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Quantitative Myocardial Distribution Volume from Dynamic Contrast-Enhanced MRI

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Abstract

The objective of this study was to investigate if dynamic contrast-enhanced magnetic resonance imaging (MRI) can be used to quantitate the distribution volume (v_e) in regions of normal and infarcted myocardium. v_e reflects the volume of the extra-cellular, extra-vascular space within the myocardial tissue. In regions of the heart where an infarct has occurred, the loss of viable cardiac cells results in an elevated v_e compared to normal regions. A quantitative estimate of the magnitude and spatial distribution of v_e is significant because it may provide information complementary to delayed enhancement MRI alone.

Using a hybrid gradient echo-echo planar imaging (GRE-EPI) pulse sequence on a 1.5T MRI scanner, 12 normal subjects and four infarct patients were imaged dynamically, during the injection of a contrast agent, to measure the regional blood and tissue enhancement in the left ventricular (LV) myocardium. Seven of the normal subjects and all of the infarct patients were also imaged at steady-state contrast enhancement to estimate the steady-state ratio of contrast agent in the tissue and blood (Ct/Cb)—a validated measure of v_e . Normal and infarct regions of the LV were manually selected and the blood and tissue enhancement curves were fit to a compartment model to estimate v_e . Also, the effect of the vascular blood signal on estimates of v_e was evaluated using simulations and in the dynamic and steady-state studies.

Aggregate estimates of v_e were $23.6\% \pm 6.3\%$ in normal myocardium and $45.7\% \pm 3.4\%$ in regions of infarct. These results were not significantly different from the reference standards of Ct/Cb ($22.9\% \pm 6.8\%$ and $42.6\% \pm 6.3\%$, $p=0.073$). From the dynamic contrast-enhanced studies, approximately one minute of scan time was necessary to estimate v_e in the normal myocardium to within 10% of the steady-state estimate. In regions of infarct, up to three minutes of dynamic data was required to estimate v_e to within 10% of the steady-state v_e value.

By measuring the kinetics of blood and tissue enhancement in the myocardium during an extended dynamic contrast enhanced MRI study, v_e may be estimated using compartment modeling.

Introduction

Delayed enhancement (DE) MRI is a widely used and powerful clinical tool for the detection of myocardial infarct. Typically, a paramagnetic contrast agent is injected into a patient to temporarily distribute in the extra-cellular, extra-vascular space (v_e) in the myocardium. In

regions of the heart where an infarct has occurred, the loss of viable cardiac cells results in an increased v_e where the contrast agent can accumulate. This increase in contrast agent shortens the T1 of the tissue, making regions of scar tissue visible when an inversion recovery sequence set to null the normal myocardium is used (1). DE MRI has become the gold standard for non-invasively identifying the presence and extent of myocardial scarring (2–4). DE MRI can also discriminate small regions of sub-endocardial infarct from viable tissue and has shown promise for reproducible sizing of infarcts and viability assessment in serial studies (5,6).

In effect, v_e directly reflects how much of an image region is comprised of extra-cellular, extra-vascular space. The remaining fraction of the image region consists of viable cells and vasculature. A quantitative estimate of the magnitude and spatial distribution of v_e may provide a complementary measure of the severity and characteristics of infarcts compared to DE imaging alone. Furthermore, the accurate estimation of regional v_e maps of the heart may provide a means to track changes in the degree of myocardial scarring in follow-up studies.

The steady-state (Ct/Cb) tissue enhancement method is one validated means of quantitating v_e in the myocardium (7). To estimate v_e using this method, a slow infusion or a bolus injection (7–10) of contrast agent is given and allowed to reach a near-equilibrium state of contrast agent transfer into and out of the tissue. At equilibrium, the ratio of the concentration of contrast agent in the vasculature to the concentration of contrast agent in the extra-cellular extra-vascular space constitutes the partition coefficient (11). When the partition coefficient is scaled to account for the blood hematocrit, then the steady-state ratio of contrast agent in the tissue and blood, Ct/Cb, directly reflects the myocardial distribution volume, v_e (10,12,13). Here, Ct is the concentration of contrast agent in the tissue and Cb is the concentration of contrast agent in the blood. The bolus and slow infusion methods require nearly 10 minutes and 20 minutes (7,9,10), respectively, for the flow of contrast agent into and out of the myocardium to reach a steady-state condition.

We hypothesize that a relatively short dynamic contrast-enhanced MRI scan can also quantitate v_e in the myocardium. With this proposed method, the kinetics of myocardial blood and tissue enhancement are imaged dynamically for one to five minutes after a bolus injection of contrast agent. The enhancement of the myocardium is assumed to increase and decrease according to a physiologically derived compartmental model (14,15). v_e is then estimated from the kinetics of tissue enhancement in the myocardium, according to the representative model. While v_e values from dynamic contrast-enhanced scans have been reported (12,16–19), they have not been validated, and the one study that included infarct regions (19) reported a decrease in v_e with infarction, contrary to expectations.

Methods

Simulation and patient studies were performed in order to evaluate the accuracy of estimating v_e from dynamic contrast-enhanced perfusion data. The simulation studies were used to investigate how imaging time and the inclusion of a vascular blood signal (Vb) in the kinetic and Ct/Cb models would affect v_e estimates in a typical case. Preliminary patient studies were also performed to determine the minimum imaging time necessary to fully capture the delayed kinetics of tissue and blood enhancement in regions of normal and infarcted tissue. The primary goals of the patient studies were 1) to compare v_e and Ct/Cb estimates in normal and infarcted regions of myocardium and 2) to investigate how well the results agreed with predictions based on simulations with the inclusion of Vb.

Simulations

For the simulation studies, dynamic tissue enhancement curves, $C_{tis}(t)$, were generated by the numerical convolution of a patient-derived blood enhancement curve, $C_{bld}(t)$, with a modified Kety model (12,14). The representative kinetic tissue enhancement model is given as:

$$C_{tis}(t) = C_{bld}(t - \Delta t) \otimes K^{trans} e^{-k_{ep}t} + V_b C_{bld}(t - \Delta t) \quad (1)$$

From this kinetic model, K^{trans} and k_{ep} are rate constants of influx and efflux of contrast agent into and out of the tissue, respectively. v_e is defined as the ratio of K^{trans} to k_{ep} for each tissue curve, scaled by an average blood hematocrit value (Hct=0.45): $v_e = K^{trans}/k_{ep} * (1-Hct)$ (10, 12). The V_b term included in $C_{tis}(t)$ represents the fractional component of the blood vasculature in the myocardium. The Δt term represents the time delay between LV blood enhancement and myocardial tissue enhancement, as blood passes through the coronary arteries. For the simulations of $C_{tis}(t)$, physiologic values of K^{trans} , k_{ep} , V_b , and Hct (12,18, 19) were used in the convolution function. For normal myocardium: $K^{trans}=0.6$ ml/g/min, $k_{ep}=1.65$ min⁻¹, $V_b=0.04$, and Hct=0.45. For infarcted myocardium: $K^{trans}=0.4$ ml/g/min, $k_{ep}=0.5$ min⁻¹, $V_b=0.04$, and Hct=0.45.

The $C_{bld}(t)$ curve used in the simulations was interpolated from two dynamic signal intensity (SI) curves that were acquired using a Siemens Avanto 1.5T MRI scanner (Siemens Medical Systems, Erlangen, Germany) using a hybrid GRE-EPI pulse sequence (20) with saturation recovery magnetization preparation. The first 300s portion of $C_{bld}(t)$ was taken from the mean SI of a manually selected region of the the LV blood pool of a healthy subject immediately after the injection of a 0.025 mmol/kg dose of gadolinium. The final 10s of $C_{bld}(t)$ was acquired from the mean SI of the same LV blood pool region after 15 minutes. The two SI segments of $C_{bld}(t)$ were interpolated with three piecewise-linear line segments to construct a continuous $C_{bld}(t)$ curve that was 900s long. To ensure realistic dynamics of blood enhancement between the acquired SI segments, the slopes of the interpolated segments of $C_{bld}(t)$ were chosen so that the ratio of $C_{tis}(t)$ to $C_{bld}(t)$ was approximately constant for the entire length of the curves. For this constraint, $C_{tis}(t)$ was numerically generated from $C_{bld}(t)$ using Eq. (1) with influx and efflux constants typical for a healthy region of myocardium (see above). $C_{bld}(t)$ was chosen to be 900s in length because tissue enhancement is nearly constant after this time duration (9, 10).

While tissue enhancement curves from regions of infarct may vary dramatically from regions of healthy myocardium, a single LV blood enhancement curve is typically assumed to serve as the input to regions of both normal and scarred myocardium in infarct patients. Thus, for the limited simulations performed here, a single $C_{bld}(t)$ curve was used for simulating normal and infarct regions. The analysis of the variability of $C_{bld}(t)$ curves in different patients was beyond the scope of this study. Finally, prior to generating $C_{tis}(t)$ from the LV blood enhancement curve, $C_{bld}(t)$ was smoothed with a temporal median filter to reduce the noise in the first-pass enhancement region of the curve.

Simulations—The effects of imaging time on estimates of v_e

In order to estimate the amount of imaging time necessary to accurately measure v_e in dynamic perfusion scans in humans, the effect of the tissue and blood enhancement curve length (the imaging time) on the estimates of v_e and C_t/C_b in simulations was evaluated. Using the simulated curves described above, progressively longer portions of the “tails” of the enhancement curves were truncated, leaving less and less kinetic data to fit to the compartmental model in Eq. (1). Using a least-squares fitting algorithm, the remaining enhancement data was fit to the kinetic model to estimate v_e . The estimated v_e values for the truncated normal and infarcted enhancement curves were compared to the known original v_e

values to measure the % error between the estimate of v_e and the true v_e as a function of the length of the enhancement curves.

Simulations—The effects of V_b on estimates of v_e and C_t/C_b

The relative steady-state change in tissue signal enhancement in the C_t/C_b model reflects the approximate change in contrast agent concentration in the myocardium, which includes the cellular and extra-cellular space *and* the myocardial vasculature, V_b . Because V_b may comprise on the order of 10% of the total myocardial tissue volume (18,21–23) and because the contrast agent concentration may be higher in V_b than in the remaining tissue, v_e and C_t/C_b can be overestimated if the vascular blood signal contribution is not accounted for in dynamic and steady-state C_t/C_b studies. To investigate how the estimates of v_e and C_t/C_b depend on V_b , we defined the steady-state C_t/C_b model in Eq. (2) to account for the physiologic V_b signal, similar to the way that V_b is included in Eq. (1). In the C_t/C_b model given below, $\Delta C_{tis}^*(t)$ is the *observed* change in tissue signal enhancement from pre-contrast to post-contrast with the V_b signal included. V_b was systematically changed when generating the simulated $C_{tis}(t)$ curves, and the resultant changes in C_t/C_b were calculated.

$$\frac{\Delta C_{tis}}{\Delta C_{bld}} = \frac{(\Delta C_{tis}^* - V_b \Delta C_{bld})}{\Delta C_{bld}} \quad (2)$$

Acquisition of dynamic image data in humans

All dynamic images were acquired with a Siemens Avanto 1.5T MRI scanner (Siemens Medical Systems, Erlangen, Germany) using a hybrid GRE-EPI pulse sequence (20) with saturation recovery magnetization preparation. Twelve normal subjects and four infarct patients were imaged at rest, after being given a low-dose (0.025 ± 0.006 mmol/kg) bolus injection of Gd-DTPA (Omniscan; Amersham Health Inc., Princeton, NJ) at 6cc/s. All the infarct patients in the study had known coronary artery disease (CAD) with stable chronic infarcts with no edema present. For these patients, imaging took place from nine months to more than 25 years post-infarct. Three of the patients had non-ST-segment elevation myocardial infarcts and one had a ST-segment elevation myocardial infarct. The contrast agent bolus was followed by a saline flush of 15mL at 6cc/s using a Medrad Spectris Solaris MR power injector (Medrad, Inc., Indianola, PA) via an antecubital vein. To speed imaging, in five of the normal subjects only half of the phase encoding lines for each image were acquired, using TSENSE acceleration (24). For each subject imaged, imaging parameters were selected in order to acquire at least three short axis (SA) slices of the LV during every heart beat. Typical imaging parameters were: delay after saturation pulse=40–70ms, TR=5.8–6.5ms, TE=0.98–1.23ms, ETL=4, flip angle=20–25, 8mm slice thickness, FOV=360×270 with an image matrix=160×90.

Dynamic stress images were acquired approximately 10 minutes after the dynamic rest scans with the same sequence and parameters described above. Prior to imaging, a continuous infusion of adenosine (140 μ g/kg/min) (Adenoscan; Astellas Pharma US, Inc., Deerfield, IL) was administered to each subject via an antecubital vein to induce vasodilation. Approximately three minutes after the start of the adenosine infusion, a low-dose (0.024 ± 0.006 mmol/kg) bolus injection of Gd-DTPA followed by a saline flush of 15mL at 6cc/s was given. During the dynamic rest and stress imaging, most patients held their breath for approximately 10–20 seconds during the first-pass of contrast agent through the LV and then breathed shallowly for the remainder of the scan. At least one minute of data was obtained in all normal subjects and at least three minutes of data was acquired for infarct patients. As time and protocol permitted, longer acquisitions were performed. Figure 1 depicts a representative timeline.

Acquisition of DE and Ct/Cb image data in humans

In all of the healthy subjects and infarct patients, additional contrast agent was injected after the rest and stress dynamic scans were completed, for a total contrast agent dose of 0.15–0.20 mmol/kg. After a 10–15 minute wait, DE imaging was performed using a phase sensitive inversion recovery (PSIR) imaging sequence (25). The approximate inversion recovery time to null the healthy myocardium was determined subjectively by experienced cardiologists. Typical inversion times ranged from 225–275ms.

To image Ct/Cb, a series of images were acquired in seven of the normal subjects and in all four infarct patients using the GRE-EPI sequence described above. Ct/Cb imaging consisted of a scan acquired prior to the injection of any contrast agent and a post-contrast scan acquired approximately 15 minutes after the final injection of contrast agent. The pre- and post-contrast scans consisted of 10 image frames with a total image time of approximately eight to 12 seconds. The same imaging parameters and SA slices were selected to match those in the dynamic scans. The images were used to estimate Ct/Cb to give v_e as described below.

Patient image processing—kinetic modeling of v_e

All image processing was performed using Matlab Version 7.2 (The MathWorks Inc. Natick, MA). The image frames for each slice of the LV were manually registered for in-plane rigid-body motion and endocardial and epicardial contours were manually drawn in each SA slice to segment the LV myocardium for analysis. Because the pre-contrast myocardium was assumed to have a uniform signal intensity, the LV was divided into eight equiangular sections and each section was normalized to the mean pre-contrast signal of the entire LV to correct for regional MRI coil sensitivity (26,27). Dynamic tissue enhancement curves, $C_{tis}(t)$, were obtained from each of the LV octants and the dynamic blood enhancement curve, $C_{bld}(t)$, was obtained from the mean SI of a manually selected region of the LV blood pool in each slice. For each subject in the study, all of the LV tissue enhancement curves were simultaneously fit to the compartment model in Eq. (1) to estimate a global time delay between LV blood enhancement and myocardial tissue enhancement. This delay was then set as a fixed parameter when estimating v_e for each LV region within each SA slice of the myocardium. During dynamic imaging, precise image acquisition times were obtained from the scanner in order to account for each patient's variable heart rate during the scan. This "time-stamp" correction process ensures a more accurate estimate of kinetic values such as v_e from the dynamic enhancement curves (28).

A non-linear least-squares curve fitting algorithm was used for the analysis. For each of the normal subjects in the study, approximately one minute of tissue and blood enhancement data was included in the model to estimate v_e . For the infarct patients, at least three minutes of tissue and blood enhancement data was acquired for the analysis. For three of the infarct patients, five minutes of enhancement data was acquired to verify that an approximate steady-state tissue enhancement had been reached. Also, in all but one of the infarct patients, the enhancement curves were acquired from a single continuous dynamic scan. In the remaining infarct patient, three dynamic acquisitions separated by approximately one minute each were acquired and then interpolated to construct a single continuous five minute long set of enhancement data. The imaging time of the blood and tissue enhancement curves was chosen based on simulations and preliminary patient studies, which revealed that v_e error estimates were within 10% of the steady-state v_e value when one minute of non-infarct enhancement data and between one and three minutes of infarct enhancement data was used in the curve fits.

Patient image processing—the effects of imaging time on estimates of v_e

To investigate the effects of imaging time on the kinetic model estimates of v_e in humans, the dynamic perfusion data for the normal subjects and infarct patients was analyzed to determine

the amount of imaging time required for the distribution of contrast agent in the myocardium to reach a “near-equilibrium” state with slowly changing kinetics. Before analysis, the acquired dynamic images were manually registered for in-plane rigid-body motion and regions of healthy and scarred myocardium were manually selected to generate average normal and infarct tissue enhancement curves. For the analysis of myocardial scar, core regions of infarct were manually identified and selected from delayed enhancement images, while peri-infarct scar was not included in the analysis. The full length acquired enhancement curves were fit to the compartmental model in Eq. (1) to estimate a “truth” value of v_e for the normal and infarcted regions of myocardium.

As with the simulation studies, progressively larger portions of the “tails” of the enhancement curves were removed and the remaining data was fit the compartmental model to estimate v_e . The estimates of v_e for the truncated normal and infarct enhancement curves were compared to the original “truth” values of normal and infarct v_e to measure the % error between the two versus different lengths of enhancement curves. This truncation process was used to determine the minimum amount of image time necessary, in both normal and infarcted regions of tissue, to estimate v_e within a desired percentage of the “truth” value.

Patient image processing of Ct/Cb

To estimate Ct/Cb in the myocardium, the 10 image frames of both the steady-state pre-contrast and the final steady-state post-contrast dynamic images were manually registered and averaged to create a mean pre-contrast and post-contrast enhancement image. The average pre-contrast and post-contrast images were then manually registered to one another. The Ct/Cb image was computed using Eq. (2) by subtracting the mean pre-contrast image from the mean post-contrast image and scaling the resultant image by removing the Vb signal contribution and then dividing the final image by the mean relative enhancement of the LV blood signal. The mean model estimate of Vb from all of the dynamic contrast-enhanced perfusion studies, $Vb=0.04$, was used in the calculation of Ct/Cb. In all of the steady-state Ct/Cb patient studies, the endocardial and epicardial boundaries of the LV myocardium and the eight equiangular LV regions were selected to match the regions in the dynamic perfusion images. Also, for the infarct patients, regions of scar in the Ct/Cb images were manually selected (based on DE image comparison) in order to compute average Ct/Cb values for infarct regions of the myocardium without partial volume effects of the surrounding normal tissue.

Statistical analysis of v_e and Ct/Cb data

Aggregate normal and infarct v_e estimates in the human studies were computed as the mean and standard deviation of v_e from each LV octant region used in the model curve fitting process. When evaluating the effect of the length of the tissue enhancement curves on v_e estimates, the error was calculated as the % difference from the steady-state value of v_e at $t=900s$ (in the simulation studies) and the % difference from the “steady-state” value of v_e (using all the enhancement data) in the human studies. Ct/Cb estimates in the simulation studies were computed using Eq. (2) and reflect the steady-state “truth” value of Ct/Cb at $t=900s$ with the inclusion of $Vb=0.04$.

In the human studies, Ct/Cb in each LV octant region reflected the mean value of Ct/Cb for all the image pixels in the region. For aggregate results, the mean and standard deviation of normal and infarct Ct/Cb values from all the LV octant regions were reported. Comparative results of v_e and Ct/Cb were reported as mean and standard deviation values for the seven normal subjects and the four infarct patients that had matched v_e and Ct/Cb analysis. A correlation plot and a Bland-Altman plot were used to compare regional v_e and Ct/Cb estimates in the patient studies and a Student’s t-test was performed to determine whether the estimates of v_e and Ct/Cb were significantly different ($p<0.05$ was considered statistically significant).

Results

Simulation results

In simulation studies of normal and infarct tissue enhancement, the effects of imaging time on the kinetic model estimates of v_e were evaluated. Figure 2 shows simulated blood and tissue enhancement curves that were extended to a “steady-state” enhancement of 15 minutes.

Approximately 30 seconds of the noise-free simulated kinetic tissue and blood enhancement data was required after contrast agent injection to estimate normal values of v_e to within 5% of the true 900s steady-state value. For the infarct curves, approximately 1.5 minutes of simulated kinetic tissue and blood enhancement data were required to estimate v_e to within 5% of truth. As more kinetic data was included to extend the “tails” of the enhancement curves, the model estimates of v_e did not change significantly. Figure 3 shows the relationship between the error of the v_e estimates versus time for simulations of normal and infarct tissue enhancement curves. These results are for this case only, and changes in the input function and kinetic parameters are expected to alter this relationship.

Next, the effects of V_b on steady-state C_t/C_b estimates were evaluated in the simulation studies. Figure 2 shows simulated tissue enhancement curves with and without V_b . In both normal and infarct tissue enhancement curves, the exclusion of modeling V_b resulted in decreased tissue enhancement and elevated estimates of C_t/C_b at steady-state enhancement. This implies that, if the vascular blood signal is not accounted for in modeling the flow of contrast agent into and out of the tissue, v_e will be overestimated. C_t/C_b was calculated using the simulated values of $V_b=0.04$, and $C_{tis}(t)$ and $C_{bid}(t)$ at $t=900s$ in Eq. (2). For the simulated normal tissue curves, the initial known value of v_e was 0.20. The estimates of normal C_t/C_b with and without the inclusion of V_b in the model were 0.21 (3% greater than the known v_e) and 0.25 (23% greater than the known v_e), respectively. For the simulated infarct curves, the initial known value of v_e was 0.45. The model estimates of infarct C_t/C_b with and without the inclusion of V_b were 0.46 (3% greater than the known v_e) and 0.50 (12% greater than the known v_e), respectively.

Human study results

For the quantitation of v_e in the human studies, Figures 4a and 4b show histograms of the aggregate v_e estimates in all the normal subjects from the rest and stress studies. Normal values of v_e at rest and stress were estimated to be $23.6\% \pm 6.3\%$ and $23.9\% \pm 4.3\%$, respectively. The estimates of v_e at rest and stress were not significantly different in normal subjects ($p=0.12$). Infarct values of v_e at rest were estimated to be $45.7\% \pm 3.4\%$ using three to five minutes of dynamic tissue enhancement data. The differentiation of v_e in normal and infarcted myocardium demonstrates the potential of dynamic imaging to distinctly identify regions of infarct and quantify the extent of increase of v_e within the myocardium. In this study, the estimates of normal and infarct v_e in the study are significantly different ($p=0.0001$).

Figure 5 shows the histogram of C_t/C_b measurements in seven normal subjects. Aggregate estimates of C_t/C_b were $22.9\% \pm 6.8\%$ and $42.6\% \pm 6.3\%$ in regions of normal and infarcted myocardium, respectively. Figure 6 shows the correlation between v_e and C_t/C_b in the normal subjects and infarct patients in the study. Figure 7 shows a Bland-Altman plot of the correlation between normal v_e and C_t/C_b results for the seven subjects that were imaged dynamically and at steady-state. The mean Bland-Altman difference has a bias of 1.5%. A summary of myocardial v_e estimates from the present study and other studies is given in Table 1. When λ was reported, a myocardial density of 1g/ml was assumed and the results were scaled by an average hematocrit of 0.45, where $v_e = \lambda * (1-Hct)$.

Figure 8 shows the decreasing error estimates of v_e for a normal and infarcted region of myocardium in a single subject, as more dynamic contrast-enhanced data is included in the

model fits. From the subjects in this study, approximately one minute of dynamic data is required to estimate v_e to within 10% of the steady-state value in normal tissue regions. Between one and three minutes of dynamic data is required to estimate v_e to within 10% of the steady-state value in infarcted tissue regions. The variations in the estimates of Vb from the kinetic modeling was 0.04 ± 0.03 . For the Ct/Cb calculations using Eq. (2), a constant value of 0.04 was used, which resulted in Ct/Cb estimates of $22.9\% \pm 6.8\%$. When the range including one standard deviation (± 0.03) is included in the calculations of Ct/Cb, the mean v_e estimates could theoretically extend from 19.9% to 25.9%.

Figure 9 shows a typical blood enhancement curve (AIF) with the corresponding tissue enhancement curves from a normal and infarcted region of the LV myocardium. Note the suppressed peak enhancement and the decreased rate of contrast agent efflux, k_{ep} , in the infarct tissue curve. Figure 10a depicts a DE image with a small infarct (bright region) in the antero-septal region of the LV. Figure 10b shows one frame of a slice-matched, dynamic contrast-enhanced perfusion image corresponding to the DE image in Figure 10a. Figures 10c and 10d show the corresponding K^{trans} and v_e maps derived from kinetic modeling and Figure 10e shows the v_e map derived from the steady-state Ct/Cb method.

Discussion

The primary finding of this study is that estimates of myocardial v_e can be quantified from dynamic contrast-enhanced perfusion MRI, using compartment models. One minute of dynamic tissue enhancement data is necessary to estimate v_e in normal regions of the myocardium and three minutes of tissue enhancement data is necessary to estimate v_e in regions of infarct. While only one minute of dynamic enhancement data was sufficient to estimate infarct v_e to within 5% of the steady-state v_e value in one infarct patient, the other patients required up to three minutes to be within 5% of the steady-state v_e estimate. A larger population is needed to determine if there is a correlation between patient characteristics or the types of infarcts imaged and the amount of imaging time required to measure the steady-state v_e value in regions of infarct.

The estimates of v_e and Ct/Cb are not significantly different ($p=0.073$) in viable and scarred myocardium when the vascular blood signal, Vb, is included in both the kinetic and steady-state models. One limitation of the study is that when computing v_e and Ct/Cb, the vascular blood volume was assumed to be a constant $Vb=0.04$, which was the mean model estimate of Vb from all of the dynamic contrast-enhanced perfusion studies. While this value of Vb is comparable to values found by another group using MRI (18,29), it is lower than estimates of Vb found by some histopathological estimates (30,31), and it may be possible that within a region of myocardium the fraction of tissue comprised of blood vasculature may not be spatially uniform.

In this study, estimates of v_e and Ct/Cb are both approximately $23 \pm 6\%$ in normal myocardium and approximately $45 \pm 6\%$ in infarcted myocardium. These results parallel the findings from numerous studies that have measured v_e in normal and infarcted myocardium, although there are some discrepancies. Table 1 summarizes these previous findings from other groups. Specifically, the estimates of v_e from this study are similar to v_e results from autoradiographic imaging and histological sectioning techniques (29–31) and are comparable to v_e estimates from the steady-state Ct/Cb method, using regional changes in signal enhancement (7,9,10, 32). v_e measurements from histological studies range from 19%–30% depending on the method of chemical fixation and histological analysis. v_e estimates from the Ct/Cb studies range from 16%–26% in normal myocardium and from 36%–48% in infarcted myocardium. Differences may vary according to whether the v_e of acute or chronic infarct was measured or whether Vb

was accounted for in the Ct/Cb model. In the current study, only stable chronic infarcts were imaged and Vb was included in the calculation of Ct/Cb.

Estimates of normal v_e from several kinetic modeling studies are slightly lower than the results presented here, ranging from 10%–20% in the normal myocardium (12,16–19), and are generally lower than histology and Ct/Cb measurements. It is hypothesized that the difference in these results may be from the techniques used to convert the measured MR signal to contrast agent concentration, or because dynamic contrast-enhanced data was acquired for too short a time to accurately measure the delayed kinetics of tissue enhancement. Differences may also be due to the exclusion of the vascular blood signal in the compartmental models.

In two studies using inversion recovery sequences and T1-mapping to estimate Ct/Cb, v_e results are higher than histological findings and the results of the current study. One author suggests that the elevation in v_e estimates may be due to partial volume effects of mixed blood-myocardium voxels that resulted from the limited spatial resolution of the imaging sequence (11) (although other studies report similar spatial resolutions and different estimates of v_e). Another author suggests the elevated measurements may be due to long-standing severe heart failure with LV remodeling in their patient population (9). The exclusion of Vb in these Ct/Cb models may also have elevated the estimates of v_e . From Eq. (2), it is clear that the inclusion of Vb in the steady-state model can only reduce the estimates of Ct/Cb from the steady-state images. Similarly, from Eq. (1), the inclusion of Vb in the compartmental model can only reduce v_e estimates.

Of the studies in Table 1 that included patients with infarct, all but one reported an increase in v_e in regions of myocardial scarring. It is hypothesized that in regions of the heart where an infarct has occurred, the loss of viable cardiac cells results in an increased distribution volume. Furthermore, (29) reports that v_e increases with increased time of coronary artery occlusion and that v_e is greater in the core of an infarct than in the peripheral infarct regions. This finding suggests that there may be a range of v_e values within an infarct that vary according to the severity of cellular damage in the region. Thus the one study that reported a decrease in v_e in regions of infarct (19) is difficult to rationalize. The reduction in v_e may be due to the short time duration of the dynamic contrast-enhanced perfusion scan or the no-reflow phenomenon (19).

Sources of inaccuracy of the v_e estimates in this study include the low SNR of the dynamic contrast-enhanced images, and missed images during the dynamic scans due to poor ECG gating in some subjects. Gating inaccuracies were minimized by using the acquisition time of each image to correct for non-uniform or spurious time sampling errors in the model fitting algorithm (28). Another source of error in the estimates is patient motion during the scan (respiratory or otherwise), which can corrupt the images with out-of-plane motion and make the image segmentation process and model curve-fitting less accurate.

Accurately measuring v_e may provide complementary information to DE imaging to objectively measure the spatial distribution or severity of scarring in infarct patients. Another practical advantage of including quantitative perfusion imaging in a DE study is that the v_e images are intrinsically registered to the perfusion images for direct comparison or subsequent analysis. This may better allow for classifying perfusion as being within-infarct or peri-infarct ischemia. Alternatively, v_e could be used to improve the specificity of perfusion imaging in the same way DE imaging has been used (33), but with better registration that matches cardiac phase and heart rate. This could better discriminate between ischemia and artifacts.

Conclusion

This study has demonstrated that dynamic contrast-enhanced imaging can be used to accurately quantitate v_e in normal and scarred myocardium. The estimates of v_e and Ct/Cb are not significantly different ($p=0.073$) in human and simulation studies, when three minutes of post-injection dynamic contrast-enhanced data is acquired in regions of infarct. One minute of dynamic contrast-enhanced data may be sufficient to estimate v_e if the patient has no myocardial scarring. To ensure that v_e and Ct/Cb estimates are not over-estimated, the dynamic and steady-state models must account for the signal intensity increase from contrast agent in the myocardial vasculature, Vb. Additional simulation and patient studies are in progress to evaluate the utility of v_e quantitation in research and clinical settings, including pathophysiology beyond chronic scar.

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Figure 1.

A schematic of the typical imaging timeline used in each patient study.

Figure 2. Simulations of extended (900s) blood and tissue enhancement curves with and without the inclusion of the vascular blood signal, V_b . Note that the change in relative tissue enhancement is reduced in the normal and infarct tissue curves when V_b is not included in the model. Subsequently, the ratio of the steady-state ($t=900s$) tissue to blood enhancement (C_t/C_b) is elevated.

Figure 3.

The % error of the normal and infarct v_e estimates versus the amount of noise-free simulated dynamic perfusion data used in the model fits. In the normal tissue curve, approximately 30 seconds of kinetic perfusion data is required to estimate v_e value to within 5% of the steady-state value. In the infarct tissue curve, approximately 1.5 minutes of perfusion data is required to estimate v_e to within 5% of the steady-state v_e value.

Figure 4.

Figure 4a. A histogram of the aggregate normal v_e estimates at rest in 248 octant regions in multiple LV slices in 12 subjects. $v_e(\text{rest})=23.6\% \pm 6.3\%$.

Figure 4b. A histogram of the aggregate normal v_e estimates at stress in 248 octant regions in multiple LV slices in 12 subjects. $v_e(\text{stress})=23.9\% \pm 4.3\%$.

Figure 5.

A histogram of the aggregate normal Ct/Cb estimates in 168 octant regions in multiple LV slices in seven healthy subjects. $Ct/Cb = 22.9\% \pm 6.8\%$.

Figure 6.

A correlation plot between v_e and Ct/Cb in the seven normal subjects and four infarct patients in the study. For the normal subjects, there are 112 points in the plot. These points represent the v_e and Ct/Cb estimates in eight octants in two short axis slices of the LV for the seven normal subjects (ie. $8 \times 2 \times 7 = 112$). For the infarct patients, there are four points representing the average v_e and Ct/Cb estimate in the core region of each patient's infarct.

Figure 7.

A Bland-Altman correlation plot of v_e and Ct/Cb estimates in the seven subjects that were imaged both dynamically and at steady-state. The mean value of v_e and Ct/Cb is $22.1\% \pm 4.6\%$ with a bias of 1.5%. The 112 points represent the v_e and Ct/Cb estimates for eight octants in two short axis slices of the LV in each of the seven patients that underwent both dynamic v_e and steady-state Ct/Cb imaging (ie. $8 \times 2 \times 7 = 112$).

Figure 8.

The % error estimates of v_e in a normal and infarcted region of myocardium in one subject. In the normal tissue region, approximately one minute of dynamic contrast-enhanced perfusion data is required to estimate v_e to within 10% of the steady-state value. In the infarcted tissue region, nearly three minutes of perfusion data is required to estimate v_e to within 10% of the steady-state v_e value.

Figure 9.

A sample blood curve (AIF) and tissue curves from a normal and infarcted region of the LV myocardium from one patient in the study. The normal region was manually selected in the lateral wall of the LV and the infarcted region was selected in the antero-septal region of the LV in the images below. The suppressed peak enhancement and the decreased rate of contrast agent efflux, k_{ep} , in the infarct tissue curve result in a v_e estimate that is higher than in the normal tissue region.

Figure 10.

Figure 10a. A phase corrected DE image with a small visible infarct (bright region) in the antero-septal region of the LV.

Figure 10b. One frame of a slice-matched dynamic perfusion image with manually drawn endocardial and epicardial contours.

Figure 10c. A 32-region K^{trans} flow map derived from kinetic modeling that shows the reduced flow in the region of infarct.

Figure 10d. A 32-region v_e map derived from kinetic modeling that shows the increased v_e in the region of infarct.

Figure 10e. A 32-region v_e map derived from the Ct/Cb model that shows the increased v_e in the region of infarct.

Table 1

Summary of average normal and infarct v_e estimates from distribution volume and partition coefficient measurement studies. In each of the studies, v_e was estimated by one of three methods: kinetic modeling, steady-state Ct/Cb analysis (either by signal difference (ΔSI) or T1-mapping), or histopathological analysis. The v_e estimates are reported as aggregate mean values from multiple subjects and regions in each of the studies. λ =the partition coefficient was reported in some studies and was manually scaled by an average myocardial density of 1g/ml and a mean hematocrit of 0.45, where $v_e = \lambda * (1 - Hct)$ (10,12,13). SR=images were acquired using a saturation recovery MR pulse sequence. IR=images were acquired using an inversion recovery MR pulse sequence. A=acute infarction. C=chronic infarction. Early=images were acquired at three weeks post infarction. Late=images were acquired at six months post infarction.

Group	Method of V_e Estimation	Mean Normal V_e (%)	Mean Infarct V_e (%)	Ref.
Current Study.	V_e using kinetic modeling ^{SR}	22.9	47.5	-
"	Ct/Cb using ΔSI ^{SR}	23.6	42.6	-
Prato et al.	V_e using ex-vivo canine model ^{λ,SR}	20.4	44	(26)
"	V_e using ex-vivo canine model ^{λ,SR}	14.3	40.7	(27)
"	Ct/Cb using ΔSI ^{λ,SR}	16.5	35.8	(28)
"	Ct/Cb using ΔSI ^{λ,SR}	24.8	44	(7)
"	Ct/Cb using ΔSI ^{λ,SR}	22.5 ^A 23.1 ^C	37.4 ^A 48 ^C	(11)
"	Ct/Cb using ΔSI ^{λ,SR}	25.3 ^{Early} 25.9 ^{Late}	45.7 ^{Early} 43.5 ^{Late}	(8)
Ritter et al.	V_e using kinetic modeling ^{SR}	10–16	-	(16)
Vallee et al.	V_e using kinetic modeling ^{SR}	15.3	-	(13)
Larsson et al.	V_e using kinetic modeling ^{λ,IR}	16.5	-	(17)
"	V_e using kinetic modeling ^{λ,IR}	18.2	-	(18)
"	V_e using kinetic modeling ^{λ,IR}	15.4	10	(19)
Flacke et al.	Ct/Cb using T1-mapping ^{λ,IR}	30.8	50.1 ^A 42.9 ^C	(9)
Klein et al.	Ct/Cb using T1-mapping ^{IR}	29	54	(10)
Arheden et al.	Ct/Cb using T1-mapping ^{IR}	18	30–90	(29)
"	V_e using histopathology (rat model)	19–30	-	"
Johnson et al.	V_e using histopathology (rabbit model)	21.2	-	(30)
Polimeni et al.	V_e using histopathology (rat model)	19	-	(31)