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Quantification of Myocardial Blood Volume During Dipyridamole and Doubtamine Stress: A Perfusion CMR Study

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ABSTRACT

***Purpose*:Myocardial blood volume (MBV) may provide complementary information about myocardial oxygen needs and viability. The aim of this study is to examine a Cardiovascular Magnetic Resonance (CMR) perfusion method to quantify the changes in MBV, in comparison with the radiolabeled ^{99m}Tc-Red-Blood-Cell (RBC) method. *Methods*: Normal mongrel dogs (n = 12) were used in this study. Eight dogs were injected intravenously with dipyridamole, and 4 dogs were given dobutamine during the MR scans. CMR first-pass perfusion imaging was performed at rest and during the pharmacological stress. An intravascular contrast agent, Gadomer (Schering AG, Berlin, Germany), was injected (0.015 mmol/kg) as a bolus during the scans. A perfusion quantification method was applied to obtain MBV maps. Radiolabeled-RBCs were injected at the end of the study to measure reference MBV at rest (n = 4), during dipyridamole vasodilation (n = 4), and during dobutamine stress (n = 4). *Results*: Myocardial blood flow (MBF) increased approximately 3-fold with both dipyridamole and dobutamine injections. Transmural MBV values measured by CMR were closely correlated with those measured by ^{99m}Tc method (CMR: MBV = 6.2±1.3, 7.2±0.8, and 8.3±0.5 mL/100g, at rest, with dipyridamole, and with dobutamine, respectively. ^{99m}Tc-RBC: MBV = 6.1 ± 0.5, 7.0 ± 0.9, and 8.6 ± 0.7 mL/100g). Dobutamine stress significantly increased MBV by CMR (33%) and ^{99m}Tc methods (35%). During dipyridamole induced vasodilation, MBV increased non-significantly by 14% with the ^{99m}Tc method and 15% with CMR method, which agreed well with other reports. *Conclusion*: First-pass perfusion CMR with the injection of intravascular contrast agents is a promising non-invasive approach for the assessment of MBV both at rest and pharmacologically induced stress.**

INTRODUCTION

Measurement of MBV can provide a unique approach to the assessment of myocardial perfusion that cannot be explained by myocardial blood flow (MBF) alone (1, 2). With the use of myocardial contrast echocardiography (MCE), MBV can be quantified non-invasively (2, 3). Of major importance to the measurement of MBV is that changes in MBV may reflect the severity of coronary artery stenosis. It was demonstrated by Jayaweera et al. (4) that MBV distal to non-critical stenoses (<50% in diameter narrowing) remained constant at rest but decreased during pharmacologically induced hyperemia. The magnitude of decrease in MBV correlated well with the severity of stenosis. Furthermore, the same group also reported that measuring changes in MBV can detect physiologically significant stenoses (<75%) at rest without recourse to any forms of stress (5). It was also stated that MBV can be used to assess myocardial viability; "if both baseline and recruitable capillaries are absent or present in very small numbers within a myocardial region, it is very unlikely that sufficient oxygen delivery occurs to myocytes within that region (1)." Furthermore, MBV value can be used as an input parameter for the calculation of myocardial oxygenation using a two-compartment model (6).

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MBV is the blood volume resident in the microvascular circulation of the left ventricle (LV) with a diameter less than 200 μm (1). This portion of blood volume is part of the coronary blood volume (CBV), which also includes blood volume resident in the epicardial conductive coronary vessels and veins. The total CBV is approximately 12 mL/100 g LV tissue, while MBV is only about 1/3 of this volume, i.e., 4.5 mL/100g LV tissue. Blood in the transmural myocardium primarily resides in capillary vessels; approximately 90% MBV is inside the capillary compartment (7).

Many attempts have been made to measure MBV under different physiological conditions. The approaches include invasive methods using radiolabeled substances (7–9), and non-invasive imaging methods such as MCE (10–12), electron beam computer tomography (EBCT) (13), and CMR (14–17). The invasive methods are usually considered to be gold standards for the measurement of MBV, and one commonly used method involves technetium-99m (^{99m}Tc) labeled RBCs (18). In normal dogs, the largest increase in MBV was observed with the injection of dobutamine and a slight to moderate increase with the intravenous injection of dipyridamole or adenosine (9, 19). In contrast, intracoronary artery injection of adenosine causes an increase in MBF, but not MBV (8, 9, 20).

CMR has been increasingly used for the diagnosis of cardiac diseases in many medical centers. First-pass perfusion CMR is the most robust method for the quantification of MBV. With the injection of an intravascular contrast agent, perfusion CMR detects a significant increase in MBV during hyperemia from MBV at rest (16), but this study provided no reference values to confirm CMR results. In one early study, the MBV in dogs was measured by using radiolabeled RBCs at rest and appeared to match with the MBV values obtained by perfusion CMR (14). However, those MBV data were significantly higher than other reported values (8, 9), and no MBV data were measured during hyperemia. The aim of this study was to test the hypothesis that a CMR first-pass perfusion mapping method can accurately measure MBV at rest and during pharmacological induced stress non-invasively. The CMR results were compared to MBV values measured by the ^{99m}Tc-labeled RBC method.

METHODS

Animal protocols

Twelve normal mongrel dogs (wt = 24.6 ± 4.0 kg) were used for this study. ^{99m}Tc RBC can only be used to quantify MBV at one condition for each dog. Because of this, ^{99m}Tc MBV measurement was performed in 4 dogs at rest, 4 dogs during dipyridamole vasodilation, and 4 dogs during dobutamine stress. The dogs were sedated with 1–2 mg/kg body weight of morphine subcutaneously and anesthetized with 12.5 mg/kg of sodium thiopental, as well as 60 mg/kg of alpha-chloralose intravenously throughout the procedure. The dogs were then intubated and ventilated with a mixture of room air and 100% oxygen at a tidal volume of 12 ml/kg and a rate of 10–15 breaths/minute with an inspiration/expiration ratio of 40/60.

Bilateral femoral arterial and venous cut-downs were then performed. An 8-French catheter was inserted into the left atrium for the injection of radio-labeled microspheres through the left femoral artery. Another catheter was inserted through the right femoral artery to withdraw reference blood samples for the measurement of MBF with microspheres. This catheter was also connected to a fluid-filled transducer for blood pressure monitoring. Another catheter was placed in one femoral vein for the administration of dipyridamole or dobutamine and fluids.

All dogs were imaged using the CMR protocol (see below) at rest and during either dipyridamole induced vasodilation or dobutamine induced stress. The heart rate and blood pressure were monitored continuously and hard copies of the record were obtained every 5 minutes using an MRI-compatible hemodynamic monitor (Vital Signs Monitoring System, Invivo Research, Orlando, Florida, USA). The dipyridamole was injected intravenously at a dose of 0.14 mg/kg/min for 4 minutes, and dobutamine was titrated at 10 μg/kg/minute increments every 5 minutes up to a maximum of 40 μg/kg/minute. Radiolabeled microspheres, ^{85}Sr and ^{46}Sc, were injected as references for measuring MBF at the rest and stress conditions respectively. ^{99m}Tc-labeled-RBCs were injected at the end of the study to measure a reference MBV. The procedure of RBC injections and analysis were described in detail elsewhere (21). The protocol time line is shown in Fig. 1. The study protocol was approved by the Animal Studies Committee of our institute.

CMR protocol

All imaging studies were performed in a 1.5T scanner (Siemens Sonata, Erlanger, Germany) with a phased-array head coil placed around the dogs' chest. Images were sequestered by a non-slice-selective saturation-prepared turbo fast low-angle shot (FLASH) sequence at a resolution of 2.1 mm × 0.9 mm and a slice thickness of 8 mm. The saturation prepared pulse is a non-slice-selective hyperbolic secant pulse with a duration of 5.12 ms. Three short-axial slices of the myocardium were acquired during each scan. The first slice was scanned in systole, followed by the second and third slice. The second slice or the middle one was obtained at the middle of diastole and was used in the subsequent analysis. There were 60 to 70 dynamic images collected for each slice and each image was collected at every RR interval. Other imaging parameters included: TR/TE/TI (from preparation pulse to acquisition of central k-space) = 2.5 ms/1.2 ms/ 90 ms, and flip angle = 18°, FOV = 220 mm × 138 mm, matrix size = 128 × 80, and image acquisition time window per cardiac cycle = 150 ms. Gadomer (Schering AG) was injected at 15 μmol/kg as a bolus. Respiratory motion was controlled by breath-hold at end expiration.

The Gadomer is a synthetic, paramagnetic complex with multiple Gd chelate moieties bonded to a dendritic backbone (22). The apparent molecular weight is 30–35 kD; therefore, the contrast media is a macromolecular Gd-based intravascular agent compared with the clinical extracellular contrast agent Gd-DTPA (<1 kD). Gadomer combines almost exclusively intravascular retention with fast and quantitative renal elimination and is

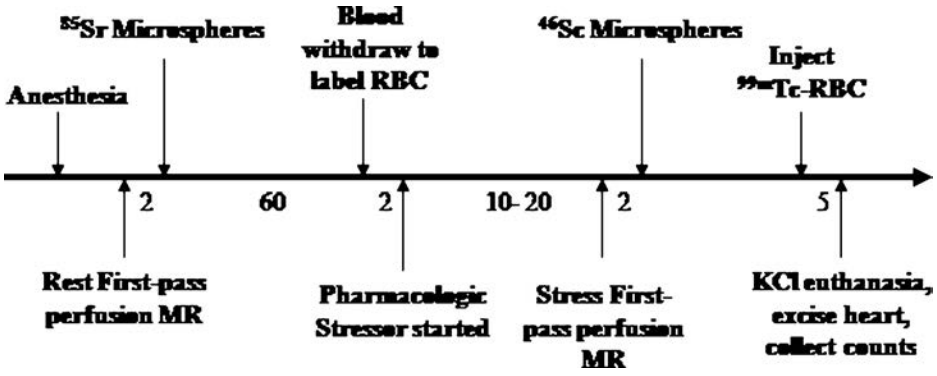

Figure 1. Timeline of study protocol. Number (in minutes) is the time between events (arrows). Rest perfusions were always performed first, with the stress perfusions approximately 60 minutes afterwards. Injecting ^{99m}Tc-labeled RBC occurred immediately after the completion of ^{46}Sc microsphere procedure. Please note, ^{99m}Tc injection can only be performed once per dog.

therefore also called a rapid clearance intravascular agent. The R_1 relaxivity ($\sim$13 $mM^{-1}s^{-1}$) of the compound is 3-fold higher than that of extracellular contrast agents at 1.5 T (23). Because of the pharmacokinetic and physical properties of Gadomer, it is well suited for first-pass perfusion imaging in our study.

Data analysis

The product of systolic blood pressure and heart rate, i.e, the rate-pressure product (RPP) values, before and after the dipyridamole or dobutamine injection were calculated for all the dogs.

Calculation of reference values of MBF and MBV

After the completion of the CMR study, the dogs were sacrificed by KCl euthanasia. The hearts were then excised. A 1 cm ring of the excised heart at the point of the middle slice was cut into 32 pieces (Fig. 2). Each dissection piece was measured by a Geiger counter to determine radioactivity of microspheres and ^{99m}Tc. The determination of MBF and MBV followed standard procedures for microsphere study (24) and RBC study (21), respectively. Global epi- and endo-myocardial MBF/MBV levels were obtained by averaging respective data from the 32 sections.

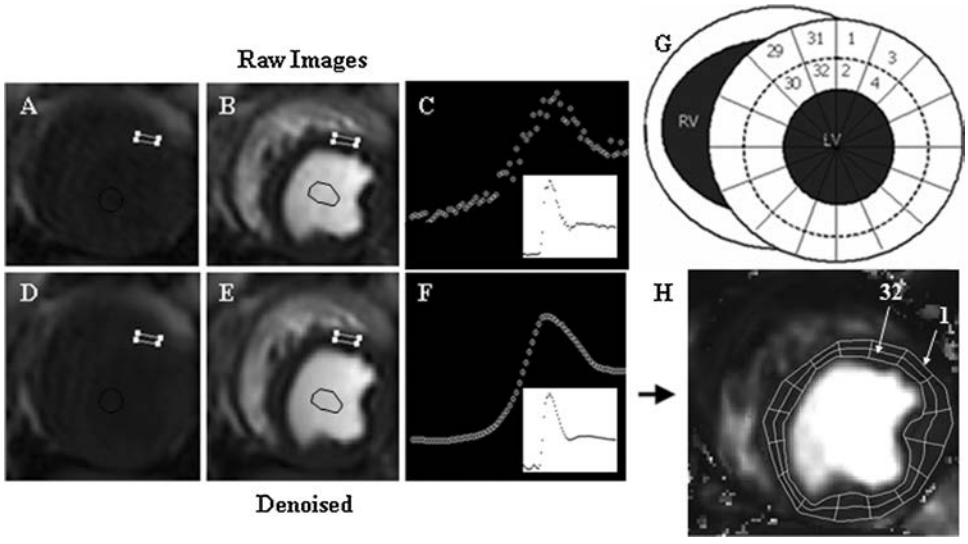

Figure 2. Examples of first-pass perfusion original images and the denoised images using a wavelet denoised algorithm developed in our laboratory. (A) A short-axis view of baseline image before the passage of contrast agent; (B) the same image during the peak contrast administration; (C) the mean intensity curve of the original images showing the signal fluctuations due to the low SNR. (D) and (E) are corresponding images after being denoised, and (F) is the mean curve after the denoising, demonstrating a more uniform curve. The arterial input function ROI can be seen in the LV blood pool in (B) and (E). The small plots in (C) and (F) show that denoising does not distort the arterial input signal. (H) MBV map, constructed from the denoised images, was segmented into 32 pieces that match the pieces dissected for ^{99m}Tc count, as shown in the schematic graph (G). Global epi- and endocardium values were later calculated by averaging the regional values.

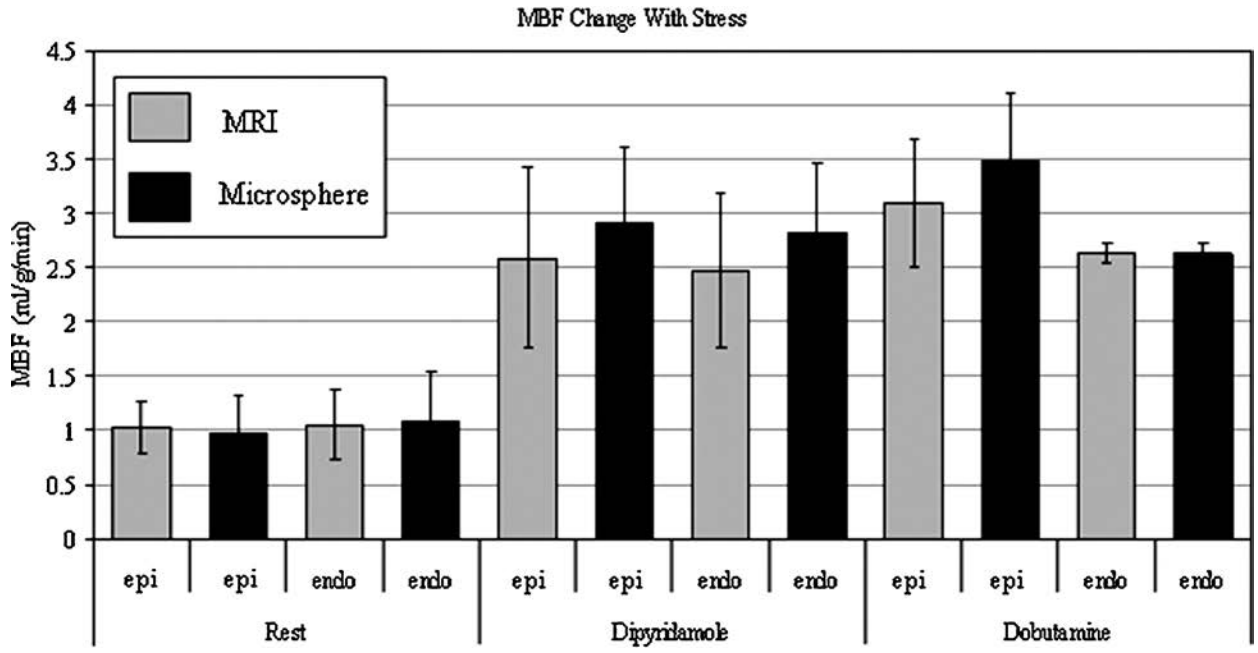

Figure 3. Comparison of MBF data measured by CMR and microsphere methods. MBF increases approximately 3-fold from rest (n = 12) during both dipyridamole (n = 8) induced vasodilation and dobutamine (n = 4) induced stress.

Because capillary hematocrit was not measured directly, the ^{99m}Tc-RBC data was calculated with the capillary hematocrit equaling half the ventricular hematocrit (8):

$$MBV_{corrected} = MBV_{observed} {}^{*} HCT_{ventricle} / HCT_{capillary} \quad [1]$$

Calculation of MBF and MBV from CMR measurements

First-pass dynamic CMR images were first denoised with a method developed in our laboratory (25), and both MBF and MBV maps were obtained using a newly developed deconvolution method (26) that is comparable to the established B-spline method (27) and is validated by microsphere data in dogs. Briefly speaking, the algorithm used a model-independent deconvolution method. The measured MBF values were in excellent agreement with data from microsphere measurements ($R^2 = 0.96$), and from B-spline method ($R^2 = 0.95$). The algorithm was implemented in JAVA (Java Runtime Environment Version 5.0, Sun Microsystems, Inc., Palo Alto, CA, USA) in our laboratory. Once maps were created from the raw images, two rings were manually drawn (Fig. 2). One inner ring surrounded the LV blood pool, while the outer ring encircled the epicardium. This created a region of interest (ROI) as the space between the two rings. The ring ROI can be segmented further into 32 small ROIs resembling the 32 dissected cuts. Epi- and endomyocardial MBF/MBV levels were obtained by averaging regional values from the 32 ROIs. Because the intravascular agent Gadomer distributes only in the plasma volume of blood, the concentration of the contrast agent is a function of blood hematocrit or the ratio of RBC volume to total blood volume. A correction was derived previously (15) for the difference in hematocrits in the large arteries or ventricles and the capillaries since 90% MBV is resident in the capillary compartment:

$$MBV_{corrected} = MBV_{observed} {}^{*} \lambda {}^{*} (1 - HCT_{ventricle}) / (1 - HCT_{capillary}), \quad [2]$$

with λ (the blood-tissue partition coefficient) = 0.95 mL/g, $HCT_{ventricle} = 0.4$, and $HCT_{capillary} = 0.5 {}^{*} HCT_{ventricle}$. Again, capillary hematocrit is approximately half of the ventricular hematocrit (8).

RESULTS

The average RPP values of dogs at rest, during dipyridamole induced vasodilation, or during dobutamine induced stress were 6710 ± 1468, 6981 ± 2609 (P = NS vs. rest), 14705 ± 2755 ($P < 0.02$ vs. rest), respectively. MBF values measured by CMR first-pass perfusion are in good agreement with the results from microsphere measurements (Fig. 3). No statistical differences were found between the CMR and microsphere MBF data (P = NS, n = 12, 8, and 4 for rest, dipyridamole, and dobutamine, respectively). Nearly a 3-fold increase in MBF was seen for both dipyridamole and dobutamine. CMR determined MBV values show excellent agreement with the ^{99m}Tc-RBC results (Fig. 4). No statistical differences were found between the CMR and ^{99m}Tc-RBC data (P = NS). ($N = 4$, 4, and 4 for rest, dipyridamole, and dobutamine, respectively). Transmural MBV of 6.2 ± 1.3 mL/100g tissue at rest was obtained by CMR, while MBV values were 7.2 ± 0.8 and 8.3 ± 0.5 mL/100g tissue for

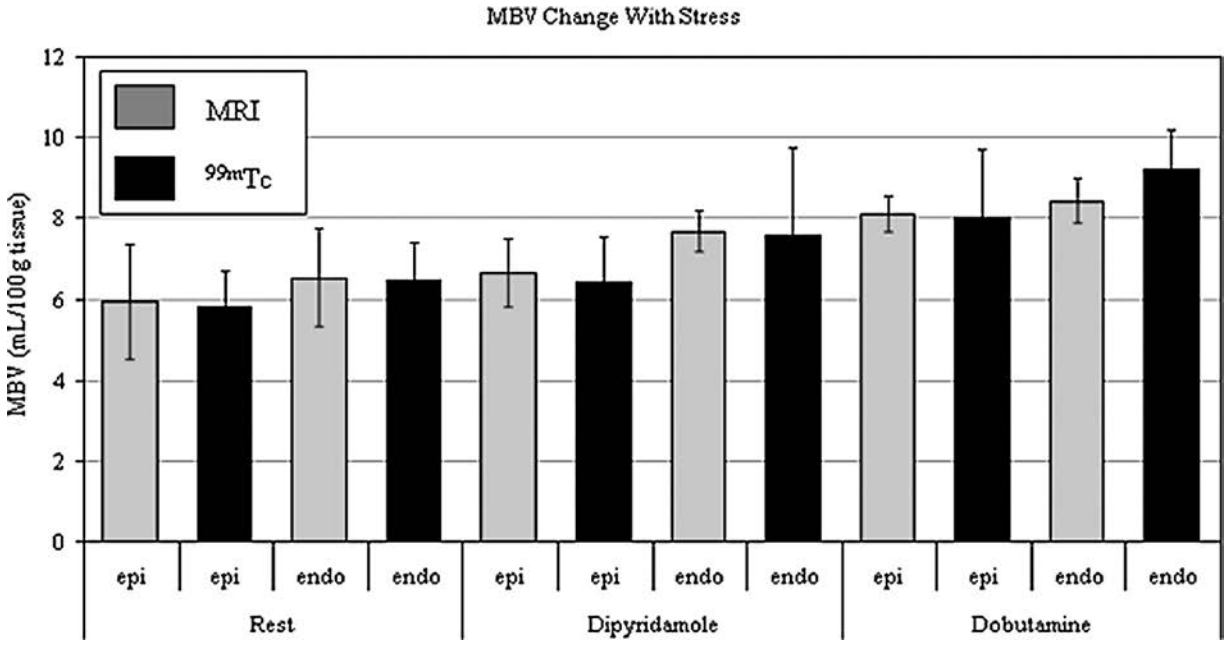

Figure 4. Comparison of MBV data measured by CMR and ^{99m}Tc-labeled RBC methods. Dipyridamole (n = 4) injection induces a small, nonsignificant increase in MBV; Dobutamine (n = 4) stress induces a significant 33% increase in MBV ($P < 0.05$), compared with MBV at rest (n = 4).

dipyridamole and dobutamine, respectively. This relates as CMR detecting a 15% (P = NS) increase from rest in MBV following dipyridamole injection and a 33% increase ($P < 0.05$) following the injection of dobutamine. While CMR and ^{99m}Tc data do not significantly differ, ^{99m}Tc-RBCs measured a 14% increase (P = NS) in MBV from dipyridamole and a 35% ($P < 0.03$) increase during dobutamine. Bland-Altman plots are shown in Fig. 5 to show any biases between ^{99m}Tc-RBC and CMR data. For the epicardium, the mean difference is -0.02 ± 1.5, indicating CMR measurement is consistent with the ^{99m}Tc results. The endocardium has a mean difference of 0.45 ± 1.5, showing that CMR slightly underestimated ^{99m}Tc in this region.

With the use of both CMR and ^{99m}Tc approaches, the endocardial MBV value was measured being constantly larger than that of the epicardium. At rest, the endocardium MBV by CMR was 11% larger (P = NS), and during dipyridamole the difference

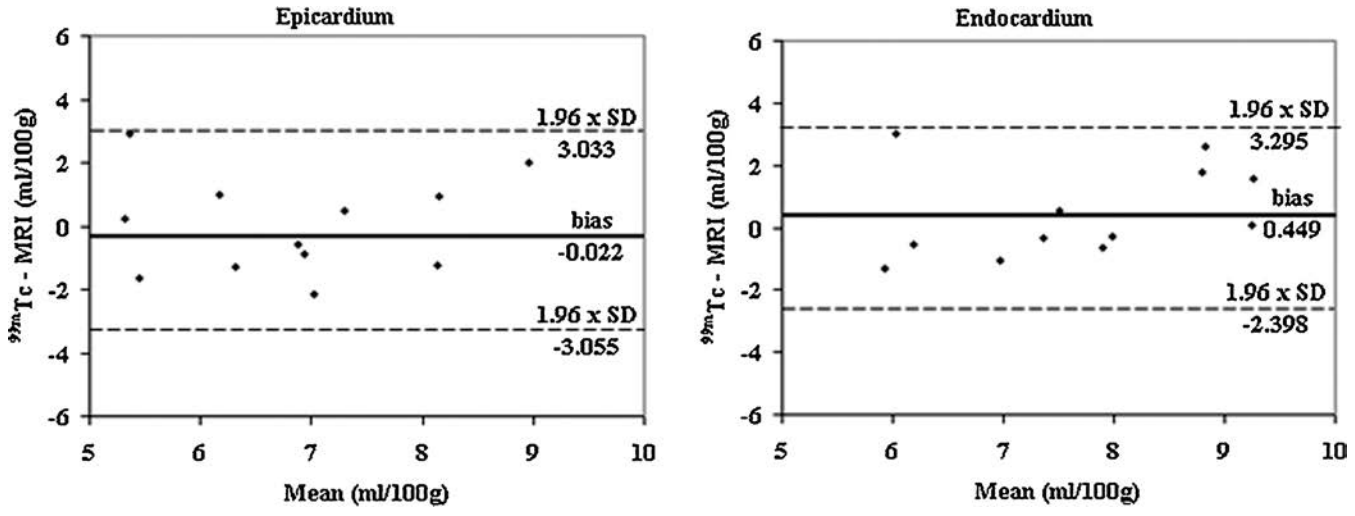

Figure 5. Bland-Altman plots of MBV measurements in epi- and endo-myocardium. Solid lines represent the mean (bias) and the dotted lines represent the limits of agreement (1.96 × SD). CMR tends to overestimate ^{99m}Tc in the epicardium; while ^{99m}Tc slightly overestimates in the endocardium.

increased to an average of 18% (P = NS). In a similar way, ^{99m}Tc measurements showed the endocardial MBV being 12% ($P = 0.02$) and 18% (P = NS) larger at rest and during dipyridamole (P = NS), respectively. While ^{99m}Tc detected an average 17% (P = NS) difference between endo and epicardium during dobutamine, CMR measurement yielded only a 4% difference (P = NS).

DISCUSSION

In the present study, we demonstrated that the CMR first-pass perfusion method with an injection of intravascular agents provides an accurate method for quantifying MBV and is in reasonable comparison with the standard ^{99m}Tc-RBC method. Furthermore, our results are in good agreement with the several existing studies regarding MBV changes under pharmacologically induced stress using myocardial contrast echocardiography. Both dipyridamole and dobutamine increased MBF dramatically but caused only a moderate increase in MBV. Unlike other reported MBV data (~12 mL/100 g tissue) measured by CMR in dogs (14), our measurements indicate that MBV values, either at rest or during pharmacologically induced hyperemia, were below 10 mL/100g tissue. If we use the same hematocrit value of 0.95 mL/g and correction factor from Eq. [2], the reported MBV value would be 8.3 mL/100g tissue and is approximately 33% higher than the MBV we measured at rest, either with the MRI method or the ^{99m}Tc method. This discrepancy warrants further investigation.

CMR measurements

Although the detail of the algorithm for calculation of MBV with the first-pass perfusion imaging was not presented, its capability for the accurate determination of MBF was reported previously (26) and will be submitted separately. This algorithm was selected because of its fast and accurate mapping of both MBF and MBV. The established B-spline method (27) was also used to compare with MBF and results were consistent with our findings.

A saturation-recovery turboFLASH sequence was used here for the data acquisition of dynamic MR images because of its ability for the quantitative determination of MBF, demonstrated by many investigators (14, 16, 28). One of its drawbacks is a relatively low signal-to-noise ratio (SNR) that may be detrimental to the accuracy of the calculation of MBV and MBF. We have adopted our wavelet denoising method (25) to reduce this adverse effect. While no comparison was made in this study, our early study has strongly suggested denoising can significantly increase the accuracy and reduce the spatial variation in the maps of MBF and MBV. One may argue that using trueFISP sequence would yield better SNR in perfusion images. However, there is a concern about dramatic phase change due to the susceptibility effect during the fast bolus passage of the contrast agent in the blood pool. This may affect signals from both myocardium and left ventricle blood. Further systematical investigation is warranted for full understanding about the role of the true FISP sequence in first-pass perfusion imaging.

MBV comparison between CMR and ^{99m}Tc

Our findings suggest that first-pass myocardial perfusion imaging with the injection of blood pool agents can readily quantify not only MBF, but also MBV, with minimal invasiveness. The MBV at transmural, endo-, and the epicardium strongly agreed with the results from the invasive ^{99m}Tc method. In addition to the close agreement between CMR and ^{99m}Tc findings, data from both ^{99m}Tc-RBC and CMR measurements agrees with other reports in dogs (1, 8) showing that there were no significant changes in MBV during vasodilation but significant increases in MBV during dobutamine stress (19, 20). This may be explained by the lack of changes in capillary dimensions because capillaries do not have smooth muscle cells and thus cannot dilate during exogenously induced vasodilation (90% of blood volume within the microvasculature is in capillaries). The small increase (15%) of MBV from rest to vasodilation conditions may be attributed to the increases in the arteriolar and venular dimensions (29), or may be associated with slightly increased RPP values when the dipyridamole was systemically administrated. MBF increased a similar amount with both dipyridamole and dobutamine, while MBV increased more with dobutamine than dipyridamole. This may be explained by a larger amount of capillary recruitment occurring due to the greater increase in myocardial O_2 demand with the administration of dobutamine (19).

With millimeter spatial resolution, the CMR method allows differentiation of MBV values in the endocardial and epicardial regions. Greater difference in MBV was found with either vasodilation or stress using ^{99m}Tc method, in comparison with rest. This finding agrees with other reports (1, 8). Our CMR data has shown similar MBV differences between epicardium and endocardium with vasodilation. The much smaller difference observed by CMR with the dobutamine induced stress is likely due to the errors listed in the limitation sections below, as well as the fluctuation of MBV during the CMR and ^{99m}Tc measurements.

MBV comparisons with other studies

At rest, MBV determined by CMR was 6.2 mL/100g tissue. Crystal et al (8) reported a similar value of 6.5 mL/100g tissue determined by ^{51}Cr-RBC. Our MBV during dipyridamole vasodilation was 7.2 mL/100g tissue (a 14% increase from rest). This compares to other adenosine studies using dogs that reported values of 18% increase (20) and 20% increase (24). In a CMR study using pigs, Jerosch-Herold et al (16) reported a rest MBV of 7.8 and hyperemic value of 10.2 (31% increase). With CMR, we measured MBV during dobutamine stress to be 8.3 mL/100 g tissue, which gives a 33% increase and is also in agreement with Bin et al (20) who reported a 28% increase in dogs with dobutamine using the MCE approach.

Limitations

Some errors may be present for the calculations in both CMR and ^{99m}Tc. First, transmural hematocrit differences likely affected both CMR and ^{99m}Tc MBV results. There was no direct

measurement of the hematocrit of the dogs in this study, but values from literature were applied to calculate MBV. Half the value of the hematocrit in large arteries was used for that in the capillary (8). Other studies have suggested a 60% (8) or even 75% (30) of hematocrit in larger arteries. If this is true, our MBV values would be underestimated by the CMR method and overestimated by the ^{99m}Tc calculation. In addition, there may be inter-subject difference in hematocrit and/or difference between rest and vasodilation (19), as well as the difference between epi- and endocardium (8). The fact that endocardial MBV measured by CMR is lower might be explained by the possible higher value of hematocrit in the capillary. On the other hand, the agreement in epicardial MBV between CMR and ^{99m}Tc methods may indicate the heterogeneity of hematocrit in the myocardium, i.e., capillary hematocrit may be different between epi- and endomyocardial tissue. Secondly, because MR signals included signals from both large and small vessels in the myocardium, MBV measured by CMR may reflect the CBV, rather than microvascular MBV. We have partially corrected this compartment issue with Eq. [1] and by drawing ROIs within transmural myocardial regions. However, some larger arterioles may still exist within our ROIs. This would not be the case for ^{99m}Tc measurements because the hearts are rinsed with saline before the dissection. This causes blood from the larger vessels to be washed out, leaving blood mainly in vessels $< 100\ \mu$m in diameter (31). Our ^{99m}Tc vs. CMR values are fairly consistent, however, this would explain any slight overestimation for epicardial MBV with our CMR method. Thirdly, the water exchange effect was not accounted for in our deconvolution model calculation of MBV (32). This is particularly important when an intravascular contrast agent is used. Nevertheless, water exchange effect is not expected to produce a significant error in MBV. This is because we have injected only 0.015 mmol/kg of Gadomer, which would yield peak plasma concentration of 0.0045 mM, assuming a cardiac output of 4 L/min in dogs (33). Given that Gadomer has a similar T1 relaxivity as NC100150 used in another study (31), the fast exchange regime remains valid in our study and measured perfusion signal intensity and thus MBV may not be affected significantly by the water exchange effect. Finally, although we match the segments of MR images with the segments of tissue for ^{99m}Tc counting as much as we could, mismatched segments are still possible because the dissection segments only approximated those in MR images.

CONCLUSION

Our quantitative approaches with first-pass perfusion CMR permit fast evaluation of changes in MBV at rest and during pharmaceutically induced vasodilation or stress. This mapping method, shown in a normal canine heart, may allow for the regional assessment of changes in MBV quantitatively in the ischemic heart and provide complementary information on myocardial flow and viability.

ABBREVIATIONS

^{99m}Tc	technetium-99-metastable
CBV	coronary blood volume
CMR	cardiovascular magnetic resonance
EBCT	electron-beam computed tomography
ENDO	endocardium
EPI	epicardium
FLASH	fast low-angle shot
HCT	hematocrit
LV	left ventricle
MBF	myocardial blood flow
MBV	myocardial blood volume
MCE	myocardial contrast echocardiography
RBC	red blood cell
ROI	region of interest
RPP	rate-pressure product
SNR	signal-to-noise ratio

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