Introduction

Aorto-coronary bypass grafting, including the left internal mammary artery, is a widely established treatment for ischemic heart disease. Overall myocardial ischemia after aorto-coronary bypass surgery could be evaluated by exercise electrocardiography, dobutamine stress echocardiography, and thallium scintigraphy. However, these methods cannot evaluate the bypass territory independently.

Myocardial contrast echocardiography (MCE) using intracoronary injection of microbubbles provides new data, such as the no re-flow phenomenon or the distribution of collateral perfusion [1-5]. Also, Spotnitz et al. reported that MCE had a potential value for assessing the adequacy of coronary artery bypass grafting [6]. In their study, the contrast agent was injected directly into the aortic root during bypass surgery. In this sense, MCE for evaluating bypass graft was limited either in the operating room or the catheterization room.

Intravenous MCE is a new method for assessing myocardial perfusion without coronary catheterization. A combination of the intermittent and second harmonic modes improves the quality of myocardial perfusion images [7-9], and intravenous MCE is an acceptable procedure for clinical use [10-12]. In many experimental studies, pharmacological stress testing has been shown to be useful for detecting coronary artery stenosis [13-15]. However, there have been few reports about intravenous MCE after coronary bypass. It

Delayed Opacification of the Coronary Bypass Region Detected by Intravenous Myocardial Contrast Echocardiography*

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Abstract
Objective: To examine the efficacy of the intravenous myocardial contrast echocardiography (MCE) for detection of the territory of the coronary bypass graft.

Methods: The subjects were 5 beagles having a bypass tube between the left circumflex and carotid artery. MCE was performed with bolus injection of Optison during short axis view recording using harmonic and ECG-triggered modes of every two cardiac cycles. Time video-intensity curve was obtained at the lateral (perfused by the bypass) and the septal wall (perfused by the native coronary artery). Their peak intensities and time interval between these two peaks were measured. Selective MCE into the bypass tube was performed to confirm the territory of the bypass. Flow volume of the bypass was also measured.

Results: The bypass area was clearly recognized by delayed opacification in comparison with the native coronary artery’s area. Time lag of opacification between the two areas showed a good hyperbolic correlation with bypass flow, and was almost identical to the theoretically calculated time lag (r=0.889, p<0.0001).

Conclusion: Both the area and flow volume of coronary bypass were diagnosed by using intravenous MCE.

Key words: Coronary circulation, Hypertension, Ultrasound

Abbreviations list: MCE: Myocardial contrast echocardiography, PI: Peak intensity, LCx: The left circumflex coronary artery, LAD: the left anterior descending coronary artery

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should be beneficial if the area of territory of bypass can be demonstrated by intravenous MCE. We speculated that the time of peak intensity should be delayed in the area of bypass in MCE.

Methods

Animal Preparation

Five healthy beagles weighing 9.8 to 11 kg (mean ± SD, 10.5 ± 0.6 kg) were used to assess myocardial contrast echocardiography. This study was approved by the Osaka University medical school animal care and use committee, and was performed in compliance with the Osaka University medical school guidelines for the care and use of laboratory animals. Dogs were anesthetized with an intravenous bolus of pentobarbital sodium (35 mg/kg) for initial induction, and then infusion of the drug (6 to 8 mg/kg per hour) was continued during the experiment. They were intubated and ventilated with a Harvard-type respirator (Model SN-480-3, Shinano, Tokyo), supplementing room air. Left-sided thoracotomy was performed in the 5th intercostal space, and the heart was suspended in a pericardial cradle.

The left circumflex coronary (LCx) and left common carotid arteries were exposed and carotid-to-LCx bypass (simulating left internal mammary artery bypass) was done using a thin tube, as described previously [16]. The tube length was 42 cm and its net volume was 2 ml. The proximal portion of the LCx was completely ligated. Both flow volume of the bypass tube and that of the left anterior descending coronary artery (LAD) were measured with ultrasonic transducers (2 SB 1212 probe & T106 blood flowmeter, Transonic Systems Inc. NY, USA).

Myocardial Contrast Echocardiography

Myocardial contrast echocardiography was performed using a Power Vision 6000 echo-Doppler system (Toshiba, Tokyo, Japan). The transducer was placed on the heart wall via an acoustic interface with a width of 1 cm (Sonar-AID. Geistlich-Pharma. Switzerland) [17]. The position of the transducer was fixed with a clamp to obtain a stable short axis view. The second harmonic mode (transmission at 1.8 MHz and receiving at 3.6 MHz) was used and the mechanical index was set at 1.4. The overall gain settings and image depth were optimized and the focus was set at the center of the left ventricular cavity at the beginning of each experiment, and then were kept constant throughout the experiment. Optison (Molecular Biosystems, Inc., San Diego, USA) (0.1 ml) was given as a bolus followed by 3 to 5 ml of saline (1 ml/sec) via a forearm vein. Intermittent imaging triggered at end-systole after every 2 cardiac cycles was used to obtain myocardial perfusion images. All images were recorded on videotape with a high-fidelity S-VHS recorder.

Fig. 1. A representative case of two serial video intensity curves (raw data). Closed circles shows serial video intensities of the area supplied by the native LAD and open circles shows serial video intensities of LCx area supplied by coronary bypass. (Peak 1: PI at LAD area, Peak 2: PI at LCx area)
MCE images were analyzed using a special computer for image analysis (Color Cardiology Workstation, Tom-Tec, USA), as described previously [2]. The region of interest was set as follows: one region was the septal myocardium perfused by the left anterior descending coronary artery (LAD: native coronary artery), and the other was the lateral myocardium perfused by the bypass tube. The baseline subtracted video intensity of the myocardium in the two regions was measured at every triggered frame and the time video intensity curve was obtained in each region (Figure 1).

**Time to peak of myocardial opacification via the bypass**

As shown in the results, a peak of intensity curve in the lateral wall was later than that in the septum, and the time lag between the two peaks was measured from the curve (Figure 1). The blood via a coronary bypass takes a roundabout route to the perfusion bed. As the proximal portion of the bypass is placed just above the aortic valve, flow time from the aortic valve to the entrance of the bypass can be neglected. The time for passage through the bypass tube is calculated as a quotient in which the net volume of the tube is divided by the flow volume through the tube (Appendix). The tube used in this experiment was equivalent, the net volume of which was 2 ml. Transit time (in seconds) for the tube was calculated as \(2 \times 60 / \text{bypass flow volume}\), when the flow volume is expressed as volume per minute (60 seconds). Time lag between two peaks of intensity of the lateral and septal walls was examined at various bypass flow volumes ranging from 9 to 62 ml/min by controlling the systemic blood pressure with noradrenalin infusion.

**Statistical Analysis**

Data were expressed as the mean ± SD. Linear regression analysis was done by the least squares method and \(p<0.05\) (two-tailed) was considered statistically significant for all comparisons. The bias was expressed as the mean difference between measured time lag and calculated time lag which were compared with the corresponding averages.

**Results**

**Detection of the Bypass Territory**

Soon after left ventricular opacification, only the LAD territory was opacified, but the bypass territory was not (Figure 2). After several seconds, the bypass territory was opacified, followed by the identical opacification of both wall segments. Thus, the bypass territory was identified as a negative opacified area during the early phase of myocardial opacification. In order to confirm the area of bypass territory, Optison was injected into the bypass tube directly at the end of

![Fig. 2.](image_url)
The perfusion defect areas and % defect ratio of MCE image during LCX occlusion were 4.12±0.69 cm² and 38.5±3.8 % in 5 dogs. The perfusion areas and % ratio of LCX, which were determined by the direct injection of Optison from the carotid-to-LCX bypass, were 4.65±0.85 cm² and 39.3±4.1 %. There was a good relationship between the both areas measured by those two methods (r=0.887, p<0.05). The maximum difference of % area ratio between those two methods was only 2.9%.

**Bypass Flow Volume and Time Lag**

The bypass flow ranged from 9 to 62 (27.4 ± 13.6) ml/min and LAD flow ranged from 12 to 98 ml/min. There was a good correlation between bypass flow and LAD flow (r=0.896, p<0.001). The mean systemic blood pressure ranged from 41 to 206 (96 ± 48) mmHg and the heart rate ranged from 146 to 213 (170 ± 18) beats/min. In any situation of bypass flow, time of PI in the LCx bed was later than that of PI in the LAD bed (Figure 1). The time lag between these two peaks was related to the bypass flow volume (Figure 3). The scatter plots were almost aligned on the regression line, which was calculated as time lag = 120 / bypass flow volume. There was a good linear correlation between the measured and calculated time lag (y= 0.76x – 1.8, r=0.889, p<0.001) showing a small bias (Figure 4). It was expected that the measured time was slightly longer than calculated time, because the calculated time only allowed for the bypass tube.

**PI of Bypass Territory and Bypass Flow Volume**

Peak video intensity of bypass area increased with the flow volume of bypass below 30 ml/minute of flow volume, but plateaued above 30 ml/minute of flow volume. This relation was fitted to the exponential curve: y=71.7(1-e^{-0.07x}) (Figure 5).

**Discussion**

New techniques of echocardiography for the evaluation of coronary heart disease have developed rapidly.
and application to coronary bypass grafting has been proven. Hozumi et al. succeeded in evaluating the flow reserve of internal mammary bypass grafts using transthoracic Doppler echocardiography [18]. Akasaka et al. also assessed the function and flow reserve of internal mammary bypass grafts using the Doppler flow-wire method [19]. Regarding evaluation of the bypass territory, Spotnitz et al. reported the potential for intraoperative assessment of the adequacy of coronary artery bypass grafting using MCE with intra-aortic injection [6]. However, this is the first report to investigate the usefulness of intravenous MCE for the assessment of coronary artery bypass grafting.

Detection of the Bypass Territory

In a case with regional wall motion abnormality after aorto-coronary bypass surgery, it is very important to determine whether the related coronary artery is the native artery or the bypass graft. Selective angiography reveals stenosis of the bypass graft, but not the perfusion territory. MCE, on the other hand, can reveal the bypass territory by selective contrast echocardiography performed during open-heart surgery, as was done by Spotnitz et al. [6], or by selective contrast injection via a catheter. Radioisotope methods indicate the ischemic area but cannot identify the bypass territory. Intravenous MCE could correctly and easily distinguish the bypass territory by showing delayed opacification of the bypass territory without any need of a selective catheterization procedure.

Time delay depending on the bypass flow volume

The territory of the bypass graft was not opacified until after the territory of the LAD. It is conceivable that delayed opacification of the lateral wall was caused by a roundabout pathway via carotid-coronary bypass. The time of delayed opacification could be calculated from the flow volume of the bypass tube, because the net volume of the tube was determined. Actual and calculated time of delayed opacification was almost simultaneous, although the actual time was slightly longer than the calculated time. The excess time should be required for blood flow from the aortic valve to the ostium of the bypass, which could be ignored because the orifice of bypass was placed just above the aortic valve. Nevertheless, it should be noted that the time of delayed opacification was inversely correlated with the bypass flow volume. Intravenous MCE has the potential to be used for the assessment of blood flow volume after coronary artery bypass grafting.

Peak Video Intensity and Flow Volume

PI of the bypass territory related roughly with the bypass flow volume. Even in a case with low bypass flow volume, PI was over 20, high enough to identify its opacification visually. On the other hand, PI was saturated when the flow volume exceeded about 30 ml/minute. Wei et al. reported that the video intensity from microbubbles flowing along the coronary microcirculation depended on the pulse interval and reached plateau, when the flow volume was constant [15]. Inversely, video intensity depends on the flow volume until the plateau, when the pulse interval is constant, which was shown in our experiment.

Study Limitations

In this model, the native LCx was totally occluded and the LCx territory was completely perfused by the aorto-coronary bypass. On the other hand, in clinical cases of aorto-coronary bypass grafting, the native coronary artery is not always totally occluded. We did not have any data about such cases. We speculate that the time-intensity curve at the double supplied area by both native and bypass vessels may make two peaks, one is composed by the native artery and the other is by the bypass graft. The shape of the time intensity curve should depend on the predominance of either vessel. We suppose that the native coronary artery
may be patient if the time delay is not definite. If delayed opacification becomes definite during follow-up of such patience, it can be diagnosed that the native coronary artery has become occluded. Naturally, it is definite that the bypass graft has been occluded, when the area is not opacified.

MCE was examined at various levels of bypass flow volume by infusion of noradrenaline in this study. We did not examine the influence of accelerated contractility by noradrenaline, which should affect the coronary circulation. However, the influence on the myocardial perfusion by infusion of catecholamine should be equivalent between beds supplied by the native coronary artery and that by the bypass graft. This consideration was supported by a good correlation between the LAD flow and bypass flow irrespective of noradrenaline administration.

Another limitation using this method was to evaluate the stenosis of bypass graft directly. However, it might be possible to presume the stenosis of bypass graft during some stress tests. In addition, it would be very difficult to determine the graft volume in the clinical setting. However, it might be still useful to follow up the graft function through serial assessments.

**Clinical Implications**

Clinically, there are several methods to diagnose myocardial ischemia in a patient with coronary bypass graft. However, even if myocardial ischemia has been diagnosed, it should be useful to recognize the exact area perfused by a coronary bypass graft. Intravenous MCE is a useful tool for identification of that area. Moreover, this technique can be applied to any patients even in an outpatient clinic.

Change of the aorto-coronary bypass flow volume can be evaluated by measuring the time lag, even if the exact net volume of the graft is not determined. This may be a clue for evaluating the changes of flow during pharmacological stress testing using dipyridamole or adenosine.

**References**


**Appendix**

**Formula of the calculated time lag (seconds)**

Calculated Time Lag = Time from aortic valve to proximal bypass + Time from proximal to distal bypass

(Time from aortic valve to proximal bypass can be neglected because it is too short.)

= Time from proximal to distal bypass

= Bypass volume (mL) x 60 seconds / Bypass flow (mL/minute) Bypass volume = 2ml

= 120 / Bypass flow (seconds)