

INTRAVASCULAR DETECTION OF ISCHEMIA BY NEAR-INFRARED SPECTROSCOPY

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ABSTRACT

The interruption of myocardial oxygen supply in acute ischemia alters the O_2 content of coronary venous blood. The oxygenation status of coronary sinus blood was assessed by intravascular application of near-infrared spectroscopy in 10 domestic pigs under in-vivo conditions. Calibration of the catheter was performed in vitro by perfusion of blood with gas mixtures of various O_2 concentrations. The catheter was placed into the coronary sinus, and anterior wall ischemia was induced by temporary occlusion of the left anterior descending coronary artery. Spectroscopic and hemodynamic data were obtained. The main differences between oxygenated and deoxygenated hemoglobin were found with O_2 concentrations < 30%, corresponding to the coronary sinus blood O_2 content. Spectrographs showed variations related to CO_2 concentration, pH, and temperature. Spectral analysis showed significant differences between pre-ischemia and ischemia. Variations in spectrographs could be observed in both in-vitro and in-vivo experiments. The intravascular application of near-infrared spectroscopy is technically feasible and can be used as a reliable tool in detection and follow-up of tissue deoxygenation, particularly in acute myocardial ischemia.

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INTRODUCTION

Near-infrared (NIR) is the wavelength interval between 700 nm and 2,000 nm. Good penetration of NIR light into soft tissue allows reliable in-vivo monitoring of blood or tissue-bound chromophores by spectroscopic analysis. The first clinical application of NIR spectroscopy was described by Jöbsis[1] in 1977 for noninvasive monitoring of cerebral and myocardial oxygen sufficiency. Further development made this technique viable for virtually any organ, based on the specific absorption spectra of oxygenated and deoxygenated blood or tissue-bound chromophores such as cytochromes.[2–5] This allows noninvasive continuous perfusion monitoring in the early diagnosis of ischemia.

For NIR spectroscopic analysis under in-vivo conditions, specific light diodes (optodes) must be placed in a dual configuration with one emitting and the other collecting the light transmitted through the tissue sample (Figure 1).[1,3,6] The collected NIR light is transferred to a photomultiplier by fiberoptic couplings, and converted into an electric signal. Signal analysis and data processing

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are performed by computer.[5] The distance between emitting and collecting optodes in current NIR spectroscopic devices is defined as the pathlength. Because of the essential face-to-face positioning of pairs of optodes, clinical application of NIR monitoring is currently limited to external use only. The objective of this study was to evaluate the possibility of online detection of ischemia by continuous intravascular spectral analysis of oxygen-bound chromophores. To allow spectroscopic access to the vascular system, a small diameter (< 7F) fiberoptic catheter was developed, which makes possible the transport of NIR light to virtually any intravascular location.

MATERIALS AND METHODS

The NIR catheter is a flexible fiberoptic device (length, 1.5 m; diameter, 2.6 mm) with coaxially configured fibers. The fibers are bundled in a concentric array of two groups: the NIR light is transported into blood by one group of fibers and collected by the other group (Figure 2). The tips of both emitting and collecting fibers are located at the catheter head. The NIR light transferred by emitting fibers to the catheter head is partly absorbed and partly reflected (back-scattered) from blood cells to the collecting fiber group of the NIR catheter. Continuous electronic conversion of the difference between emitted and collected NIR light gives the actual absorption spectra of oxygenated and deoxygenated hemoglobin. For spectrometric measurements, an Ocean Optics S 2000 (Ocean Optics Inc., Dunedin, FL, USA) miniature fiberoptic spectrometer (2,048 pixels; wavelength range, 200 to 1,100 nm) with a stabilized tungsten-halogen light source was used. The spectral acquisition time was 2 seconds per sample. SpectraWin version 4.1 software (Top Sensor Systems, Eerbeek, Holland) was used for data acquisition, graphing, and data manipulation.

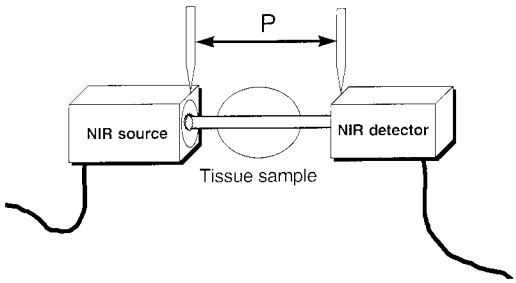


Figure 1. Typical configuration for the clinical application of near-infrared (NIR) monitoring. Defined pathlength (P) between the NIR source and detector (optodes) is the standard for algorithms of the spectral analysis. In cerebral oxygenation monitoring, optodes are placed on frontoparietal areas.

The technical feasibility of the fiberoptic catheter was evaluated by an in-vitro calibration experiment. Changes in the oxygen affinity of blood were simulated using a closed circulation system with a roller-pump, oxygenator (perfusion with O_2), and deoxygenation technique (perfusion with N_2 to eliminate O_2) at different levels of saturation with O_2 and CO_2 and various temperatures (Figure 3). The tip of the catheter was inserted into the bloodstream. Differences in O_2 and CO_2 binding of hemoglobin in arterial and venous blood were simulated using pre-bottled constant gas mixtures (Table 1) at temperatures of 37°C, 30°C, and 23°C. The tests started with arterial-configured blood (CO_2 5.6% v/v) at the lowest O_2 level (10.0% v/v). After an appropriate circulation time, the temperature was gradually reduced from 37°C to 30°C and then to 23°C. NIR graphs were registered at each concentration of O_2 and temperature in arterial and venous states of blood. Simultaneously, blood gas analyses were performed.

The effects of acute myocardial ischemia on the O_2 saturation of myocardial venous blood backflow was evaluated in 10 domestic pigs in an open-chest procedure (median sternotomy). The Institutional Animal Care and Use Committee at the Texas Heart Institute, Houston, Texas, USA, approved all procedures. Animals were maintained in accordance with the "Principles of

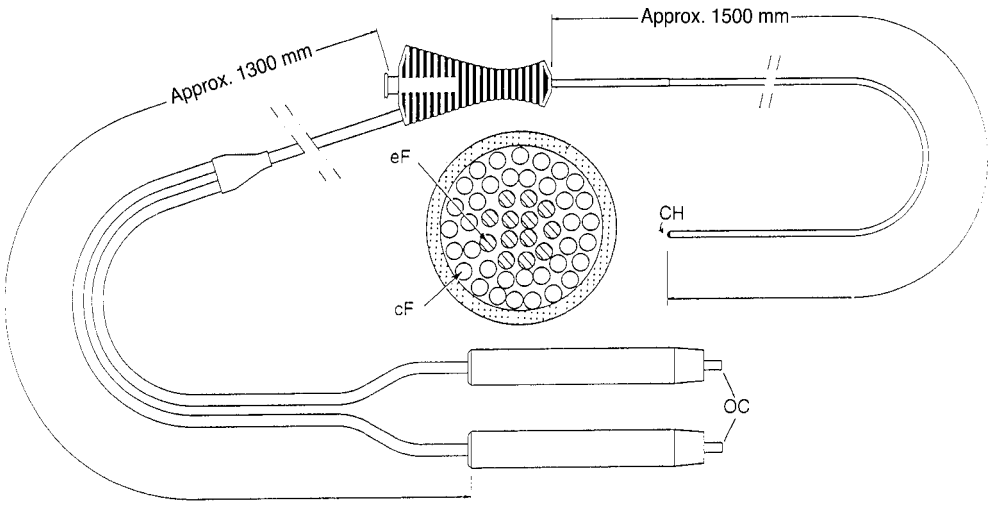


Figure 2. The intravascular near-infrared catheter. CH = catheter head, OC = optical couplings (cross-section: cF = collecting fiber group, eF = emitting fiber group).

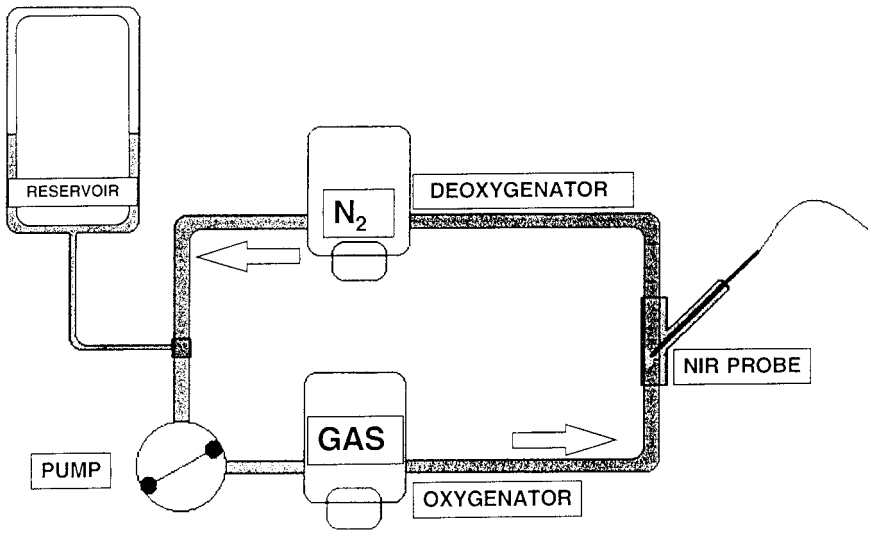


Figure 3. In-vitro perfusion experiment. The perfusion of blood with standardized gas mixtures and the elimination of dissolved oxygen with nitrogen was carried out by oxygenators. The near-infrared catheter (NIR) was inserted into the bloodstream.

Laboratory Animal Care" as formulated by the National Society for Medical Research and the "Guide for Care and Use of Laboratory Animals" (NIH Publication No. 85-23, rev. 1985). The NIR catheter was inserted into the coronary sinus through the right atrial appendage. A second NIR catheter was placed in the femoral artery as an arterial reference. Ischemia was induced by temporary occlusion of the left anterior descending artery (LAD) immediately distal to the 1st diagonal branch, on the beating heart. Hemodynamic parameters were recorded via a Swan-Ganz catheter (right jugular vein) and a left ventricular Millar catheter. After 90 minutes of ischemia, the occluder was released to initiate reperfusion for 90 minutes. Electrocardiogram (ECG) and hemodynamic parameters were monitored continuously. NIR data acquisition and blood gas analyses were performed every 30 minutes before, during, and after LAD occlusion. At the end of the experiment, the animals were euthanized, and infarcted areas were verified by histologic and electron-microscopic examinations of specimens from the myocardium.

Table 1. **Standardized Pre-Bottled Gas Mixtures for Perfusion of Blood in Vitro**

Bottle No.	Gas Mixtures
Arterial	
1	10.0% O_2 + 5.6% CO_2 (+ N_2)
2	30.0% O_2 + 5.6% CO_2 (+ N_2)
3	50.0% O_2 + 5.6% CO_2 (+ N_2)
4	70.0% O_2 + 5.6% CO_2 (+ N_2)
5	90.0% O_2 + 5.6% CO_2 (+ N_2)
Venous	
6	90.0% O_2 + 9.0% CO_2 (+ N_2)
7	70.0% O_2 + 9.0% CO_2 (+ N_2)
8	50.0% O_2 + 9.0% CO_2 (+ N_2)
9	30.0% O_2 + 9.0% CO_2 (+ N_2)
10	10.0% O_2 + 9.0% CO_2 (+ N_2)

RESULTS

The NIR spectroscopic analysis of arterial and venous-configured blood showed similar absorbance patterns at each temperature, with a minimum point on the graphs at 660 nm for gas mixtures with 30% to 90% O_2 concentration. At O_2 concentrations lower than 25% to 30%, the absorbance minimum was at approximately 690 nm. Only at these very low O_2 concentrations did different temperatures lead to markedly different absorbance patterns. Interruption of O_2 flow and the subsequent suppression of O_2 by N_2 in the deoxygenation system led to changes in the NIR graph pattern (Figure 4): an increase of absorbance at 660–665 nm; a shift of the minimum from 690 nm to approximately 735 nm; formation of a new peak at 770 nm; an isosbestic point between the graphs of oxygenated and deoxygenated blood at 790 nm; and reduction of the NIR absorbance at higher wavelengths. Slight differences in absorbance at 660–665 nm were observed between arterial and venous graphs at identical O_2 concentrations. Considering that the only difference between these graphs was the CO_2 concentration, these results indicate differences between deoxygenated and CO_2 hemoglobin. During deoxygenation, spectral changes in NIR graphs were visible within the first minute of O_2 elimination with N_2 and the arterial NIR curve quickly appeared more venous. At the end of 5 minutes, the graph demonstrated an entirely different pattern (Figure 5) with identical characteristics to those described above.

In the animal experiments, arterial and peripheral venous NIR graphs demonstrated no marked differences among the 10 animals compared to the baseline, due to the relatively high peripheral venous oxygen concentration in pigs. The graph for coronary sinus blood showed an NIR absorbance pattern that was identical to in-vitro NIR

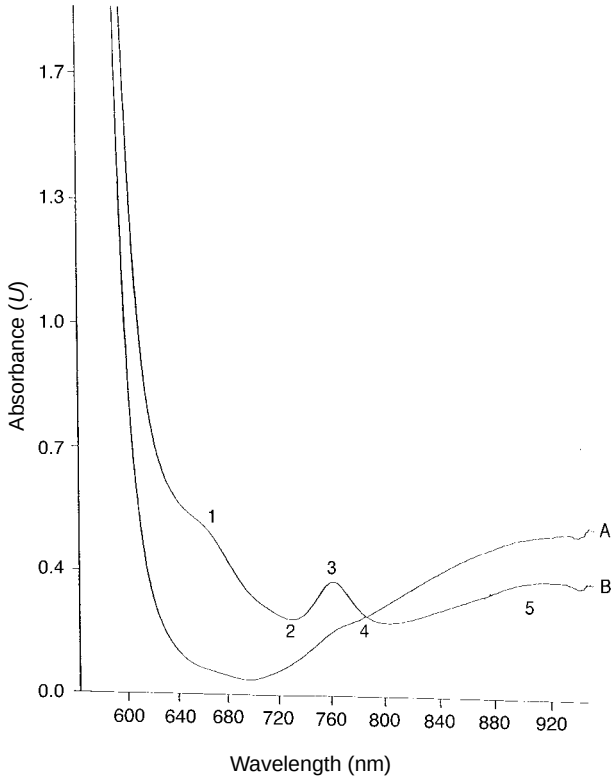


Figure 4. Changes in the NIR absorbance pattern after perfusion with a low O_2 concentration (< 30%; curve B) compared to a high O_2 concentration (> 50%; curve A). Major spectral changes are marked with numbers 1 to 5.

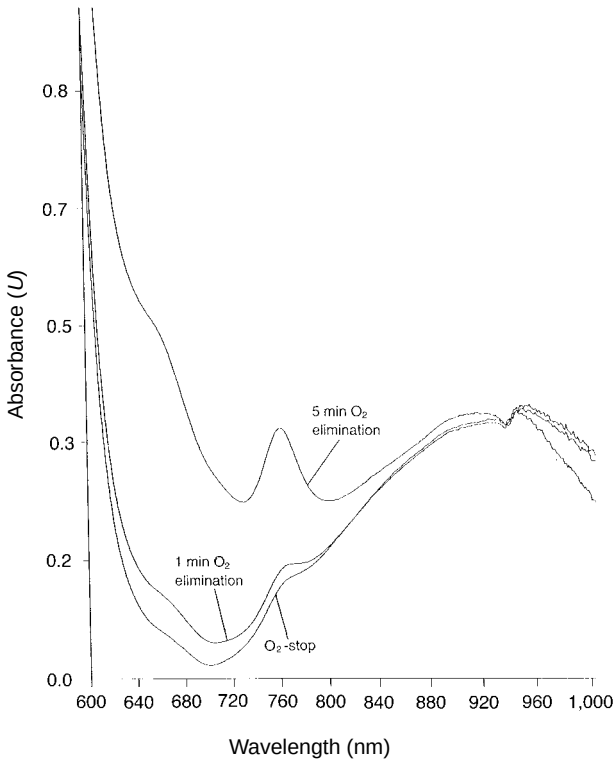


Figure 5. In-vitro deoxygenation with N_2. Changes in NIR absorbance pattern on interruption of O_2 flow; 1 minute and 5 minutes after continuous elimination of O_2 with N_2.

graphs with an O_2 saturation lower than 30%. Occlusion of the LAD led to visible motion disturbances in the ischemic region, with the local color turning to purple. The heart rate was increased during LAD occlusion but other hemodynamic parameters (mean aortic pressure and left ventricular end-diastolic pressure) did not change significantly over time or on reperfusion, compared to baseline data, although typical ischemic changes in the ECG were evident. During ischemia and subsequent reperfusion, central venous O_2 saturation showed no significant changes on blood gas analysis. In contrast, the NIR spectra of coronary sinus blood displayed a significant elevation of absorbance, particularly at the 735-nm minimum and 770-nm maximum, within the first 30 minutes of LAD occlusion (Figure 6). The absorbance at longer wavelengths (> 790–800 nm) was diminished during the ischemic period, compared to shorter wavelengths (< 780–790 nm). Metabolic recovery of the affected myocardium could be observed after initial ischemic changes between 30 and 90 minutes of ischemia. Simultaneously, hemodynamic parameters returned to almost normal values. The absorbance curves in 6 of the 10 pigs could be evaluated and summarized in a mean graph pattern (Figure 7). Regions of interest for ischemic changes in the mean NIR spectrum were registered at 735, 770, and 975 nm where there were significant absorbance shifts compared to the pre-ischemic status in these animals (Table 2). The end of the ischemic period (90 minutes) was characterized by slightly decreased absorbance at wavelengths less than 790 nm.

The macroscopic, histologic, and electron-microscopic examination of the myocardium showed demarcated infarction zones with extensive damage to cellular structures in affected areas of the myocardial specimens in all animals, confirming the clinical and spectroscopic observations during the experiments.

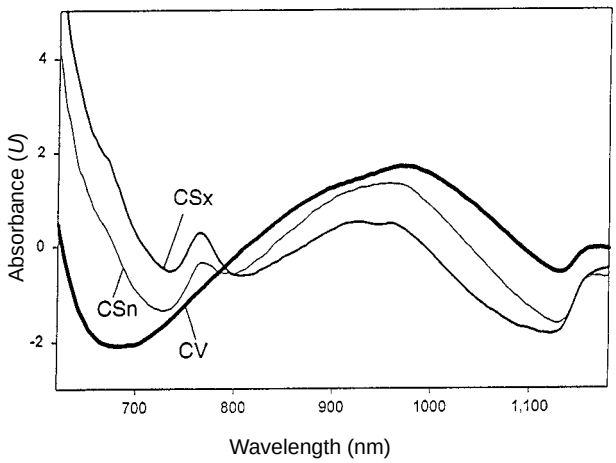


Figure 6. Differences in the NIR spectra of coronary sinus blood between the baseline central venous sample (CV), the normal control sample from the coronary sinus (CSn), and after the left anterior descending artery occlusion (CSx).

DISCUSSION

Currently, NIR-based monitoring is used mainly for the detection of tissue oxygenation, especially for cerebral measurements. The known patterns of NIR graphs in oxygenated and deoxygenated tissue samples are strongly related to changes in the oxygenation states of different chromophores such as hemoglobin and the tissue-bound chromophore cytochrome aa_3.[7–9] However, in isolated blood analysis, we found that similar NIR spectra could be obtained in blood containing no free chromophores other than hemoglobin. On this basis, the external application of NIR spectroscopy by an optode technique would be potentially misleading with less exact NIR data due to overlapping of blood-bound and tissue-bound parameters. In current literature, the characteristic NIR graphs of hemoglobin are still considered as either oxygenated or deoxygenated, regardless of the additional possibilities of structural variations of the hemoglobin molecule during transportation of oxygen.[6,10,11] Hemoglobin-CO_2 binding takes place at a different location on the hemoglobin macromolecule (N-terminal valyl group) than O_2 binding, and would generally not interfere with oxygenation. This fact, together with the effects of pH and temperature on NIR spectral analysis, is not clearly described in the literature. However, in the in-vitro part of this study, some irregularities were found in the detailed analysis of the NIR spectra, which might contain more physical information regarding the partial pressure of O_2 and CO_2, pH value, and temperature of the blood.

For the clinical application of NIR spectroscopic analysis of tissue oxygenation, the present technology requires optodes to be configured face-to-face about an object.[3,6,12] Regular optodes are pads that may be attached anywhere on the surface of the body. The optodes currently in use are bulky devices and are not well suited to in-situ monitoring of internal organs, due to the geometrical configuration and positioning required. These experiments indicate that NIR spectroscopy could be feasible for intravascular application by locating emitting and collecting optodes coaxially at the tip of a fiberoptic catheter. The NIR catheter could either be placed in the arterial system or inserted into the venous backflow from virtually any organ to detect its time-related specific oxygenation status.

Interruption of myocardial O_2 supply by occluding a coronary artery leads to rapid deoxygenation of the affected myocardial zone; hence oxygen consumption in the tissue is discontinued. As a result, coronary sinus blood shows a change in the NIR absorbance pattern, with a significant shift to a deoxygenated status. In the initial phase of ischemia, cellular damage occurs at a metabolic level, and morphology is not impaired. Laboratory parameters

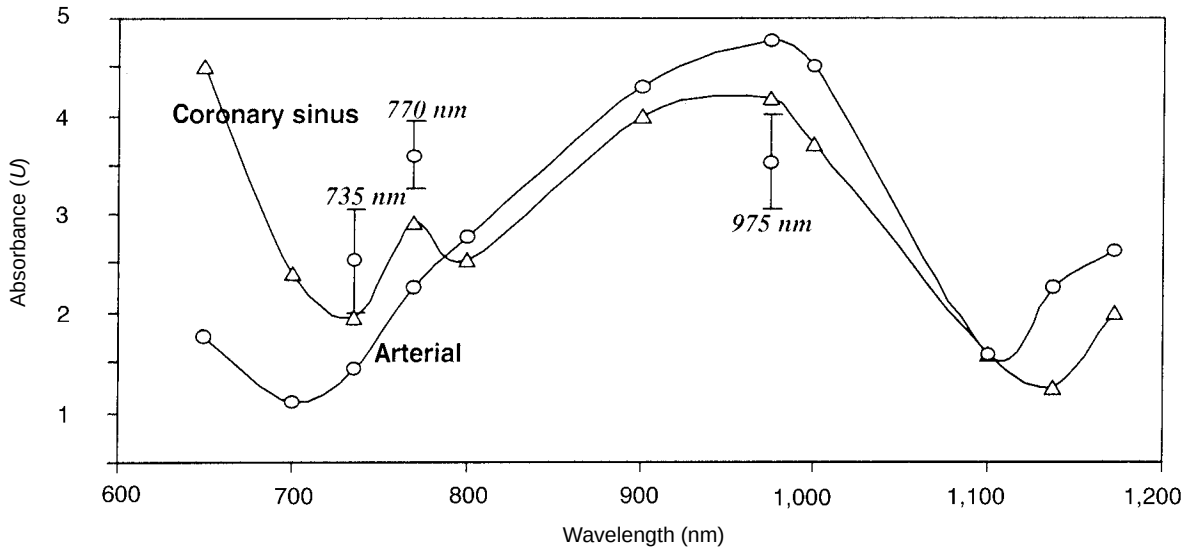


Figure 7. Mean NIR absorbance patterns of the arterial and coronary sinus baseline graphs before ischemia. Bars at points of interest (735, 770, and 975 nm) indicate the ischemia-related changes within the first 30 minutes of left anterior descending artery occlusion.

Table 2. **Changes at Points of Interest in Coronary Sinus Near-Infrared Absorbance Spectra**

	Absorbance (U)		
Wavelength (nm)	LAD Patent	LAD Occluded (30 min)	*p* Value
735	1.84 ± 0.37	2.52 ± 0.52	< 0.05
770	2.84 ± 0.10	3.60 ± 0.35	< 0.01
975	4.23 ± 0.34	3.53 ± 0.50	< 0.05

LAD = left anterior descending artery.

that indicate structural injury, such as troponin or creatine kinase-MB, would thus not show any significant elevation in this very early phase of ischemia. More reliable parameters here are the ECG, critical changes in hemodynamic data, or detection of wall motion disturbances by transesophageal echocardiography. In these animal experiments, ischemic changes in the coronary sinus NIR absorbance pattern became evident even before the ECG or hemodynamic parameters were altered.

Thorniley and colleagues[9] examined changes in hemoglobin and myoglobin oxygenation and volume to study tissue perfusion and flow in 9 pigs, using NIR spectroscopy. Although different data acquisition and processing techniques were used, their results showed a broad similarity to ours, confirming the usefulness of NIR spectroscopy in measuring changes in myocardial oxygenation in response to ischemic episodes. The same conclusion was also made by Parsons and colleagues[4,13] who used NIR spectroscopic detection of myocardial ischemia in dogs in open-chest studies, declaring that the application of NIR spectroscopy was suitable for assessing the relation of tissue oxygenation to contractile function during ischemia. Both of these studies, together with many others, demonstrate the species-independent characteristics of ischemic changes in myocardial tissue.

In-situ detection of acute ischemic events might give more definitive diagnosis and prognosis compared to current methods of monitoring ischemia. It is evident that at this stage, only global information can be received from the partially ischemic myocardium. This makes the ischemic or infarcted area difficult to locate without backup from ECG or transesophageal echocardiography. It is postulated that further development by refinement of NIR data acquisition and exact positioning of the catheter tip in the coronary sinus could offer reliable and reproducible data on the location and time course of ischemic events. For clinical application, the catheter could be placed through a central venous access (for example, jugular vein) for closed-chest monitoring in cardiac intensive care units. For open-chest procedures in cardiac surgery, the catheter could be placed directly into the coronary sinus through the right atrial appendage. The spectral acquisition time per sample was less than 2 seconds and it can be varied depending on the sensitivity required. Electronic triggering with the ECG or other important hemodynamic parameters is thus technically possible.

These results were definitely encouraging, indicating that intravascular NIR spectroscopy might become a reliable tool for online detection, follow-up, and prevention of myocardial ischemia and infarction, in the field of cardiac surgery and cardiology.

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