How NIR is the future in blood flow monitoring?

Wolfgang M. Kuebler
Institute of Physiology, Lung and Circulatory Research Laboratory, Charité-Universitätsmedizin Berlin, Berlin, Germany

CURRENTLY ESTABLISHED METHODS for the in vivo determination of tissue blood flow in humans, such as perfusion magnetic resonance imaging or positron emission tomography, are frequently not available for physiological or diagnostic purposes, which require more flexible, accessible, and rapid monitoring techniques. Shortly after the introduction of near-infrared (NIR) spectroscopy, Jöbsis and coworkers (3) recognized the potential of this approach as a rapid, safe, and relatively cheap alternative for cerebral blood flow measurements. In a study published in the Journal of Applied Physiology, Guenette and colleagues (5) followed this idea and established NIR spectroscopy as a technique to measure blood flow in human respiratory muscles, a task that was so far only possible by collecting phrenic venous effluent in anesthetized patients.

Biological tissue is relatively transparent to light in the NIR range (λ = 700–1000 nm), and NIR spectroscopy makes use of this characteristic to calculate the concentration of light-absorbing chromophores in tissue from the attenuation of emitted NIR light. For perfusion measurements, the passage of a vascular tracer through the tissue is monitored, and relative or absolute blood flow values can be calculated by a variety of different proposed algorithms.

After initial approaches to utilize a sudden increase in arterial oxygen saturation (Sao2) as a tracer failed to provide acceptable accuracies when compared with “gold standard” reference techniques (9), indocyanine green (ICG) was introduced as an alternative exogenous tracer with an almost ideal profile: 1) ICG was already established in clinical use for hemodynamic monitoring, hepatic function tests, and ophthalmic imaging, and rates of moderate to severe adverse reactions are below 0.5%; 2) ICG has an absorption peak at 805 nm and follows Lambert-Beer’s law at concentrations used in vivo; 3) intravascular injections induce a sudden step increment in tracer concentration and can be repeated ~50 times before the maximal daily dosage is reached; and 4) ICG binds to >95% to plasma proteins and thus remains within the intravascular space, from which it is eliminated by hepatic clearance with a half-life of several minutes.

Because of these characteristics, ICG has been used extensively for blood flow monitoring by NIR spectroscopy. Various algorithms have been proposed and applied for the analysis of the tracer curve, most commonly the Fick principle and a relative blood flow index derived from fluorescence flowmetry (7, 10). Initial feasibility studies yielded promising and plausible results both in animals and humans, and direct comparison with established blood flow measurement techniques showed good general agreement between methods (1, 6, 10). In the present study by Guenette and colleagues (5), a gold standard for the measurement of respiratory muscle blood flow in conscious humans did not exist. Therefore, the authors correlated data from the ICG technique against physiological parameters determined at rest and during different degrees of isocapnic hyperpnea. Pooled data on respiratory muscle blood flow correlated linearly with cardiac output, work of breathing, and transdiaphragmatic pressure, confirming the notion that NIR monitoring of ICG tracer curves presents a reliable tool for rapid and versatile blood flow measurements. Yet, is good already good enough?—or, in other words, is the validity and reproducibility of the ICG technique satisfactory for a diagnostic tool on which critical decisions in patient care may depend?

Brown and colleagues (2) and our own group (7) have reported correlation coefficients for the comparison of the ICG approach with accepted reference methods of r = 0.93 for Fick’s principle and r = 0.81 for the blood flow index. An even better estimate of the method’s accuracy is provided by Bland-Altman analyses, i.e., by plotting the difference between the data from the ICG and the reference technique against the average value from both measurements. The limits of agreement between both methods, given by the interval “mean difference ± 2 SD,” predicts the range of deviation between the measured and the actual value (under the assumption that the gold standard measures correctly). In most studies using this approach, the mean difference between the ICG technique and the standard reference was negligible, indicating the absence of a systematic bias. Yet, 2 SD of the difference between both methods amounted on average to ~35% of the absolute measured value (1, 2, 6, 7). In other words, if the true blood flow value is 40 ml·100 ml−1·min−1, only 68% of data measured by the ICG technique will lie within a range from 33 to 47 ml·100 ml−1·min−1. Most clinicians will find this variability not acceptable for a diagnostic test.

Interestingly, reported coefficients of variation for intra-subject repeated blood flow measurements by ICG are only ~10% (13), and intraindividual differences in ICG kinetics between both hemispheres identify patients with acute ischemic stroke with a sensitivity and specificity of up to 100% (12). Similarly, the method reflects changes in blood flow within individual subjects with a high level of accuracy, as demonstrated by correlation with microsphere measurements, which yielded intraindividual r values of 0.95–0.99 (10). Yet, in the same study, slopes of linear regressions varied between different animals by a factor of almost 4, suggesting that the ICG technique is less ideal for absolute blood flow measurements in a heterogeneous population of individuals. Interindividual variations will be less evident in physiological or pathophysiological studies like the one by Guenette and colleagues (5), where repeated measures are pooled at each time point, yet they limit the predictive value of a single diagnostic measurement decisively.

Considering the unique potential of this promising, flexible, and—if pulse dye densitometry rather than arterial catheterization is applied to monitor the arterial input function—noninvasive technology, it must be our aim to further improve the accuracy of the individual measurement. The finding that

Address for reprint requests and other correspondence: W. M. Kuebler, Institute of Physiology Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Arnimallee 22, 14195 Berlin, Germany (e-mail: wolfgang.kuebler@charite.de).
intraindividual blood flow measurements by the ICG technique are relatively reproducible demonstrates the basic robustness of the applied algorithms and allows one to eliminate iatrogenic factors like variable ICG injection rates as potential sources of the high variability. Individual factors that currently limit the quality of absolute quantitative measurements may include the tissue concentration and distribution of endogenous chromophores, as well as variations in the constitution of the assessed tissue volume. NIR signals are collected from a banana-shaped volume between sensor and emitter, and the variable contribution of tissues other than those of interest will interfere with the measurement to different degrees in different subjects. Recent developments, such as amplitude-modulated and time-resolved spectroscopy or the two-detector partial pathlength method, have introduced concepts of depth resolution and facilitated, e.g., the separation of intracerebral from extracerebral signals in cranial NIR spectroscopic measurements (4, 8, 11). Yet these innovative techniques still depend on model assumptions such as thickness and optical homogeneity of each tissue layer, and so far there are no data on whether they may actually increase the accuracy of quantitative measurements. Hence, at its present stage, blood flow monitoring by the ICG technique can be considered to yield reliable data on relative changes within individual subjects. Therefore, it presents an excellent tool to monitor time-dependent effects in single individuals or pooled study populations. The present study by Guenette and colleagues (5) establishes this technique for measurements in respiratory muscles and thus provides a valuable tool to advance our understanding of respiratory physiology and pathophysiology in conscious humans. However, further technological advancements to control for interindividual variability are required and must be validated in experimental and clinical studies before single measurements of absolute blood flow values can be accepted as a relevant parameter in individual patient care.

REFERENCES