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Editorial

EDITORIAL

Near-infrared spectroscopy: unfulfilled promises

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Near-infrared spectroscopy (NIRS) is a promising technology for non-invasive monitoring of cerebral blood flow (CBF), particularly in the fields of neonatal medicine, cardiac surgery, and neurocritical care. NIRS measures the relative proportion of oxy- and deoxy-haemoglobin based on the transmission and absorption of near-infrared light as it passes through tissues.[1] NIRS provides a measure of the regional cerebral oxygen saturation (rSO_2) in the first few millimetres of the frontal cortex. However, a major concern with this technology is the undesired contamination of rSO_2 with extracranial blood flow. Such limitations become more apparent when NIRS is studied in patients who meet the clinical criteria for the neurological determination of death (NDD). Despite jurisdictional differences regarding the definition of the NDD,[2] the absence of intracranial blood flow is often used as a confirmatory ancillary test when there is an uncertainty that clinical criteria have been met.[3] Previous reports examining the use of NIRS to identify the absence of CBF in patients who meet formal NDD criteria have consistently demonstrated near 'normal' values for rSO_2.[4–6] These data only serve to reinforce that the appeal of NIRS as a reliable clinical tool for CBF monitoring is predicated on empty promises.

In an attempt to improve on these limitations of conventional NIRS technology, the ultrasound-tagged NIRS (UT-NIRS) has been developed. The UT-NIRS applies low-power ultrasound to modulate near-infrared light.[7] The UT-NIRS signals (photons) then undergo a Doppler effect within the target tissue as a result of the movement of blood cells. The velocity of the blood cells can be directly measured, and serves as a surrogate for blood flow.[7,8] Rather than rSO_2, the UT-NIRS provides an uncalibrated and unit-less measure of CBF, termed the cerebral flow index (CFI), with an arbitrary value of 0–100. The UT-NIRS has a purported advantage over conventional NIRS in its ability to detect intracerebral changes in blood flow with higher accuracy rather than potentially contaminated measures of rSO_2. These characteristics make the UT-NIRS more closely related to laser Doppler flowmetry[9] and transcranial Doppler (TCD)[8] than to conventional NIRS itself.

Whether the UT-NIRS provides a 'better' surrogate measure for true intracranial blood flow is one of the drivers for the work by Caccioppola and colleagues[10] in this issue of the *British Journal of Anaesthesia*. In this context, the authors assessed the performance of a UT-NIRS monitor device (c-FLOW™, Ornim Medical, Kfar Saba, Israel) to detect the absence of CBF in 20 patients who met the formal criteria for NDD in comparison with 20 healthy volunteers. In the NDD group, the UT-NIRS data were acquired only after the formal clinical criteria for NDD were met. Importantly, the confirmatory testing demonstrated a lack of CBF in 14 of 20 patients (TCD, computerised tomography angiography, or conventional digital subtraction angiography). In the healthy volunteers, the median CFI was 33 (inter-quartile range: 27–36). In patients who met the criteria for NDD, CFI was detected in *all* patients, with a median value of 41 (36–47). This important work demonstrates that the UT-NIRS suffers the same limitations as conventional NIRS, namely, falsely identifying intracranial blood flow when it is demonstrably absent. Moreover, these findings refute the assertion that the UT-NIRS is specific to 'deep' changes in blood flow,[11] allegedly intracerebral changes. Interestingly, in one patient in the NDD group who underwent a decompressive craniectomy, the CFI over the intact skull was 41 compared with 0 on the side with the craniectomy. This observation supports the assertion that extracranial blood flow is responsible for contamination of either the rSO_2 or CFI observed by NIRS or UT-NIRS, respectively.

There have been prior studies examining the ability of both NIRS and UT-NIRS to identify the timing of NDD. A case report described a change in CFI obtained by the UT-NIRS in a 73-yr-old woman who presented with a right middle cerebral artery stroke and bilateral internal carotid artery occlusions.[12] The patient's pupils became unreactive on Day 7 and the UT-NIRS was applied on Day 9. At that time, she had absent brainstem reflexes, yet was able to trigger the ventilator. Her right and left CFI were 16 and 35, respectively. After extubation for withdrawal of life-sustaining measures, she stopped breathing and her CFI decreased to <10 bilaterally at 60 min, and cardiac arrest followed soon thereafter. Another case report using conventional NIRS demonstrated rSO_2 of 60–71% in an NDD patient with absent diastolic flow on TCD.[13] Similar findings have also been reported by Billet and colleagues.[6] They retrospectively analysed cerebral-oximetry data in five patients who progressed to NDD. The onset of NDD was accompanied by a decrease in rSO_2 from 67% to 55%, and rSO_2 remained stable thereafter. In three cases, the rSO_2 values only reached minimal values (25%) at complete circulatory arrest. It would have been interesting if the current study by Cacciopola and colleagues[10] used a similar approach and had been able to observe changes in CFI in patients as they progressed to NDD. However, all of these findings confirm the major limitation of extracranial-blood-flow contamination when using both UT-NIRS and conventional NIRS.

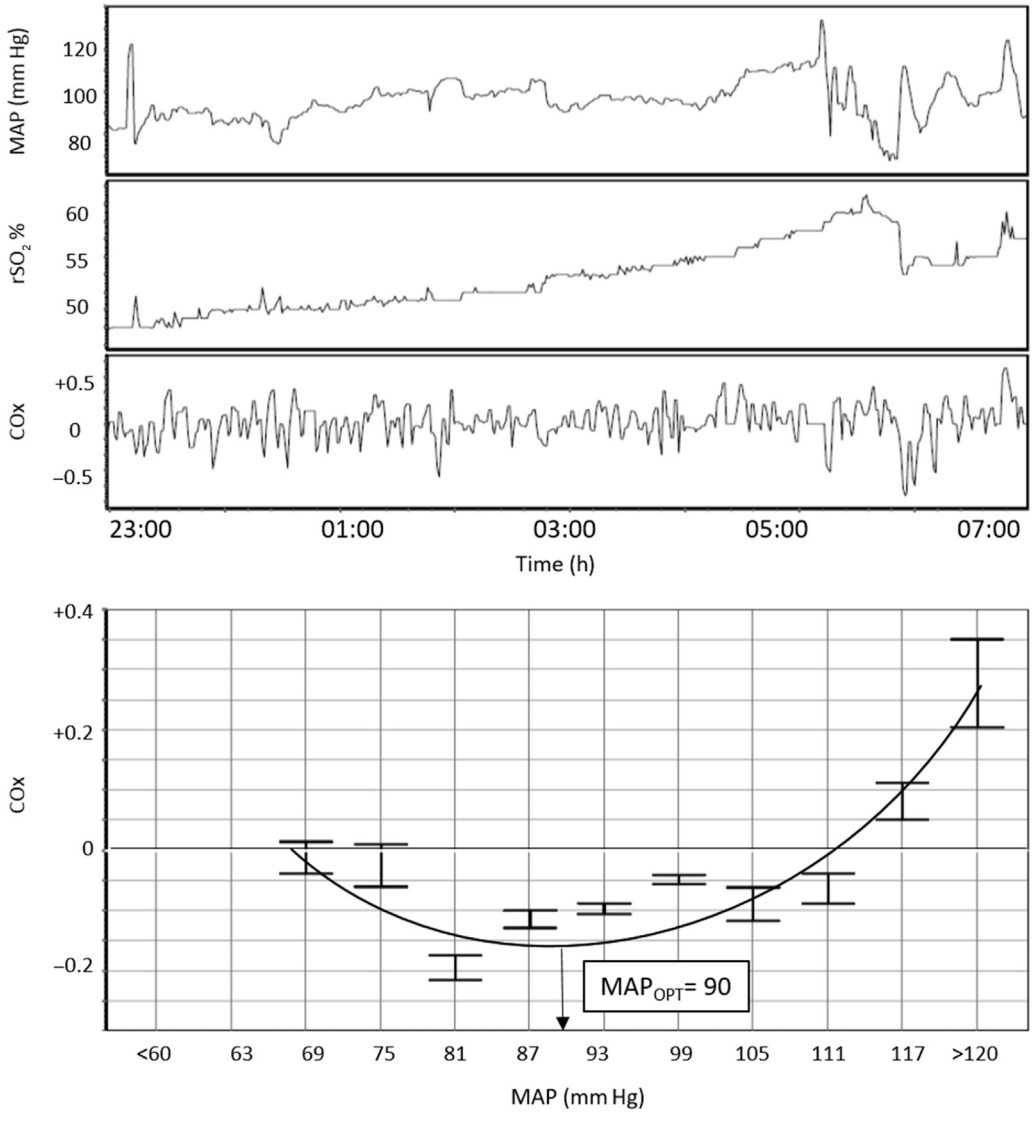

Fig 1. Recordings from a patient who remained unconscious after cardiac arrest. The first three panels are MAP, regional saturation of oxygen (rSO_2), and cerebral-oximetry index (COx). COx is a moving Pearson correlation coefficient between 30 consecutive, 10 s averaged values of mean arterial pressure (MAP) and the corresponding rSO2 signals. The bottom panel is COx plotted against the intervals of MAP in 5 mm Hg. The ICM+® brain-monitoring software (Division of Neurosurgery, Cambridge University) plots a U-shaped curve with the nadir of the curve being the optimal MAP. This figure was reproduced from our prior work.[20]

The work by Caccioppola and colleagues[10] forces us to re-examine the much broader and important question of the overall value of NIRS itself. How should we treat parameters obtained with NIRS devices? Is NIRS truly a measure or surrogate of CBF? The normal range assumed for rSO_2 lies between 60% and 75%, with a coefficient of variation of ~10%.[14] However, the absolute threshold of rSO_2 that predicts cerebral hypoxaemia or ischaemia is uncertain despite a large body of literature.[1] Despite the wide application of NIRS for cerebral monitoring during cardiac surgery in adults,[15] the clinical benefit of cerebral-oximetry measurements in this population has not been demonstrated,[16,17] although catastrophic events, such as cannula malposition during bypass, can be identified by abrupt reductions in rSO_2.[15] Importantly, there is marked heterogeneity in the literature as to what value of rSO_2 constitutes cerebral desaturation. The lack of clinical benefit holds true even when examining NIRS-based algorithms that are used to optimise rSO_2.[18] Why has the use of NIRS not translated into meaningful clinical outcomes? Aside from extracranial contamination, there are inherent physiological confounders that limit the technology, including arterial oxygen saturation, MAP, arterial carbon dioxide tension, haematocrit, cerebral blood volume, and the cerebral arteriovenous ratio.[19] Claims of an absolute NIRS threshold for cerebral ischaemia or hypoxaemia should simply be disregarded at the current state of development.

Given these inherent physiological limitations, coupled with a paucity of clinical evidence, clinicians could not be faulted for simply abandoning the use of NIRS. On the other hand, rather than using NIRS as a measure of CBF, for which it is woefully inadequate, there may be a more nuanced approach for using NIRS to assess cerebral autoregulation. Rather than relying its absolute value, we can observe how rSO_2 changes in response to fluctuations in mean arterial pressure (MAP). If cerebral autoregulation is compromised, CBF will be directly dependent on MAP, and MAP and rSO_2 will thus trend in the same direction (e.g. increasing MAP leads to increasing rSO_2). Conversely, if rSO_2 remains relatively constant during changes in MAP, then autoregulation is intact. Over time, a moving correlation coefficient (a value between -1 and $+1$) between MAP and rSO_2 can be calculated. This correlation coefficient is termed the cerebral-oximetry index (COx). A positive COx (MAP and rSO_2 moving in the same direction) indicates dysfunctional autoregulation. A negative or near-zero COx indicates intact autoregulation. Using COx, we can non-invasively identify the optimal MAP for an individual patient (Fig. 1). The optimal MAP derived using COx from NIRS demonstrates an excellent agreement with other indices of cerebral autoregulation based on intracranial pressure,[21] laser Doppler,[22] and TCD.[23] Multiple studies have used COx to assess cerebral autoregulation in different patient populations, including those with traumatic brain injury,[24] with hypoxaemic–ischaemic brain injury,[20] and undergoing cardiopulmonary bypass.[23]

In a historical cohort study by Hori and colleagues,[25] the optimal MAP and the upper limit of autoregulation were assessed using COx in 491 patients undergoing cardiopulmonary bypass. There was no specific fixed MAP threshold that identified postoperative delirium. However, the duration and magnitude above the upper limit of autoregulation were associated with a higher risk of delirium. These results reinforce that COx-based assessments allow for *individualised* MAP thresholds. Other studies have demonstrated an association between deviation from the optimal MAP (determined using NIRS) and poor neurological outcomes in traumatic brain injury,[24] hypoxaemic–ischaemic brain injury,[26] and preterm newborns at risk of intraventricular haemorrhage.[27] Aside from COx using NIRS, the UT-NIRS has been used as an autoregulation monitor to identify the optimal MAP in patients undergoing cardiopulmonary bypass.[28] There was strong agreement in the optimal MAP identified using UT-NIRS and TCD.

What is the future for NIRS? Despite significant inquiry into this technology, NIRS and UT-NIRS remain an unfulfilled promise of a reliable and clinically useful CBF monitor. This is despite the hopes of clinicians for a non-invasive method to determine the adequacy of CBF and avoid cerebral hypoxaemia. However, there is a possible path moving forward. Rather than relying absolute values of rSO_2, we may be able to identify a *patient-specific* optimal MAP by using NIRS-based technology as a monitor of cerebral autoregulation. Research in this area may be a way forward to fulfilling the promises of NIRS as a clinically useful brain-monitoring technique.

Authors' contributions

Both authors contributed to drafting and revising the manuscript and for intellectual content.

Declaration of interest

The authors declare that they have no conflicts of interest.

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