible likelihood of good outcome (2%) in the absence of recanalization, but reaching at least partial recanalization increased the odds of favorable outcome to 38%. Based on largely empirical evidence, many stroke centers have adopted recanalization therapy protocols with time windows much wider than 4.5 hours from symptom onset, which is used for stroke thrombolysis in general. This article summarizes evidence and presents a hypothesis that assists in conceiving why we can help patients with BAO even after a long period after onset.

THE TIME WINDOW IN BAO RECANALIZATION PROTOCOLS
The spontaneous recanalization rate of BAO within the natural course is not known, but is thought to be relatively low and not to exceed 20% within a clinically meaningful time window of 12–24 hours. Indeed, many centers apply thrombolysis for BAO up to 12–24 hours after symptom onset. In the systematic analysis of BAO case series, the treatment delay fluctuated between 7 and 48 hours after symptom onset. In the IVT series, the fraction treated within...
12 hours was 77%, and within 6 hours 29%. In the IAT series, the corresponding fractions were 76% and 42%, respectively. In the Helsinki IVT cohort (n = 184), favorable outcome (modified Rankin Scale [mRS] 0–3) was achieved in 39% of those treated within 6 hours, in 36% within 6–12 hours, and in 36% above 12 hours. If patients with extensive infarction already at baseline are excluded, at least 50% reached mRS 0–3 even when treated beyond 12 hours. The rates of the 2 worst outcomes (mRS 5 or 6) were comparable in these 3 time windows: 51%, 57%, and 50%, respectively. Recanalization took place in 82%, 70%, and 75%, respectively. Timing of treatment has been a significant prognostic predictor in univariate analyses, but not in multivariable analyses adjusted for extent of baseline ischemic changes. Halving the onset-to-treatment time (OTT) after 2005 in Helsinki did not translate into therapeutic improvement (Lindsberg et al., unpublished data, 2015). These data do not back a firm time window for therapies attempting to reverse BAO.

In a recent analysis of the Basilar Artery International Cooperation Study (BASICS) registry (n = 619), Vergouwen et al. found that the prognosis was related to the time from symptom onset and patients with severe strokes at presentation treated beyond 9 hours after onset had poor clinical outcome. Unlike pivotal recanalization studies in anterior circulation stroke, patients with extensive infarct signs already at baseline were not excluded in the BASICS registry. In the Helsinki series of BAO (n = 184), a similar decay of therapeutic efficacy is seen beyond 9 hours, but this time dependency disappeared when the results were adjusted for the extent of baseline ischemia (posterior circulation Alberta Stroke Program Early CT Score [pc-ASPECTS]). Patients treated later than 9 hours were simply more likely to have extensive infarctions before treatment. RCTs of stroke have usually excluded patients presenting with characteristic posterior circulation symptoms. Therefore the time window for recanalization in posterior circulation stroke has not been ascertained in RCTs. Many published case series have recruited patients with substantially longer symptom times than considered suitable for the anterior circulation; up to 4.5–6 hours for IVT or IAT and 8 hours for mechanical thrombectomies. This has created an array of speculations, where, e.g., different collateral circulation patterns or fewer hemorrhages due to lesser infarct volumes have been conceived to increase the ischemia tolerance of brain tissue in the BA territory. 

**COLLATERAL BLOOD FLOW DYNAMICS DURING BAO**

Once the trunk of the basilar artery (BA) has been occluded by a sudden (thrombo)embolus, blood pressure at the junction of posterior cerebral arteries (PCAs) drops immediately. Depending on the individual vascular anatomy, blood flow within the circle of Willis is partially diverted from the anterior circulation through posterior communicating arteries (PComs) to fill this relative void and supply blood flow to the PCAs. Depending on the level at which the BA trunk is occluded, there will probably be reverse filling (reflux) to the distal BA, maintaining the patency of the superior cerebellar artery (SCA) branching from it as well as any number of perforator trunks and lateral, circumferential arteries that remain unblocked by the clot (see figures 1, 2, 4, and 9 from reference 11). This phenomenon is observed frequently when individuals with varying degrees of vertebral artery (VA) or even BA stenosis/occlusion are examined electively with digital subtraction angiography of the anterior circulation, and reversed filling of the distal BA can be observed to augment distal basilar patency also during the acute phase of BAO (figures 1C, 2C, and 3, A and B).

The significance of reverse flow gradient into BA also underlies the rationale of therapeutic stepwise VA occlusion in the treatment of true giant fusiform BA aneurysms. Before the advent of flow-diverting stents, this procedure was the only way to try to prevent rupture by lessening the pressure and flow inside the sac. Naturally, the sufficiency of the BA reverse flow had to be tested during acute temporary occlusion, which proves its existence also in the acute setting of complete vertebrobasilar occlusion. Detecting the reverse flow in the upper BA in the acute BA setting would require selective catheterization of the cerebral arteries. This is not routinely done if the BAO has been diagnosed with CT angiography (CTA). CTA may demonstrate minute blood flow around the clot, but not its direction. Time-of-flight (TOF) magnetic resonance angiography (MRA) is ineffective in showing very slow or reverse flow in the BA because physical properties of TOF MRA require fast blood flow to produce visible flow enhancement.

Reverse flow from the PCom may augment residual circulation in the branches distal to the BA clot and, depending on the pressure gradient, may help maintain minute flow within the oligemic region. A small BAO series (n = 20) raised the idea that effective collateral flow to the BA may prolong ischemia tolerance and lead to more favorable outcomes. Of patients with collateral filling of the distal BA, 5 (83%) had a good neurologic outcome and 1 did not. Of those without collateral flow, 1 (17%) had a good neurologic outcome and 5 did not. Additional recent studies have corroborated the significance of collaterals as a prognostic predictor.

A second distinctive feature of collateral flow in BAO is the redundant blood supply from the VAs.
When the BA is blocked usually one VA remains open, i.e., the origin of at least one and often both posterior inferior cerebellar arteries (PICAs) are open. In addition, PICAs can be supplied by reverse flow in the anterior spinal artery, which originates unilaterally or bilaterally from the distal VA or PICA. In the cervical segment, the anterior spinal artery is well supplied by branches of the ascending and profound cervical arteries, which can compensate unilaterally or bilaterally occluded VAs. PICA is a strong collateral to the anterior inferior cerebellar artery (AICA) and SCA and thus to the brainstem perforating arterioles (figures 2, E–G, 3E, and 4, A–D). In BAO, this system may as well maintain brainstem vitality for significant periods if the clot does not gradually extend to block the perforating arteries.

THE RADICULAR AND ANASTOMOTIC BRAINSTEM VASCULAR SUPPLY

One way to comprehend the delicate layout of the vasculature arising from the BA is to inspect the conceptual homology of the anatomical layout of vertebrobasilar and spinal arteries. The BA can be viewed to be formed by fusion of the longitudinal neural system, which in its most primitive form consists of loosely connected channels running along the ventral surface of the brainstem. Later during fetal development, the channels will form longitudinal arterial circulations that will fuse on the ventral pontine surface to form the BA. Lasjaunias et al. viewed the arterial circulation of the brainstem and cerebellum as natural extensions of the segmental, radicular vascular layout found in the spinal cord (figure 5; see www.neuroangio.org). Lescher et al. have recently utilized high-resolution angiographic techniques to further visualize this concept.

If one considers the BA to be an extension of the anterior spinal artery, and its branches and perforators as homologs of the coronary and sulco-commissural arteries of the segmental spinal circulation, the relationship between the sequential buildup of an ascending clot and stepwise intensified clinical course reflecting successive brainstem infarctions makes perfect sense (figure 6A). This concept of stepwise growth of the BA thrombus is compatible with the clinical course characterized by repeated periods of sudden worsening of clinical symptoms before...
full-blown BAO with locked-in syndrome, tetraplegia, and coma.

Detailed anatomical studies have demonstrated that a considerable amount of artery-to-artery anastomoses exist between the superficial brainstem arteries, but there is a lack of anastomoses between the internal brainstem arteries.19 So, a considerable network of anatomical anastomoses, and recruitment of potential anastomoses and above described collaterals arising from anterior and vertebral circulation, can assist in maintaining the larger supplying superficial arteries patent in acute BAO (figure 2, E–G and 3E). However, once the penetrating internal brainstem arteries lose patency, the irreversible necrosis will ensue rapidly.

CHARACTERISTICS OF BASILAR CLOT

Empirical knowledge from long-lasting endovascular facilities supports a few distinctive features of BA clots. These clots are not so tightly compacted or tethered to the vascular wall compared with clots lodged elsewhere in the cerebral vessels. In fact, on repeated imaging, the clots seem to be roving a bit. This may relate to systolic-diastolic pressure amplitudes lower than, e.g., the anterior circulation, and to the fact that the distal pressure is not zero and is fluctuating through the cardiac cycle. 4D phase-contrast MRI pulsatile flow velocities have revealed that the systolic pressure peak is mounted a few milliseconds sooner to the internal carotid artery (ICA) bed than in the BA.20 On lateral projections, often a thin layer of open lumen exists...
between clot and the dorsal origins of the brainstem perforators. Milliseconds apart, the systolic pressure waves are pounding the clot from the opposite directions. This may permit an element of plasma flow, facilitated by the minute piston-like migrations of the still nontherethed blood clot. This oil around the piston may keep the perforators patent longer than if their origins were occluded by a tightly attached clot. Examples of the described plasma flow are seen in figures 2, F and G, and 4, D and E, and illustrated schematically in figure 6B. This is exclusively seen in the BA, but not at all in occlusions in the anterior circulation such as middle cerebral artery (MCA) occlusions.

This scenario would explain the common empirical observation that BAO is seemingly much more prone to reocclusion after thrombolysis compared with anterior circulation. The short-acting fibrinolytics may initially only detach the clot from the vascular wall, but without anticoagulation, thrombectomy, or longer lasting fibrinolytics, the clot will build up again, allowing the clinical syndrome to reappear.

The above considerations may also explain why thrombus aspiration is generally much easier in the BA than in the anterior circulation. The BA clots may also be less compacted, perhaps reflecting a higher water content. Due to the bidirectional arterial access, fibrinolytics may penetrate the clot more efficiently than in the MCA or ICA, which could explain why the recanalization rates of systemic thrombolysis are significantly higher in the BA. The degree of collateral circulation was recently shown to significantly promote recanalization. Furthermore, we have shown that contrary to the MCA clot, where 8 mm has been demonstrated to be a cutoff length for efficacy of IVT, there is no such cutoff for BAO thrombus.

**IS THERE A PENUMBRA IN BAO?**

In their report of 10 individuals with acute BAO, Ostrem et al. obtained brain scans on average 4 hours 10 minutes after onset and found evidence of diffusion-weighted imaging (DWI)—perfusion-weighted imaging (PWI) mismatch in 5 patients, which included brainstem, cerebellum, and posterior cerebral hemispheres. This mismatch comprised 49%–99% of the total perfusion abnormality on early scans and did not entirely proceed to infarction following post-thrombolytic clinical improvement. Furthermore, in no case was there a reversal of diffusion abnormality in the brainstem or cerebellum. It could not be determined whether the pretreatment perfusion deficit represented oligemia rather than penumbra. We have not found additional reports of reversal of prethrombolytic DWI or PWI lesions within the posterior fossa, but there are technical difficulties in imaging penumbra-like flow conditions in the posterior fossa, as noted by others. However, the absence of BA territory circulation in the vast literature of ischemic penumbra is striking. In fact, considering perforant internal brainstem arteries as the other cerebral end arteries would actually suggest that, in line with the vulnerable region of hemispheric deep penetrating arteries, no penumbra can exist in the pons after the internal arteries have been occluded.

**OTHER POTENTIAL EXPLANATIONS FOR LONG TIME WINDOW**

In BAO, the exact onset of symptoms has often been an issue. In a series of 85 patients with postmortem verified basilar or bilateral distal VA occlusions, onset was sudden in 20 patients; sudden, but preceded by prodromal symptoms in 11 patients;
and progressive in 54 patients. Twenty-five patients had prodromes that cleared completely (TIA) before the start of a progressive or sudden onset. Half of these patients had their first symptoms during the 2 weeks before admission, but the rest had their TIA longer ago. In our understanding the onset of BAO should be limited to the monophasic course of acute BAO symptoms, which can be gradual, progressive, and full-blown at the outset.

It has been suggested that the presumably longer time window for BAO recanalization therapies could be attributed to the relative scarcity of post-thrombolytic symptomatic intracerebral hemorrhage (sICH), the most feared complication ruining the benefits of stroke thrombolysis. To this end, Sarikaya et al. compared the post-thrombolytic outcomes of 99 patients with posterior circulation stroke (PCS) with those of 788 patients with anterior circulation stroke and found that PCS was an independent predictor of lower sICH frequency ($p = 0.001$). In our large consecutive series of BAO thrombolysis, where good outcomes were strikingly not limited to short OTTs, increased OTT did not influence rates of sICH.

The caudal brain has physiologically longer tolerance against tissue ischemia. Indeed, paramount ultrastructural differences exist between phylogenetically diverse CNS structures. For example, the human cerebellum contains more neurons than the rest of the brain combined and the blood supply is characterized by a lack of anastomoses between the cortical penetrating branches. Not much is known of the patency of CBF autoregulatory capacity in the cerebellum and brainstem. Using transcranial Doppler and inhalation of CO$_2$, Reinhard et al. demonstrated that cerebellar autoregulation was at least as efficient as that in the MCA territory. The vertebrobasilar circulation has less developed autonomic innervations, which has been linked to a lower autoregulatory ability in the PCA, while the autoregulatory response and CO$_2$ reactivity of the BA have been found equal to the MCA. However, these observations cannot be extended beyond hemodynamic and physiologic fluctuations to provide an answer.

**HYPOTHESIS** Why should the benefit of recanalization be less time-dependent in BAO than in anterior circulation occlusions? This counterintuitive point could arise from the anatomical vascular layout of the brainstem being different from that in usual anterior circulation strokes. To explain this, we
propose several vascular mechanisms that most often act simultaneously, but this depends on the individual clot location, location of local atherosclerotic plaques, and individual developmentally determined vascular anatomy.

1. A blood clot lodged in the BA will create a reverse circulation, arterial backflow from the circle of Willis through the PComs to the distal BA, which either directly from BA perforators or through recruiting and fueling the anastomotic and collateral vascular networks will maintain the vital brainstem structures viable for a considerable time if the clot does not enlarge and the brainstem does not have lethal ischemia. The prerequisite for this in terms of individual anatomy would, of course, be sufficient patency of PComs, and a relative importance of the fetal anterior circulation in the mesencephalic blood supply. In our understanding, in the anterior circulation there is no similar chance of emergency reserve of arterial blood to supply a relatively small volume but critical brain area that would be prognostically as decisive as the brainstem. Who knows if this peculiar arrangement represents a phylogenetic construct to secure the vitality of brainstem in various vascular or hemodynamic catastrophes.

2. While arterial backflow (reflux) maintains the brainstem viable, at least with the progressively symptomatic proximal or midbasilar presentations, the blood clot may be building up stepwise by new layers of clot, each blocking the small circumferential and perforating brainstem arteries (figure 6A). In fact, the reflux may furnish a continuous supply of coagulable blood to the site of thrombus formation. As the clot grows stepwise distally, ischemia at each sequential level of perforators triggers a crescendo of multiple new infarcts. This would be clearly at variance with the situation in anterior circulation large artery strokes, where a thromboembolus will initially become lodged and create a substantial penumbral tissue at risk, which the persistent ischemia will time-dependently necrotize into the eventual infarct core. In such infarctions, there is no successive clot formation and the extent of eventual infarction is
determined by the patency of collateral blood flow recruited at the outset in the infarct periphery. Indeed, it was shown recently that there is an interaction of time and collaterals in tissue loss. In the anterior circulation stroke, time alone is not a significant predictor of outcome but collaterals are. When collaterals are removed from the multivariable models, time becomes significant.\textsuperscript{15} The time window in which the tissue at risk can survive is determined by a physiologic tissue clock that starts to tick immediately.\textsuperscript{24} This clock limits the tolerable period to a few hours, as we know from the pooled pivotal trials of thrombolysis.

3. In the proposed fundamentally different stepwise BAO clot growing either in anterior or caudal direction, in any patient with BAO who has survived the first hours without extensive brainstem infarction, the brainstem may be kept alive by multiple sources of residual and compensatory blood circulation. Besides backflow (reflux) from the anterior circulation through the PComs, considerable blood supply can be provided caudally from anastomotic vascular networks as well as the PICA-derived collaterals to both AICA and SCA systems. Anastomoses between the superficial brainstem arteries may become recruited by abnormal hemodynamic and blood pressure gradient circumstances.

4. Finally, in some occasions a layer of plasma flow between the nonadherent and sometimes migrating blood clot and the vessel wall can maintain brittle patency of the BA side branches and brainstem perforators (figures 2, F and G, and 4, D and E), which in turn maintains brittle patency of the brainstem perforator vasculature. Fibrinolytic therapy may detach a tethered clot and reinstate tissue circulation along with neurologic function, but this may be transient if the thrombus cannot be extracted or dissolved.

Figure 6 Distinctive features of the evolution of clot in basilar artery

(A) In this drawing, the clot is building up sequentially onto the initial thromboembolus (clot 1) to the rostral direction. Analogous stepwise thrombus growth can naturally occur also to the caudal direction. The clinical syndrome is changing abruptly corresponding to stepwise advances in the deeply ischemic brainstem territory whenever a new set of perforating brainstem arteries is being occluded by new clot layers (2 and 3). (B) This drawing represents the situation where substantial reflux of arterial pressure gradient is being conveyed from the anterior territory through the posterior communicating arteries (arrows). In some instances, the initial thromboembolus may not lodge to the basilar tip but rather floats on this arterial reflux, thus avoiding attachment to the arterial wall. Instead, a piston-like or migrating clot movement can occur due to the systolic pressure waves separated by milliseconds pounding the clot from anterior and caudal directions. This can generate plasma flow between the clot and arterial wall (figures 2, F and G, and 4, D and E), which in turn maintains brittle patency of the brainstem perforator vasculature. Fibrinolytic therapy may detach a tethered clot and reinstate tissue circulation along with neurologic function, but this may be transient if the thrombus cannot be extracted or dissolved.
However, once the brainstem perforating internal arteries have been occluded, there is no more time for rescue therapies. This concept is coherent with the observation that the presence of extensive posterior circulation infarctions as determined by pc-ASPECTS score is the single most significant prognostic baseline factor. To require lack of extensive brain infarction in the area supplied by the occluded artery before approving the patient for recanalization therapy is conceptually no different from what we require when we attempt to salvage the penumbra in the anterior circulation strokes.

THE WAY FORWARD The clinical management will probably shift towards rapid deployment of efficient endovascular techniques in reversing BAO. Our concepts emphasize that delay from symptom onset should not be regarded as an argument against aggressive therapies, if the parenchyma of the critically ischemic posterior circulation territory is still viable. On the other hand, MRI or noncontrast CT imaging of brainstem and additional parenchyma of the BA territory need to be systematically evaluated to reveal extended infarctions prior to costly treatments. Novel developments such as artefact-free CT image acquisition algorithms may assist evaluation of parenchymal structures in the posterior fossa.

The hypotheses proposed here can potentially be tested using novel techniques of determining microvascular perfusion and tissue viability in conjunction with ever perfecting recanalization techniques. It remains to be seen whether dynamic CT perfusion imaging or multimodel MRI can be refined to produce reliable estimates of tissue viability as in the anterior circulation. Centers that use primary angiography for patient selection will be able to use dynamic 3D rotational angiography and test in clinical trials tissue viability algorithms based on microvascular perfusion such as capillary index score. Clearly, evaluation of the patency of collaterals will be more important than today.

AUTHOR CONTRIBUTIONS
Drs. Lindsberg and Schroth conceptualized and designed the study. Drs. Schroth, Mattle, Pekkola, Sairanen collected data and participated in data analysis. Drs. Schroth and Pekkola analyzed all radiologic data. Dr. Lindsberg made the first draft and all others wrote parts of it and/or reviewed it critically.

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Perttu J. Lindsberg, Johanna Pekkola, Daniel Strbian, et al.

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