

Detection of Small Vessel Knock using Transcranial Doppler Ultrasonography - Implications for the Ischaemic Penumbra and the Treatment of Small Vessel Occlusive Stroke

The ischaemic penumbra has been defined in a variety of ways, but the most clinically relevant definition is that portion of the ischaemic territory that is still potentially salvageable, if an appropriate treatment is given.¹ Following large vessel occlusion, the benefit of revascularisation is time-dependent with penumbral tissue present in a significant proportion of cases around 3-6 hours but rarely up to 48 hours.² Transcranial Doppler ultrasonography (TCD) has recently been shown to increase revascularisation in association with recombinant tissue plasminogen activator (tPA) within 3 hours of middle cerebral artery occlusive stroke but no clear clinical benefit was identified.³ However, the time-dependence for beneficial revascularisation following small vessel occlusion (SVD) of the brain, which is the commonest form of ischaemic stroke, is unknown. Here, I would like to report a new Transcranial Doppler ultrasonography (TCD) finding in ischaemic stroke due to SVD which I have named "small vessel knock" (SVK). I will show preliminary evidence that SVK is the ultrasound finding of SVD and that targeted insonation, using only diagnostic ultrasound of 2 Mhz (EZ Dop, DWL elektronische), can recanalise SVD resulting in clinical recovery over a considerable time window.

"Knock" is the name given to the TCD finding of a high intensity thump-like sound occurring at peak systole and has been found in circulatory arrest due to brain death⁴ (see figure 1a) and traumatic brain injury.⁵ It has been proposed that this is due to reflected sound from vessel wall motion.⁵ However, I have found similar knock in association with middle cerebral artery occlusion (see Figure 1b). SVK is also associated with peak systole and is found in the ± 300 Hz range of the spectrum, which is automatically "filtered-out" by most TCD machines. It is often obscured by the signal obtained from the main supplying artery and has a characteristic high-intensity, low-velocity systolic wave often associated with a reversed

diastolic wave (Figures 2 to 4). The diastolic component is likely to be due to aortic valve closure since it coincides with the second heart sound on auscultation. SVK closely resembles the systolic and diastolic knock found in extracranial internal carotid artery occlusion just proximal to the flow void area (see figure 1c)⁶. Figure 2 shows that SVK results from occlusion of a small perforating artery. Targeted insonation results in changes to the SVK signal within a few minutes (broadens and changes in intensity) revealing a small vessel waveform. Clinical improvement is associated with either full arterial opening or the appearance of a black area of low intensity in the high intensity systolic SVK signal (an "SVK insonation window"). I have found SVK in association with MRI-negative stroke-like deficits⁷ and in both anterior and posterior circulation stroke. As examples, I will now briefly discuss 3 cases of SVK-positive posterior circulation stroke. Video evidence of complete clinical recovery associated with SVK opening during insonation can be seen in Case 3.⁸

Cases:

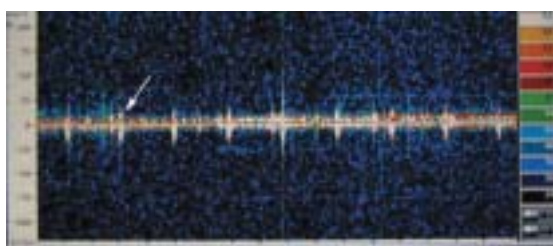
Case 1. (Figure 3) is a 67 year old man who presented with sudden onset of left face, arm and leg weakness with mild dysarthria. A T2-weighted MRI slice through the pons showed a hyperintensity signal consistent with an infarct. TCD performed 12 hours post-onset showed an abnormal high intensity low velocity signal occurring at peak systole with an inverted signal during diastole, to the right of the main basilar artery, at a depth of 103 mm. Continuous insonation improved flow (not shown) but did not result in any recovery.

Case 2 (Figure 4) is a 44 year old woman with a 7 week history of intermittent, left sided weakness, dizziness and mild paraesthesia. The figure shows two FLAIR MRI slices, one with left basal ganglia hyperintensity signals

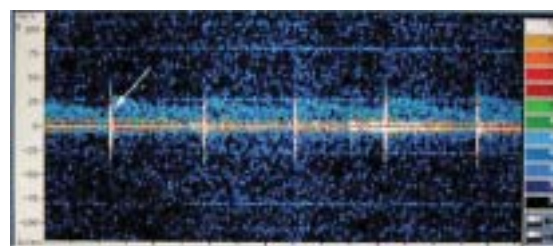


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Figure 1. Shows knock in association with (a) cerebral death (b) Left MCA occlusion and (c) Right internal carotid artery occlusion.



(a) Knock (arrow) in the Right middle cerebral artery of a 40 year old woman with brain death following a right internal carotid artery dissection



(b) Knock (arrow) associated with a Left MCA occlusion in a 40 year old man with dysphasia and dense hemiplegia, 48 hours post-hip surgery. A patent foramen ovale was identified.



(c) Right internal carotid artery occlusion with systolic knock (arrow) followed by vessel wall motion due to aortic valve closure in a 53 year old with a large Right MCA infarct. This patient also had knock in the Right middle cerebral artery, increased velocity in the Left anterior cerebral artery and flow reversal in the Right ophthalmic artery.

Basilar artery depth 95 mm (sequential changes during 6 minutes of continuous insonation)

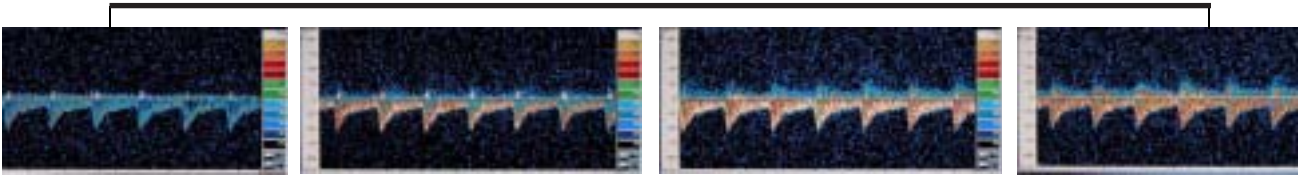


Figure 2. Shows SVK (white triangles) occurring at peak systole. During insonation the SVK disappears (left to right) to reveal a small vessel waveform. This patient had trigeminal neuropathy for 6 weeks prior to insonation. Sensation returned on opening the SVK signal.

Case 1.

Basilar artery depth 98 mm

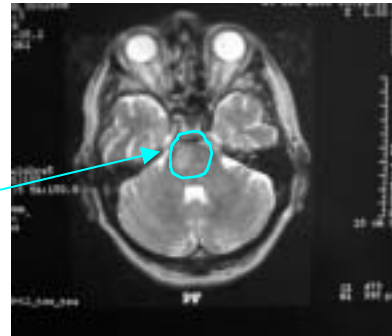
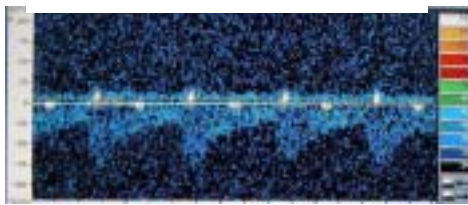
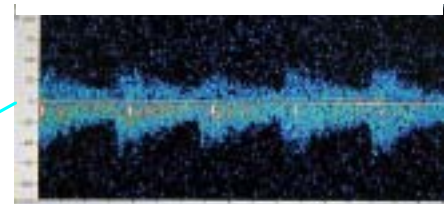


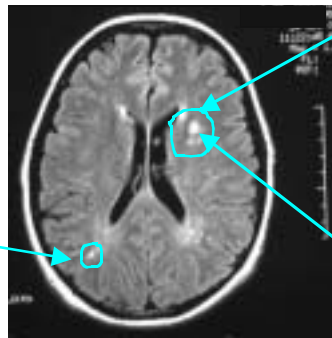
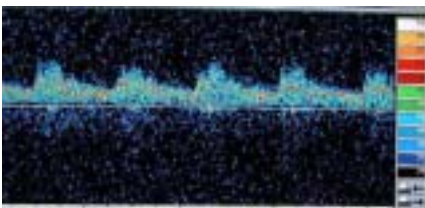
Figure 3. SVK (white triangles) seen in spectra obtained from the basilar artery (Left). This was associated with a hyperintense area in the right paramedian area of the Pons on T2-weighted MRI (Right)

Case 2.

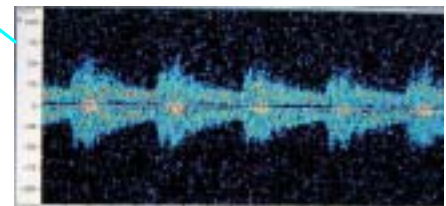
Anterior cerebral artery depth 68 mm



Posterior cerebral artery (P1)
depth 60 mm



Middle/Anterior cerebral artery
bifurcation depth 60 mm



Basilar artery depth 103 mm

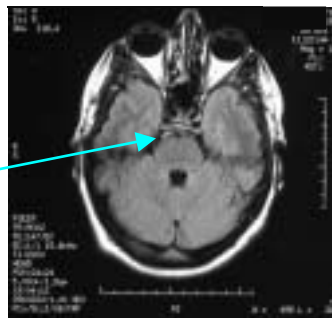
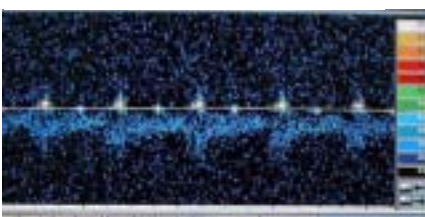


Figure 4. Knock is shown at peak systole in the anterior cerebral artery (top right) and Posterior cerebral artery (top left). A bruit was found at the MCA/ACA junction (middle right). This was associated with hyperintense areas on FLAIR MRI (middle top). SVK was found in the Basilar (bottom left). The brain stem was normal (middle bottom).

consistent with small vessel occlusive disease (SVD). These signals were associated with knock in the left anterior cerebral artery (ACA), the posterior cerebral artery and a bruit at the ACA/middle cerebral artery junction. This patient also had SVK to the right of the basilar artery as per Case 1 with a normal brain-stem image on MRI. Prior to insonation she had been symptomatic for over 48 hours. Continuous insonation of the basilar SVK improved flow and relieved her symptoms. Recovery occurred on arterial opening.

Case 3⁸ is a 58 year old woman with known hypertension and hyperlipidaemia with a strong family history of ischaemic heart disease who presented with sudden onset of right hemisensory loss, tinnitus, vertigo and mild right hemiplegia. She was examined at 21 hours post-onset and then again at 26 hours post-onset (24 hour cut-off for the WHO definition of stroke) with no change in her signs or symptoms. SVK was then identified at 72 mm through the transforaminal window and this opened during targeted insonation. This was associated with immediate and full clinical recovery. This patient was CT and MRI negative. For a 'Quicktime' movie clip, see [rtsp://pilton.ucs.ed.ac.uk:554/gmed/psyme/newtreat.mov](http://pilton.ucs.ed.ac.uk:554/gmed/psyme/newtreat.mov)⁸ NB. You will need a minimum 256k connection to view this 98mb clip.

Conclusions and implications:

These cases serve to illustrate that TCD can detect SVD in the form of "small vessel knock" in patients who have either MRI positive or negative^{7,9} stroke-like deficits. If the MRI and CT scans are negative, targeted SVK insonation consistently results in small vessel recanalisation and clinical recovery over an extensive therapeutic window. This discovery provides evidence that salvageable brain tissue in the ischaemic penumbra of SVD can be found over a much larger time period than that following large vessel occlusion. This may explain the difference in clinical benefit following recanalisation between large³ and small vessel occlusion. It is possible that the ischaemic penumbra for SVD may last as long as the collateral blood flow persists. It is also possible, that variations in the degree of collateral flow could mean that SVK will be found in a spectrum of disease ranging from asymptomatic occlusion (excellent collateral flow) through transient ischaemia, to salvageable stroke (Cases 2 & 3) and finally to established permanent stroke (poor collateral flow, MRI and CT positive) (Case 1).

The mechanism by which ultrasound induces SVK recanalisation is unknown but has to be either a direct physical action on the clot^{10,11} or indirectly via the endothelium. The low power and higher frequency used here with diagnostic TCD favours the latter mechanism. Ultrasound produces cellular shear stress by cavitation¹² and it has also been shown that minimal endothelial shear stress results in the release of both endogenous tPA¹³ and nitric oxide¹⁴ from endothelium. Thus, targeted insonation may simulate flow stress resulting in vasodilatation, endogenous thrombolysis and recanalisation. Clinical recovery occurs if salvageable brain tissue still exists distal to the site of occlusion and is likely to depend on both the size of the ischaemic area and collateral blood flow. Targeted SVK insonation is also likely to be important since non-targeted ultrasound could redirect collateral blood flow away from the ischaemic area by vasodilating arteries supplying non-ischaemic areas. This is

analogous to the paradoxical fall in cerebral blood flow ipsilateral to a critically stenosed carotid artery when contralateral arteries are dilated during CO₂ inhalation.

Randomised control trials are now needed to confirm these findings, to optimise treatment and to answer some of the above hypotheses. However, this discovery offers the exciting possibility of an effective, non-invasive, safe treatment for all SVD stroke, including vascular dementia, which can be provided over a considerable time window.

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Conflict of interest: A patent has been applied for the targeted ultrasound treatment of small vessel occlusive disease with an exclusive licence to the NHS.

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