The Heart Surgery Forum #2001-6973
5 (4), 2002

Online address: www.hsforum.com/vol5/issue4/2001-6973.html

Near-Infrared Fluorescence Coronary Angiography: A New Noninvasive Technology for Intraoperative Graft Patency Control

(#2001-6973 … June 27, 2001)

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ABSTRACT

Background: Intraoperative graft patency verification is of major clinical importance for quality control after coronary artery bypass grafting (CABG), especially if surgery is performed on the beating heart. This is one of the first reports of fluorescence coronary angiography (FCA) using the dye indocyanine green (ICG), a noninvasive technology for direct visualization of coronary arteries, bypass grafts, and myocardial perfusion.

Methods: Twenty-three domestic pigs (weight, 45-72 kg) underwent FCA of the left anterior descending coronary artery (LAD). In the first group (n = 6 pigs), FCA was used to visualize the native coronary vessels and myocardial perfusion. In the second group (n = 8 pigs), 14 stenoses of various degrees and 4 total vessel occlusions were created by snares on different segments of the LAD, and FCA was used to visualize the effects of these obstructions. In the third group (n = 9 pigs), a coronary bypass procedure on the beating heart was performed by a left internal mammary artery or a human saphenous vein graft to the LAD, and FCA was used to visualize graft patency. Three pigs were removed from the study because of ventricular fibrillation. ICG was intravenously applied, and the heart was illuminated with near-infrared light emitted by laser diodes. The fluorescence emission was detected by an adapted charge-coupled device camera system. The images were displayed in real time on a high-resolution monitor. Subsequently, images obtained with FCA were compared to those obtained with coronary angiography (n = 10 pigs).

Results: In all cases, high-quality FCA images of coronary arteries and myocardial perfusion were obtained. All stenoses resulted in an impairment of the myocardial perfusion visualized by FCA. Occlusion of the LAD or the diagonal branch resulted in a total perfusion defect of the corresponding anterior myocardial wall with immediate reperfusion after releasing the snare. In 5 cases a patent bypass graft with an apparent homogenous perfusion of the corresponding myocardium was detectable. In one procedure, FCA images indicated total occlusion of the bypass graft and a total perfusion deficit in the distal LAD region. Correlation between FCA and coronary angiography in detection of stenoses and graft patency was excellent.

Conclusion: With the fluorescence technique using ICG, visualization of blood flow in coronary vessels and bypass grafts, as well as of myocardial perfusion, is feasible. FCA is a highly sensitive and reproducible method and an excellent technique for intraoperative quality control in CABG.

INTRODUCTION

Coronary artery bypass grafting (CABG) with or without cardiopulmonary bypass (CPB) is the most frequently performed cardiac surgical procedure. More than 76,000 patients per year in Germany and approximately 400,000 patients per year in the United States undergo CABG.

Within the past few years, since commercially cardiac stabilizers became available and satisfying results were reported, interest in minimally invasive techniques for myocardial revascularization performed on the beating heart without CPB has increased worldwide [Cremer 2000, Arom 2000, Puskas 2001].

Despite widespread acceptance of this procedure, concerns have been raised regarding the accuracy of coronary anastomosis performed on a beating heart. Furthermore, the identification of the correct vessel in minimally invasive direct coronary artery bypass (MIDCAB) procedures through a small thoracotomy can be rather difficult [Schmid 1999]. Thus, several cardiac centers perform a postoperative angiography for quality control and verification of graft patency. Reports of angiographic studies indicate that the total patency rate of the coronary anastomoses ranges from 90% to 99% [Mack 1999, Detter 2001]. However, postoperative angiography is an invasive technique that incurs additional

Presented at the Fourth Annual Scientific Meeting of the International Society for Minimally Invasive Cardiac Surgery, June 27-30, 2001, Munich, Germany.

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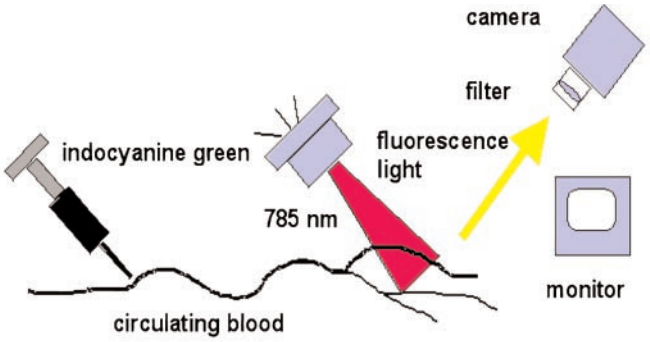

Figure 1. The principle of fluorescence coronary angiography.

risk for the patient. To improve the quality control for coronary procedures, intraoperative graft patency verification is of major importance and may eliminate the need for reoperation by facilitating correction of the anastomosis or bypass graft at the primary procedure.

In cooperation with the Institut für Lasertechnologien (ILM), University of Ulm, and the Section for Minimally Invasive Surgery, University of Tübingen, we developed fluorescence coronary angiography (FCA) using the dye indocyanine green (ICG) as a new noninvasive technology for intraoperative visualization and documentation of coronary vessels, bypass grafts, and myocardial perfusion.

The aim of the study was to evaluate this new FCA technique as a clinically usable imaging system.

MATERIAL AND METHODS

Indocyanine Green

ICG is a water-soluble fluorescent dye with a molecular weight of 775 d. When injected into the blood, ICG immediately binds to plasma proteins and is distributed in circulating blood volume [Fox 1956]. Thus, it is almost completely bound to globulins (80%), mainly α_1-lipoprotein, and to albumin (20%), and this binding guarantees that the fluorescent dye will remain intravasal [Baker 1966]. Because ICG is rapidly eliminated exclusively by the liver, it does not accumulate in the body [Cherrick 1960]. The dye is nontoxic, and side effects other than a rare iodine allergy have not been reported [Cherrick 1960, Paumgartner 1975, Hope-Ross 1994]. The plasma clearance for patients with normal liver function is between 18.5% [Cherrick 1960] and 28.2% [Leevy 1967, Ott 1998], a rate that corresponds to an effective half-life of 3.4 minutes and 2.4 minutes, respectively, after receipt of 0.5 mg ICG per kg. Thus, repeated injections of ICG with only a slight delay between injections are possible. In plasma, ICG displays an absorption maximum at 805 nm and an emission maximum at 830 nm [Cherrick 1960].

ICG was first introduced by Fox and Brooker in 1956 and was used primarily in hepatology as a liver function test [Leevy 1967, Paumgartner 1975] and in cardiologic diagnostics for estimation of cardiac output [Fox 1956]. In 1973, the fluorescence technique was introduced for fluorescence angiography of the choroidea [Flower 1973]. Enhanced imaging was made possible by the development of digital ICG videoangiography [Yannuzzi 1992].

Fluorescence Coronary Angiography

The principle of FCA is depicted in Figure 1 ◎. The fluorescent dye ICG was intravenously applied, and the heart was illuminated with near-infrared (NIR) light at a wavelength of 785 nm. The light was provided by IR laser diodes. The excited dye showed fluorescence with an emission maximum at 830 nm. The emission of the excited fluorescent dye was detected by an adapted infrared charge-coupled device (CCD) camera system (KamPro02; EHD Imaging, Damme, Germany). A bandpass filter was placed in front of the laser light to reach only light of the required spectrum. The camera was mounted on the operating table and the exposed surface of the heart was focused at a distance of approximately 25 cm at a perpendicular angle. The FCA images were displayed in real time on a high-resolution monitor and recorded with a digital video-recording system (Sony GV-D900E). Selected images were analyzed using a computer system and software provided by LLS (Ulm, Germany).

Animal Experiments

This study was reviewed and approved by the Animal Care Committee of our institution. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH, publication 86-23, revised 1985).

Prior to initiation of the series of animal experiments, the technique was tested on 10 ex vivo pig hearts from a slaughterhouse to verify the parameters obtained in the in vitro model and optimize the image acquisition.

Twenty-three domestic pigs of both sexes, body weight 54.3 ± 6.4 kg (range, 45-72 kg) were used in the investigation. Premedication was performed by intramuscular injection of atropine (0.02 mg/kg), ketamine (10 mg/kg), and stresnil (8 mg/kg). After intravenous injection of dormicum (0.1 mg/kg), etomidate (0.2 mg/kg), and fentanyl (6 μg/kg) the pigs underwent endotracheal intubation. The anesthesia was maintained under volatile narcotics with isoflurane (1.5%-2%), continous infusion of fentanyl (0.3 mg/h), and controlled positive-pressure ventilation with 40% to 50% O_2. To ensure a stable cardiac rhythm and adequate oxygenation, a 5-channel electrocardiograph (ECG) for continuous monitoring of the electrocardiogram was applied and blood gas analyses were regularly performed. After operative preparation of the right carotid artery, a 6F arterial lock was inserted for arterial pressure monitoring and for blood gas analysis. A standard coronary angiography via the right carotid artery was performed in 10 pigs using the 6F catheter. A double-lumen central venous catheter was inserted into the right jugular vein for delivery of saline, heparin (10,000 IU initial dose; 15,000 IU prior to CABG), and ICG. At the end of the experiments, the animals were killed by an intracardiac injection of T 6.

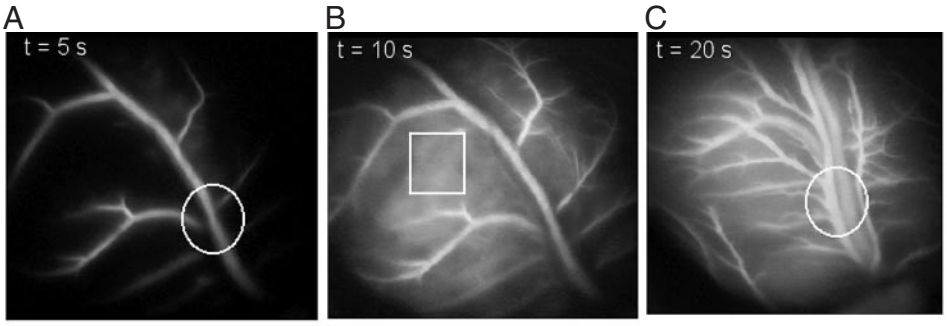

Figure 2. Fluorescence coronary angiography of the LAD and its side branches at different time intervals. The chronological blood perfusion of the heart with arterial inflow into the coronary arteries (A), capillary perfusion (B), and venous filling (C) can be observed.

Surgical Technique

The operation was carried out on the beating heart through a median sternotomy. The left internal mammary artery (LIMA) or a human saphenous vein graft (SVG) was used as graft material. LIMA was harvested using standard techniques. Deep pericardial traction sutures were placed on the left side for exposure of the LAD. The Octopus 2 stabilizer (Medtronic, Minneapolis, MN) was employed to achieve local immobilization of the target vessel. During temporary interruption of the coronary flow, the LAD was incised and an intracoronary shunt was inserted. Coronary anastomosis between LIMA or SVG and the LAD was performed on the beating heart with a single 7-0 polypropylene (Ethicon, Somerville, NJ) running suture.

Study Protocol

For FCA we applied an ICG concentration of 0.03 mg/kg body weight as obtained from the previous in vitro and ex vivo models. The CCD camera system with the laser light was positioned and focused on the exposed surface of the heart. In our animal experiments, the LAD was chosen for FCA examinations because of the optimal topographical situation.

Of 23 domestic pigs, 20 pigs underwent FCA of the LAD. The animals were randomly divided into 3 different groups.

In the first group (n = 6 pigs), the native coronary vessels and the myocardial perfusion were visualized and the chronological blood perfusion of the heart was documented.

In the second group (n = 8 pigs), stenoses of various degrees and total vessel occlusion were created by snares on different segments of the LAD. Initially, a baseline FCA was performed for detection of the coronary artery. Another FCA was performed to document and evaluate the grade of stenosis. For documentation of the ischemic myocardial area, the LAD or the diagonal branch were occluded completely by snaring the coronary artery. The occlusion was released and the reperfusion was recorded by FCA.

In the third group (n = 9 pigs), a baseline FCA was performed to visualize the coronary arteries and to demonstrate the noncompromised myocardial perfusion of the left ventricle. Subsequently, a coronary bypass procedure was performed on the beating heart, anastomosing an LIMA or an SVG to the LAD. Three animals were dropped from the study because of ventricular fibrillation after the coronary bypass procedure. In the remaining 6 pigs, FCA was performed at the end of the bypass procedure to document graft patency.

To demonstrate the feasibility of the FCA technique in detection of the coronary vessels, stenoses, and bypass grafts, the FCA images were compared to standard coronary angiographic images. Standard coronary angiography via the right carotid artery was performed in a total of 10 pigs in the 3 groups (group 1, n = 2; group 2, n = 5; group 3, n = 3). Both types of angiographic images were visually quantified to evaluate and compare the results.

RESULTS

Visualization of Native Coronary Vessels and Myocardial Perfusion (First Group)

In all cases, high-quality FCA images of the coronary arteries and of the myocardial perfusion were obtained. Figure 2 ◎ shows an FCA of the LAD and its side branches at different time intervals. Approximately 5 seconds after injection of the dye, arterial inflow into the coronary arteries was observed, with visualization of the LAD and its side branches (Figure 2A ◎). Then, myocardial perfusion was visible as a diffuse fluorescence of the anterior wall of the left ventricle (Figure 2B ◎). Thereafter, the fluorescent dye reached the venous vasculature, and the fluorescent signal from the coronary arteries decreased (Figure 2C ◎). Thus, the chronological blood perfusion of the heart with arterial, capillary, and venous filling could be observed.

Figure 3 ◎ shows the LAD and its side branches detected by FCA and coronary angiography. With both angiographic techniques, excellent and comparable images of the native coronary arteries were obtained.

Stenoses and Occlusion of the Coronary Arteries (Second Group)

In 8 pigs, 14 stenoses of various degree and 4 total vessel occlusions on different segments of the LAD were performed. All stenoses were visualized by FCA and resulted in an impairment of the myocardial perfusion. Occlusion of the LAD or the diagonal branch resulted in a total perfusion defect of the corresponding anterior myocardial wall within the LAD region. Figure 4 ◎ shows an occlusion of the proximal part of the LAD. FCA demonstrated normal perfu-

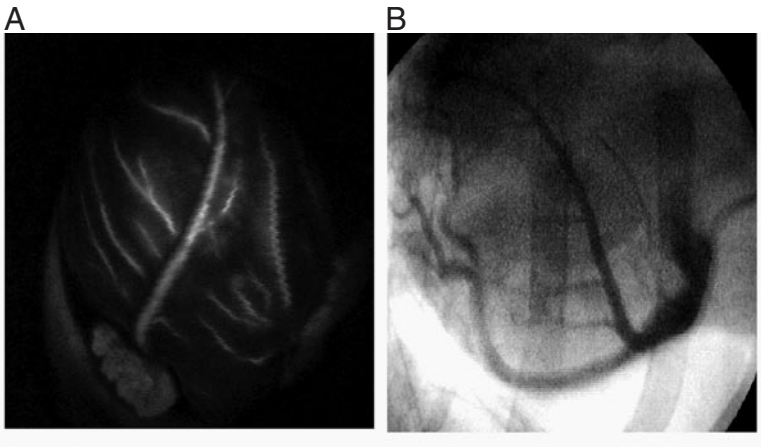

Figure 3. Left anterior descending coronary artery and its side branches detected by fluorescence coronary angiography (A) and coronary angiography (B).

sion of the right ventricle and the proximal part of the left ventricle. The absence of a fluorescence signal distal to the LAD occlusion indicated the ischemic area. After the interruption of blood flow was released, the distal part of the LAD and the capillary perfusion of the corresponding myocardium were visualized, indicating immediate reperfusion of the previously ischemic area.

Figure 5 ◎ shows a significant stenosis of the proximal part of the LAD as depicted by FCA and coronary angiography. The stenoses of the LAD were detected in all cases with both angiographic techniques.

Graft Patency Control (Third Group)

Baseline FCA resulted in high-quality images of the LAD, and excellent myocardial perfusion of the left ventricle could be demonstrated. At the end of the bypass procedure, we documented graft patency by FCA in 6 pigs. In 5 cases, a patent bypass graft was detected (Figure 6A ◎). FCA was used to visualize the bypass graft and the distal part of the LAD. An apparent homogenous perfusion of the corresponding myocardium was observed in all 5 cases, indicating good antegrade bypass flow. In one procedure, FCA indicated total occlusion of the bypass graft and a total perfusion deficit in the distal LAD region (Figure 6B ◎). In this case, neither the bypass graft nor the LAD could be visualized by FCA. The absence of a fluorescence signal of the corresponding myocardium indicated a total perfusion deficit in the LAD region.

To demonstrate the feasibility of the FCA technique for detection of graft patency, results of standard coronary angiography and FCA for 3 pigs were compared. Both types of angiographic techniques showed a patent bypass graft in 2 cases and an occluded bypass in 1 case.

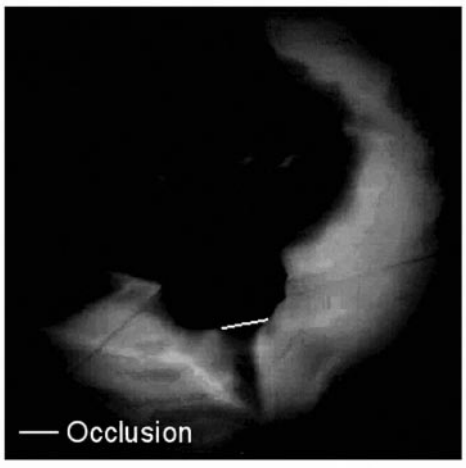

Figure 4. Fluorescence coronary angiography showing an occlusion of the proximal part of the left anterior descending coronary artery (LAD). No fluorescence signal was detected distal to the LAD occlusion indicating the ischemic area.

DISCUSSION

Off-pump coronary artery bypass grafting (OPCAB) for myocardial revascularization on the beating heart is an evolving technique and represents a popular alternative to standard bypass surgery in a growing patient population. With the increasing number of OPCAB procedures, there is a need to confirm graft patency and to document the success of the operative technique. Thus, intraoperative graft patency control is important to avoid serious complications due to graft failure.

With the introduction of ultrasound-based flowmeters such as Doppler [Segadal 1982] and transit time flow measurement [Lundell 1993, Laustsen 1996], interest has been revived in intraoperative documentation of graft patency as well as graft and anastomosis quality assessment [Canver 1997]. However, these techniques are limited to the measurement of the bypass flow rate without visualization of the grafted vessel and provide no information about myocardial perfusion. In addition, blood flow measurements cannot be used to identify significant graft stenoses or predict graft patency [Hol 2001]. Thermal coronary angiography (TCA) is a technique for imaging of small temperature differences between adjacent structures. This technique, in contrast to ultrasound, provides a noninvasive angiographic picture of the graft and the anastomosed vessel and allows the verifica-

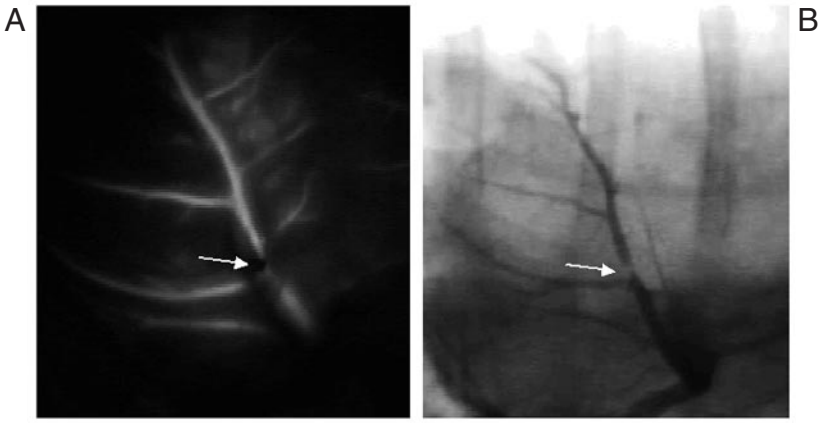

Figure 5. Significant stenosis of the proximal part of the left anterior descending coronary artery depicted by fluorescence coronary angiography (A) and coronary angiography (B).

tion of graft patency [Mohr 1989]. Initially, TCA did not work as well for OPCAB procedures because the small temperature differences could not be detected. Recent technical improvements have allowed the TCA technique to be successfully used in MIDCAB and OPCAB procedures [Falk 1997, Suma 2000]. Nevertheless, the TCA technique has not become commonplace. Coronary angiography is still considered the "gold standard" in assessment of stenoses of coronary arteries and evaluation of stenoses or patency of bypass grafts. However, coronary angiography using ionizing radiation is an expensive, invasive technique with the risk of severe complications. Furthermore, intraoperative angiography is usually not available in most hospitals, and postoperative angiography entails an additional expense and adds a slight risk to the patient. This method does not provide any information for assessment of myocardial perfusion or bypass flow.

This report is one of the first to describe FCA using the dye ICG, a new noninvasive technology for direct visualization of coronary vessels and bypass grafts. This technique allows visualization of blood flow without the need for contrast medium or radiation. In this study, the FCA technique resulted in high-quality images of the coronary vasculature in all cases. In addition, the technique allowed assessment of myocardial perfusion, providing further information on the blood supply of the corresponding myocardium. Indeed, FCA enabled us to detect occlusion of the LAD or the diagonal branch, resulting in a total perfusion defect of the corresponding anterior myocardial wall in the LAD region, with immediate reperfusion after release of the snare. Thus, the ischemic area was detected by the FCA technique. In addition, FCA enabled detection of all created LAD stenoses, a result verified by coronary angiography. Nevertheless, FCA, in contrast to coronary angiography, provides images in only one plane. Thus, stenoses parallel to the surface plane may not be directly visualized. FCA diagnosis is confined to the upper 4 mm because of the limited penetration of NIR light in myocardial tissue. However, coronary stenoses result in impairment of myocardial perfusion, which can be detected by FCA and may give further information for interpretation of stenotic vessels.

Concerning intraoperative verification of bypass graft patency, FCA enabled visualization of the bypass graft and the distal coronary vessel. Thus, a patent bypass graft was detected in 5 cases and graft occlusion in 1 case, and these findings were confirmed by intraoperative coronary angiography. In all 5 patent graft cases, apparent homogenous perfusion of the corresponding myocardium was observed, indicating good antegrade bypass flow. In contrast, in the case of graft occlusion, a perfusion defect of the myocardial wall dis-

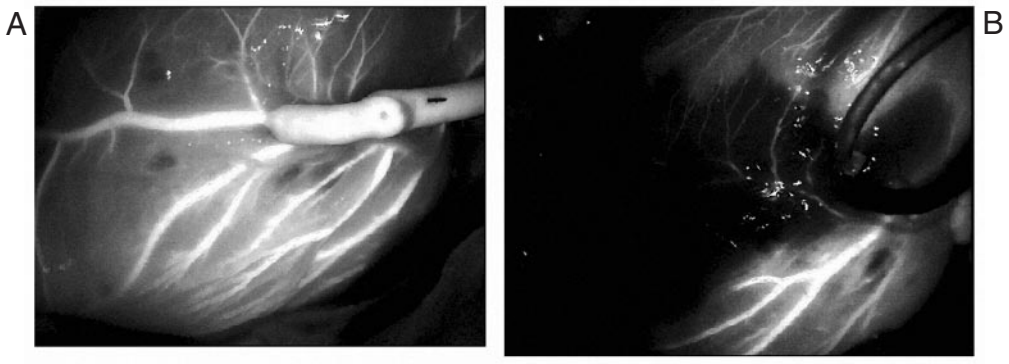

Figure 6. Fluorescence coronary angiography demonstrating the patency of the bypass graft without narrowing of the anastomotic side (A) compared to a total occlusion of the bypass graft with a perfusion deficit in the distal left anterior descending coronary artery region (B).

tal to the graft occlusion was detected. We believe that the visualization and the impairment of myocardial perfusion may provide further important information in the assessment of graft stenoses or occlusion.

Our findings have limitations. First, no attempts were made to perform quantitative analyses based on the fluorescence angiograms, but adapted imaging algorithms are under development. In the meantime, these early experiences prove the feasibility of FCA in visualization of coronary vessels, presence of stenoses, and bypass graft patency. Second, the impairment of myocardial perfusion was visualized by FCA but was not quantitatively defined. Thus, further studies are necessary to evaluate the feasibility of quantification of this new technique.

In conclusion, FCA is a highly sensitive, simple, and reproducible method for visualization of blood flow in coronary vessels and bypass grafts. In addition, myocardial perfusion can be assessed, providing further information on the blood supply of the corresponding myocardium. The patency of the bypass graft can be evaluated. Thus this new technique may serve as an excellent method for intraoperative verification of bypass graft patency.

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