Quantitative Assessment of Myocardial Perfusion Using Real-Time Three-Dimensional Echocardiographic Imaging

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Abstract

The new real-time three-dimensional (RT3D) echocardiographic technology offers an opportunity for myocardial perfusion imaging in the entire heart without the need for reconstruction from multiple slices and repeated contrast maneuvers. Our aims were to develop and validate a technique for quantitative volumetric assessment of myocardial perfusion. Studies were conducted in 5 isolated rabbit hearts and in 5 patients with ischemic heart disease. In rabbits, RT3D datasets were acquired over 30 sec, during which infusion of contrast agent Definity was initiated and reached steady-state myocardial enhancement. Data were obtained at 3 different levels of coronary flow. At each level, myocardial videointensity (MVI) was measured over time in 3 LV short-axis slices of fixed thickness and peak contrast inflow rate (PCIR) was calculated. Administration of contrast resulted in clearly visible and measurable dynamic changes in MVI. PCIR followed the changes in coronary flow ($p<0.01$). Feasibility in humans was tested by imaging the interventricular septum during initiation of infusion of Definity at rest and during adenosine infusion. Dynamic changes in MVI were visible and suitable for quantitative analysis. In 2 patients, adenosine resulted in dark regions, reflecting lack of myocardial filling in stenosis-related territories. RT3D imaging and quantification of myocardial perfusion using our algorithm are feasible. This approach can potentially allow more accurate assessment of the extent of perfusion defects than 2D myocardial contrast echocardiography.

1. Introduction

Multiple studies have demonstrated the feasibility of contrast-enhanced, two-dimensional echocardiography to image myocardial perfusion [1]. This methodology provides information only on a single slice of the heart, and is limited because the extent of a perfusion defect cannot be accurately assessed from a single plane. Obtaining such information for the entire heart requires 3D imaging, which has been until recently mainly based on consecutive acquisition of multiple planes followed by off-line volume reconstruction [2,3]. Furthermore, quantification of perfusion from 3D reconstructed data requires contrast maneuvers, such as boluses of contrast or microbubble destruction with high-energy ultrasound pulses during contrast infusion [4], to be repeated for each imaging plane. Accordingly, this methodology is tedious and impractical for clinical use.

The recently developed real-time three-dimensional (RT3D) echocardiographic technology offers an opportunity for online perfusion imaging in the entire heart without the need for volume reconstruction from multiple slices and repeated contrast maneuvers. Despite the ability of real-time volumetric contrast imaging to demonstrate perfusion defects [5,6], there are no tools for 3D quantitative analysis of myocardial perfusion. Also, the use of the above contrast maneuvers with RT3D imaging is problematic and technologically unresolved. Accordingly, our approach is based on tracking changes in myocardial contrast during the transition from no enhancement to steady-state enhancement. In this study, our aims were: (i) to test the feasibility of RT3D myocardial perfusion imaging; and (ii) to develop and validate an algorithm for quantitative volumetric analysis of myocardial perfusion. We tested this approach in an isolated rabbit heart model, which allowed for almost artifact-free imaging, and then tested its feasibility in human subjects.

2. Methods

2.1. Isolated rabbit heart model

Studies were conducted in a Langendorff isolated rabbit heart preparation (New Zealand White rabbits, 2-3.2 kg, N=5). Hearts were perfused retrogradely via the aortic root with Krebs-Henseleit solution at constant pressure of 86 mmHg, resulting in global coronary flow between 32 and 52 ml/min at baseline (Transonic). A latex balloon was placed in the left ventricle and filled with fluids to allow the heart generate physiologic pressures during isovolumic contractions. The heart was then placed in a container filled with fluid to allow

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ultrasound imaging through the container wall. EKG-triggered harmonic RT3D datasets were acquired (X4 probe, Philips 7500) at mechanical index of 0.5 over 30 sec, during which infusion of Definity (20 ml/hr) into the perfusion line was initiated and reached steady-state myocardial contrast enhancement.

Coronary flow was varied by partially obstructing the perfusion line. Data were obtained at 3 different levels of coronary flow: baseline (BL), 40 to 60% of baseline flow (F1) and 10 to 20% of baseline flow (F2). The duration of flow reduction was kept under 5 min to minimize ischemic damage.

The data were analyzed using custom software. The pyramidal wide-angled RT3D datasets were initially reviewed to allow selection of three LV short-axis slices of a fixed thickness. In each slice, a ring-shaped region of interest containing the myocardium was defined manually, and myocardial videointensity (MVI) was measured over time at each flow level. These MVI time curves were used to assess myocardial perfusion in each slice. The time derivative of the MVI curve, which reflects the rate of contrast inflow, was computed using a second order Savitzky-Golay smoothing filter. Myocardial peak contrast inflow rate (PCIR) was calculated as the maximum of MVI time derivative, normalized by the increase in MVI at the steady state relative to the MVI level prior to contrast infusion. Then PCIR values were averaged for all animals and changes between different flow levels were tested using paired t-test.

2.2. Human studies

Feasibility of RT3D perfusion analysis was tested in 5 patients (3 males, 2 females, age 56±11) with known ischemic heart disease in the left anterior descending coronary artery confirmed by coronary angiography and good acoustic windows. Two patients had significant coronary narrowing, one patient had mild diffuse coronary disease, and the remaining two patients were studied following successful percutaneous revascularization. Since it was not possible to image the entire heart because of the limited spatial aperture angle of the transducer, we acquired zoomed EKG-triggered harmonic RT3D images of the interventricular septum. Imaging was performed using mechanical indices between 0.5 and 0.8, following initiation of i.v. infusion of Definity (6 ml/min) at rest and during adenosine infusion (0.142 ml /kg/min).

3. Results

In rabbits, RT3D imaging allowed high quality volumetric rendering of the entire heart (fig. 1). This mode allowed the visualization of myocardial perfusion

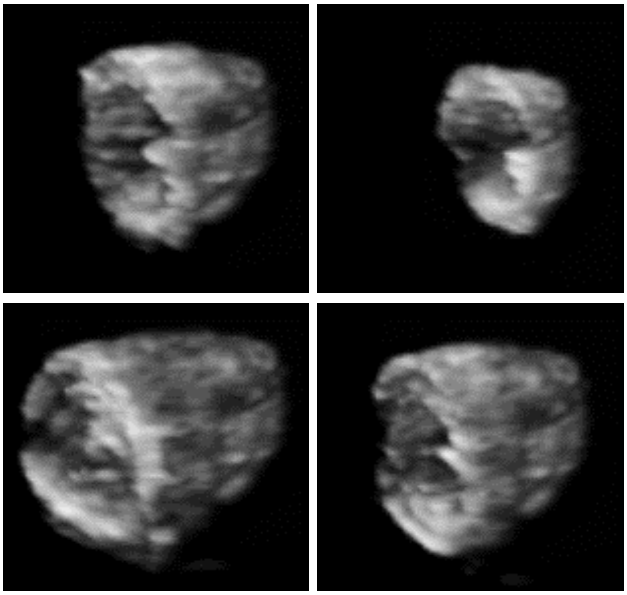

Figure 1. 3D rendering of an isolated rabbit heart obtained from the RT3D dataset. The heart can be sliced at any level for off-line 3D analysis of myocardial perfusion.

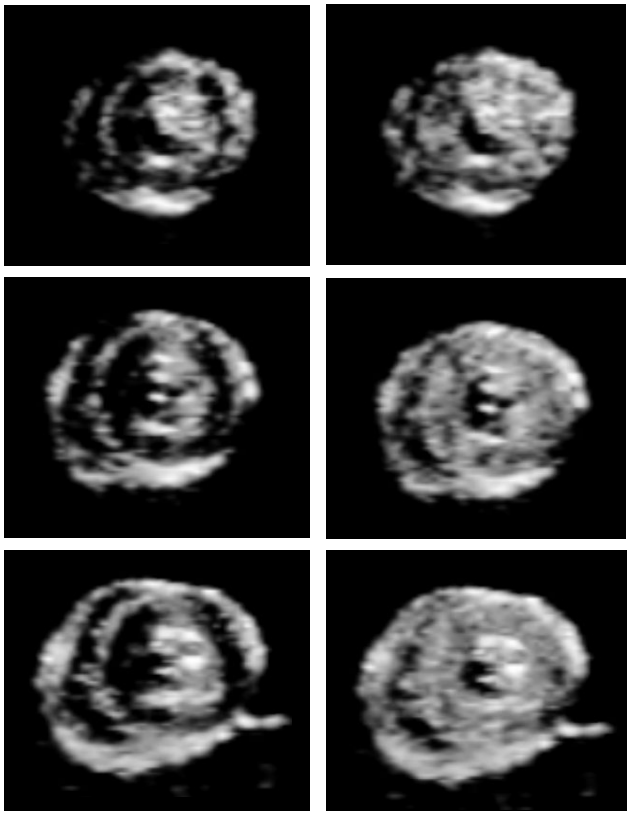

Figure 2. Short axis LV slices at three levels of the heart extracted from the 3D volumetric data, before contrast infusion (left) and during steady-state contrast enhancement (right).

in the entire left ventricle in a single acquisition during a single contrast maneuver. The administration of contrast resulted in clearly visible dynamic changes in MVI in all LV slices (fig. 2).

These changes in myocardial contrast resulted in MVI time curves (fig. 3) with high signal-to-noise ratios (6 to 33). From these curves, MVI time-derivatives were obtained and were found to be sufficiently smooth to allow reliable calculation of PCIR (fig. 3). At BL coronary flow, PCIR in the 3 different LV slices varied less than 4% in all rabbits.

Coronary flow reductions resulted in changes in MVI time curves (fig. 4, top), including lower levels of steady-state enhancement and slower contrast inflow. Accordingly, PCIR changed significantly between the three levels of coronary flow (fig. 4, bottom).

In human subjects, dynamic changes in MVI were visible and suitable for quantitative analysis. We found that the transition from no enhancement to steady-state enhancement occurred in all 5 patients within less than 45 sec, which were captured in a single data acquisition EKG-triggering resulted in uniform contrast enhancement, reflecting minimal bubble destruction despite the relatively high mechanical indices used in this protocol. In the two patients with significant coronary stenosis, adenosine resulted in dark regions, reflecting the lack of myocardial contrast inflow (fig 5) in stenosis-related territories. These defects could be visualized in multiple views by cropping the dataset, thus providing the observer with additional spatial information on the extent of the defect. The patient with diffuse coronary disease and the two patients studied following revascularization did not show any localized perfusion defects.

4. Discussion and conclusions

This is the first study aimed at volumetric quantitative assessment of myocardial perfusion with contrast-enhanced real-time 3D echocardiography. Since current RT3D technology does not allow the use of destructive, high-energy ultrasound pulses, we used the transition from no enhancement to steady-state enhancement, as an alternative maneuver necessary to assess flow dynamics.

The isolated heart model proved to be a valuable tool in developing the quantitative approach to volumetric assessment of myocardial perfusion. This model provided near ideal conditions for contrast-enhanced echocardiographic imaging [7,8], including: (i) excellent image quality with minimal acoustic shadowing, since there is no flow through the LV cavity, (ii) absence of cardiac translation due to respiration, (iii) no recirculation-related artifacts, since the heart is continuously perfused with fresh solution, and (iv) a readily accessible, wide range of coronary flows.

Our results obtained in this protocol confirmed the

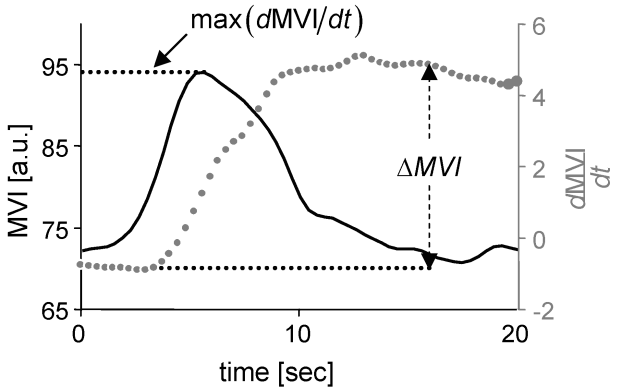

Figure 3: Myocardial videointensity (MVI) measured in a 3D slice obtained in an isolated rabbit heart (solid circles). Peak contrast inflow rate was determined from the MVI time-derivative (solid line).

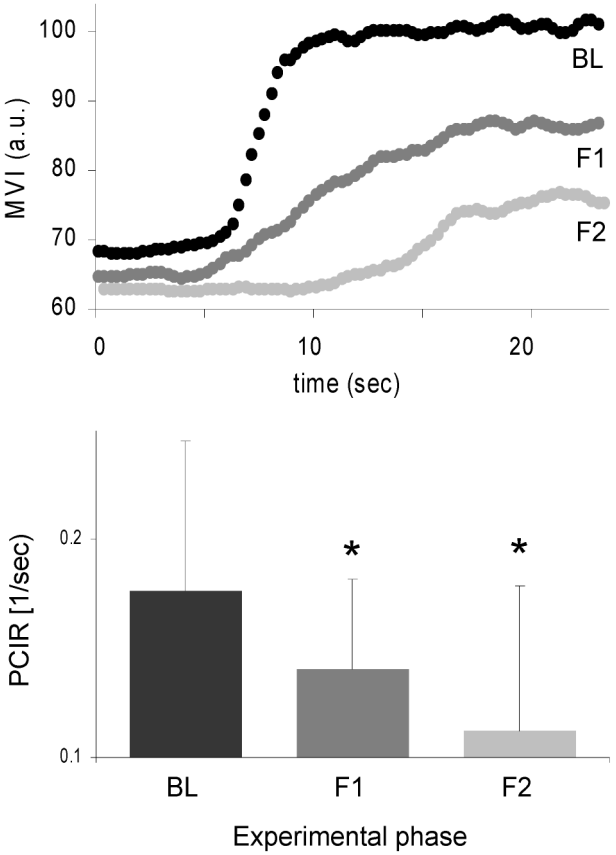

Figure 4. Top: example of MVI time curves obtained from one 3D slice of an isolated rabbit heart at 3 levels of coronary flow: BL – baseline, F1 – 40-60% of baseline flow, F2 – 10-20% of baseline flow. Bottom: average values of myocardial peak contrast inflow rate (PCIR) measured at the different levels of coronary flow (* $p<0.01$ compared to BL, paired *t*-test).

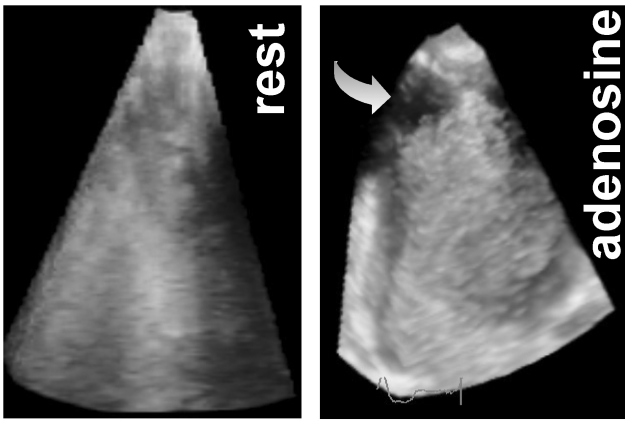

Figure 5. RT3D images obtained at rest and during adenosine infusion in a patient with a near complete occlusion of the left anterior descending coronary artery past the first diagonal branch. Note the dark area in the distal septum during adenosine infusion.

feasibility of RT3D imaging and quantitative volumetric assessment of myocardial perfusion from the RT3D data. We observed marked changes in videointensity between baseline and steady state contrast enhancement. The high quality of the data obtained from the isolated heart enabled the extraction of almost noise-free videointensity time curves, which were used to assess the dynamic properties of myocardial flow. EKG triggering allowed us to use relatively high mechanical indices without compromising image quality. Our approach to the analysis of MVI time curves provided consistent values of PCIR in the different slices of the heart, indicating that this parameter is a reliable index of myocardial perfusion. In addition, we found that the PCIR values corresponded to the directly measured coronary flow values. Since calculating the PCIR from the MVI curves does not involve curve-fitting algorithms [4], our technique may be more robust to noise than other, previously used methods, which were based on fitting the measured data to an exponential curve.

In humans, we were able to visualize the dynamics of myocardial blood flow during the transition from no contrast enhancement to steady-state enhancement within a short time suitable for image acquisition in the clinical setting. Although the spatial aperture angle of the transducer did not allow imaging the entire ventricle, we were able to test the feasibility of our technique by focusing on the interventricular septum. Although the number of patients in this study was very small, we observed myocardial perfusion patterns that could be explained in each patient by the findings of coronary angiography. This observation needs to be extended to a larger group of patients in future studies, wherein regional quantitative analysis of myocardial perfusion will also be applied.

In conclusion, we found that RT3D imaging of myocardial perfusion within a single contrast maneuver is feasible and allows quantitative volumetric assessment of tissue blood flow. This approach can potentially allow more accurate assessment of the extent of perfusion defects than 2D myocardial contrast echocardiography.

Acknowledgements

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