Echocardiographic Detection of Stress-Induced Myocardial Ischemia Using Quantitative Analysis of Contrast-Enhanced Parametric Perfusion Images

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Abstract

Echocardiographic assessment of myocardial perfusion is currently achieved by measuring indices of contrast replenishment following destructive high-energy ultrasound impulses (flash-echo). We developed a technique for automated detection of perfusion defects based on quantitative analysis of parametric perfusion images created from these indices. Parametric images were obtained at rest and during dipyridamole stress in 18 pts with suspected coronary artery disease. Each image was divided into 6 segments, and mean parameter value (MPV) was calculated for each segment. Changes in MPV from rest to stress were used to automatically detect stress-induced perfusion defects. ROC analysis was used to optimize (1) the threshold for MPV stress-to-rest ratio, and (2) the minimal number of abnormal segments, required for the diagnosis of ischemia, using coronary stenosis >70% as the "gold standard". The sensitivity, specificity and accuracy of the automated detection of ischemia were 63, 75 and 69% in the LAD, and 67,100 and 75% in the non-LAD territories. In conclusion, automated quantitative analysis of echocardiographic parametric perfusion images is feasible and may be useful for objective detection of myocardial ischemia.

1.   Introduction

Objective noninvasive detection of stress-induced myocardial ischemia is a clinically important goal. With the recent technological developments in contrast echocardiography, myocardial perfusion imaging has become easier, more reliable and more reproducible. One of the latest developments is parametric perfusion imaging, based on analysis of "flash-echo" sequences [1]. These parametric images were developed to visualize perfusion defects. However, the interpretation of parametric images is subjective.

With flash-echo, a packet of high energy ultrasound pulses is transmitted to destroy microbubbles during continuous infusion of contrast. Multiple previous studies have shown that analysis of post-flash contrast inflow allows the assessment of flow dynamics [2-3].

Regional myocardial videointensity is measured in a specific phase of the heart cycle, typically end-systole, over time to create a videointensity time curve. This process is repeated for every pixel in a myocardial region of interest (ROI). A typical videointensity time curve is shown in figure 1, with the highest videointensity reflecting the saturated image caused by the flash. The time point immediately following reflects peak bubble destruction and the subsequent increase in videointensity reflects the build-up of contrast concentration due to inflow of fresh contrast.

Since contrast concentration, which follows indicator dilution dynamics, determines the instantaneous videointensity $VI(t)$, the latter can be expressed by:

$$VI(t) = A\left(1 - e^{-\beta t}\right) + C \qquad (1)$$

where A represents the difference between maximal bubble destruction and steady-state contrast enhancement, C is pre-contrast intensity and β is the characteristic constant. The values of these parameters are computed for each pixel within the myocardial ROI and displayed as a color-coded image overlay, or a parametric perfusion image. In figure 1, right panel, dark pixels inside the myocardial ROI indicate low values and bright pixels indicate high values. Theoretically, β is proportional to myocardial flow and $A \cdot \beta$ is the filling rate immediately after the flash. Thus, reduced flow is expected to result in low values of both parameters.

Our aims in this study were to develop a technique for automated analysis of parametric perfusion images and test the feasibility of objective detection of stress-induced perfusion defects based on this analysis.

2.   Methods

2.1.   Patients

18 patients (13 men, 67±8 years old) referred for coronary angiography for suspected coronary artery disease were imaged (Sonos 7500, Philips) during continuous intravenous infusion of contrast agent
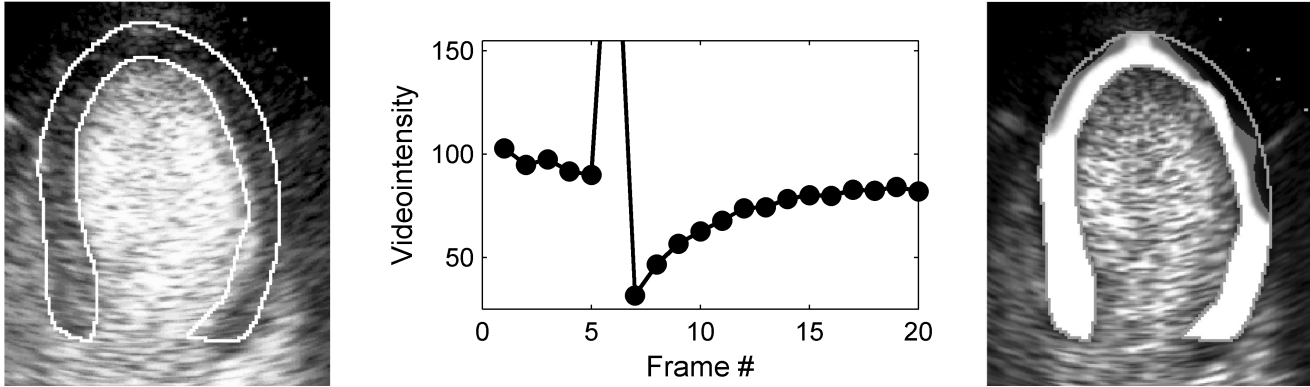
Figure 1. Pre-flash contrast enhancement and the myocardial region of interest (left). Regional videointensity time curve which reflects the destructive effects of high energy pulse followed by contrast replenishment (middle, see text for detail). Parametric image of β shown here in gray levels, with dark areas that represent low levels of β, indicating reduced perfusion in the corresponding territory (right).

Definity (10 ml/h, Bristol-Myers Squibb). Apical 2-, 3- and 4-chamber views were obtained in the power modulation mode with mechanical index of 0.1. Flash-echo image sequences were acquired in each view during non-triggered image acquisition. Imaging was performed at rest and during pharmacologic stress, achieved by infusion of dipyridamole (0.14 mg/Kg/min for 4 min, imaging started 10 min after onset of infusion).

2.2. Image analysis

Parametric images of both β and $A \cdot \beta$ were generated using QLab software (Philips) and displayed as color overlays. We used custom software to analyze these images. Each image was divided into 6 segments using a standard segmentation scheme. In each segment, mean value of the displayed parameter was computed. Then, the ratio of each mean parameter value (MPV) between stress and rest was calculated. This ratio is expected to be high in normally perfused segments that respond to dipyridamole by increasing blood flow (normal flow reserve), and low in areas that are supplied by a partially occluded artery that fails to produce a normal response. Stress-induced perfusion defects were automatically detected using the following scheme. A myocardial segment was considered abnormal if the stress-to-rest MPV ratio was less than a certain threshold value.

In addition, parametric images were visually assessed by two expert echocardiographers, who jointly graded perfusion in each segment as normal or abnormal.

2.3. Data analysis

Segments in the left anterior descending (LAD) and non-LAD territories were analyzed separately. In each territory, we used a receiver operating characteristic (ROC) analysis to optimize the threshold for stress-to-rest MPV ratio and the cutoff number of abnormal segments required for calling a perfusion defect.

For both the automated and visual interpretation of perfusion images, angiography data were used as the anatomical gold standard. Coronary stenosis of over 70% was considered significant and perfusion defect was expected at stress in the corresponding area of the myocardium.

For each perfusion territory, the optimal threshold values were used to calculate the sensitivity, specificity and accuracy of the automated detection of stress-induced perfusion defects. In addition, the sensitivity, specificity and accuracy of the visual interpretation of perfusion images were calculated.

3. Results

Coronary angiography indicated that 6 patients did not have significant stenosis, 2 patients had single-vessel LAD stenosis, 4 patients had either single of double vessel non-LAD stenosis and the other 6 patients had triple-vessel disease. Figure 2 shows an example of images extracted from two flash-echo sequences of apical 4-chamber images and corresponding parametric images, obtained at rest (left) and during stress (right) in a patient with no significant coronary stenosis. The relatively uniform pixel intensity in the parametric image reflected normal perfusion pattern both at rest and under stress (middle panels). The stress-to-rest MPV ratio was relatively high in all 6 segments in this view (bottom panel), reflecting normal coronary flow reserve.

Figure 3 shows an example of images obtained in a patient with isolated 90% LAD stenosis. While the parametric perfusion image calculated from the resting sequence appeared normal, as reflected by the shades of light gray throughout the ROI, the stress parametric image showed a defect in the mid and apical septum (darker gray) corresponding to the LAD territory in this

Rest **Stress**

4.0   3.8
2.3   1.3
1.8   0.9

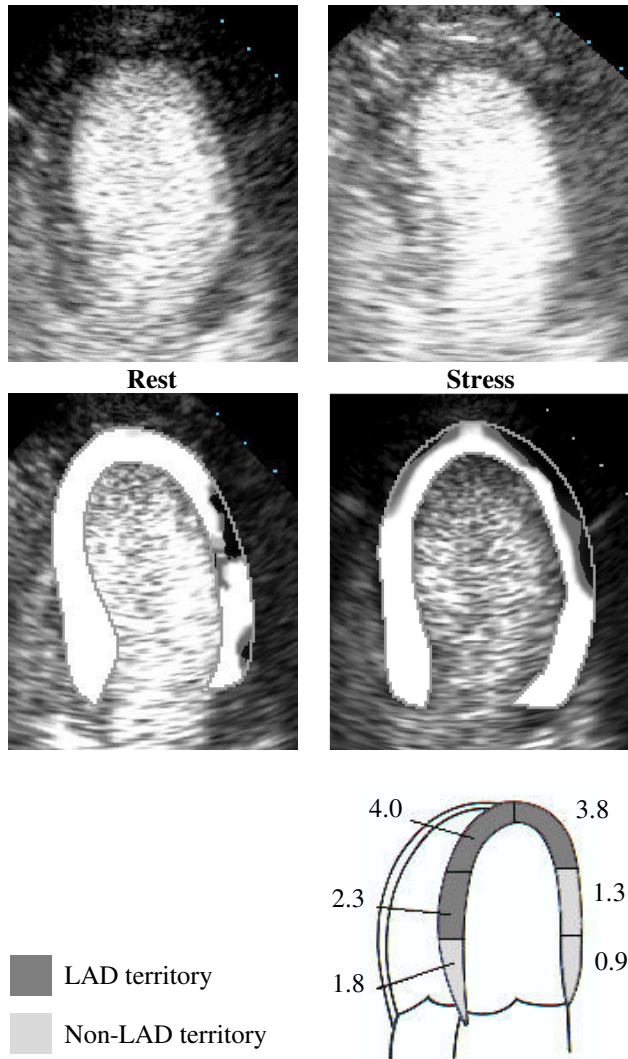■ LAD territory

□ Non-LAD territory

Figure 2. Top: contrast enhanced echocardiographic images of a 67 year old patient with no significant coronary stenosis (mild diffused LAD disease, 40% proximal lesions in both the RCA and LCx), obtained at rest (left) and during stress (right). Middle: the corresponding parametric images of $A \cdot \beta$. Bottom: calculated stress-to-rest ratio of mean parameter value in each segment.

view. Indeed, the stress-to-rest MPV ratio in these two septal segments was only 0.4 (bottom panel), reflecting reduced coronary flow reserve.

Figure 4 shows the results of ROC analysis for the threshold value for stress-to-rest MPV ratio, performed separately for the LAD and non-LAD territories. The optimal threshold value was 0.8 for the LAD territory and 0.65 for the non-LAD territory. The optimal cutoff number of segments for the detection of stress-induced perfusion defects was 3 for both perfusion territories.
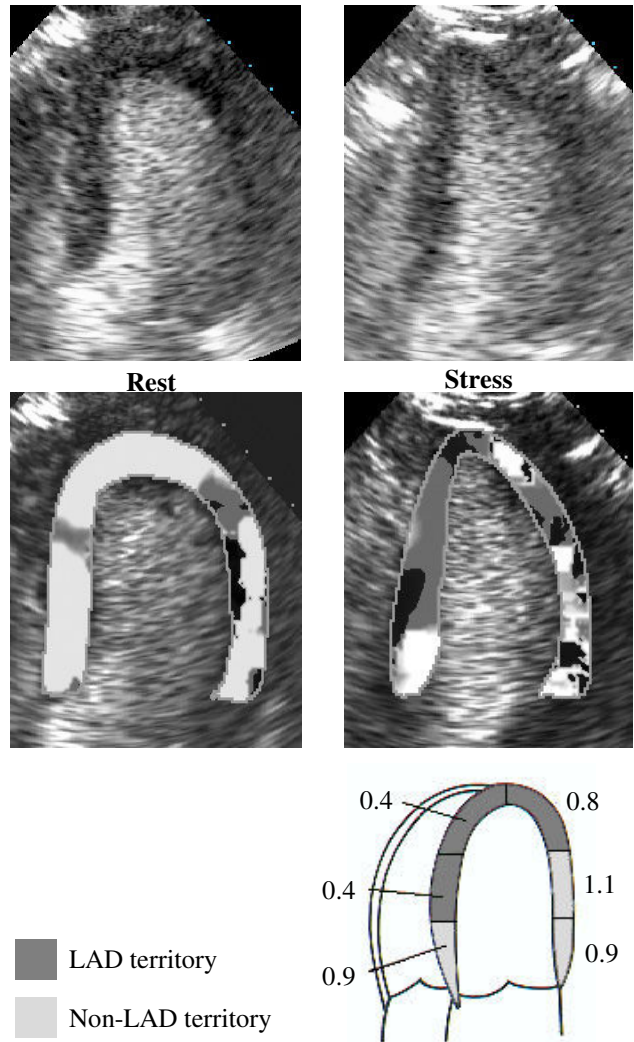

Rest **Stress**

0.4   0.8
0.4   1.1
0.9   0.9

■ LAD territory

□ Non-LAD territory

Figure 3. Data obtained in a 55 year old patient with 90% isolated LAD stenosis (same format as in figure 2).

	Automated Detection		Expert readings	
	LAD	Non LAD	LAD	Non LAD
Sensitivity	78%	78%	75%	60%
Specificity	63%	67%	63%	67%
Accuracy	69%	75%	69%	63%

Table 1. Performance of the automated and subjective visual detection of perfusion defects against coronary angiography.

The sensitivity, specificity and accuracy of the automated detection scheme against coronary angiography (table 1) were compared with those of the visual interpretation of the same parametric images. Of note, the modest values of sensitivity, specificity and accuracy in the table were comparable for both techniques.
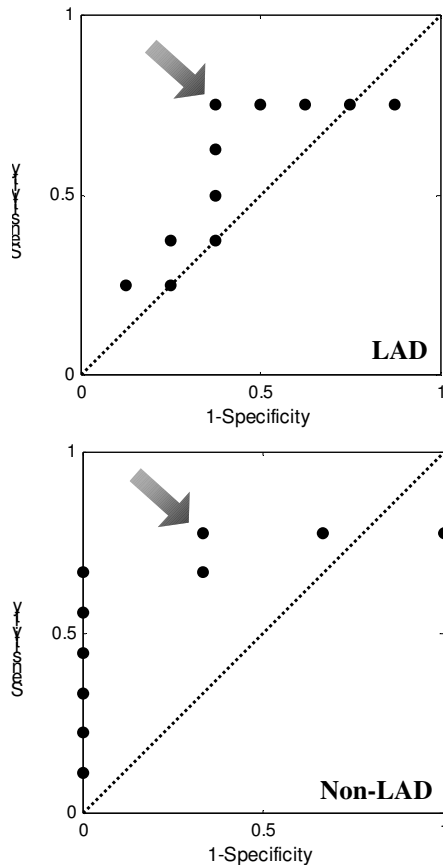

Figure 4. ROC curves obtained by varying the threshold of the stress-to-rest MPV ratio (see text for detail) for the LAD (top) and non-LAD (bottom) territories. Points of optimal performance are shown by arrows.

4.   Discussion and conclusions

Parametric perfusion imaging was recently developed to facilitate the visualization of perfusion defects from flash-echo image sequences. The goal of this work was to develop a technique for automated and objective detection of stress-induced perfusion defects from these parametric images. The free parameters of this technique were optimized against angiography, which served as an anatomical gold standard. It is important to note that although angiography is considered the gold standard for clinical perfusion measurements, it is unable to directly determine myocardial perfusion, as assessed by the flash-echo technique. Rather, it assesses coronary flow, which correlates with perfusion. Nevertheless, the performance of our technique was fond to be at least as good as the subjective visual interpretation by expert echocardiographers.

One of the limitations of this study is the quality of flash-echo image sequences, many of which were obtained in patients with suboptimal acoustic windows as a result of previous surgery. Also, these sequences were obtained without triggering which is known to affect myocardial contrast by partial microbubble destruction. With triggering, the automated technique is expected to be more accurate. This needs to be tested in future studies. In addition, this technique with the calculated threshold values needs to be tested prospectively in a larger group of patients.

In conclusion, this study demonstrated the feasibility of the automated detection of stress-induced perfusion defects by analysis of parametric perfusion images. This new technique may aid in objective echocardiographic diagnosis of ischemic heart disease.

References

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