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Image-Guided Quantification of Cardioplegia Delivery during Cardiac Surgery

Edward G. Soltesz, MD, MPH¹, Rita G. Laurence, BS¹, Alec M. De Grand, BS², Lawrence H. Cohn, MD¹, Tomislav Mihaljevic, MD¹, and John V. Frangioni, MD, PhD^{2,3}

¹Division of Cardiac Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA 02115

²Division of Hematology/Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215

³Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA 02215

Abstract

Objectives—Homogenous distribution of cardioplegia delivered to the myocardium has been identified as an important predictor of post-cardiopulmonary bypass ventricular recovery and function. Presently, a method to determine adequate distribution of cardioplegia in patients during cardiac surgery does not exist. The goal of this study was to evaluate the feasibility of quantifying cardioplegia delivery using a novel, non-invasive optical method. Such a system would permit instantaneous imaging of jeopardized myocardium and allow immediate, intraoperative corrective measures.

Methods—We have previously developed a portable, intraoperative near-infrared (NIR) fluorescence imaging system for use in large animal cardiac surgery, which simultaneously displays color video and NIR fluorescent images of the surgical field. By introducing exogenous, non-isotopic NIR fluorophores, specific cardiac functions can be visualized in real-time.

Results—In a cardiopulmonary bypass porcine model, we demonstrate that the FDA-approved intravascular fluorophore indocyanine green (ICG) permits real-time assessment of cardioplegia delivery. ICG was injected into an aortic root and/or transatrial coronary sinus catheter during delivery of cold crystalloid cardioplegia solution. Segmental distribution was immediately noted at the time of injection. In a subset of animals, simulated coronary occlusions resulted in imaging defects consistent with poor cardioplegia delivery and jeopardized myocardium. Videodensitometric analysis was performed on-line to quantify right and left ventricular (RV, LV) distribution.

Conclusions—We report the development of a novel, non-invasive, intraoperative technique which can easily and safely provide a visual assessment of cardioplegia delivery (antegrade and/or retrograde) and which offers the potential to quantify the relative segmental distribution during cardiac surgical procedures.

ULTRAMINI ABSTRACT—Intraoperative near-infrared fluorescence imaging is a novel, non-invasive technique that can safely and easily visualize and quantify cardioplegia distribution during cardiac surgery. This system should permit surgeons to identify regions of poor myocardial protection, and guide interventions, intraoperatively and in real-time.

Keywords

Cardioplegia; Coronary Artery Bypass Grafting; Image-Guidance; Intraoperative Imaging; Near-Infrared Fluorescence

INTRODUCTION

Conventional cardiac surgery utilizes cardiopulmonary bypass for circulatory support while the aorta is occluded and the heart arrested in order to create a bloodless, motionless operative field for efficient coronary grafting or valve surgery. Aortic occlusion, however, results in a period of warm ischemia and subjects the heart to a time-dependent hazard for myocardial injury. Typically, the heart is protected during this phase by injecting cardioplegia solution either in an antegrade or retrograde fashion.¹

The adequacy of myocardial protection during this obligate period of ischemia is dependent upon uniform distribution of cardioplegia to the myocardium.² Antegrade administration of cardioplegia via the aortic root is by far the most common delivery method.³ However, significant coronary stenoses and poor collateral supply may limit its distribution to compromised areas of myocardium. Retrograde delivery of cardioplegia through the coronary sinus has a theoretical advantage in patients with high-grade coronary lesions since it might supply regions of the myocardium inaccessible by the antegrade route.⁴ Retrograde cardioplegia, though, suffers from poor preservation of the right ventricle⁵, regional heterogeneity, and a significant delay before diastolic arrest.⁶ Often, a combination of antegrade and retrograde delivery techniques is used to optimize myocardial protection. The adequacy of cardioplegia distribution, though, is difficult to ascertain and quantify. At present, surgeons rely on the generation of an asystolic and motionless heart⁷ together with the delivery of an optimal volume⁸ of cardioplegia solution as a guide to the adequacy of cardioplegia distribution and the resultant myocardial protection. These measures, however, are all surrogates for real-time visualization of cardioplegia delivery. Contrast echocardiography utilizing sonicated renografin-76 microbubbles can provide an indirect assessment of injected cardioplegia, yet this method is operator-dependent and lacks resolution.⁹ The optimal method for assessing the adequacy of cardioplegia distribution is direct intraoperative visualization of cardioplegia flow. This method allows the cardiac surgeon to identify territories of poor delivery prior to ischemic damage, to direct the sequence of grafting based on territories at risk, and to determine the need for retrograde cardioplegia supplementation. Additionally, the direct visualization of retrograde cardioplegia flow would permit early identification of a malpositioned coronary sinus catheter and allow immediate correction.

Our goal was to provide the cardiac surgeon with highly sensitive, real-time intraoperative imaging of cardioplegia distribution and regional cardiac ischemia using noninvasive methods. We recently developed a near-infrared (NIR) fluorescence optical imaging system that permits real-time, intraoperative imaging using the FDA-approved NIR fluorescent agent indocyanine green (ICG).^{10,11} NIR light, otherwise invisible to the human eye, provides extremely high signal to background ratios without changing the look of the surgical field. In this present study, we investigated the feasibility of using ICG for intraoperative visualization and quantification of cardioplegia distribution in a large animal model of cardiac surgery.

METHODS

NIR Imaging System

The large animal intraoperative NIR fluorescence imaging system used in this study has been described in detail previously.¹⁰ Briefly, it is composed of two wavelength-isolated excitation

sources, one generating 1 mW/cm² of 400-700 nm “white” light, and the other simultaneously generating 5 mW/cm² of 725-775 nm light over a 15 cm diameter field of view. Photon collection is achieved with custom-designed optics that maintains separation of the white light and near-infrared fluorescence (>795 nm) channels. The system has variable zoom capability, achieving a spatial resolution of 625 µm at a field-of-view of 20 × 15 cm, and 125 µm at a field-of-view of 4 × 3 cm. After computer-controlled camera acquisition, anatomic (white light) and functional (near-infrared fluorescent light) images can be displayed separately and merged. Images acquired with the 12-bit Orca-AG (Hamamatsu, Bridgewater, NJ) NIR camera were within its linear range. All screen images are refreshed 15 times per second. The entire apparatus consists of a portable console with an articulating arm that suspends the camera over the operative field, at a distance of 18”. No contact is made with the subject. Data were acquired and quantified on a Dell computer using LabVIEW 6.0 (National Instruments, Austin, TX).

NIR Fluorophores and Cardioplegia

Indocyanine green (ICG, IC-Green™) was purchased from Akorn, Inc. (Decatur, IL). A 2.5 mg/ml stock solution in saline was prepared fresh for each surgical procedure and stored at room temperature in the dark. ICG is FDA-approved for indicator dilution studies in humans and remains intravascular after injection, with a half-life of 30-60 sec. It is also, however, a NIR fluorophore, with peak excitation at 779 nm and a peak emission at 806 nm in aqueous buffer. Since its approval in 1958, ICG has had a remarkable safety record with minimal adverse reactions.^{12,13}

Standard cold (4°C), hyperkalemic crystalloid cardioplegia was used in this study and consisted of 154 mmol sodium, 154 mmol of chloride, 4 mEq of MgSO₄, and 40 mEq of KCl per liter. 100 µg of ICG was added to 150 ml of cardioplegia solution resulting in a 860 nM final injection concentration.

Surgical Preparation

Adult Yorkshire pigs (n=10, mean weight 35 kg) of either sex were used in this study. Animals were purchased from EM Parsons and Sons (Hadley, MA). All animals received humane care in compliance with approved institutional protocols. General anesthesia was induced with 4.4 mg/kg of intramuscular Telazol (Fort Dodge Labs, Fort Dodge, IA) and 2.2 mg/kg xylazine. Once sedated, the animals received oxygen and 5% isoflurane to effect. Animals were intubated with a cuffed endotracheal tube and ventilated with 100% oxygen. Anesthesia was maintained with 1.5% to 2% isoflurane. Continuous oxygen saturation and 3-lead electrocardiographic tracing were monitored throughout the experiment. An intravenous catheter was placed in the left marginal ear vein, and maintenance intravenous fluid was infused. The left internal jugular vein was cannulated for central venous access, and a Millar pressure-transducing catheter (Millar Instruments, Houston, TX) was placed in the left carotid artery to monitor arterial pressure. Animals received intravenous lidocaine (50 mg) and dexamethasone (4 mg) prior to sternotomy. After a median sternotomy was performed, the heart was suspended in a pericardial cradle and the azygous vein ligated. Following systemic heparinization (3 mg/kg), a 14 Fr arterial cannula was placed in the left femoral artery and a two-stage, single-venous cannula was placed through the right atrial appendage into the right atrium. These were connected in the standard fashion, and cardiopulmonary bypass was initiated at 36°C.

Following establishment of cardiopulmonary bypass with adequate flow, a purse-string stitch was placed in the right atrium and a retrograde cardioplegia catheter (auto-inflating balloon catheter, 15 Fr, Medtronic, Grand Rapids, MI) for retrograde cardioplegia administration was advanced transatrially into the proximal coronary sinus and sutured in place. The left anterior descending coronary artery (LAD) was identified and isolated just proximal to its first diagonal

branch. The ascending aorta was occluded, and a 14-gauge cannula was inserted into the proximal aorta for antegrade cardioplegia administration.

Images of the surgical field were obtained prior to the administration of cardioplegia in order to document background autofluorescence. Cardioplegia containing ICG was then administered via the aortic root and/or coronary sinus catheters according to protocols detailed below. Cardioplegia was injected at a rate of 100 ml/min. Continuous real-time NIR fluorescence imaging was obtained during cardioplegia injection and for 5 minutes thereafter. In 4 animals, hearts were explanted, sectioned along their short-axes, and then re-imaged. In the remaining animals, hearts were allowed to wean from cardiopulmonary bypass. All images were archived for videodensitometric analysis.

Cardioplegia was infused according to the following protocols:

1. Antegrade cardioplegia delivery (n=4);
2. Retrograde cardioplegia delivery (n=2);
3. Antegrade cardioplegia delivery with temporary ligation of the proximal LAD followed by re-injection of cardioplegia after ligature removal (n=2);
4. Antegrade cardioplegia delivery with temporary ligation of the proximal LAD (n=2).

Videodensitometric Analysis

Distribution of cardioplegia delivery was analyzed by review of the recorded NIR fluorescent imaging sequences. NIR fluorescent density was determined in four reproducible regions of the heart: mid-anterior right ventricular free wall, mid-anterior left ventricular free wall, lateral left ventricular free wall, and posterior left ventricular free wall. Background-subtracted pixel-intensity was normalized for each imaging sequence by dividing each background-subtracted pixel-intensity by the maximum pixel intensity for that imaging sequence. Similar videodensitometric measurements were made of the short-axis cross sections at the epicardial, myocardial, and endocardial levels. A Student's t-test was used to compare regional NIR fluorescent cardioplegia density between control and ligation animals.

RESULTS

Real-Time NIR Fluorescence Imaging System

The NIR imaging system was able to unobtrusively provide real-time images to the surgeon during the entire procedure. Despite cardiac motion, real-time images of cardioplegia flow were easily obtained at high-resolution. While operating, the surgeon can view color video, NIR fluorescent, and pseudo-colored merged images of the operative field in real-time. This latter image is particularly useful to the surgeon because it permits visualization of cardioplegia flow against a background of normal regional cardiac and coronary anatomy. By using a nonanatomic color such as lime green (i.e., a pseudo-color) for this overlay, cardioplegia flow and any regions of inadequate myocardial protection can be clearly delineated. The imaging system's variable field of view allows zooming capability for more precise visualization of coronary anatomy if needed. The invisible nature of the light does not disturb the operative field. Finally, the entire imaging system is portable and easily maneuverable.

Quantification of Antegrade Cardioplegia

Tissue autofluorescence of the heart was negligible (Figure 1). Upon injection of 150 ml of cardioplegia solution in an antegrade fashion via the aortic root, immediate fluorescence of the coronary vessels was visible in real-time (Figure 1). Myocardial distribution of cardioplegia was evident within 5 seconds after injection, and by 8 seconds, homogenous fluorescence of

all surfaces of the heart was easily appreciated. Visual assessment alone confirmed homogenous cardioplegia distribution to the right and left ventricles.

Background-subtracted videodensitometric analysis demonstrates relatively homogenous distribution of cardioplegia throughout regions of the left ventricle (Figure 2A). Compared to the RV, only the lateral region of the LV demonstrates proportionately more fluorescence, suggesting more cardioplegia distribution to this portion of the heart. Quantitative analysis of ventricular cross sections shows that distribution of cardioplegia to the myocardium predominated distribution to the epicardium and endocardium (Figure 2B).

Quantification of Retrograde Cardioplegia

As in the previous animals, tissue autofluorescence of the heart was negligible. Following aortic cross-clamping, 300 ml of cardioplegia was infused via the transatrial coronary sinus catheter. Preliminary experiments demonstrated that a larger volume of cardioplegia was necessary to adequately visualize retrograde distribution. Fluorescence of the coronary veins followed by coronary arteries was immediately visible. By 15 seconds after injection, myocardial uptake was visible. Unlike the homogenous fluorescence seen with antegrade cardioplegia delivery, retrograde delivery resulted in a patchy heterogeneous fluorescence pattern indicating less efficient cardioplegia delivery (data not shown).

Acute Coronary Occlusion Imaging

Injection of 150 ml of cardioplegia solution in an antegrade fashion via the aortic root following temporary proximal ligation of the LAD resulted in an immediate flow defect throughout the LAD territory (Figure 3A). On-line background-subtracted videodensitometric analysis confirmed significantly less fluorescence in the LAD territory as compared with other regions of the heart (Figure 2B). Additionally, fluorescence in the LAD territory was significantly less in occluded than in control animals. During LAD occlusion, the right ventricle received relatively more cardioplegia flow as evidenced by increased fluorescence in this region (Figure 2B). When the temporary ligature was removed and 150 ml of cardioplegia was re-injected, NIR fluorescence imaging confirmed patency of the previously ligated vessel (Figure 3B). Regional myocardial fluorescence in the LAD territory demonstrated adequate delivery of cardioplegia to this previously unprotected area. Immediately explanted cross-sections of the hearts show homogenous re-perfusion of the LAD territory (Figure 3C). Since myocardial tissue fluorescence is cumulative and complete wash-out of ICG would require either injection of cardioplegia devoid of ICG contrast or cardiac reperfusion, the LAD territory is less fluorescent than other territories since it effectively received half the ICG concentration.

In a subgroup of animals, hearts with LAD ligations were immediately explanted following cardioplegia injection in order to determine if surface imaging defects correlated with cross-sectional defects. Cross-sectional analysis of these hearts demonstrated significantly less fluorescence in the LAD territory compared to control hearts (Figure 2B). Importantly, epicardial fluorescence in the occluded LAD territory was similar to myocardial and endocardial fluorescence. Thus, surface imaging of cardioplegia delivery correlated strongly with cross-sectional imaging.

DISCUSSION

Despite significant advancements in cardioplegia solutions and techniques, inadequate myocardial protection during cardiac surgery continues to be a potential source of intraoperative injury. Intraoperative myocardial protection has been identified as an important predictor of post-cardiopulmonary bypass ventricular recovery and function.¹⁴ Although overall morbidity and mortality rates for cardiac surgery are low, a growing number of patients

with advanced coronary artery disease are experiencing increasing rates of delayed postoperative ventricular recovery attributable to inadequate intraoperative myocardial protection.¹⁵ As such, recent efforts at improving outcomes in cardiac surgery have focused on optimizing cardioplegia delivery to high-risk patients in hopes of ameliorating postoperative low-output syndrome.

Presently, there is no reliable method for intraoperatively determining the distribution of cardioplegia infusion during cardiac surgery. The presence of asystole is an unreliable surrogate marker for global arrest and can exist despite large territories of poorly protected myocardium. Septal temperature measurements have also been used as markers for the adequacy of cardioplegia delivery. Yet, septal temperature is only a regional measurement and might not reflect a more distant area of poor myocardial protection.¹⁶ Myocardial tissue pH probes have recently shown promise for identifying regions of myocardial acidosis, a correlate of regional myocardial ischemia.¹⁷ Although the presence of regional myocardial acidosis has been clinically shown to predict postoperative outcomes¹⁴, the probe technology can be obtrusive to the surgeon and only allows for measurement of two regions of the heart - anterior and posterior. Finally, contrast echocardiography utilizing sonicated microbubbles has been used to image the distribution of injected cardioplegia, however, this method is highly operator dependent, lacks resolution, and requires probe contact with the patient.

In this study, we report a novel technique for real-time intraoperative visualization of cardioplegia distribution during simulated cardiac surgery. Our system takes advantage of the unique properties of NIR fluorescence imaging and provides the cardiac surgeon with precise, instantaneous, high-resolution visualization of cardioplegia distribution, and as such, overcomes many of the limitations of current techniques. Importantly, the system is not operator dependent or invasive; the entire imaging system is portable and does not obstruct the operative field. The NIR fluorescent contrast agent, ICG, is inexpensive, is already FDA-approved for other indications, and has an excellent safety profile. The system allows rapid assessment of the presence or absence of cardioplegia perfusion and provides for quantitative estimates of flow.

In this study, NIR fluorescence imaging of control animals rapidly confirmed homogenous distribution of cardioplegia to the right and left ventricles when antegrade delivery is used. Quantitative analysis demonstrated more fluorescence in regions of the left ventricle compared to the right ventricle, suggesting better cardioplegia distribution to the left ventricle. This finding has been corroborated in many other studies examining cardioplegia distribution in normal hearts.¹⁸ When a temporary ligature was placed on the LAD, NIR fluorescence imaging detected an immediate flow defect in the LAD territory, suggesting a lack of cardioplegia distribution to this region. Images of ventricular cross-sections in a subgroup of these animals confirmed a transmural flow defect. As expected during proximal LAD ligation, right ventricular distribution of cardioplegia flow actually increased compared to baseline. Imaging of retrograde cardioplegia demonstrated less uniform distribution of cardioplegia as compared to antegrade cardioplegia delivery. Malposition of the coronary sinus catheter and inadequate pressure of retrograde cardioplegia in our studies may have contributed to less than ideal visualization.

ICG is a non-toxic dye used for over 40 years in ophthalmologic angiography, liver function testing, and cardiac output measurement. It is a partially water-soluble dye excreted unchanged by the liver into bile. As such, it poses no risk of renal toxicity. Adverse reactions are rare; Carski, et al. reported only 4 adverse reactions in 24,000 administered doses.¹⁹ Our imaging system combined with the biodistribution and pharmacokinetics of ICG allow for repeated injections and imaging. Within 15 seconds following ICG injection, the vascular fluorescence signal rapidly declines while the myocardial signal remains for approximately 10 minutes.

Since the myocardial signal during this time is far less than the vascular signal peak, computerized background subtraction allows for repeated injections during this obligate period of myocardial signal wash-out.

A major limitation of the simple reflectance imaging system used in this study is its depth penetration and surface weighting. Although it can detect fluorescent lymph nodes through up to 1 cm of solid tissue²⁰ and 5 cm of lung tissue²¹ against a low autofluorescent background, the epicardium and outermost myocardium will contribute almost all of the measured signal after intravascular ICG injection. Clinically, this might lead to visualization of presumably adequate epicardial cardioplegia distribution in the presence of subendocardial or septal ischemia, regions which cannot be presently visualized with this technology. Recent advances in optical tomography suggest that depth penetration up to 4 cm may someday be possible.^{22,23} A second limitation of this method is its inability to measure the functional metabolic response to cardioplegia delivery; in essence, adequate flow of cardioplegia does not always correlate with protection from myocardial ischemia. Nevertheless, without the technology we describe in this study, there is no simple way to even assess cardioplegia distribution prior to cardiac arrest. Although our system does not directly assess functional myocardial protection, protection always does begin with adequate flow. As our data show, if a myocardial region does not exhibit epicardial evidence of cardioplegia delivery, there is likely poor protection in this region, which must be surgically addressed.

In addition to visualizing cardioplegia distribution, our NIR imaging system is capable of providing real-time intraoperative high-definition coronary angiography.¹⁰ This allows surgeons to precisely locate the areas of critical stenoses that were seen on preoperative catheterization images. Additionally, our imaging system can provide intraoperative graft patency confirmation similar to the SPYTM imaging system (Novadaq Technologies, Concord, ON, Canada).^{24,25} In a series of 100 patients, Balacumaraswami, et al. used intraoperative cardiac fluorescence imaging with ICG to evaluate graft patency and found 8 graft failures in 241 total grafts.²⁶ Such immediate intraoperative quality control is becoming increasingly important as coronary operations become more complex.

In summary, this study demonstrates the development of a novel, non-invasive, intraoperative technique using NIR fluorescence imaging that can easily and safely delineate and quantify relative regional cardioplegia distribution during cardiac surgery. This system can also provide optical coronary angiography¹⁰ and post-bypass graft patency evaluation without the attendant hazards of ionizing radiation.^{25,26} Such a system should allow surgeons to more readily identify regions of poor myocardial protection and guide interventions to ameliorate intraoperative myocardial injury in the hopes of improving patient outcomes.

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Figure 1. Kinetics of Antegrade Cardioplegia Delivery to the Porcine Heart during Cardiopulmonary Bypass

The autofluorescence of the heart is minimal (top row). Antegrade cardioplegia delivery can be visualized in real-time, with 1 sec (second row), 5 sec (third row), and 30 sec (posterior) images displayed. Shown are color video images (left), NIR fluorescence images (middle), and a merge of the two with NIR fluorescence pseudo-colored in lime green (right). All NIR fluorescence images have identical exposure times (67 msec) and normalizations.

A.

B.

Figure 2. Quantification of Cardioplegia Delivery by Surface and Cross-Sectional Imaging

NIR fluorescence signals were quantified from reflected surface images (A) and cross-sectional imaging (B) of the same heart. (RV = right ventricle; LV Ant = anterior left ventricle; LV Lat = lateral left ventricle; LV Post = posterior left ventricle; Epi = epicardial; Myo = myocardial; Endo = endocardial). * indicates $p < 0.05$.

A.

B.

C.

Figure 3. Inadequate Cardioplegia Delivery to the Porcine Heart during Cardiopulmonary Bypass and Corrective Action

- A. Antegrade cardioplegia delivery after clamping of the LAD instantly reveals a large wedge-shaped defect.
- B. Correction of the defect in (A) can also be visualized in real-time. Shown are color video images (left), NIR fluorescence images (middle), and a merge of the two with NIR fluorescence pseudo-colored in lime green (right).
- C. Cross-sectional analysis from base (left) to apex (right) of the heart from (B). All NIR fluorescence images have identical exposure times (67 msec) and normalizations.