Published in final edited form as:

Magn Reson Med. 2013 September ; 70(3): 766–775. doi:10.1002/mrm.24517.

Assessment of Left Ventricular 2D Flow Pathlines during Early Diastole Using Spatial Modulation of Magnetization with Polarity Alternating Velocity Encoding (SPAMM-PAV): a study in normal volunteers and canine animals with myocardial infarction

Ziheng Zhang¹, Daniel Friedman^{1,†}, Donald P. Dione², Ben A. Lin², James S. Duncan¹, Albert J. Sinusas³, and Smita Sampath^{1,*}

¹Department of Diagnostic Radiology, PO Box 208043, TAC N153

²Section of Cardiovascular Medicine, PO Box 208017, LSOG 125-130

Yale University School of Medicine, New Haven, CT 06520-8043, USA

Abstract

A high temporal resolution 2D flow pathline analysis method that describes the spatio-temporal distribution of blood entering the left ventricle during early diastolic filling is presented. Filling patterns in normal volunteers (n=8) and canine animals (baseline (n=1) and infarcted (n=6)) are studied using this approach. Data is acquired using our recently reported MR technique, SPAMM-PAV, which permits simultaneous quantification of blood velocities and myocardial strain at high temporal resolution of 14 ms.

Virtual emitter particles, released from the mitral valve plane every time frame during rapid filling, are tracked to depict the propagation of 2D pathlines on the imaged plane. The pathline regional distribution patterns are compared with regional myocardial longitudinal strains and regional chamber longitudinal pressure gradients. Our results demonstrate strong spatial inter-dependence between left ventricular (LV) filling patterns and LV mechanical function. Significant differences in pathline-described filling patterns are observed in the infarcted animals.

Quantitative analysis of net kinetic energy for each set of pathlines is performed. Peak net kinetic energy of 0.06 ± 0.01 mJ in normal volunteers, 0.043 mJ in baseline dog, 0.143 ± 0.03 mJ in three infarcted dogs with nominal flow dysfunction, and 0.016 ± 0.007 mJ in three infarcted dogs with severe flow dysfunction is observed.

Introduction

Diastolic dysfunction in patients with myocardial infarction is associated with worsened progressive LV remodeling and is an independent predictor of poor outcome [1–2]. Doppler echocardiography (DE) is the current gold standard and the most commonly employed

*Corresponding author: Department of Diagnostic Radiology, Yale University School of Medicine, The Anlyan Center, 300 Cedar Street, N131, New Haven, CT 06520-8043., Tel.: +1 203-737-5398, Fax: +1 203-785-6643, smita.sampath@yale.edu.

†Current address: Department of Mechanical Engineering and Applied Mechanics, University of Pennsylvania School of Engineering and Applied Science, 229 Town Building, Philadelphia, PA 19104-6315, USA.

clinical approach used in the assessment of diastolic dysfunction. Typically, E/A ratios obtained from measurements of mitral valve inflow velocity are used to assess global diastolic function [3]. However, it has been shown that this ratio sometimes reflects a pseudo-normal measurement during disease progression [4]. While regional quantification of early diastolic function may provide more accurate diagnosis of disease progression, it is a challenging problem that involves the characterization of rapidly changing functional interactions between tissue mechanics and chamber hemodynamics.

The spatio-temporal study of LV chamber blood flow pathlines and streamlines has recently become an active research subject with both clinical and academic focus [5, 6]. Here, as a step towards improved characterization of regional diastolic function, we present the temporal evolution of regional diastolic patterns of two-dimensional (2D) flow pathlines using a novel high-temporal resolution MRI technique - SPAMM-PAV [7]. We study the relationships between pathline trajectories and regional myocardial mechanics during early diastole. From regional pathline analysis, an index of diastolic dysfunction is also computed and presented.

In recent studies, regional/spatial indices based on color M-mode echocardiography have been used to better discriminate stages of diastolic dysfunction in patients [8]. For example, at the instant of peak mitral to apical pressure difference, the critical normalized distance into the left ventricle when the pressure relative to the base saturates was computed from spatial patterns of chamber pressure gradients. This critical distance enabled better separation of patient groups with different disease stages than conventional global indices of E/E', E/A, or flow propagation velocity used in the clinic today. Spatial patterns of chamber pressure gradients dictate spatial distribution of flow. In this paper, we will study the relationships between our novel flow pathline analysis with regional pressure gradient patterns in normal volunteers and infarcted dogs. Such contextual regional flow analysis in relation to regional mechanics may provide a better understanding of diastolic dysfunction post myocardial infarction and lead to improved diagnostic and prognostic imaging indices.

Magnetic resonance (MR) imaging offers an alternative to echocardiography overcoming some typical limitations. For example, data acquisition with uniform scan sensitivity in the entire imaged plane, and flexibility in image plane orientation with respect to flow direction is easily achievable using MR imaging [9]. It provides reliable multi-dimensional and multi-directional flow measurements [10–12], and permits the application of specific flow-analysis techniques, e.g. streamline and pathline tracking, for a more comprehensive understanding of the studied complex flow fields [13–15]. Time-resolved cine phase contrast (PC) MR imaging is the technique typically applied in cardiovascular MR studies to characterize intra-cardiac blood flow [16–21]. With recent advances in hardware, parallel imaging and navigator technology, time-resolved three-dimensional (3D) cine PC MR imaging is now commercially available and gaining popularity [6]. The 3D three-directional PC datasets acquired using this package naturally lends itself to pathline analysis, and has been applied in MR angiography [22, 23] and cardiovascular MR imaging [5, 9, 16, 24–25]. However, the current temporal resolution of 3D PC MR imaging (~ 40 ms) [6], is insufficient to capture rapidly changing events during early diastole. For example, peak mitral inflow velocities are typically over 100 cm/s. With a temporal resolution of 40ms, one or two samples at most

can be obtained before the blood particle travels down to the apex and details in flow structures maybe lost. Thus higher temporal resolution is desired during early diastole to ensure sufficient sampling density of pathline trajectories [15].

In this study, 2D early LV diastolic function was assessed using a novel MR imaging technique, **S**Patial **M**odulation of **M**agnetization with **P**olarity **A**lternating **V**elocity encoding (SPAMM-PAV), which provides simultaneous measurements of myocardial displacement and chamber blood velocity [7] at high temporal resolutions of 14 ms, sensitive to the rapid early-diastolic mechanical and hemodynamic events. In addition to excellent temporal sampling of the flow data, the simultaneous acquisition of regional myocardial strain and chamber flow datasets using SPAMM-PAV also offers distinct advantages in overall time savings, spatial and temporal registration of the two measurements with matched protocol parameters, and registered transient physiological manifestations, with no loss in quality of each measurement. It also greatly increases the time efficiency in imaging and simplicity in post-processing due to spatial co-registration. The SPAMM-PAV pulse sequence was used to quantify the 2D in-plane blood velocity field and myocardial displacement field on select long axis imaging planes.

Flow pathlines describe the paths of massless particles over time in the flow, and are strongly related to the dynamic behavior of flow fields [24]. They are also highly suitable for studying intra-cardiac blood flow given its unsteady, time-dependent feature [13–15]. In this paper, using the SPAMM-PAV pulse sequence, we study the spatio-temporal distribution of blood entering the left ventricle during early-mid diastole at high temporal resolutions by tracking the 2D flow pathlines of virtual blood emitter particles dynamically released from the mitral valve plane. Its spatial relation to longitudinal pressure gradient patterns (computed from acquired chamber blood velocity data) and to the regional myocardial longitudinal strain patterns (computed from acquired myocardial displacement data) are also characterized. The flow pathlines are studied in eight normal volunteers, one baseline dog and six infarcted dogs imaged 3 days post infarction and reperfusion. Quantitative analysis of net kinetic energy along pathlines for each set of released emitter particles is also performed and the peak net kinetic energy is presented as a novel pathline-derived index of diastolic dysfunction.

Methods

MR Imaging Pulse Sequence

All the experiments reported in this study were performed on a 1.5 Tesla (T) Siemens Sonata scanner (Siemens Medical Solutions, Erlangen, Germany), equipped with gradient coils capable of imaging at 33 mT/m and with maximum slew rates of 100 T/m/s. The SPAMM-PAV imaging sequence, discussed in detail in Ref [7], was employed for all the human subject and canine measurements. Displacement encoding is achieved using a 1-1 spatial modulation of magnetization (1-1 SPAMM) tagging preparation. Bipolar gradients sensitive to blood velocity with alternating polarity each time frame are played out before the readout gradients to encode blood velocity. A cine segmented gradient-echo echo planar imaging readout is employed. By integrating displacement encoding and phase velocity encoding approaches, the SPAMM-PAV technique provides simultaneous measurements of

1-D myocardial displacement and 1-D chamber blood velocity with a high temporal resolution of 14 ms in a single breath-hold acquisition (see Fig. 1). In reality, the temporal resolution of the velocity measurements is 28 ms, but view-shared to match the temporal resolution of the strain measurements. The parallel imaging technique, GRAPPA, was implemented to reduce the scan time to a clinically feasible image acquisition time.

The SPAMM-PAV datasets were acquired using imaging parameters as follows: image matrix = 192×192 , spatial resolution = $1.5 \times 1.5 \text{ mm}^2$, slice thickness = 8mm, views per cardiac phase = 3, echo train length = 3, TR/TE = 14/4.6ms, tag separation = 8mm, tagging flip angle = 90° , effective VENC 75cm/s (150 cm/s +, 150 cm/s -), an incrementing train of imaging flip angles was employed (to maintain constant tagging contrast-to-noise ratio during the acquisition window) with final flip angle $\alpha_n = 15^\circ$, receiver bandwidth = 500Hz/pixel. At the beginning of each heartbeat, a delay ($D_1 = 30\%$ of R-R cycle) was inserted to limit the number of RF pulses for improved tag contrast during diastole. Parallel imaging with accelerating factors of 4 was used resulting in acquisition times of around 19 s.

Our previous results [7] in flow phantoms demonstrate good suppression of spurious phase errors due to concomitant gradient and inhomogeneity effects with flow measurement accuracy of 96% using SPAMM-PAV as compared to 99% using conventional PC techniques. These results demonstrate good reliability of SPAMM-PAV to perform flow analyses.

Volunteer Studies

Volunteer studies were performed in eight normal volunteers. Relationships between the filling patterns, the longitudinal pressure gradient patterns, and the regional longitudinal strain patterns were studied, and quantitative kinetic energy analysis of flow pathlines was conducted. All the studies were approved by the Institutional Review Board of Yale University and all subjects provided written informed consent. All datasets were obtained with the subject in the supine position on the MR scanner bed. The volunteers [3 females, 5 males; age: 34 ± 9 (mean $\pm$ SD) yrs; height: 1.73 ± 0.09 m; weight: 69.39 ± 14.23 kg] had no prior diagnosis or symptoms of any heart disease.

A long-axis slice in the 4-chamber view was acquired for all normal volunteer studies. The tag encoding direction was set along the readout direction, and the flow encoding direction was set along the phase-encode direction. For each slice, two breath-hold acquisitions with orthogonally swapped readout directions were acquired to obtain two-dimensional (2-D) displacement and velocity sensitivity. Datasets acquired by the SPAMM-PAV sequence were reconstructed and analyzed offline by post-processing software developed in Matlab (MathWorks, Natick, MA).

Canine Studies

Studies were also performed in one normal dog for baseline measurements and a set of six infarcted dogs. All the canine studies were performed with approval of the Institutional Animal Care and Use Committee, according to the guiding principles of the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council, Washington, DC, 1996).

One dog was imaged at baseline and six dogs (30–35 kg) were imaged 3 days post infarction and reperfusion. All six infarcted animals were fasted overnight prior to surgical intervention. The dogs were anesthetized with halothane (0.6–1.5%), nitrous oxide (70%) and oxygen (30%), intubated, and placed on a respirator for mechanical ventilation. An angioplasty catheter was placed in the proximal left anterior descending (LAD) artery, following which a 5–6 hour balloon occlusion was performed with subsequent reperfusion with aim of creating an antero-septal transmural infarct.

The animals were placed in the head-first-left-lateral position. SPAMM-PAV datasets were acquired in the 4-chamber long-axis slice orientation as described in the normal volunteer section, and were reconstructed and analyzed offline by the same post-processing software aforementioned.

2D Flow Pathlines

Velocity maps acquired in both in-plane directions from SPAMM-PAV datasets were used for pathline analysis to investigate the spatial propagation patterns of virtual blood particles continuously emitted from the mitral valve plane during early diastolic rapid filling. A region around the mitral valve was first selected and the flow velocity within this region was averaged, as shown in Fig. 2, to depict the mitral inflow velocity curve. At each time frame, the number of emitter particles released from the mitral valve plane was proportional to the area under the inflow velocity curve. The pathlines of each set of released emitter particles was tracked in time using the acquired multi-time frame 2D velocity fields. All pathline analysis was performed in the Matlab programming environment. A Catmull-Rom Splines interpolation technique [28], with 100 points interpolated between any two sequential propagation points was used to form the pathline. Note that since these pathlines are obtained from 2D velocity fields, the emitter particles are replaced by particles that are moving in and out of the slice plane. Despite this, 2D pathlines provide a meaningful illustration of the temporal distribution of flow patterns within the imaged plane from 2D velocity fields that are reflective of the temporal evolution of spatial pressure patterns in that imaged plane.

Kinetic Energy Analysis of 2D Flow Pathline—In flow pathline analysis, two kinds of information are typically extracted, scalar values and time series, with the former describing local or global properties of a pathline and the latter collecting information along a pathline [24]. A typical time-series based flow pathline analysis, kinetic energy, was performed in eight normal volunteers, baseline dog and the six infarcted dogs to quantitatively assess LV early diastolic filling patterns.

The instantaneous kinetic energy was first calculated based on the knowledge of the volume covered by the pathline during that time step, its velocity and the density of the blood. The particle velocity between interpolated time points was assumed to be constant and was therefore calculated via $v = l / t$, where v is the instantaneous velocity, l is the linear distance between two interpolated time points, and t is the time-span between points, 14 ms.

The mass of the group of particles was determined by $m = \rho V$ where m , ρ and V represent overall particle mass, human blood density (assumed to be constant at 1060 kg/m^3), and

volume of the particle region respectively. The particle was defined as a curved cuboid with constant horizontal cross-sectional area, A , (the product of the width of the pixel, 1.6 mm, and the slice thickness, 8 mm) and length, D , (the distance traveled by the particle from the first to the second frame). As such, the volume of the region was defined as:

$$V = \int_0^D A dL = A \times D, \text{ where } D = \sum_{n=1}^{100} \sqrt{(x_{n+1} - x_n)^2 + (y_{n+1} - y_n)^2} \quad (x_n \text{ and } y_n \text{ were latitudinal and longitudinal coordinates respectively}) \text{ and the overall mass was therefore: } m = \rho V = \rho AD.$$

The kinetic energy of a region was then calculated by substituting $l/\Delta t$ for v between the two frames in question and substituting ρAD for m . As a result, the kinetic energy equation can be expressed as:

$$KE = \frac{mv^2}{2} = \frac{(\rho AD) \left(\frac{l}{\Delta t} \right)^2}{2} = \frac{(\rho AD)(l)^2}{2(\Delta t)^2}. \quad (1)$$

The kinetic energy of each emitting particle is calculated for each time frame. The net kinetic energy experienced by each set of released pathlines (computed as the average kinetic energy of all pathlines released at each time frame) was then computed [26]. The net kinetic energy for each set of released pathlines is then plotted for all normal volunteers, and canine animals and the peak net kinetic energy is compared between volunteers and animals.

Longitudinal Axial Pressure Gradient

In our earlier work, we described the existence of a basal to apical pressure gradient within the left ventricle creating suction and facilitating filling during the acceleration period of rapid filling. We also described how this pressure gradient is reversed during the latter part of rapid filling (or the deceleration period). In this paper, we relate regional pressure gradients to pathline trajectories. From the reconstructed blood velocity images, longitudinal pressure gradients were computed using the reduced Euler Equation [27]. The spatio-temporal variation of the longitudinal pressure gradient within the LV chamber was then investigated as follows. The average longitudinal pressure gradient within ten central regions, uniformly dividing the length of the ventricle as illustrated in Fig. 3, was computed and plotted as a function of time to represent the temporal variation of each central region of interest (ROI) from base to apex.

Longitudinal Lagrangian Strain

Myocardial longitudinal strain evolution was analyzed from the tagged images acquired by SPAMM-PAV using the harmonic phase (HARP) methodology [28, 29]. The myocardial ROIs, i.e. basal, mid-cavity, and apical regions of the septal and lateral LV myocardial walls, were contoured according to a standard from the American Society of Echocardiography's Guidelines [30], as illustrated in Fig. 3. The reference frame for Lagrangian strain computations was selected at the onset of isovolumic relaxation (IVR), which is empirically defined in this study as 80 ms ahead of the onset of rapid filling [7].

Results

2D Flow Pathlines

Normal Volunteer Studies—Figure 4a shows the pathline trajectories for each set of emitter particles released during early diastolic rapid filling in a representative normal volunteer. The pathlines are color-coded to depict the instantaneous KE of the pathlines. In the first figure, the position of the virtual emitter particles at each time frame along the pathlines is depicted by red dots. The large number of dots along each pathline highlights the high temporal resolution of our method. Also, observing the organization of the dots for each time frame, one can visualize the wavefront like propagation of blood from base to apex. As expected, the instantaneous KE increases in particles released during the acceleration period of rapid filling and decreases in particles released during the deceleration period. Also kinetic energy is higher closer to the mitral valve. The temporal evolution of these trajectories follow a specific pattern, with uniform distribution of blood throughout the left ventricle in the early time frames followed by a more centric filling pattern restricted to the basal regions and away from the walls during later time frames. This is more clearly visualized when the pathlines are overlapped using the temporal color scheme as shown in Fig. 4b. An upward propagation of flow pathlines is observed closer to the lateral wall at later time frames in the normal volunteer. While it appears that blood is flowing through the mitral valve flow into the left atrium (LA), we believe these particles in actuality originate above the mitral valve due to partial closure of the mitral valve leaflet during those time frames. The pathline trajectories of these particles represent the movement of these blood particles along the LA wall.

Infarcted Dog Studies—Figure 5 displays the overlapped pathline trajectories for (a) a normal baseline dog, (b) a representative infarcted dog from a subset of three infarcted dogs with qualitatively observed nominal flow dysfunction, and (c) a representative infarcted dog from a subset of three infarcted dogs with qualitatively observed severe flow dysfunction. In comparison to results obtained in a normal volunteer, the pathline trajectories shown in Fig. 5a exhibit a clockwise rotational flow. As the pathlines propagates down to the apex, a near uniform distribution of blood throughout the left ventricle is observed. For both infarcted dogs, patterns of flow dysfunction is observed using pathline visualization. In Fig. 5b, the pathline trajectories are similar to the baseline animal at regions closer to the basal region. However, as the pathlines propagate down to the apex, the pathlines closer to the septal wall turn around generating a vortex in the mid-basal regions of the septal wall. The infarct region which lies in the apical antero-septal wall, closely matches the region of the observed flow abnormality. The presence of the vortex may also result in a compensatory accentuation of filling. This pattern of filling was observed in three of the six infarcted animals that were imaged, and was categorized as a nominal flow dysfunction. The other three animals exhibited a different flow pattern as represented in Fig. 5c. In these animals, the pathline trajectories during very early time frames traveled straight down to the apex without much spread to the two walls and the pathline trajectories of particles released at most later time frames appeared mostly stagnated in the basal region. This pattern, completely different from the baseline animal, was qualitatively categorized as a severe flow dysfunction.

Longitudinal Pressure Gradient

Normal Volunteer Studies—Figure 6a depicts average longitudinal pressure gradient curves in ten central regions, defined from base to apex in the diagram on the left, with the symbols and curves color-coded to match the color of the defined ten regions. The trends of the curves are examined during the two physiological periods, acceleration and deceleration, of the rapid filling phase. A definite pattern is observed. During acceleration, the apical pressure gradient is lowest and the basal pressure gradient is highest, while during deceleration this pattern reverses. The curves obtained from the ten regions are more-or-less equally separated from each other at the positive peak observed at the center of the acceleration period and the negative peak observed at the center of the deceleration period. The curves from all ten regions are also temporally matched in behavior and all the curves pass through the zero point at the same moment coincident with the time when the mitral inflow velocity reaches its peak.

Infarcted Dog Studies—The regional pressure gradients for the baseline dog and two representative infarcted dogs are illustrated in Figs. 6b–d. A similar trend in the pressure gradient curves as seen in the normal volunteer is observed in the baseline animal in Fig. 6b. During the acceleration phase, the apical pressure gradient is lowest and the basal pressure gradient is highest, which is reversed during the deceleration phase. Again, the curves are temporally matched and more-or-less equally separated at the time point of peak positive and negative pressure gradient.

In Fig. 6c, although the apical and basal pressure gradients are respectively the lowest and the highest during the acceleration phase and reversed during the deceleration phase, differences in the separation between regions are observed. We find that there is no relative pressure gradient from the seventh to the tenth region (as counted from the base). The curves in these regions lie close to each other. Interestingly, the seventh region spatially corresponds with the region around which the flow pathline trajectories turn around creating the septal vortex. In addition, the curves from the ten regions are not temporally matched. For example, the basal pressure gradient curve exhibits a longer duration with the onset prior to the rapid filling phase and the return to zero after the rapid filling phase. While, the apical pressure gradient curve exhibits a shorter duration initiating after the rapid filling phase begins and ending before the rapid filling phase ends. This temporal mismatch further changes the equidistance between the curves from subsequent regions, and in effect alters the linear pressure gradient that exists from base to apex.

In Fig. 6d, we observe a shorter acceleration period followed by a much longer deceleration period, representing reduced overall filling. The relative pressure in the apical regions is lower than the basal regions for only the first 25% of rapid filling. As a result, propagation of blood flow down to the apex stops early, as observed in the pathline trajectories.

Longitudinal Lagrangian Strain

Normal Volunteer Studies—Fig. 7a and b illustrate the diastolic strain curves for basal, mid and apical regions on the septal and lateral walls of a representative normal volunteer. The mitral inflow velocity curve is superimposed for temporal reference. Again, the rapid

filling phase is divided into two distinct phases, acceleration and deceleration. It is evident from the regional strain curves in Fig. 7a and b that an increase in basal, mid, and apical strain begins prior to the rapid filling phase. The regional strain curves plateau in a sequence, with apical regions at the end of acceleration filling phase, basal regions at early diastasis, and mid regions at sometime in between. The curves also reflect a relatively higher rate of longitudinal strain in the apical regions during acceleration and a relatively higher rate of longitudinal strain in the basal regions during deceleration. The basal regions exhibit a bi-phasic strain pattern with higher slopes (or rates of longitudinal strain) during the acceleration period and lower slopes during deceleration.

Infarcted Dog Studies—Figs. 7c and d depict strain patterns in the baseline dog. Similar trends as observed in the normal volunteer are seen, with highest strain rate in the apical region and lowest strain-rate in the basal regions during the acceleration phase. However, there is not much strain change during the deceleration phase in the baseline dog in comparison to the normal volunteer. Figs. 7e and f depict strain patterns in a representative infarcted dog with nominal flow dysfunction. Here, in Fig. 7e, we find an abnormal pattern in strain in the apical region of the septal wall. The strain-rates in this region are lower than the mid and basal region and the maximum strain at saturation is much lower than the baseline animal. The curves in Fig. 7f (lateral wall) exhibit a normal strain response. Thus, a nominal strain dysfunction restricted to the septal apical region is observed in this animal in the 4-chamber slice. Figs. 7g and h depict strain patterns in a representative infarcted dog with severe flow dysfunction. Here, in Fig. 7g we observe an abnormal pattern in strain in the apical region of the septal wall, as was observed in the infarcted animals with nominal flow dysfunction. In addition, we also observe abnormal strain patterns in the mid region of the septal wall and the apical, and mid regions of the lateral wall. Thus, a more severe strain dysfunction is observed in this animal.

Kinetic Energy Analyses of 2D Flow Pathline

The net kinetic energy for each set of pathlines created by releasing emitter particles during the rapid filling phase is plotted in Fig. 8 for the normal volunteers, baseline dog and six infarcted dogs. The curves are temporally scaled and eighteen points on the curve are re-sampled. The results show a bell shaped curve, with peak kinetic energy observed at the center of rapid filling for the baseline volunteers, baseline animal and the animals with nominal flow dysfunction. The peak of the curves is shifted slightly to the right in the animals with severe flow dysfunction. Peak net kinetic energy of 0.06 ± 0.01 in normal volunteers, 0.043 in the baseline dog, 0.143 ± 0.03 in three infarcted dogs with nominal flow dysfunction, and 0.016 ± 0.007 in three infarcted dogs with severe flow dysfunction is observed. The peak net kinetic energy is significantly increased in the three infarcted dogs with nominal flow dysfunction (partially due to the presence of a large vortex and related accentuated filling), and is significantly decreased in the three infarcted dogs with severe flow dysfunction (partially due to reduced filling during acceleration and prolonged deceleration times with mostly stagnated flow in the basal regions). The values of peak net kinetic energy for normal volunteers and each individual animal is shown in Table 1. The corresponding saturated strain value at end of rapid filling for segmented regions is also tabulated. From this table, we observed that nominal flow dysfunction is associated with a

considerable increase in peak net kinetic energy and strain dysfunction restricted mostly to the apical regions. In animals with severe flow dysfunction, we observe a considerable drop in peak net kinetic energy with strain dysfunction in the apical and mid regions of both the septal and the lateral walls. While the infarct region is designed to be created in the antero-septal region, strain dysfunction observed in the lateral wall in these animals may be a result of diastolic stunning in adjacent risk regions.

Discussion

We present a high-temporal resolution 2D pathline analysis-based method to evaluate regional and global diastolic function in normal volunteers and infarcted dogs. While global indices such as E/A ratios are susceptible to pseudonormal readings, pathline visualization during early diastole, as described in this paper, in combination with such global indices may provide a more comprehensive evaluation in the clinic.

We demonstrate that the patterns of diastolic filling, as observed using pathline analysis, are closely dictated by patterns of chamber pressure gradients and are related to myocardial function (or strain). A close relationship is observed between myocardial longitudinal strain at the end of the rapid filling phase and peak net kinetic energy derived from pathline analysis during early diastole. Time-dependent imaging of both these quantities in context with qualitative pathline visualization may provide greater insight into the mechanisms of LV remodeling in various cardiac disease states.

Relation between filling patterns and longitudinal pressure gradients

Our results in normal volunteers and infarcted dogs show a close relation between pathline propagation into the left ventricle and patterns of intraventricular pressure gradients.

In the normal volunteer curves and the baseline animal in Fig. 6 (a and b), the longitudinal pressure gradient during the acceleration period of rapid filling varies nearly linearly from the basal to the apical regions, with the lowest pressure gradient in the apex. This efficiently promotes the suction of blood down to the apex resulting in an even distribution of the pathlines throughout the LV. During deceleration, this pattern reverses. Correspondingly, the pathline distribution pattern during this period contributes mainly to basal and mid-ventricular filling during the early part and mostly basal filling during the later part. Thus filling of the left ventricle occurs in a spatially definite pattern with the apex completing filling first followed by the mid-ventricular and basal regions.

In the first infarcted animal curves in Fig. 6c, we notice that a loss of pressure gradient between the mid-apical septal regions during acceleration results in the inability of the pathlines to propagate down to the apex in the septal region forming a large mid-basal septal vortex. The flow in the lateral regions in this animal is normal. In the second infarcted animal in Fig. 6d, we notice that the acceleration period is much shorter than the deceleration period. The relative pressure in the apex very quickly increases in comparison to the mid-ventricular and basal regions resulting in the loss of the suction needed to maintain filling during the acceleration period. As a result the pathline trajectories are mainly stagnated in the mid-basal regions during most of the filling. The filling is affected

throughout the ventricle, and not just in the septal wall as seen in the previous infarcted animal.

Regional pressure gradients, created due to longitudinal relaxation and untwisting [31], are affected during myocardial infarction, and is responsible for abnormalities in diastolic filling patterns. In animals with a greater degree of infarction, greater loss of suction will result in shorter pathline propagation distances and reduced overall filling with longer deceleration times.

Relation between filling patterns and longitudinal strain

Our results in normal volunteers and infarcted dogs show a close relation between pathline propagation into the left ventricle and regional strain patterns.

In the normal volunteer, the pathline trajectories, as seen in Fig. 4a, spread uniformly when emitter particles are released during early time frames, but are gradually restricted away from the apex and the walls when particles are released during later time frames. During the deceleration phase, the blood entering mostly contributes towards basal filling. These results correspond closely with the regional strain results in Figs. 7 a and b, where apical strain rates are highest during the acceleration phase, while basal relaxation dominates during the deceleration phase.

As illustrated in Figs. 5b and c, abnormalities in the filling pattern of the infarcted dogs is observed. In Fig. 5b, we observe that blood in the septal region does not propagate down to the apex and curls around to form a mid-basal septal vortex. The longitudinal strain curves from this animal correspondingly depict decreased longitudinal strain and strain-rate indicating increased stiffness in this region. In Fig. 5c, we observe a more severe flow dysfunction with a short central filling pattern followed by stagnation in the mid-basal regions. The longitudinal strain curves in this animal correspondingly depict decreased strain and strain-rates in the apical and mid regions on the septal and lateral wall indicating increased stiffness in these regions. Studies have shown the presence of edema in the adjacent risk regions of reperfused infarcts. We believe that a larger infarct size combined with diastolic stunning in the lateral wall due to the presence of edema may be responsible for the greater extent of strain dysfunction seen in this animal.

As seen in the table, a relationship exists between mechanical dysfunction and peak net kinetic energy computed through pathline analysis. In animals with a septal vortex like pattern, we observe increased peak net kinetic energy and the strain dysfunction is limited mainly to the apical region. In animals with shortened centric flow during early rapid filling and stagnated basal flow during late filling, we observe decreased peak net kinetic energy with strain dysfunction on both walls extending at times to the mid and basal regions. The peak net kinetic energy represents a novel index of diastolic dysfunction. In combination with qualitative pathline visualization, it would offer unambiguous interpretation of flow dysfunction with additional quantitative insight into the nature/function of the flow distribution patterns.

Limitations

The methods presented in this paper are 2D based approaches. As a result, substantial particle exchange would occur during the pathline propagation process. A reasonable assumption can be made that the particle exchanged into the pathline inherits the properties of the previous particle it replaced. Although a 3D flow pathline, extracted from a 3D velocity dataset depicts the trace of a single particle moving in space, the 2D flow pathline depicts the pathline trace within a single imaging plane, which can be analyzed from 2D datasets using the same well established pathline-analysis methodologies. Thus, in contrast to the 3D flow pathline, the 2D flow pathline represents a summation of the influence of all the blood particles passing through a certain region of the left ventricle. It also directly correlates to the corresponding local longitudinal strains and local pressure gradients, which are investigated in this study for both normal volunteers and infarcted dogs. 2D flow-pathline analysis for the assessment of early diastolic LV dysfunction also has the advantage of providing a rapid imaging technique that can be easily translated into the clinic. However, a full-chamber investigation as can be assessed through 3D MR imaging techniques will not be achievable.

In this study, GRAPPA with an acceleration factor of 4 was applied, with five receiver coils. Although the results are acceptable, further improvement to the hardware will significantly improve the SNR and performance of the measurement.

For the strain measurements, the HARP methodology, which extracts the harmonic peaks from the Fourier transform of the reconstructed tagged images, was applied. To avoid spectral contamination from the DC peak, a fairly narrow filter bandwidth is usually selected, as a result limiting the resolution of the strain maps. The MICSr technique [32] could be implemented to increase the resolution of the strain maps, but would require an additional acquisition with complementary spatial modulation of magnetization (CSPAMM) [33]. Thus, the choice of the acquisition strategy will depend on the specific needs of each scan and the application.

Our pressure gradients were measured in small regions defined at the center of the left ventricle. In the future, the pressure gradient patterns on the entire slice will be related to regional pathline trajectories.

Conclusion

In conclusion, 2D pathline analysis provides a direct regional assessment of early diastolic filling patterns. From our preliminary studies in normal volunteers and infarcted dogs, 2D flow pathlines are sensitive to abnormalities in early diastolic filling, and may provide a reliable diagnostic indicator of diastolic dysfunction for a range of cardiac diseases with diastolic disorders. Quantitative kinetic energy analysis may enable risk stratification of patients. In the future, we will study the value of flow pathline trajectories in acutely predicting the extent and pattern of chronic remodeling post myocardial infarction.

Acknowledgement

This publication was made possible by CTSA Grant Number UL1 RR024139 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on Re-engineering the Clinical Research Enterprise can be obtained from the [NIH website](#).

References

1. Moller JE, Pellikka PA, Hillis GS, Oh JK. Prognostic importance of diastolic function and filling pressures in patients with acute myocardial infarction. *Circulation*. 2006; 114:438–444. [PubMed: 16880341]
2. Moller JE, Sondergaard E, Poulsen SH, Egstrup K. Pseudonormal and restrictive filling patterns predict left ventricular dilation and cardiac death after a first myocardial infarction: a serial color M-mode doppler echocardiographic study. *Journal of the American College of Cardiology*. 2000;1841–1846. [PubMed: 11092654]
3. Claessens TE, De Sutter J, Vanhercke D, Segers P, Verdonck PR. New echocardiographic applications for assessing global left ventricular diastolic function. *Ultrasound Med Biol*. 2007 Jun. 33:823–841. [PubMed: 17434662]
4. Khouri SJ, Maly GT, Suh DD, Walsh TE. A practical approach to the echocardiographic evaluation of diastolic function. *Journal of the American Society of Echocardiography*. 2004; 17(3):290–297. [PubMed: 14981433]
5. Eriksson J, Carlhäll CJ, Dyverfeldt P, Engvall J, Bolger AF, Ebbers T. Semi-automatic quantification of 4D left ventricular blood flow. *J Cardiovasc Magn Reson*. 2010; 12:9. [PubMed: 20152026]
6. Ebbers, Tino. Flow Imaging: Cardiac Application of 3D Cine Phase Contrast MRI. *Curr Cardiovasc Imaging Rep*. 2011; 4:127–133.
7. Zhang Z, Dione DP, Brown PB, Shapiro EM, Sinusas AJ, Sampath S. Assessment of early diastolic strain-velocity temporal relationships using spatial modulation of magnetization with polarity alternating velocity encoding (SPAMM-PAV). *Magn Reson Med*. 2011; 66:1627–1638. [PubMed: 21630348]
8. Stewart KC, Kumar R, Charonko JJ, Ohara T, Vlachos PP, Little WC. Evaluation of LV diastolic function from color M-mode echocardiography. *J Am Coll Cardiol Img*. 2011; 4:37–46.
9. Fyrenius A, Wigström L, Ebbers T, Karlsson M, Engvall J, Bolger AF. Three dimensional flow in the human left atrium. *Heart*. 2001; 86:448–455. [PubMed: 11559688]
10. Firmin DN, Nayler GL, Kilner PJ, Longmore DB. The application of phase shifts in NMR for flow measurement. *Magn Reson Med*. 1990; 14:230–241. [PubMed: 2345505]
11. Pelc NJ, Herfkens RJ, Shimakawa A, Enzmann DR. Phase contrast cine magnetic resonance imaging. *Magn Reson Q*. 1991; 7:229–254. [PubMed: 1790111]
12. Powell AJ, Geva T. Blood flow measurement by magnetic resonance imaging in congenital heart disease. *Pediatr Cardiol*. 2000; 21:47–58. [PubMed: 10672614]
13. Wigström L, Sjöqvist L, Wranne B. Temporally resolved 3D phase-contrast imaging. *Magn Reson Med*. 1996; 36(5):800–803. [PubMed: 8916033]
14. Buonocore MH. Visualizing blood flow patterns using streamlines, arrows, and particle paths. *Magn Reson Med*. 1998; 40:210–226. [PubMed: 9702703]
15. Kilner PJ, Yang GZ, Wilkes AJ, Mohiaddin RH, Firmin DN, Yacoub MH. Asymmetric redirection of flow through the heart. *Nature*. 2000; 404:759–761. [PubMed: 10783888]
16. Wigström L, Ebbers T, Fyrenius A, et al. Particle trace visualization of intracardiac flow using time resolved 3D phase contrast MRI. *Magn Reson Med*. 1999; 41(4):793–799. [PubMed: 10332856]
17. Kozerke S, Hasenkamp JM, Pedersen EM, Boesiger P. Visualization of flow patterns distal to aortic valve prostheses in humans using a fast approach for cine 3D velocity mapping. *J Magn Reson Imaging*. 2001; 13(5):690–698. [PubMed: 11329190]

18. Markl M, Chan FP, Alley MT, et al. Time-resolved three-dimensional phase-contrast MRI. *J Magn Reson Imaging*. 2003; 17(4):499–506. [PubMed: 12655592]
19. Markl M, Harloff A, Bley TA, et al. Time-resolved 3D MR velocity mapping at 3T: improved navigator-gated assessment of vascular anatomy and blood flow. *J Magn Reson Imaging*. 2007; 25(4):824–831. [PubMed: 17345635]
20. Uribe S, Beerbaum P, Sorensen TS, et al. Four-dimensional (4D) flow of the whole heart and great vessels using real-time respiratory self-gating. *Magn Reson Med*. 2009; 62(4):984–992. [PubMed: 19672940]
21. Dyverfeldt P, Kvitting JP, Sigfridsson A, et al. Assessment of fluctuating velocities in disturbed cardiovascular blood flow: in vivo feasibility of generalized phase-contrast MRI. *J Magn Reson Imaging*. 2008; 28(3):655–663. [PubMed: 18777557]
22. Bogren HG, Buonocore MH. 4D magnetic resonance velocity mapping of blood flow patterns in the aorta in young vs. elderly normal subjects. *J Magn Reson Imaging*. 1999; 10:861–869. [PubMed: 10548800]
23. Markl M, Draney MT, Miller DC, Levin JM, Williamson EE, Pelc NJ, Liang DH, Herfkens RJ. Time-resolved three-dimensional magnetic resonance velocity mapping of aortic flow in healthy volunteers and patients after valve-sparing aortic root replacement. *J Thorac Cardiovasc Surg*. 2005; 130(2):456–463. [PubMed: 16077413]
24. Shi, K.; Theisel, H.; Hauser, H.; Weinkauff, T.; Matkovic, K.; Hege, HC.; Seidel, HP. Path line attributes - an information visualization approach to analyzing the dynamic behavior of 3D time-dependent flow fields. In: Hege, HC.; Polthier, K.; Scheuermann, G., editors. *Topology-Based Methods in Visualization II, Mathematics and Visualization*. Grima, Germany: Springer; 2009. p. 75-88.
25. Heiberg E, Ebberts T, Wigström L, Karlsson M. Three dimensional flow characterization using vector pattern matching. *IEEE Trans Vis Comp Graphics*. 2003; 9:313–319.
26. Bolger AF, Heiberg E, Karlsson M, Wigström L, Engvall J, Sigfridsson A, Ebberts T, Kvitting JPE, Carlhäll CJ, Wranne B. Transit of blood flow through the human left ventricle mapped by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2007; 9(5):741–747. [PubMed: 17891610]
27. Axel L. Biomechanical dynamics of the heart with MRI. *Annu Rev Biomed Eng*. 2002; 4:321–347. [PubMed: 12117761]
28. Osman NF, Kerwin WS, McVeigh ER, Prince JL. Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. *Magn Reson Med*. 1999; 42(6):1048–1060. [PubMed: 10571926]
29. Osman NF, Prince JL. Visualizing myocardial function using HARP MRI. *Phys Med Biol*. 2000; 45(6):1665–1682. [PubMed: 10870717]
30. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005 Dec; 18(12):1440–1463. [PubMed: 16376782]
31. Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, Thomas JD. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol*. 2008; 294:H505–H513. [PubMed: 18032523]
32. NessAiver M, Prince JL. Magnitude image CSPAMM reconstruction (MICSAR). *Magn Reson Med*. 2003; 50(2):331–342. [PubMed: 12876710]
33. Fisher SE, McKinnon GC, Maier SE, Boesiger P. Improved myocardial tagging contrast. *Magn Reson Med*. 1993; 30:191–200. [PubMed: 8366800]

Figure 1.

Color-coded blood velocity maps with myocardial tag overlay for fifteen continuous representative time frames during early diastolic filling obtained in the four-chamber view with a high frame rate of 14 ms. Data was obtained from a normal volunteer in a single breath-hold SPAMM-PAV acquisition.

Figure 2.

Schematic depicting the relative number of emitter particles released at each time frame during rapid filling. The number of particles released at a given time frame is proportional to the area under the mitral inflow velocity curve at that time frame. The inflow velocity curve is obtained by averaging the velocity in the circled area illustrated in the insert.

Figure 3. Standard used for myocardial strain, mitral valve inflow velocity and longitudinal pressure gradient segmentation in the four-chamber view, reproduced according to the American Society of Echocardiography's Guidelines.

Figure 4.

(a) Time series (row1: acceleration, row 2: deceleration) of particle traces emitted from the mitral valve plane in a normal volunteer, color-coded to depict instantaneous kinetic energy. The number of blood particles, represented by the red circles, emitted at each time frame is determined by the area under the velocity curve at each time interval as shown in Fig. 2. The red dots on the pathlines, shown on the top left sub-figure, illustrate the position of the emitter particles (released at the first time frame) at each subsequent time frame as it propagates into the LV chamber. A wavefront like propagation is observed. (b) Overlapped

particle trace trajectories of emitter particles released at all time points in a normal volunteer. Blood propagating into the left ventricle at an early stage distributes uniformly throughout the left ventricle, while blood entering at later time frames contributes to a more centric filling (away from the walls and the apex).

a

b

C

Figure 5.

Overlapped pathline trajectories for (a) a normal baseline dog, (b) a representative infarcted dog with nominal flow dysfunction, and (c) a representative infarcted dog with severe flow dysfunction. A large vortex is observed around the mid-basal region of the septal wall in (b) depicting a compensatory accentuated filling pattern and nominal flow dysfunction as compared to baseline. In (c), the filling pattern is severely impaired and depicts shortened centric filling towards the apex, and stagnation in the basal regions (severe flow dysfunction).

a

b

c

d

Figure 6.

Longitudinal pressure gradient time curves during rapid filling, averaged in ten regions defined along the central long-axis, as shown in Fig. 3, for (a) a normal volunteer, (b) a normal baseline dog, (c) a representative infarcted dog with nominal flow dysfunction, and (d) a representative infarcted dog with severe flow dysfunction. The left sub-figure of each case illustrates the relative position of the investigated regions with the pathlines. Case (a) and (b) exhibit a regular pattern and variation of regional pressure gradient with time, while

case (c) and (d) show irregular patterns and regional variations. Mitral valve inflow velocity curve is superimposed as a temporal reference.

a

b

C

d

e

f

g

h

Figure 7.

Time plots comparing the mean of longitudinal strain in basal, mid-cavity, and apical regions of septal and lateral walls during early diastole, in normal volunteers (a and b), normal baseline dog (c and d), a representative infarcted dog with nominal flow dysfunction (e and f), and a representative infarcted dog with severe flow dysfunction (g and h). The strain pattern in the baseline dog is close to the normal volunteers. The dog with nominal flow dysfunction exhibits decreased strain in the apical region on the septal wall, while the dog with severe flow dysfunction exhibits decreased strain in the apical and mid regions on

both the septal and lateral walls. Mitral valve inflow velocity curve is superimposed as a temporal reference.

Figure 8.

The net kinetic energy for each set of pathlines during the rapid filling phase (temporally scaled and resampled) for the normal volunteers represented by black (■) with standard deviation, a baseline dog represented by light grey (●) and six infarcted dogs, respectively represented by red (●), blue (◆), green (▲), cyan (●), purple (◆), and orange (▲), where the former three are the infarcted dogs with nominal flow dysfunction and corresponds to dogs 1, 2 and 3, shown in Table 1, and the latter three are the infarcted dogs with severe flow dysfunction, corresponding to dog 4, 5 and 6 in Table 1. The large vortex present in dogs with nominal flow dysfunction may contribute to the increase in the net kinetic energy, while the reduced filling observed in the dogs with severe flow dysfunction may contribute to the decrease in the net kinetic energy.

Table 1

Peak net kinetic energy and the corresponding saturated strain value at end of rapid filling for segmented regions for normal volunteers and each individual animal.

	Peak KE	Peak Septal Strain			Peak Lateral Strain		
		Apical	Mid	Basal	Apical	Mid	Basal
N-Vol	0.06±0.01	18.1±0.4	17.9±1.2	12.5±0.6	13.6±0.8	17.5±0.6	17.1±1.4
Baseline	0.043	17.1±0.2	12.7±0.2	9.5±0.2	16.1±0.8	12.7±0.4	8.5±0.2
Dog 1	0.17	5.5±0.3	14.2±0.3	9.4±0.3	11.1±0.4	9.3±0.3	7.2±0.2
Dog 2	0.15	2.9±0.2	20.7±0.6	13.3±1.6	2.3±0.4	11.4±0.4	5.7±0.5
Dog 3	0.11	-0.03±0.04	8.8±0.4	14.9±0.3	-0.1±0.03	0.8±0.3	8.5±0.2
Dog 4	0.022	1.0±0.2	7.2±0.4	9.9±0.4	0.4±0.5	0.6±0.5	2.2±0.5
Dog 5	0.019	-0.5±0.2	10.6±0.1	9.5±0.06	7.5±0.2	5.0±0.1	5.6±0.4
Dog 6	0.0075	-1.3±0.7	1.5±0.4	16.8±0.5	-2.4±0.4	-0.3±0.4	5.6±0.3