QUANTIFICATION OF LEFT VENTRICULAR REGIONAL FILLING PATTERNS WITH CORRELATION TO SYSTOLIC EVENTS

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL
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To those who persevere in the setting of left ventricular dysfunction

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I thank the members of my advisory committee for their mentoring, guidance and motivation throughout this project. I thank my parents for their support of my academic pursuits. I thank my wife for sacrificing while understanding why pursuits of knowledge are important to me. I thank my daughters for inspiring me to make them proud.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Abstract of Thesis Presented to the Graduate School
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Growing knowledge suggests that normal filling of the left ventricle (LV) is dependent on events that occur during systole. During systole potential energy is stored which during diastole allows for deformation of the LV. This deformation allows for a decrease in pressure in the LV. The greatest decrease in pressure in the LV during diastole is likely at the apex. Therefore, we hypothesized that in patients with normal systolic events the apical region of the LV will fill with blood the earliest.

We performed a retrospective evaluation of cardiac MRI images obtained as a part of routine clinical care between January 1, 2007 and July 31, 2008. We analyzed MRI images off-line and generated volume-time curves for both the basal and apical regions. These curves were transformed to display the percent of filling achieved over the percent of the cardiac cycle for both the basal and apical regions. These graphs allowed determination of the point in the cardiac cycle at which 10% and 20% of filling was achieved in the apical and basal regions. Additionally, apical and basal ejection fractions (EF) were determined to assist in the classification of a patient's systolic pattern.

Among the 21 patients with a normal pattern of systolic events, i.e. the apical EF was greater than the basal EF, filling occurred earlier in the apical region as compared to the basal region. On average the apical region reached 10% of filling 57msec earlier than the basal region. This difference represented 7% of the cardiac cycle (P value<0.001). Also, on average the apical region reached 20% of filling 28msec earlier than the basal region. This difference represented 3.5% of the cardiac cycle (P=0.011). In the 4 patients with an abnormal pattern of systolic events, i.e. the basal EF was greater than the apical EF, parameters of LV filling occurred earlier in the basal region as compared to the apical region. On average the basal region reached 20% of filling 57msec earlier than the apical region. This difference represented 6.9% of the cardiac cycle (P value 0.043). The mean difference between the points in the cardiac cycle at which the apical and basal regions reached 10% of filling was different between the patients with a normal pattern of systolic events and those patients with an abnormal pattern of systolic events (P value=0.001). Also, the mean difference between the points in the cardiac cycle at which the apical and basal regions reached 20% of filling was different between the patients with a normal pattern of systolic events and those patients with an abnormal pattern of systolic events (P value=0.006).

The pattern of LV systolic events predicts the pattern of LV diastolic events. Those patients whose apical EF was greater than their basal EF had earlier filling in the apical region relative to the basal region. This finding supports the relationship between systolic and diastolic events. Further, this supports the concept that systolic events can contribute to the generation of diastolic suction.

CHAPTER 1
INTRODUCTION

Mechanisms of Left Ventricular (LV) Filling

Diastolic Suction

Diastolic dysfunction of the left ventricle (LV) can lead to significant morbidity and mortality (1). The primary function of diastole is LV filling. Therefore, understanding the mechanisms of normal and abnormal LV filling is important. LV filling has long been considered a passive process. However, growing knowledge suggests that normal LV filling depends on active processes. These active processes occur during both diastole and systole. Specifically, during systole, shortening of the myocardium places strain on elastic elements in the LV, such as the protein titin, that allows for the storage of potential energy (2). During isovolumic relaxation (IVR) this stored energy is released allowing the LV to deform back to its pre-ejection configuration. This deformation of the LV, in the setting of an isovolumic state, allows for a decrease in intra-ventricular pressure. The generation of a decreasing intra-ventricular pressure during IVR and the early part of LV filling is referred to as diastolic suction (3).

Intra-Ventricular Pressure Gradient

Deformation of the LV during IVR and the early part of LV filling is felt to be dependent on, and correlate with, the potential energy that is stored during systole. The apical region of a normal LV has a more vigorous systolic contraction as compared to the basal region. For example, the apical region typically twists 15 degrees counterclockwise during systole, whereas the basal region twists only 3 degrees clockwise (4). Therefore, the apical region, as compared to the basal region, will store more potential energy during systole allowing for a more vigorous change in LV configuration during IVR. Because of this vigorous change in apical LV configuration during IVR, the greatest decrease in pressure during IVR exists in the apical region of the LV cavity (5). The discrepancy between the decrease in pressure at the apex and basal region of the LV creates an intra-ventricular pressure gradient that starts during IVR but reaches peak in the early part of diastolic filling (5). Blood should preferentially accelerate toward the area of the LV with the lowest pressure. Therefore, in patients with an intact intra-ventricular pressure gradient, we expect that after mitral valve opening blood would first accelerate toward the apical region.

Quantification of the Effects of Diastolic Suction

A number of studies have documented the temporal sequence of myocardial segment deformations that contribute to the generation of diastolic suction (6-9). However, no previous study has evaluated the temporal sequence of regional changes in the intra-ventricular cavity during LV filling. Patterns of regional LV filling could allow for the diagnosis of abnormal LV function and serve as a therapeutic target. We developed a technique to evaluate and compare the filling patterns of the apical and basal intra-ventricular regions. Because we expect that after mitral valve opening blood will first accelerate toward the apical region in normal patients, this technique should reveal that the apical region will fill prior to the basal region.

CHAPTER 2
METHODS

Patient Selection

After obtaining approval from the IRB, we performed a retrospective evaluation of cardiac MRI images obtained between January 1, 2007 and July 31, 2008. All cardiac MRIs were ordered as a part of routine clinical care and performed at Shands Hospital at the University of Florida. Only the cardiac MRIs of patients who also had an echocardiogram within 6 months of the cardiac MRI and prior to July 31, 2008 were considered. Between January 1, 2007 and July 31, 2008, 236 adult patients had cardiac MRIs performed. Of these patients, 141 also had an echocardiogram within 6 months of the cardiac MRI and prior to July 31, 2008. Because we compared data between the MRIs and echocardiograms, only the 75 patients with the shortest time interval between their MRI and echocardiogram were enrolled into the study population. Of these 75 patients, 8 patients with normal ejection fraction (EF) and normal diastolic echocardiographic parameters, 6 patients with normal EF and abnormal diastolic echocardiographic parameters, and 11 patients with abnormal EF were included in the current analysis. The remaining 50 patients were not included in the current analysis because they had congenital abnormalities or had severe LV systolic dysfunction. Specifically, those patients with an apical or basal EF <10% were not included in the current analysis because the filling volumes were too small to permit an accurate interpretation of the filling curves.

MRI Analysis

We used a Pie Medical work station (BV, Maastricht, The Netherlands) to analyze the cardiac MRIs. First, we determined which short axis cine slices encompassed the entire LV. Second, we determined which of these slices correlated with either the basal or apical regions of the left ventricle. The two slices chosen to represent the apical region included the most apically positioned slice at end-systole that contained a circular portion of the LV cavity as well as the slice basal to it. The two slices chosen to represent the basal region included the slice closest to the mitral annulus that did not include a portion of the LV outflow tract and the slice apical to it. Next, within the slices included in the basal region, the endocardium was traced in the end-systolic frame and all diastolic frames included in the cine series. These tracings were then used to generate a graph of volume over time. This procedure was then repeated for the apical region. Therefore, a separate graph of volume over time was produced for the basal and apical regions.

This data was transformed in two ways. First, to account for differences in heart rate between patients, time in msec was transformed to represent the percent of a single cardiac cycle. Systole began at 0% of the cardiac cycle and diastole was complete at 100% of the cardiac cycle. Second, to account for the difference between basal and apical regional volumes within subjects, volume in mL was transformed to represent the percent of filling volume achieved in a given region. Filling volume was defined as the difference between maximal volume and minimal volume in a given region. An example of the raw and transformed data for the apical and basal regions is shown in Figure 2-1. These graphs allowed determination of the point in the cardiac cycle at which 10% and 20% of filling was achieved for the apical and basal regions.

Classification of LV Systolic State

MRI images were analyzed with a Pie Medical work station (BV, Maastricht, The Netherlands) to determine the regional ejection fraction (EF) for the apical and basal regions. Previous work has demonstrated that in normal subjects the apical region of the LV has a more vigorous systolic contraction as compared to the basal region (4). Therefore, those patients whose EF was greater in the apical region as compared to the basal region were classified as having a normal pattern of LV systolic function. Those patients whose EF was greater in the basal region as compared to the apical region were classified as having an abnormal pattern of LV systolic function.

Statistical Analysis

A paired T test was used to determine if the point in the cardiac cycle at which 10% and 20% filling was achieved was different between the apical and basal regions of the LV in all 25 patients. Then a separate paired T test was performed in those with a normal pattern of LV systolic function and those with an abnormal pattern of LV systolic function to determine if the point in the cardiac cycle at which 10% and 20% filling was achieved was different between the apical and basal regions of the LV. Finally, an independent sample T test was then used to determine if the mean difference between the time to achieve 10% and 20% filling in the apical and basal regions was different between those with a normal pattern and an abnormal pattern of LV systolic function. Power calculations were not performed, as this is a pilot study.

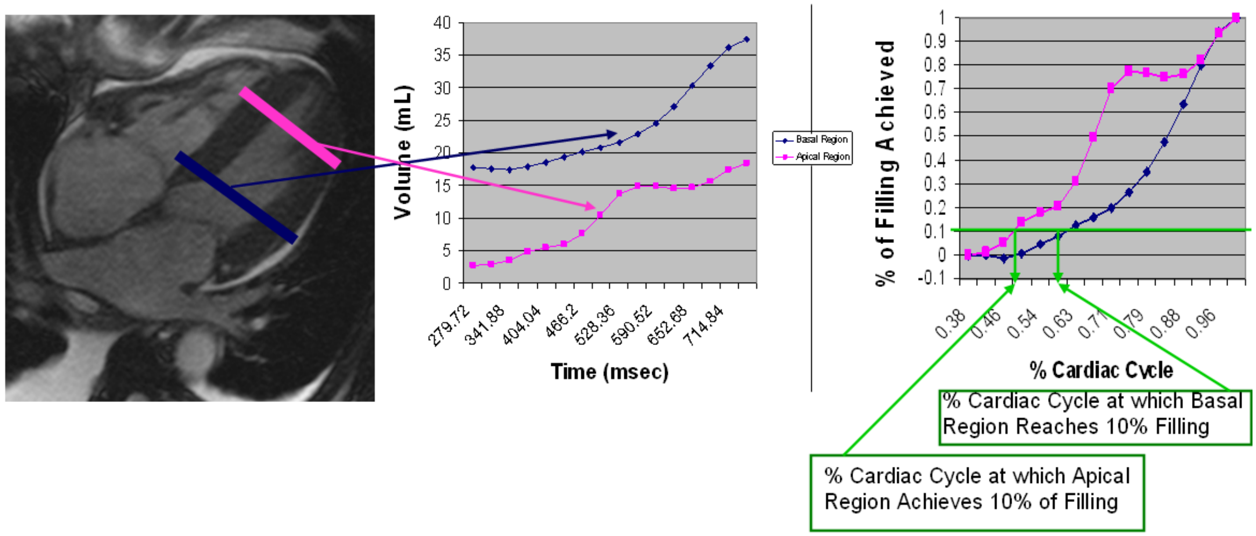

Figure 2-1. Cardiac MRI image demonstrating the typical position of the apical and basal slices used for this analysis. An example of the raw data of volume vs. time for the apical and basal regions is shown in the center. This raw data was transformed to demonstrate the % filling achieved over the % cardiac cycle (right). The green arrows show the points in the cardiac cycle when the apical and basal regions achieve 10% of filling.

CHAPTER 3
RESULTS

Patients

Twenty-five patients were enrolled in the current analysis. For all 25 patients, the average age was 58 years, the average EF was 57%, and 60% were male. Twenty-one had a normal pattern and 4 had an abnormal pattern of LV systolic function. The average age, EF, QRS duration, and proportion male for the 21 patients with a normal pattern of LV systolic function and the 4 patients with an abnormal pattern of LV systolic function are shown in Table 3-1.

Differences in Time to Achieve Filling in the Apical and Basal Regions

Differences in All Patients

The variables used in this analysis are shown in Table 3-2. In the 25 patients included in this analysis, parameters of LV filling occurred earlier in the apical region as compared to the basal region. The mean difference between the points in the cardiac cycle at which the apical and basal regions reached 10% of filling represented 5.2% of the cardiac cycle (P value=0.001). Similarly, on average the apical region of the LV achieved 20% of filling prior to the basal region. The mean difference between the points in the cardiac cycle at which the apical and basal regions achieved 20% of filling represented 1.8% of the cardiac cycle. This difference in time to 20% filling between the apical and basal region was not statistically significant (P value=0.186).

Differences in LV Systolic Groups

In the 21 patients with a normal pattern of systolic events, parameters of LV filling occurred earlier in the apical region as compared to the basal region. On average the apical region reached 10% of filling 57msec earlier than the basal region. This difference represented 7% of the cardiac cycle (P value<0.001). Also, on average the apical region reached 20% of filling 28msec earlier than the basal region. This difference represented 3.5% of the cardiac cycle (P=0.011).

In the 4 patients with an abnormal pattern of systolic events, parameters of LV filling occurred earlier in the basal region as compared to the apical region. On average the basal region reached 20% of filling 57msec earlier than the apical region. This difference represented 6.9% of the cardiac cycle (P value=0.043). Similarly, on average, in these 4 patients, the basal region achieved 10% of filling 40 msec earlier than the apical region. This difference represented 4.4% of the cardiac cycle, but was not statistically significant (P value=0.317).

The mean difference between the points in the cardiac cycle at which the apical and basal regions reached 10% of filling was different between the patients with a normal pattern of systolic events and those patients with an abnormal pattern of systolic events (P value=0.001). Also, the mean difference between the points in the cardiac cycle at which the apical and basal regions reached 20% of filling was different between the patients with a normal pattern of systolic events and those patients with an abnormal pattern of systolic events (P value=0.006). Figure 3-1 summarizes the mean difference between the points in the cardiac cycle at which the apical and basal regions reached 10% and 20% of filling.

Table 3-1. Patients' baseline characteristics

	Normal systolic pattern	Abnormal systolic pattern	P value
n	21	4	
Average age (years)	57.75	62.13	0.61
Average EF (%)	59.33	45.38	0.051
Average QRS duration (msec)	96.5	111	0.12
Proportion male	62%	50%	

Table 3-2. Analyzed variables for all patients

Patient ID	% cycle at which apex reaches 10% filling - % cycle at which base reaches 10% filling	Time (msec) at which apex reaches 10% filling - time at which base reaches 10% filling	% cycle at which apex reaches 20% filling - % cycle at which base reaches 20% filling	Time (msec) at which apex reaches 20% filling - time at which base reaches 20% filling	Overall EF	Apical EF	Basal EF	Gender	Age (years)	RR interval (msec)	Diastolic time (msec)	QRS (msec)
49	-0.063	-46.99296	-0.052	-38.78784	80	79.2703	54.849	f	20.40	745.92	497.28	90.00
76	0.015	9.3744	0.02	12.4992	63	91.3635	51.6023	m	39.60	624.96	390.60	90.00
63	-0.067	-61.68288	0.005	4.6032	70	84.2759	45.4644	m	44.90	920.64	690.48	76.00
14	-0.085	-74.3376	0.015	13.1184	68	88.5694	67.4838	f	75.70	874.56	546.60	90.00
26	-0.01	-6.4128	0.01	6.4128	67	87.7005	62.3254	f	57.50	641.28	427.52	86.00
18	-0.075	-67.968	0.02	18.1248	62.5	78.658	41.3923	m	47.90	906.24	641.92	96.00
44	-0.083	-73.46496	-0.023	-20.35776	63	75.2865	53.3275	m	69.60	885.12	590.08	80.00
66	-0.105	-78.3216	-0.123	-91.74816	67	85.3534	52.5597	m	64.40	745.92	466.20	84.00
71	-0.148	-88.23168	-0.018	-10.73088	68	89.7014	53.7321	m	59.30	596.16	397.44	84.00
48	-0.093	-98.58	-0.083	-87.98	62	75.2484	37.3792	f	71.50	1060.00	706.40	84.00
94	0.002	1.80288	0	0	62.5	83.4856	67.1661	f	52.00	901.44	600.96	96.00
75	-0.02	-15.7248	-0.003	-2.35872	62.5	94.2314	57.8928	m	63.60	786.24	589.68	135.00
23	-0.005	-4.1472	0.038	31.51872	62	90.092	53.4953	m	64.90	829.44	518.40	82.00
80	-0.0155	-13.42176	-0.03	-25.9776	57.5	40.207	31.7582	f	66.20	865.92	577.28	114.00
65	-0.02	-15.5904	0.007	5.45664	46	73.3309	48.3133	f	43.70	779.52	519.68	118.00
95	0.078	73.15776	0.09	84.4128	49	63.22	65.3563	f	64.80	937.92	664.36	96.00
99	-0.132	-99.85536	-0.132	-99.85536	54	84.9345	18.1537	m	54.60	756.48	535.84	106.00
20	-0.105	-87.7968	-0.072	-60.20352	44	62.9898	29.3853	m	83.10	836.16	487.76	118.00
42	-0.125	-131.04	-0.117	-122.65344	43	73.9832	43.0926	f	70.20	1048.32	653.88	90.00
29	-0.1075	-94.944	-0.0075	-6.624	52	74.6158	43.1624	m	68.30	883.20	552.00	100.00
60	-0.05	-27.552	-0.028	-15.42912	66	73.9581	34.8153	m	26.10	551.04	183.68	88.00

Table 3-2. Continued.

Patient ID	% cycle at which apex reaches 10% filling - % cycle at which base reaches 10% filling	Time (msec) at which apex reaches 10% filling - time at which base reaches 10% filling	% cycle at which apex reaches 20% filling - % cycle at which base reaches 20% filling	Time (msec) at which apex reaches 20% filling - time at which base reaches 20% filling	Overall EF	Apical EF	Basal EF	Gender	Age (years)	RR interval (msec)	Diastolic time (msec)	QRS (msec)
74	0.127	103.0224	0.11	89.232	57.5	46.7753	51.9428	m	54.80	811.20	574.60	110.00
58	-0.187	-123.15072	-0.155	-102.0768	26	22.8115	13.2367	m	69.30	658.56	439.04	120.00
9	-0.037	-23.72736	0.06	38.4768	22	16.34	29.7243	m	77.10	641.28	320.64	138.00
1	0.007	7.17696	0.016	16.40448	53	35.7876	36.9613	f	51.80	1025.28	512.64	100.00

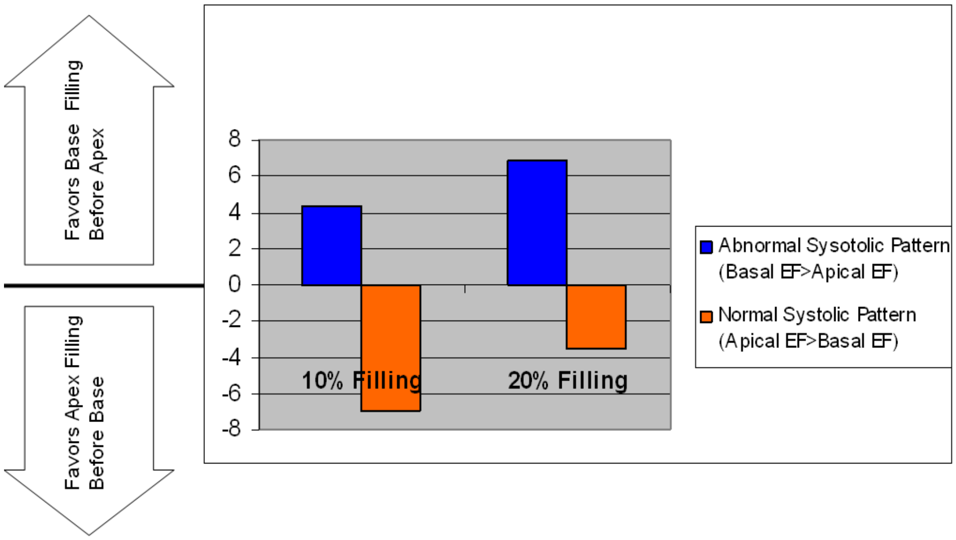

Figure 3-1. Mean difference between points in the cardiac cycle (in %) at which the apical and basal regions reached 10% and 20% of filling.

CHAPTER 4
DISCUSSION

Our results suggest that in patients with a normal pattern of LV systolic function, in which the apical systolic contraction is more vigorous then the basal systolic contraction, the apical LV region achieves parameters of early LV filling prior to the basal LV region. Further, our results suggest that in patients with an abnormal pattern of LV systolic function, in which the basal region has a more vigorous systolic contraction, the basal LV region achieves parameters of early LV filling prior to the apical LV region. Together these findings support the concept that events in systole contribute to changes in the pattern of filling during early LV filling. Specifically, these findings suggest that the region of the LV with the most vigorous systolic contraction will fill earliest. This process is likely explained by the fact that during systole potential energy is stored. This stored energy allows for the deformation of the LV during diastole and creates a decrease in intra-ventricular pressure.

In patients with a normal pattern of LV systolic function, the most vigorous region of the LV is the apex. Therefore, the apex has the greatest decrease in intra-ventricular pressure during isovolumic relaxation and early diastole. After mitral valve opening there is a suction of blood toward the apex. This theory of diastolic suction is supported by research which demonstrates a declining pressure within the apical region of the LV and documents the movement of blood toward the apex during isovolumic relaxation and early LV filling (5, 10-11). By demonstrating that the apical region achieves parameters of filling earlier then the basal region, our described method of quantifying LV regional filling may allow for a universal means of measuring the effects of intact diastolic suction.

Additionally, our method of quantifying LV regional filling may allow for improved classification of LV function. Figure 4-1 displays the filling patterns of two patients with normal echocardiographic parameters of global LV systolic and diastolic function. Patient A's apical region achieves early filling parameters prior to the basal region, whereas Patient B's basal region achieves early filling parameters prior to the apical region. Quantification of regional filling patterns may improve classification of LV dysfunction. This improved classification may allow for personalized selection and follow up of pharmaceutical, mechanical and electrical interventions.

Our findings that systolic events correlate with events in diastole are supported by recently published research. Systolic longitudinal and radial strain, at rest and after exercise, were significantly lower in patients with diastolic heart failure as compared to healthy controls (12). Additionally, systolic apical rotation, at rest and after exercise, was significantly lower in patients with diastolic heart failure as compared to healthy controls (12). Similarly, Wang et al. demonstrated a reduction in longitudinal and radial systolic strain in patients with diastolic heart failure as compared to healthy controls (13).

Limitations and Future Directions

Future efforts can overcome the limitations of our study. The sample size for our current analysis is small. Our results should be confirmed with a prospective analysis that would include normal volunteers as well as patients with defined systolic and diastolic LV abnormalities. The retrospective design of our study prevented the determination of symptom classification at the time of cardiac imaging. We expect that patients with abnormal diastolic suction, as suggested by an abnormal regional filling pattern in which the basal region of the LV achieves filling prior to the apex, would be more likely to have elevated left atrial and pulmonary venous pressures. Therefore, we suspect that patients with abnormal regional filling patterns would be more likely to have a worse symptom classification. A prospective cohort study could help determine the correlation of regional filling patterns with symptom classification in addition to symptom progression and incidence of hospitalization.

Our method of measuring volume has two limitations. First, our measurements of volume are based on short axis images only and do not include long axis images. These short axis images are obtained at set positions in the thorax with no ability to account for through plane movement of a LV region. Therefore, our technique has limited appreciation of long axis components of volume change. This limitation could ultimately be overcome by full volume acquisition, using technologies such as 320 slice computed tomography or newer echocardiographs. These non-MRI based modalities would also allow analysis of the effects of right ventricular and left ventricular pacing on regional filling patterns. Second, our measurements depend on accurate determination of the endocardial border. In certain patients' images this determination is challenging and subjective. This limitation could be overcome by improved automated endocardial border detection techniques.

Our study suggests that the pattern of apical and basal systolic function correlate with the pattern of regional LV filling. Identifying the pattern of apical and basal systolic function may therefore be an important aspect of a patient's evaluation. Our evaluation of the systolic pattern of the LV was limited to the determination of the apical and basal regional EF. More sophisticated techniques, such as those with strain imaging, might lead to a more detailed understanding of the pattern of systolic events that contribute to a "normal" pattern of regional LV filling. Specifically, determination of the relative strength and timing of apical and basal longitudinal, radial, and circumferential strain and twist could lead to a more advanced understanding of the appropriate pattern of systolic events.

Our defined parameters of filling were limited to the point in the cardiac cycle at which a given region achieved 10% or 20% of filling. These discrete measures of filling were selected arbitrarily with the hopes of serving as an appropriate parameter of early LV filling. The most clinically relevant parameter of filling is currently unknown. Longitudinal comparison of the entire apical and basal filling curves may be more relevant then assessment of the discrete parameters evaluated in this study.

Conclusions

Our study suggests that events in systole contribute to changes in the pattern of LV filling during early diastole. Further, in patients with a normal pattern of LV systolic function, the apical LV region achieves parameters of early LV filling prior to the basal LV region. Our results support the evolving concept that normal LV filling includes suction of blood toward the apex after mitral valve opening. We suspect that this suction of blood toward the apex is dependent on the storage of potential energy at the apex during systole. Understanding the timing of an individual’s regional LV filling provides improved classification of the mechanical deficits of that individual. Understanding the specific mechanical deficits of an individual may allow for personalized selection and follow up of pharmaceutical, mechanical and electrical interventions.

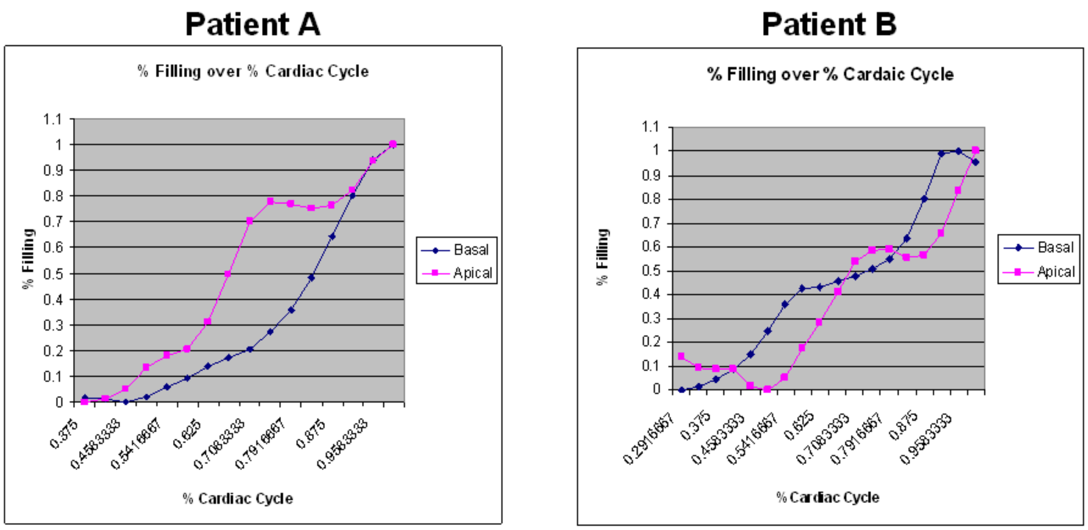

Figure 4-1. Two patients with normal echocardiographic parameters of global LV systolic and diastolic function but different regional filling patterns.

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BIOGRAPHICAL SKETCH

John William Petersen, M.D. was born in 1979 in Chicago, Illinois. He graduated from Bishop Verot High School and then enrolled at the University of Florida. He was accepted into the Junior Honors Medical Program, a combined seven year B.S. and M.D. program. He was awarded his B.S. in interdisciplinary basic medical sciences in 2001 and his M.D. in 2004. He completed his internal medicine residency training at Duke University in 2007. He is scheduled to complete his cardiology fellowship training at the University of Florida in June 2010. John's current research focuses on the use of non-invasive imaging techniques to advance the understanding of normal and abnormal LV mechanics.

John is married to Kimberly Register Petersen and has two daughters, Kendall Joy and Kylee Grace.