

Quantitative Analysis of Myocardial Perfusion and Regional Left Ventricular Function from Contrast-Enhanced Power Modulation Images

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Abstract

Our goal was to test the feasibility of using power modulation, a new echocardiographic imaging technique, for combined quantitative assessment of myocardial perfusion and regional LV function. Coronary balloon occlusions were performed in 18 anesthetized pigs. Images were obtained during iv contrast infusion at baseline, during coronary occlusion and reperfusion, and analyzed using custom software. At each phase, regional myocardial perfusion was assessed by calculating mean pixel intensity and the rate of contrast replenishment following high-power ultrasound impulses. LV function was assessed by calculating regional fractional area change. All ischemic episodes caused detectable and reversible changes in perfusion and function. Perfusion defects were visualized in real time and confirmed by a significant decrease in pixel intensity in the LAD territory following balloon inflation and reduced rate of contrast replenishment. Fractional area change significantly decreased in ischemic segments, and was restored with reperfusion. Power modulation allows simultaneous on-line assessment of myocardial perfusion and regional LV wall motion.

1. Introduction

Although the use of ultrasound contrast media to assess myocardial perfusion has been long under investigation [1-5], their mainstream implementation remains LV opacification for improved endocardial visualization [6]. Quantification or even imaging of myocardial perfusion remains a goal for future research [2;4;7], and the assessment of LV function with contrast remains subjective, since no established technique for endocardial border detection is applicable to contrast-enhanced images. We hypothesized that power modulation would allow real-time visualization of perfusion defects and automated border detection. Our goal was to test the feasibility of combined assessment of myocardial perfusion and regional LV function in an animal model of acute ischemia.

2. Methods

2.1. Power modulation imaging

The basic assumption underlying power modulation imaging (PMI) is that, unlike microbubbles, the reflective properties of cardiac structures are mostly linear. Power modulation uses this assumption by transmitting repeated pulses of different intensities in the same direction and analysing the reflections in a way that uses the differences in acoustic properties to selectively enhance microbubble-generated reflections, while suppressing reflections from cardiac structures and tissues.

2.2. Animal preparation

Experiments were carried out in 18 male farm pigs (20-30kg). Animals were pre-treated with telazol (2.2mg/kg, i.m.) and atropine sulfate (0.05mg/kg, i.m.), mechanically ventilated and anesthetized with isoflurane (0.5-2.5%). Electrocardiogram, body temperature, blood pressure and expiratory gases were monitored (Datex). Lidocaine was administered (1mg/kg, i.v. bolus + 4mg/kg/hr infusion) to prevent ventricular arrhythmias. An intracoronary balloon catheter (2.5-3.5 mm balloon diameter) was introduced via the right femoral artery into the LAD coronary artery under fluoroscopic guidance. The balloon was positioned near the origin of the artery to maximize the perfusion territory affected by balloon inflations.

2.3. Imaging

Transthoracic images were obtained using a S3 transducer (SONOS 5500, Agilent). Parasternal short-axis views were obtained at the level of the papillary muscles. Power modulation was activated at mechanical indices of 0.1-0.2, gain 65-75, pulse repetition frequency 3.7, and low line density. Contrast enhancement was achieved using intravenous infusion of Definity (DuPont). Infusion rates were optimized for dense opacification of the LV cavity without attenuation, and with clearly visualized intramyocardial contrast.

2.4. Protocol

To track ischemic changes in myocardial perfusion, PMI images triggered every end-systole were acquired over 60sec, including 15sec baseline, 30sec complete coronary occlusion, and 15sec reperfusion. During each phase, a high-energy ultrasound pulse (mechanical index 1.7) was transmitted to image contrast destruction and subsequent replenishment (figure 1). To quantify changes in regional wall motion, images were acquired continuously over three cardiac cycles under control conditions, 30sec after coronary occlusion, and again after balloon deflation.

2.5. Image analysis

Images were analyzed using custom-designed software. Initially, six myocardial regions of interest were manually drawn. In each region, mean pixel intensity was measured frame-by-frame. The position of each region was adjusted when necessary to compensate for translation, and mean pixel intensity was plotted over time. To represent regional pixel intensity at a steady state during baseline, ischemia and reperfusion phases, 6 consecutive heartbeats were averaged, starting 5 beats following each high-energy pulse. The slope of the linear regression of the first 5 beats after each pulse was used as an index of contrast replenishment rate.

To evaluate regional LV function, the endocardial border was first detected frame-by-frame by thresholding PMI intensity. A binary image was created using a depth-dependent threshold and further processed using standard morphological operators to extract the LV cavity. The LV was then divided into six 60° sectors, corresponding to the regions of interest used to assess perfusion. For each segment, cavity area was measured frame-by-frame during each experimental phase, expressed in percent of regional end-diastolic area and plotted over time, and regional fractional area change was calculated (figure 2).

3. Results

High-energy pulses resulted in a saturated image and in destruction of microbubble reflective properties, which were then gradually restored to baseline level (figure 1). In all animals, the loss of pixel intensity in the LAD territory during coronary occlusion was followed by an increase during reperfusion (figure 3). No concurrent changes were noted outside the LAD territory.

PMI intensity measured in the myocardium followed similar patterns in all animals (figure 4, left). The three sharp peaks in each curve reflect the high-energy pulses that caused image saturation. The intensity drop following each peak reflects the loss of microbubble reflectivity.



Figure 1. Contrast-enhanced PMI images obtained in a pig. A high-energy ultrasound pulse destroyed the reflective properties of the contrast agent that are then gradually restored as microbubbles re-enter the imaging plane.

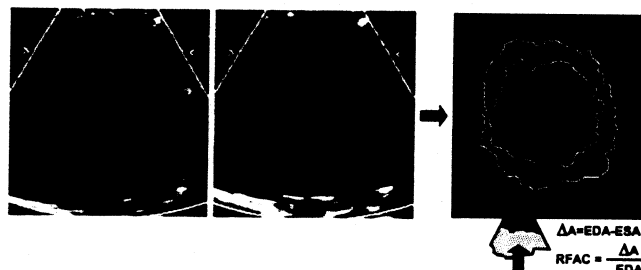


Figure 2. End-diastolic and end-systolic images with the extracted endocardial borders superimposed. The origin of segmentation is the centroid of the LV cavity at end-diastole, shown in the right panel with the end-systolic and end-diastolic borders and the segmentation scheme, which was used for analysis of endocardial motion.

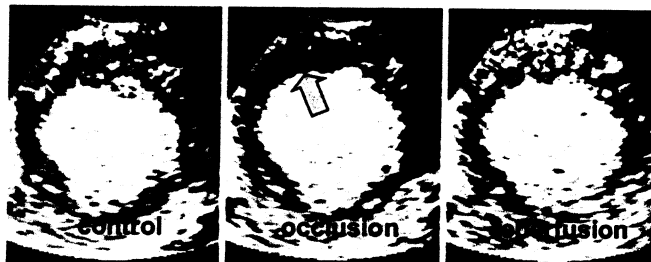


Figure 3. Intracoronary balloon inflation caused a loss of contrast enhancement in the anterior and anteroseptal walls (arrow), which was reversed during reperfusion.

Contrast replenishment rate is reflected by the slope of intensity increase following the pulse. Balloon inflation caused a gradual decrease in pixel intensity in the LAD territory, reflecting lack of blood flow, where little or no replenishment was noted following the second pulse. Balloon deflation resulted in rapid contrast replenishment, confirming the reversal of the perfusion defect. The third pulse demonstrated rapid contrast replenishment consistent with reperfusion. In contrast, inferior, posterior and lateral segments were not affected by coronary occlusion.

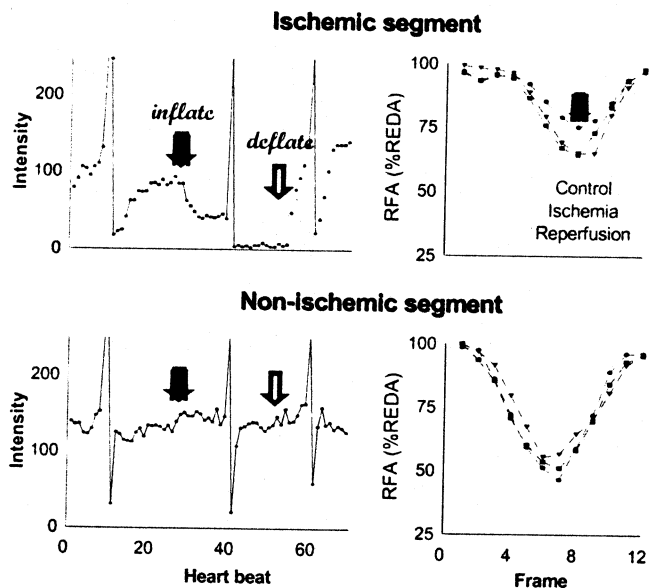


Figure 4. Perfusion (left) and function (right) data obtained in an ischemic (top) and a non-ischemic (bottom) myocardial region. In the ischemic region only, pixel intensity dropped after intracoronary balloon inflation and no contrast replenishment was noted after a high-energy pulse until balloon deflation (left, top). Regional fractional area (RFA) time curve flattened as a result of coronary occlusion in the ischemic region (right, arrow).

occlusion and reperfusion are shown in figure 4 (right). In the LAD-related segments, coronary occlusion resulted in an increase in end-systolic fractional area with a consequent decrease in fractional area changes. These indices were restored during reperfusion.

Figure 5 presents the summary of control-normalized perfusion and function indices obtained from all animals at the different experimental phases. Both perfusion indices, i.e. pixel intensity and contrast replenishment rate decreased significantly as a result of coronary occlusion in the anterior and anteroseptal segments, while other segments showed no significant changes. Reperfusion caused an increase in these indices to levels higher than the corresponding controls in all segments. These ischemic changes in perfusion coincided with a significant decrease in regional fractional area change in the anterior and anteroseptal regions with no significant evidence of hyperdynamic motion during reperfusion.

4. Discussion

Although echocardiography is one of the major noninvasive tools used in the diagnosis of coronary artery disease, the detection of wall motion abnormalities is based on subjective visual interpretation [8]. The sensitivity of this methodology is limited since even severe stenosis may not cause a wall motion abnormality at rest. Accordingly, there is a strong need for techniques capable of extracting more information from ultrasound images that may provide additional insights into myocardial physiology.

It is widely accepted that the ability to assess myocardial perfusion would be diagnostically invaluable. Contrast echocardiography is increasingly referred to as a technique that could allow quantification [2-4] or at least imaging of myocardial perfusion [1;5]. However, this goal still remains a great challenge. Although LV opacification for improved endocardial visualization is better established than perfusion imaging, it is qualitative because there is no technique to automatically detect the endocardial border from contrast-enhanced images. Our goal was to test the feasibility of using PMI for combined quantitative assessment of regional myocardial perfusion and LV function [9].

Contrast-enhanced PMI images may be prone to artifacts, including false positive perfusion defects [10]. Therefore, a clear connection had to be established between ischemia and regional changes in PMI images, presumably reflecting abnormal perfusion. We used a pig model, where regional myocardial perfusion and LV function were assessed during acute myocardial ischemia. To minimize the effects of changes in gain settings and/or imaging plane, all perfusion data were obtained in a single image sequence

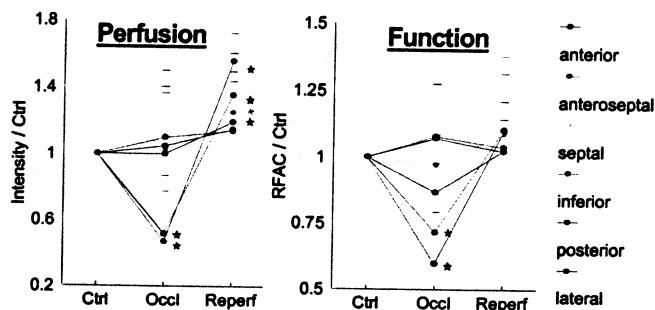


Figure 5. Control-normalized indices of myocardial perfusion and regional LV function measured under control conditions (Ctrl), during LAD occlusion (Occl) and reperfusion (Reperf).

In all animals, coronary occlusions resulted in visible wall motion abnormalities in the LAD territory, which were reversed during reperfusion. Endocardial border detection worked accurately throughout the cardiac cycle in 11/13 animals, which were included in statistical analysis. Regional fractional area curves obtained throughout one cardiac cycle under control conditions, during coronary

that included control conditions, ischemia and reperfusion. To minimize bubble destruction and allow uniform LV cavity opacification essential for border detection, low mechanical indices were used.

Perfusion was quantified using mean pixel intensity and contrast replenishment rate. While the former parameter has been used previously, the latter had required repeated image acquisitions at variable pulsing intervals [7;11], which made both data acquisition and analysis complicated and time-consuming. In contrast, the use of PMI with high-energy ultrasound pulses allowed this index to be measured from a single image acquisition. Our preliminary studies showed that contrast-enhanced PMI images provided more uniform LV cavity enhancement than gray-scale imaging. This observation led us to the assumption that PMI could be used for automated endocardial border detection, which was achieved by applying standard border detection techniques.

We found that acute ischemia resulted in reproducible, gradual and reversible perfusion defects and reproducible and reversible wall motion abnormalities that were visualized using PMI and confirmed quantitatively. In addition to control data obtained from ischemic segments at baseline, perfusion territories of other coronaries provided a simultaneously obtained reference for comparison. The comparisons with these established the connection between ischemia and changes in contrast-enhanced PMI images. The increase in perfusion indices following balloon deflation is consistent with the well-documented reperfusion hyperemia [12].

The major limitation of PMI is its low temporal resolution (~15 frames/sec), an intrinsic feature of this technique, which relies on transmitting repeated pulses and real-time processing to create a single scan line. Although the assessment of perfusion and function in this study was not truly simultaneous, simple software modifications could resolve this issue. A major limitation of a closed-chest pig model is that it does not allow imaging from the apical views, which provide important information in humans. Therefore, the accuracy of the ischemic markers described here remains to be determined in future clinical studies in all standard views. Also, the ability to detect ischemia induced by partial coronary occlusions needs to be tested. Nevertheless, our findings reinforce the basis for the diagnostic use of this technique.

This experimental study was designed to investigate the effects of acute myocardial ischemia on contrast-enhanced power modulation images of the left ventricle. This goal was achieved by acquiring and analyzing data in pigs undergoing coronary occlusion. Our findings demonstrated that ischemia results in noninvasively detectable and quantifiable changes in myocardial perfusion and regional

LV function. Therefore, current echocardiographic techniques provide the basis for on-line, objective and simultaneous assessment of regional myocardial perfusion and wall motion. The availability of this information promises to improve the accuracy of echocardiographic diagnosis of coronary artery disease.

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