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Potential of Delayed Gadolinium Enhancement Magnetic Resonance for Quantification of Reverse Remodeling of the Peri-Infarct Zone in Patients with Ischemic Cardiomyopathy Treated with Chronic Vasodilator Therapy: Initial Experience

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Abstract

Purpose—The peri-infarct zone represents the morphological substrate for re-entry ventricular tachycardia after myocardial infarction (MI) and its extent is a strong predictor of major cardiac events. Although delayed gadolinium enhancement magnetic resonance (DGE-MRI) was shown to allow for detailed characterization of MI by quantifying infarct core zone and peri-infarct zone volume, potentials of DGE-MRI for measuring changes in peri-infarct zone volume are unknown. Therefore, we aimed to assess changes in volume of the peri-infarct zone among patients with ischemic cardiomyopathy treated with chronic vasodilator therapy.

Materials and Methods—Core and peri-infarct zone volumes as assessed with DGE-MRI were measured in 5 patients at baseline and following 6 months treatment with sustained-release dipyridamole.

Results—Core zone volume remained stable during follow-up [median(range): 19ml(9–42) vs. 16ml(11–46); $p=0.785$]. The ratio between the peri-infarct zone and the core zone volume decreased significantly at 6 month as compared to baseline [median(range): 0.22(0.19–0.42) vs. 0.18(0.09–0.32); $p=0.043$], and a trend towards reduction in peri-infarct zone volume was found [median(range): 5ml(2–8) vs. 3ml(2–6); $p=0.059$]. The peri-infarct zone volume decreased in all but 1 patient over the follow-up.

Conclusions—This initial experience suggests that reverse remodeling of the peri-infarct zone with reduction in peri-infarct zone volume may take place in patients with ischemic cardiomyopathy. Quantification of this process may be feasible with DGE-MRI, but further studies are needed to confirm this hypothesis and to further clarify the role of DGE-MRI for the assessment of changes in peri-infarct zone volume in patients with ischemic cardiomyopathy.

Keywords

Peri-infarct zone; magnetic resonance imaging; delayed gadolinium enhancement; myocardial infarction

Introduction

Areas of myocardial infarction (MI) are composed by a core zone of scar tissue and a peri-infarct zone. The latter represents the morphological substrate of re-entry ventricular tachycardia after MI, and is characterized by a heterogeneous tissue containing both, myocardial fibrosis and viable myocardial cells [1,2]. Extent of the peri-infarct zone as assessed with delayed gadolinium enhancement magnetic resonance imaging (DGE-MRI) has been correlated with ventricular arrhythmias and mortality in patients with ischemic cardiomyopathy in multiple studies [3–5]. Notably, the extent of the peri-infarct zone has been found to be a stronger outcome predictor as compared to left ventricular ejection fraction (LVEF) and total amount of myocardial scar [3]. Although dynamic changes in myocardial scar characteristics and size take place during the early phase after acute MI, little is known about the behavior of the peri-infarct zone in chronic MIs [6]. Since viable cells are present in the peri-infarct zone, dynamic changes and reverse remodeling process with consequent reduction in size of the peri-infarct zone may take place. Frequently, myocardial cells in the peri-infarct zone are ischemic and hibernated due to residual stenosis of the supplying coronary artery, or to microvascular injuries related to the prior MI. Therefore, as suggested by histopathological studies, therapeutic interventions aimed to improve perfusion of the peri-infarct zone may promote reverse remodeling and reduction of peri-infarct fibrosis [7–9]. However, the concept of using DGE-MRI as an in-vivo diagnostic tool for qualitative and quantitative assessment of the remodeling process of the peri-infarct zone has not been evaluated. This may be of particular interest, since the size of the peri-infarct zone is a major outcome determinant after MI [3–5]. Therefore, we aimed to determine if changes in size of the peri-infarct zone among patients with ischemic cardiomyopathy occur. For this study we evaluated patients who were treated over a six month period with chronic sustained-release dipyridamole in order to augment myocardial blood flow [10].

Materials and Methods

Patient population

This study was approved by the institutional committee of human research and in accordance with HIPAA regulations. All patients gave written informed consent before enrollment. As reported in the study by Akhtar et al. [10] from which we retrospectively studied patient population, 6 patients with ischemic cardiomyopathy demonstrated by at least one of the following: (1) angiographically documented $\geq 75\%$ stenosis of a major epicardial coronary artery, and/or $\geq 50\%$ left main coronary artery stenosis or (2) typical symptoms of angina and ischemia documented by exercise electrocardiography or single photon emission computed tomography (SPECT), reduced ejection fraction (LVEF $<40\%$) within 1 year by echocardiogram or SPECT, were treated with chronic sustained-release dipyridamole 200 mg twice daily for 6 months. Patients did not undergo cardiac revascularization during follow-up. New York Heart Association class IV, unstable angina, acute MI and coronary revascularization within 6 month were exclusion criteria. Change in myocardial blood flow as assessed with rest and hyperemic coronary sinus flow was the main outcome in the original study design. Coronary sinus flow was measured with phase-contrast MRI. Therefore, all patients underwent repeated MRI studies including DGE-MRI

at baseline and after 6 months. In the current analysis 1 patient was excluded due to absence of MI by history and no evidence of delayed myocardial enhancement on DGE-MRI images at baseline. Therefore, our study population consisted of 5 patients.

Imaging study

All scans were acquired with a 1.5-Tesla scanner (Intera I/T, Philips Medical System, Best, the Netherlands) using a 4-channel cardiac coil. All patients underwent a standardized imaging protocol including: 1) Contiguous short-axis stack of breath-hold steady-state free precession cine loop images with full coverage of both ventricles from the base to the apex to quantify ventricular size and function (8mm thick, 0 mm gap, 18 phases/cardiac cycle, TR=1.4–3.0 ms, TE=1.4–3.2 ms, flip angle=70°, FOV=340 mm, acquisition matrix= 144 × 256, number of acquisitions=1). 2) Short axis DGE-MRI images were obtained by use of a 3-dimensional inversion-recovery turbo spin-echo sequence (10 mm thick, inversion time=220–300 ms, TR=7.6 ms, TE=2.0 ms, flip angle=150, FOV=260 mm, acquisition matrix=256×256, number of acquisitions=1) 10–15 minutes after administration of 0.15 mg/kg of gadolinium chelate for DGE-MRI assessment. Inversion-time scouts were used to set proper nulling times.

Image analysis

Volumetric analyses were performed in a dedicated workstation (VPRO, Philips Medical System, Best, The Netherlands). The following measures were calculated: left ventricular end-diastolic and end-systolic volumes indexed to the body surface area (LVEDVi, LVESVi), and LVEF. Myocardial scar analyses were performed using a freely available and validated software Segment (<http://segment.heiberg.se>) [11]. The endocardial and epicardial contours on delayed enhancement images were traced manually. A region of interest containing non-infarcted myocardium was traced in each short-axis slice to determinate the signal intensity of remote myocardium. Using a semiautomatic detection algorithm, we applied a signal-intensity threshold of >2 standard deviations (SDs) above the intensity of the reference remote myocardial region on the same slice to quantify the total scar volume. The core zone volume of the MI was then determined by applying a second threshold of >3 SDs above the intensity of the remote myocardial region. The peri-infarct zone volume was calculated as the subtraction of the total scar volume and the core zone volume as previously described by Yan et al. (peri-infarct zone volume = total scar volume–core zone volume) [5]. An example of scar quantification as assessed with DGE-MRI is illustrated in figure 1. All scar volumes were expressed in milliliters. The ratio between peri-infarct zone volume and core zone volume, and peri-infarct zone volume and total scar volume were then calculated. The physician who analyzed the MRI images was blinded in regards to the time of data collection. All the above mentioned measurements were done at baseline and after 6 month at the end of the study.

Statistical analysis

Continuous data are presented as median (range). Categorical data are presented as percentages. Differences of the tested variable between baseline and month 6 were tested with a Wilcoxon test. This test was used considering the small number of patients and the absence of a normal distribution. A p-value of ≤ 0.05 was considered statistically significant (2-tailed). Analyses were performed using the commercially available statistical package SPSS version 15.0.

Results

Baseline characteristics of the patients are shown in table 1. Notably, this was a group of patients with chronic MI. The average time since MI was of approximately 5 years, with a

minimal time interval of 1 year between the MI event and the first MRI study. Results of the imaging study, including total scar volume, core zone volume and peri-infarct volume at baseline and at the end of the follow-up period are shown in table 2. The total scar volume and core zone volume did not change significantly between baseline and month 6. However, there was a trend towards a reduction in peri-infarct zone volume, and a significant reduction in ratio of peri-infarct zone volume to core zone volume, and in ratio of peri-infarct zone volume to total scar volume, respectively. As previously reported for this group of patients the global myocardial tissue perfusion, measured as the coronary sinus blood flow, increased significantly [10]. Individual changes in core zone volume, peri-infarct zone volume and ratios of peri-infarct zone volume to core zone volume, respectively, are illustrated in figure 2. Notably, the peri-infarct zone volume diminished in all but 1 patient, in whom the peri-infarct zone volume was the smallest at baseline and remained unchanged at the follow-up study.

Discussion

Although DGE-MRI was shown to allow for detailed characterization of infarcts by differentiation of core zone and peri-infarct zone, there are no reports addressing the potentials of DGE-MRI for the assessment of remodeling process of the peri-infarct zone in patients with chronic MI [3–5,12]. Results of this feasibility study suggest that reverse remodeling with reduction in peri-infarct zone volume may take place, and that quantification of this process is feasible with DGE-MRI. However, considering the small number of patients included in the current study, these results are not conclusive and need to be confirmed in a larger patient population. Furthermore, due to the lack of a control group, the causative correlation between the observed reduction in peri-infarct zone volume and the treatment with chronic vasodilator therapy is speculative. However, results of the current study are supported by histopathological reports on patients with chronic MI, showing that hibernated myocytes in the peri-infarct zone undergo a dedifferentiation process with depletion of contractile filaments and substantial increase in interstitial fibrosis. These structural changes are reversible after restoration of adequate myocardial perfusion [7–9,13]. In this context, reverse remodeling process with reduction of interstitial fibrosis after increase in tissue perfusion, as in the present model of chronic vasodilator therapy, may lead to decrease in distribution volume of gadolinium chelates in the peri-infarct zone and subsequent measurable changes in peri-infarct zone volume as assessed with DGE-MRI [14]. Potential beneficial effects of chronic vasodilator therapy on cardiac remodeling in patients with ischemic cardiomyopathy are also supported by a large randomized trial, showing that long-term nitroglycerin prevents left ventricular dilation and remodeling after MI [15]. These results on functional recovery are also confirmed with dipyridamole administration by other several studies in literature [16–19].

The observations of the current study indicate a dynamic state of the peri-infarct zone and that DGE-MRI may allow for qualitative and quantitative assessment of peri-infarct remodeling process related to therapeutic interventions, such as revascularization procedures, with the intention of influencing the remodeling process in the peri-infarct-zone. The latter is of particular interest, since the extent of the peri-infarct zone was shown to be a strong predictor of major cardiac events in patients with chronic ischemic cardiomyopathy. In this context, results of this first experience should stimulate research on this topic to further define the role of DGE-MRI for the assessment of peri-infarct zone remodeling in patients with ischemic cardiomyopathy.

Conclusions

Reverse remodeling of the peri-infarct zone may take place in patients with chronic MI. These preliminary results support that quantification of this process may be feasible with DGE-MRI, but further studies are needed to confirm this hypothesis and clarify the role of DGE-MRI as an in-vivo diagnostic tool for the assessment of changes in peri-infarct zone volumes in patients with ischemic cardiomyopathy.

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Figure 1. Measurement of the peri-infarct zone

Delayed gadolinium short axis image (A), and illustration of the delineation of the total scar tissue (yellow line) and the core zone of the scar (pink line) obtained with the semiautomatic technique for quantifying scar volumes (B). The peri-infarct zone is the tissue between the 2 lines.

Figure 2. Changes in core zone volume and peri-infarct zone volume over follow-up

Graphic illustrating the individual values in core zone volume (A), peri-infarct zone volume (B), and ratio between peri-infarct zone volume and core-zone volume (C) at baseline and after 6 months.