Coronary Tree Assessed With Contrast Harmonic Imaging

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Abstract

**Background.** There have only been a few studies that visualized the human coronary tree continuously from coronary arteries to capillaries in the clinical setting. The purpose of this study was to visualize the human coronary tree non-invasively with myocardial contrast echocardiography (MCE) by changing frame rates.

**Methods.** MCE was performed intravenously using \(^{15} \text{Levovist.}\) Study population consisted of 20 patients with ischemic heart disease. We performed 3 kinds of MCE: intermittent, semi-real, and real-time harmonic imaging.

**Results.** 1. Myocardial blood flow velocity and volume were obtained from the time-intensity replenishment curve with intermittent imaging. Curve fitting was possible in 75% of the targeted region of interest. 2. Semi-real-time perfusion image was obtained with a frame rate of 5/sec. We observed a cyclic variation of echo-intensity in one cardiac cycle in only viable region (Peak subtracted signal intensity: 53±29 in end-diastole and 33±27 in end-systole, p<0.05). This phenomenon may result from the compression of arterioles according to cardiac beat. 3. Real-time perfusion image was obtained at a rate of 26 frames/sec. We observed line-form small artery flows in 80 % of the viable area.

**Conclusions.** Thus, coronary tree following major epicardial coronary arteries was visualized non-invasively from the small artery to the capillary bed with 3-staged intravenous-MCE in the clinical setting.

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**Key words:** Coronary tree, Intermittent imaging, Myocardial contrast echocardiography, Real time imaging
Methods

Study population consisted of 20 patients with ischemic heart disease. Mean age was 63 years (35 – 82). Five patients were female. All patients gave informed consent for all MCE procedures.

Levovist (Schering), a suspension of monosaccharide (galactose) microparticles in sterile water, was used as the ultrasound contrast agent in this study and was administered as either a continuous infusion or slow bolus injection. For the intermittent imaging, continuous infusion was performed at a concentration of 125 mg/ml and speed of 5 ml/min using an infusion pump. Slow bolus injection was performed at a concentration of 250 mg/ml and a speed of 0.5 ml/sec in the semi-real-time and real-time imaging.

Sonos 5500 (Philips) was used as the echo equipment for this study with T3S3 transducer. All imaging were performed using Ultra harmonic (Philips), in which ultrasound was transmitted at 1.3 MHz and received at 3.6 MHz. The mechanical index was set at high ranging from 1.4 to 1.6. Three kinds of frame rate dependent MCE were performed: intermittent imaging by low frame rate, semi-real-time imaging by intermediate frame rate, and real-time imaging by high frame rate. The identification of the infarct region was performed with 2D echocardiography. We defined the infarct region as that showing more severe asynergy than hypokinesis.

Blood flow is visualized because microbubbles in the contrast agent are of strong echo origin in the blood. Ultrasonic transmission destructs microbubbles. Transmission with higher frame rate destructs more bubbles. Therefore, higher frame rate imaging visualizes only faster blood flow due to the destruction of almost all microbubbles in the slower blood flow. Thus circulation of the coronary tree can be visualized at several different levels by changing frame rate.

1. Evaluation with intermittent perfusion imaging

Intermittent MCE was designed to reduce the destruction of microbubbles using a low frame rate and to visualize slow capillary circulation. MCE was performed by changing the pulsing interval from 1:1 to 1:8 in end-systole. Peak background-subtracted contrast intensity of myocardium versus pulsing interval plots were fitted to an exponential function: $y = A \left(1 - \exp^{-\beta t}\right)$, where $A$ is the plateau contrast intensity reflecting the myocardial blood volume, and $\beta$ reflects the rate of raise of contrast intensity and, hence, blood flow velocity [6]. We measured $A$ and $\beta$ in the normal segments from the time-intensity replenishment curve using an on-line image analyzer.

2. Evaluation with semi-real-time imaging

This MCE was designed using the intermediate frame rate of 5 frames per second (fps) to visualize pre-capillary circulation including arterioles that have more rapid flow than capillary. Peak background-subtracted contrast intensity of myocardium was obtained in both end-systole and end-diastole at 55 normal and 11 infarcted segments. Frames acquired over 3 entire cardiac cycles were transferred to an on-line image analyzer. A region of interest (ROI) was placed over the mid myocardium of normal and infarcted segments. Pre-contrast intensity obtained from end-systolic and end-diastolic frames before microbubble administration were subtracted from their respective contrast-enhanced values.

3. Evaluation with real-time imaging

Using a high frame rate of 26 fps, this MCE was designed to visualize intramyocardial small arteries that have more rapid flow and to destruct more microbubbles within slow flow such as capillary or pre-capillary circulation. It was evaluated that real-time MCE could detect intramyocardial arterial flow in normal segments.

Results

1. Assessment with intermittent perfusion imaging

Curve fitting was possible in 15 of 20 (75%) ROIs for the equation of $y = A \left(1 - \exp^{-\beta t}\right)$ in the time-intensity replenishment curve (Fig. 1). Value $A$ was measured to be $5.3 \pm 3.8$ AU, and the rate constant $\beta$ was measured to be $1.0 \pm 1.0$ in the normal 15 segments expressed by mean $\pm$ SD, respectively. Capillary circulation was assessed with myocardial perfusion image obtained with low frame rate.

2. Assessment with semi-real-time perfusion imaging

Myocardial opacification was good in the normal segment and poor in the infarcted segment. Therefore, it was possible to differentiate the infarcted region from the normal region with MCE by intermediate frame rate. Moreover, we observed phasic changes of echo-intensity in one cardiac cycle in viable myocardium (peak background-subtracted signal intensity: $53 \pm 29$ in end-diastole and $33 \pm 27$ in end-systole, $p<0.05$) (Fig. 2). Echo intensity that increased in diastole and decreased in systole might reflect the pha-
Phasic changes of pre-capillary circulation. Phasic changes were less prominent in the infarcted region than in the normal region (Fig. 3). Pre-capillary circulation was assessed with myocardial perfusion image obtained with intermediate frame rate.

3. Assessment with real-time vascular imaging

We observed intramyocardial line-form small artery flows in high frame B-mode images in 80% of the viable myocardium (Fig. 4). The linear structures traversing the myocardium represent the intramyocardial small arteries that have a velocity high enough to fill in 40 ms. It was possible to assess intramyocardial arterial flow with pulse Doppler technique in 25% of those small arteries. Small artery flow was assessed with...
Discussion

1. The flow that can be assessable with low frame rate MCE

Myocardial blood flow can be quantified with MCE during a venous infusion of microbubbles. In high mechanical index ultrasonography, signal intensity has a strong linear correlation with the concentration of the ultrasound contrast agent under conditions of constant applied acoustic pressure. Therefore, we can assess coronary circulation with contrast signal intensity [7-9]. Destruction of microbubbles and measurement of their reappearance rate within the myocardium during a continuous infusion provide an estimation of mean myocardial microbubble velocity. Similarly, the plateau contrast intensity at long pulsing interval reflects myocardial blood volume. Knowing both the mean myocardial microbubble velocity and the myocardial blood volume can then provide a measure of mean blood flow. Excellent correlations were found between flow and $\beta$, as well as flow and the product of $A$ and $\beta$ [6].

Because 90% of myocardial blood volume resides in capillaries [10,11], contrast intensity at a pulsing interval of more than 5 seconds mostly represents capillary blood volume that does not change between end diastole and end systole when cardiac function and coronary blood flow are normal [12].

However, the correlation between flow and $\beta$ is influenced by several examination variables, including depth, angle, and instrument settings [13, 14]. Therefore, MCE refilling measures are best applied by comparing baseline values with those of stress studies [15].

Thus, myocardial image with low frame rate could assess capillary circulation.

2. The flow that can be assessable with intermediate frame rate MCE

Microbubbles fill only arterioles before being destroyed by the next ultrasound pulse because the interval between frames during semi-real-time imaging is only 250msec. Thus, myocardial perfusion image obtained with intermediate frame rate visualized pre-capillary circulation including arterioles.

Full-motion MCE utilizing an intravenous fluorocarbon-based agent and pulse inversion power Doppler techniques identifies stunned myocardium and accurately predicts recovery of segmental left ventricular function in patients with recent myocardial infarction [16,17]. In our study, myocardial opacification decreased significantly in the infarcted segment than in the normal segment which means there was damage to not only capillary circulation but also pre-capillary circulation including arterioles.

Phasic changes in intramyocardial arteriolar dimensions have been documented during cardiac contrac-

Fig. 4. Visualization of intramyocardial small artery with real time imaging

This is a MCE image of a patient with anterior myocardial infarction in the chronic stage. Intramyocardial line-form flows were observed in high frame B-mode images in viable myocardium (arrow in the middle panel). The linear structures traversing the myocardium represent the intramyocardial small arteries that disappear in the systolic phase.
This phenomenon may result from the compression of arterioles according to cardiac beat [19, 20]. However, there is controversy regarding changes in capillary dimensions during this period [21-24]. Changes in intramyocardial pressures during the cardiac cycle could potentially affect phasic changes in myocardial contrast intensity because microbubbles are sensitive to ambient pressure [25]. Wei et al [12] showed that phasic changes in myocardial contrast intensity with continuous MCE using high mechanical index allow the detection and quantification of coronary stenosis at rest without need for pharmacological or exercise stress. Thus, the measurement of phasic changes in contrast intensity has the potential to detect myocardial ischemia or myocardial viability.

3. The flow that can be assessable with high frame rate MCE

Microbubbles within the myocardium are destroyed by pulses of ultrasound at a sampling rate of 26Hz with real-time imaging using high mechanical index [12]. Any myocardial opacification could occur only from partial or complete filling of vessels whose velocity would allow significant replenishment at 40ms. In this manner, there is no backscatter from capillaries and arterioles. Therefore, only vessels with a high enough velocity could be detected at the high sampling rate used.

Doppler technique would be able to assess intramyocardial small artery flow under real-time MCE. Thus, real-time MCE has potential to widen Doppler approach for intramyocardial small artery flow.

4. Each phase of coronary tree

We have defined a novel method for visualizing the coronary tree that is based on the bubble destruction by ultrasound.

1. Perfusion image obtained with intermittent MCE using low frame rate visualizes capillary flow of speeds less than 1 mm/sec and does not show phasic change of contrast.

2. Pre-perfusion image obtained with semi-real-time MCE using intermediate frame rate visualizes precapillary circulation including arterioles and shows phasic change of echo intensity depending on cardiac cycle.

3. Vascular image obtained with real-time MCE using high frame rate visualizes intramyocardial small artery flow of speeds more than 10-20 cm/sec.

MCE with different frame rates provides several information about the different levels of the coronary tree using a venous administration of microbubbles that is likely to be a feasible clinical technique. This novel method gives us a new possibility about the identification of myocardial infarction. Namely, we can assess the infarcted region from the view of not only perfusion but also vasculature damage of precapillary using 3 kinds of MCE in the clinical setting.

At present, epicardial coronary arteries can be assessable with transthoracic Doppler technique.

![Visualization of Coronary Tree](image)
Coronary tree following major epicardial coronary arteries will be visualized from the small artery to the capillary bed with 3-stage intravenous-MCE (Fig.5).

5. Limitation

A large dose of ultrasound contrast agent needs to be injected to be able to detect small arterial flow. This amount of microbubbles caused significant far-field shadowing that makes assessment of the posterior wall impossible. Therefore, we could not assess myocardial perfusion with short axis view or parasternal view in MCE. The sensitivity of harmonic imaging has to improve in order to obtain the same information from a continuous infusion of a small dose of microbubbles without producing far-field attenuation [12]. Imaging at higher harmonics improves sensitivity because the tissue signal is less and it is easier to filter the second harmonics. Therefore, we used ™Ultra harmonic imaging technique in this study, but we could not completely neglect far-field shadowing. Recently, several advanced harmonic imagings that use high or sub-harmonics have emerged as new harmonic technologies. These new imaging technologies will overcome a problem of far-field attenuation and bring us marked improvement of signal to noise ratio [26]. In this study, we did not measure direct blood velocity of capillary, arteriole and small artery using Doppler signal. Therefore we do not have clear proof that our findings indicate coronary tree circulation.

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