Mechanics, Mechanisms and Clinical Implications of Impaired Ventricular Filling

Internal Medicine Grand Rounds

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SUMMARY

Impaired ventricular filling is an important determinant of prognosis in patients with the syndrome of congestive heart failure, and may be the principal determinant of functional status. Excluding obstruction to ventricular inflow in mitral stenosis, atrial dysrhythmia and constrictive pericarditis, impaired filling occurs in two broad (potentially coexisting) forms:

1. impaired ventricular relaxation, manifested as a reduced rate of early diastolic filling and resulting in most cases from delayed re-uptake of calcium into the sarcoplasmic reticulum. This may reflect deficient expression of SERCA, disordered regulation of SERCA and/or myofibrillar calcium affinity, or disordered myocardial energetics.
2. elastic resistance to ventricular distension, manifested as abbreviated early ventricular filling and reduced mid- and late-diastolic compliance. This may be due to viscoelastic properties of hypertrophied myocardium, an increase in myocardial collagen content and/or active contraction of cardiac myofibroblasts. Angiotensin II - both circulating and produced locally in the heart, and aldosterone appear to play important pathophysiologic roles, and their effects may be mediated in part through TGF-β. Ultimately, the result is a restrictive filling pattern, in some cases complicated by ventricular interdependence.

Doppler echocardiography is the most informative modality for the evaluation of ventricular filling, supplemented in some cases by invasive hemodynamic measurements and/or one of several ventricular imaging techniques. Clinical trials to date provide little guidance in management. Beta-adrenergic receptor antagonists and calcium channel antagonists may beneficially alter ventricular relaxation, but the data in support of the latter, at least, is very limited. ACE inhibitors and AT1 receptor antagonists appear to favorably effect myocardial fibrosis in experimental models, and favorable effects have been observed in limited clinical trials. Ventricular interdependence is more common than generally appreciated, and has important implications for management. Both the clinical management of patients and future clinical trials must be guided by attention to the specific physiology underlying impaired ventricular filling.

Cases:

Case 1:

J. A. is a 43 year old gentleman carrying a diagnosis of hypertension for four years after presenting with headache and a BP of 220/130. At the time of original presentation, examination revealed grade II retinopathy, a fourth heart sound, and a serum creatinine of 1.6 mg/dl. Since that time, he has been readmitted on 3 occasions, the last two of which were precipitated by progressive exertional dyspnea limiting walking to less than 2 blocks. Examinations and CXRs on these two admissions demonstrated pulmonary congestion, improved with re-initiation of antihypertensive and diuretic therapy. Echocardiography demonstrated concentric left ventricular hypertrophy with minimally depressed left ventricular systolic function. For the last six months, he has been unable to work as a security guard due to exercise intolerance.

Case 2:

R. T. K. is a 74 year old physician who presented 1 year ago to his cardiologist with recent onset and progressive angina inadequately controlled by medical therapy prescribed by his internist. Cardiac catheterization revealed multivessel coronary disease with normal left ventricular volumes, pressures and function. He underwent 3-vessel coronary bypass grafting. His post-operative course was complicated by mediastinal bleeding requiring re-exploration, at which time a roughly 200 cc hematoma was evacuated from the pericardial space. His remaining hospital course was relatively uneventful, but he represented 2 months later with fatigue and mild exertional dyspnea. Examination revealed distended neck veins but was otherwise unremarkable. Echocardiography showed normal ventricular function and trace mitral regurgitation. Therapy with diuretics produced little improvement in his symptoms. Repeat echocardiography showed a restrictive filling pattern of transmitral flow and normal left ventricular systolic function. Cardiac catheterization showed right atrial pressure 18, pulmonary capillary wedge pressure 19, cardiac output 3.4 l/min with calculated SVR 1620. Chest CT scan showed mediastinal scarring with a possible organized hematoma lining the posterolateral pericardial border.

Case 3:

R. B. is a 38 year old gentleman with a family history of sudden cardiac death at young age in his father and an older brother. He presented with symptoms of progressive exercise intolerance over 2-3 years due to exertional dyspnea. He was no longer able to participate in recreational athletics and for ~3 months had difficulty functioning as a construction laborer. Initial evaluation revealed a BP 120/70, a soft murmur of mitral regurgitation but was otherwise unremarkable. Echocardiography revealed marked concentric ventricular hypertrophy with systolic near-obliteration of the left ventricular cavity, systolic anterior motion of the anterior mitral valve leaflet, and diminished early diastolic transmitral flow with reversal of the E/A ratio.

Case 4:

A. S. is a 42 year old African woman who presented with a two year history of progressive fatigue, edema and ascites. Efforts at medical therapy for congestive heart failure by her personal physician had resulted in minimal improvement. On presentation to the emergency department with worsening dyspnea, examination revealed jugular venous distention, diminished pulse volumes, hepatomegaly, moderate ascites and severe pitting edema of the lower extremities. Echocardiography revealed biatrial and right ventricular enlargement with normal left ventricular chamber size, moderately

depressed global left ventricular systolic function, and a restrictive transmitral flow profile. Right heart catheterization revealed a right atrial pressure of 20, pulmonary artery pressure 44/24, pulmonary capillary wedge pressure 22 and cardiac index 1.8 l/min with SVR 2200. Cardiac MRI showed no evidence of pericardial thickening. Cardiac catheterization confirmed high filling pressures and low output, showed normal coronary arteries and right ventricular biopsy showed endo- and myocardial fibrosis.

Case 5:

L. N. is a 55 year old woman diagnosed at age 48 with congestive heart failure. Evaluation at that time included echocardiography showing left ventricular end-diastolic diameter 65mm, end-systolic diameter 54 mm, severely depressed global left ventricular function without identifiable segmental wall motion abnormalities. Cardiac catheterization showed normal coronary arteries, LVEDP 24 and LVEF 0.22. She was treated with digoxin, lasix and captopril with marked improvement in her symptoms. Since that time, she has been followed in the Cardiology clinic with a diagnosis of idiopathic dilated cardiomyopathy on ACE inhibitor and diuretic therapy able to carry out essentially all of her activities of daily living. She has been hospitalized on one occasion with decompensated heart failure rapidly responsive to parenteral diuretic therapy. She is currently able to walk 5 blocks without limiting symptoms.

The first four cases share three common threads that distinguish them from Case 5:

i. each of the first four patients has relatively preserved global left ventricular systolic function,
ii. each demonstrates compromise of left ventricular diastolic filling, and, in contrast to Case 5,
iii. each is severely limited by symptoms referable to their cardiac disease.

Common indices of left ventricular performance - cardiac index, stroke volume, left ventricular ejection fraction and similar measures - are long recognized predictors of survival in the syndrome of congestive heart failure. For almost as long its been recognized that isolated ("diastolic heart failure") or concomitant ("diastolic dysfunction") abnormalities of left ventricular filling can precipitate congestive symptoms. More recently, it has become appreciated that parameters of left ventricular filling (and, at least in part, derivative right ventricular function) are often more important than contractile function as determinants of functional status.

On a macroscopic scale, the physiology of impaired ventricular filling was described more than 20 years ago. In the last several years, however, molecular events underlying the deposition and remodeling of the cardiac interstitial matrix have been described. The connective tissue matrix of the heart now appears a dynamic component of the syndrome of congestive heart failure. In the process, new insight into the mechanisms by which commonly used therapeutic agents beneficially affect the course of congestive heart failure has been gained, and paths toward new therapeutic strategies have been opened.

My objectives for this Grand Rounds are to review:

i. the physiology of ventricular filling,
ii. the mechanics and diagnostic evaluation of various forms of impaired ventricular filling (focusing on differential physiologic rather than differential etiologic diagnosis),

iii. implications of different patterns of impaired ventricular filling for the therapy of congestive heart failure,
iv. insights into molecular mechanisms operative in the remodeling of the cardiac interstitial matrix, and
v. potential directions in the evolution of novel therapeutic approaches to congestive heart failure arising from these insights.

I have made no attempt to be comprehensive. Specifically excluded are the special cases of obstruction to ventricular inflow in mitral stenosis and loss of atrial systole in dysrhythmia, and discussion of specific etiologies of dilated, restrictive or infiltrative cardiomyopathies, and constrictive pericarditis. Excellent reviews of diastolic heart failure (Brutsaert 1993, Goldsmith 1993, Lenihan 1995, Wheeldon 1994, Clarkson 1994, Shah 1992), echocardiographic evaluation of diastolic function (Vitarelli 1998, Poulsen 1997), restrictive cardiomyopathy (Shabetai 1992), diastolic function in hypertrophic cardiomyopathy (Wigle 1995), constrictive pericardial disease (Fowler 1995) and management of heart failure associated with diastolic dysfunction (Ruzumna 1996, Vasan 1996) have been published, and complement omissions and deficiencies in the discussion that follows.

Prognosis and Response to Therapy in Congestive Heart Failure

In the setting of acute myocardial infarction, residual left ventricular function – most often assessed as ejection fraction - is the most important determinant of prognosis. Similarly, in chronic congestive heart failure, indices of ventricular systolic performance convey prognostic information, but a substantial fraction of patients with the syndrome of congestive heart failure have preserved left ventricular function (Vasan 1995). Moreover, a number of variables not directly reflective of systolic ventricular performance impact prognosis. For example, Pernenkil (1997) reported that in elderly patients, LVEF is a significant predictor of 3 month, but not 1-year survival. Jouillier (1997) reported that survival free of transplantation in a population of patients with class III-IV congestive heart failure was related to better clinical class, lower pulmonary artery pressure, higher cardiac index and lower right ventricular volumes in addition to left ventricular ejection fraction. In multivariate analysis, both left and right ventricular ejection fractions conveyed independent prognostic information.

Lee (1993) reported that severe LV dilation independently and adversely impacts survival in advance heart failure. In this study, the authors reported that although 183 patients with LV end-diastolic dimension indexed > 4.4 cm/m^2 had a similar hemodynamic impairment to 199 patients with only moderate dilation, their actuarial 2-year survival without transplantation was much lower (49% vs 75%).

De Salvo (1994) published an analysis based on a retrospective review of 528 consecutive patients hospitalized for advanced heart failure (mean LVEF 0.20) and transplant evaluation who were stabilized with medical therapy and discharged. Within 1 year, 11% died suddenly and 13% died of heart failure or required urgent transplantation. Independent predictors of clinical deterioration or death included serum sodium < 134 mEq/liter, pulmonary arterial diastolic pressure > 19 mm Hg, left ventricular diastolic dimension index > 44 mm/m^2, peak oxygen consumption during exercise testing < 11 ml/kg/min and the presence of a permanent pacemaker. In the absence of these factors, risk of hemodynamic deterioration was only 2% vs. > 50% in the presence of hyponatremia and any 2 additional risk factors.

From these and similar studies, a consistent observation that indices of pulmonary congestion, ventricular size, neurohumoral activation and clinical status/functional capacity influence prognosis in patients with congestive heart failure independent of left ventricular systolic performance has emerged.

Tailored therapy and clinical course

Shortly after the emergence of vasodilator therapy for congestive heart failure, Milton Packer and colleagues (Packer 1980) described a relationship between ventricular size and acute hemodynamic and clinical response to vasodilator therapy. They reported left ventricular end-diastolic dimension (LVEDD) measured by M-mode echocardiography correlated significantly with the percent change in stroke volume ($r = 0.77$), left ventricular filling pressure ($r = -0.68$), and stroke work index ($r = 0.87$) during short-term therapy. Despite similar ejection fractions (< 0.30) 15/24 patients with an LVEDD > 60 mm improved in response to vasodilator therapy, while only 2/16 patients with an LVEDD < 60 mm improved. In the latter group, 10/16 patients showed clinical deterioration (hypotension, pre-renal azotemia), indicating that left ventricular chamber size is an important factor in the acute response to vasodilator therapy.

In 1989, Lynne Stevenson and colleagues (Stevenson 1989) described "tailored" therapy for pre-transplant patients with advanced congestive heart failure. In the initial series, 50 consecutive patients (mean LVEF 0.16) referred for urgent transplantation underwent intensive afterload reduction therapy, initially with intravenous and subsequently with oral vasodilators and diuretics tailored to specific hemodynamic goals. In particular, therapy was tailored in an effort to achieve a pulmonary capillary wedge pressure of 15 mmHg. In response to aggressive therapy, mean cardiac index increased from 1.9 to 2.8 $l/min/m^2$, mean PCWP decreased from 30 to 15 mmHg and mean systemic vascular resistance decreased from 1,800 to 1,100 dynes-s-cm^{-5}. Forty of these 50 patients were ultimately discharged on medical therapy, and actuarial survival for 24 discharged patients receiving sustained medical therapy alone was 67% at 1 year. Two-thirds of survivors returned to employment, and 88% survived until transplantation.

Subsequently, these studies have been extended to demonstrate sustained hemodynamic improvement in patients receiving "tailored" therapy (Steimle 1997). Twenty-five patients referred for transplantation and stabilized on aggressive angiotensin converting enzyme inhibitor, diuretic and with/without digoxin, hydralazine or nitrate therapy underwent hemodynamic reassessment 8+/-6 months after initial treatment. On essentially the same medical program as initially established, these patients demonstrated persistent improvement in PCWP (means pre-treatment 24, acute 15, chronic 12) and SVR (means pre-treatment 1651, acute 1207, chronic 1003). Sustained improvement in functional class and freedom from resting symptoms were also observed.

While now virtually dogma in the management of advanced congestive heart failure, the aggressive effort to normalize left ventricular filling pressure in its time violated conventional wisdom. Aggressive efforts to relieve congestive symptoms were often proscribed in response to fears that cardiac output would be further compromised by movement down the Frank-Starling relationship. Persistent pulmonary congestion was often accepted as the price of preserved forward output, at a cost of reduced functional status and more frequent rehospitalization.

What does this have to do with diastolic function or impaired ventricular filling? More later, but for now suffice it to say that *the Frank-Starling relationship between sarcomere length and force development in cardiomyocytes now well established to apply even in failing myocardium* (e.g. Vahl 1998, Vahl 1997, Holubarsch 1998) *cannot be blanket extended to describe the hemodynamic response to left ventricular filling pressure in humans with the syndrome of congestive heart failure*

Right ventricular function and prognosis in congestive heart failuree

Indices of right ventricular performance have historically received limited attention in the assessment of patients with "left" heart failure. Recent studies suggest, however, that right ventricular performance is an independent predictor of survival and functional status in advanced CHF. For example:

Gorsican (1996) examined right ventricular pressure-volume loops in 16 pre-transplant patients. They observed that RV elastance (ratio of peak systolic pressure to end systolic volume) and improvement in RV elastance in response to dobutamine infusion correlated with a favorable short-term prognosis.

Spinar et al. (1996), studying a transplant evaluation population (n=67), have reported that RVEF >0.35 by radionucleide angiography was a significant and better predictor of 6 month event-free survival than cardiopulmonary stress testing. In their series, LVEF was not associated with either overall or event-free survival.

In a study of 62 patients with class III-IV heart failure (LVEF 0.30), Jouillier (1997) reported transplant-free survival was related to better clinical class and LVEF, lower pulmonary artery pressure, higher cardiac index and lower right ventricular volumes. In multivariate analysis, LVEF and RVEF were independent predictors of survival.

Gravazzi (1997) studied short-term prognosis in 142 class III-IV patients referred for transplant evaluation. During a mean follow-up of ~11 months, heart failure score and right ventricular ejection fraction were significantly associated with outcome. Right ventricular ejection fraction (<0.24) was the single variable highly correlated with an increased risk of early death.

Similarly, Karatasakis (1998) reported that in 40 patients with class III-IV heart failure and LVEF < 30%, survival was strongly (sensitivity 90%, specificity 80%) associated with right ventricular shortening > 1.25 cm measured echocardiographically.

Finally, De Groote (1988) reported that in 205 patients with NYHA class II-III heart failure (mean LVEF 0.29) followed for ~2 years, three variables-NYHA classification, percent of maximal predicted VO2 and RVEF-were independent predictors of both survival and event-free cardiac survival. Left ventricular ejection fraction had no predictive value. The event-free survival rates from cardiovascular mortality and urgent transplantation at 2 years were 59% vs. 93% for patients with RVEF <25% or >35% respectively.

In the absence of chronic pulmonary hypertension, right ventricular systolic performance is very sensitive to afterload. As pulmonary artery systolic pressure increases in a roughly linear manner with pulmonary venous pressure, to an extent, right ventricular ejection fraction varies as a function of left ventricular filling pressure. Several studies have identified pulmonary artery (PA) hypertension in transplant recipients as a risk factor for early post-transplant mortality. Similarly, persistent pulmonary hypertension in pre-transplant patients despite aggressive medical therapy correlates with reduced event-free survival. While not carefully studied, several observations suggest that improvement in pulmonary artery systolic pressure with therapy of advanced CHF largely parallels improvement in PCWP. For example, in a study of 50 pre-transplant patients, Levine (195) observed that patients with a decrease in PA pressure were those with a significant fall in PCWP. A mean decrease in PCWP from 27 to 14 mmHg was associated with a mean decrease in PAS from 57 to 37 mmHg. Patients with hemodynamic improvement on aggressive medical therapy in this study had roughly half the 10-month mortality rate of patients failing to improved pulmonary vascular hemodynamics. In this context, it appears that often

pulmonary artery systolic pressure and pulmonary vascular resistance are increased reactively in response to pulmonary venous hypertension.

In summary, whether the correlation between RVEF and prognosis in patients with congestive heart failure reflects the presence or absence of right ventricular myocardial dysfunction, or rather identifies those patients with persistently elevated left sided filling pressures has not been carefully studied. There is accumulating evidence, however, that indices of left ventricular filling, like those of right ventricular systolic function, convey important prognostic information.

Diastolic Function and Prognosis in Congestive Heart Failure

For many years, abnormalities of left ventricular compliance or diastolic dysfunction have been recognized as a cause of congestive symptoms in patients with hypertrophic cardiomyopathy or those with heart failure in the setting of preserved left ventricular systolic performance (restrictive and hypertensive cardiomyopathies). More recently, however, impaired left ventricular filling has been identified as a common component of dilated cardiomyopathy generally, and abnormal left ventricular filling patterns have been identified as important indicators of prognosis in patients with DCM. For example:

Lupa-Bula (1998) investigated Doppler-echocardiographic left ventricular filling parameters as predictors of survival in 197 patients with DCM (LVEDD > 60 mm and fractional shortening <25%). Over a period of 62 months, transplant-free survival was inversely related peak transmitral flow velocity (E) and E/A ratio (restrictive filling pattern). Age, peak E velocity, LVEF, and systolic blood pressure independently predicted cardiac deaths.

Temporelli (1998) has reported that the change in left ventricular filling pattern (assessed by Doppler transmitral deceleration time) in response to optimal oral therapy for heart failure could identify patients with a favorable subsequent clinical course. 62/144 patients with CHF and a deceleration time < 125 msec at the time of initial evaluation had prolongation of deceleration time toward normal over 6 months of therapy. Cardiac mortality during follow-up was 11% in patients with, vs. 37% in patients without improvement in deceleration time with therapy.

Indices of left ventricular filling have been reported to convey prognostic information in patients with acute myocardial infarction as well. Poulsen (1997) examined transmitral and pulmonary venous flow velocities obtained within 1 hour of a first acute myocardial infarction in 65 patients. Regression analysis identified age, LVEF < 0.45, mitral E deceleration time < 130 msec, E/A ratio > 1.5, and peak pulmonary venous flow velocity > 30 cm/sec as predictors of subsequent CHF, with age and mitral E deceleration time < 130 ms the most significant independent variables.

Left ventricular filling is an important determinant of clinical course in CHF

While, in general, the studies to date are not large and the data correlating specific variables with prognosis not entirely consistent, the evidence available makes a fairly compelling case that parameters of left ventricular systolic function do not adequately characterize the patient with dilated cardiomyopathy and congestive heart failure. Specifically, it appears that *patients with evidence of impaired ventricular filling – high early diastolic filling velocity, rapid deceleration of early transmitral flow, increased E/A ratio (discussed below), persistently elevated pulmonary capillary wedge pressure, high pulmonary artery pressures, and/or depressed right ventricular systolic performance – have a worse prognosis. In particular, even when survival differences have not been seen, more frequent episodes of decompensation and lesser functional class have been consistently observed.*

From that perspective, let me turn to a discussion of the mechanics of left ventricular filling.

Mechanics of Ventricular Filling

Ventricular pressure-volume relationship

Figure 1A is a schematic representation of a left ventricular pressure-volume relationship throughout the cardiac cycle. Figure 1B shows a magnified view of this relationship during ventricular filling, and Figure 1C shows a transformed view of this relationship in which both pressure and volume are plotted as a function of time during diastole. I'll refer to versions of these diagrams as I review the mechanics of ventricular filling.

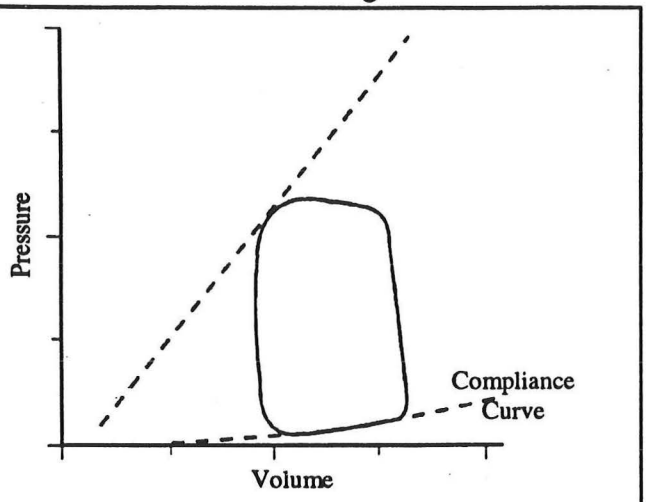

Figure 1A

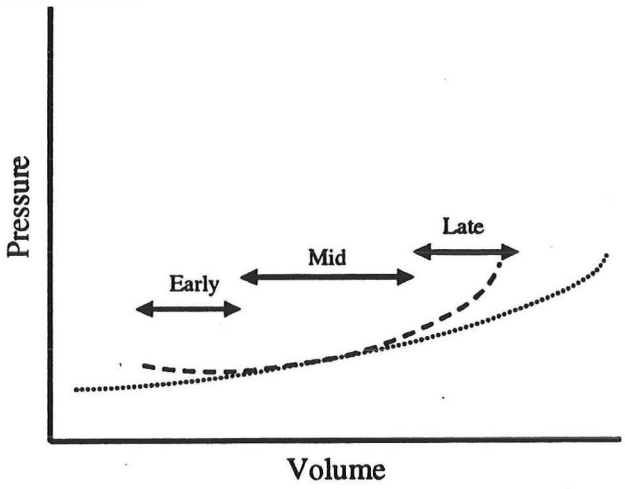

Figure 1B

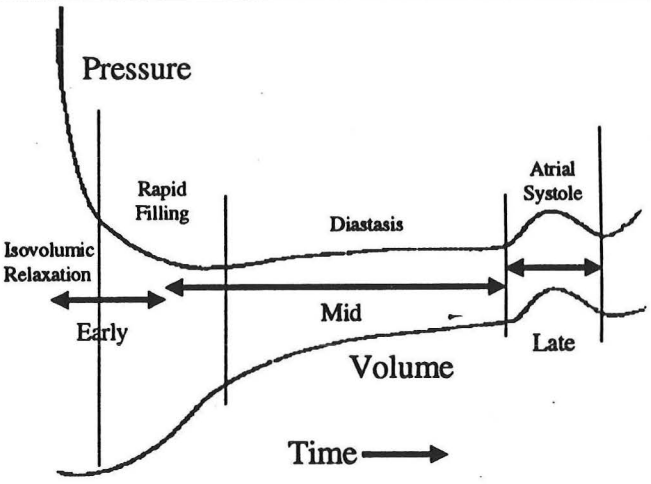

Figure 1C

Phases of diastolic filling

Conventionally, diastole has been described in three phases defined hemodynamically – early rapid ventricular filling, diastasis, in which LA and LV pressures differ little and little ventricular filling occurs, and atrial systole. ***Physiologically, I believe diastolic filling is better conceptualized in three phases defined by the mechanics of ventricular filling, as the factors that may impair filling during each of these phases differ. For the purposes of this discussion, early diastole extends from mitral valve opening until nominal ventricular volume (volume at 0 transmural pressure), which occurs before the end of the rapid phase of ventricular filling. Stated another way, the terminal portions of rapid ventricular filling are mechanically part of mid-diastole, which spans the period from nominal ventricular volume to atrial systole; and atrial systole.***

Early Diastolic Filling:

Ventricular filling during the initial phase of diastole - from mitral valve opening until nominal ventricular volume (volume at 0 transmural pressure) is influenced by 5 factors: left atrial pressure,

mitral valve orifice area, inertial factors related to the mass of blood and ventricular myocardium, the rate of ventricular relaxation and ventricular elastic recoil. The first of these is largely a dependent variable, and inertial factors are essentially a constant. The special case of obstruction to ventricular inflow in mitral stenosis is beyond the scope of this discussion. In general, then, the rate of early ventricular filling may be conceptualized in term of competing influences, ventricular relaxation – impairment of which may delay early filling, and elastic recoil of the ventricle toward nominal volume – which accelerates early filling.

Ventricular relaxation

Relaxation of the ventricular myocardium is an active, energy-dependent process. The rate of ventricular relaxation is governed by re-uptake of calcium from the sarcolemma into the sarcoplasmic reticulum, largely via the SR calcium-dependent ATPase (SERCA). The rate of calcium re-uptake is a regulated process. The pentomeric protein phospholamban inhibits SERCA. Phosphorylation of phospholamban by protein kinases A and/or C relives SERCA inhibition, and enhances the rate of calcium re-uptake into the SR.

Similarly, the rate of sarcomeric cross-bridge release is regulated. Phosphorylation of troponin I reduces calcium affinity, right-shifting the activation curve of the contractile apparatus with respect to sarcoplasmic calcium concentration.

Abnormal ventricular relaxation can affect ventricular filling in three ways. First, slowed ventricular relaxation (e.g. delayed rate of calcium re-uptake, reduced phosphorylation of phospholamban and/or troponin I) as seen, for example in hypothyroidism (Morgan 1989), reduces the slope (-dP/dT) of ventricular relaxation and splays the early portion of the diastolic pressure volume relationship. In experimental animal models of hypertensive cardiomyopathy, SERCA mRNA and protein expression are decreased. Treatment with ACE inhibitors or AII receptor antagonists normalize SERCA expression in parallel with improvement in ventricular relaxation, suggesting that a cellular defect in calcium re-uptake may underlie impaired ventricular relaxation in patients with ventricular hypertrophy (Flesch 1997). A similar change in this relationship can arise from dyshomogeneity in ventricular relaxation in the setting of, for example, ischemia (Heyndrickx 1990). Finally, incomplete or very delayed relaxation – true luisitropic dysfunction - (e.g. hibernating or stunned myocardium, Serizawa 1980) increases the elastic constant of myocytes, resulting in an upward displacement of the pressure volume relationship (Figure 2).

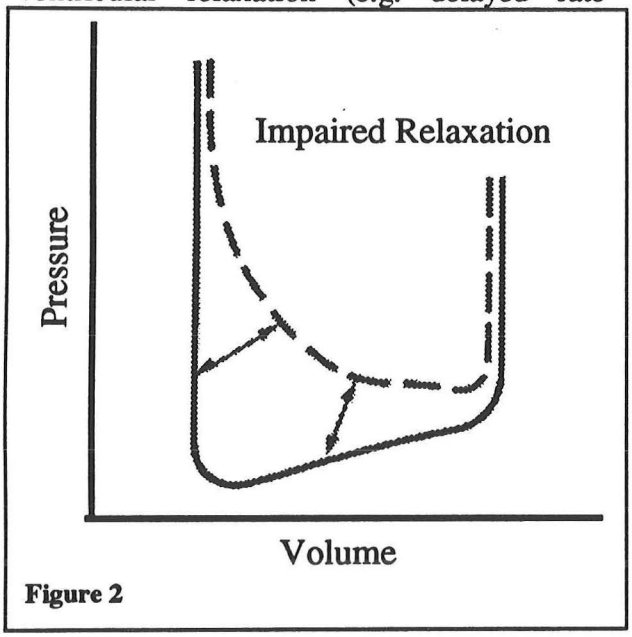

Figure 2

Ventricular Recoil

The force of ventricular systole, in addition to ejecting blood from the ventricular chamber, compresses ventricular myocardium and interstitial connective tissue. During systole, the ventricle also "coils" counterclockwise on its longitudinal axis (Matter 1996). With myocardial relaxation, elastic forces analogous to a compressed spring act to restore the ventricle to nominal volume (Gilbert 1989).

Because inertial factors related to acceleration of the blood mass and the impedance to flow arising from a normal mitral valve are minimal, under physiologic conditions this elastic recoil produces little measurable transmitral pressure gradient. It does contribute, however, to the rapid fall in ventricular and left atrial pressures observed at the end of ventricular relaxation in normal humans.

Changes in ventricular recoil can be of several types. First, increased systolic contraction reduces left ventricular end-systolic volume, essentially increasing compression of the "spring", and accentuates early diastolic recoil and, as a result, early diastolic filling. Conversely, systolic dysfunction results in a larger end-systolic volume and reduces the magnitude of recoil forces acting in early diastole. Increases in interstitial connective tissue mass essentially increase the spring constant, thereby accelerating recoil.

Physiologically, it is essentially impossible to separate cleanly the opposing effects of ventricular relaxation and ventricular recoil on early diastolic filling. *In general, slowed early ventricular filling in the setting of dilated cardiomyopathy reflects some combination of abnormal of ventricular relaxation and reduced compression resulting from systolic dysfunction. Increased early ventricular filling in a hyperdynamic heart is likely physiologically enhanced ventricular relaxation, while in the setting of abnormally increased ventricular wall thickness and impaired mid-diastolic filling (see below) is likely to reflect pathologically increased ventricular recoil associated with restrictive physiology.*

Mid-diastolic filling

Mid-diastolic ventricular filling extends from nominal ventricular volume until atrial systole. In normal humans (absent obstruction to ventricular inflow), the onset of mid-diastole is marked by virtual diastasis of left atrial and ventricular pressures. Filling of the ventricle during this period is driven by left atrial filling/pressure, and resisted by the elastic distensibility of the ventricle – i.e. ventricular compliance. Four "independent" factors influence mid-diastolic filling:

Series elastic resistance

While separating intrinsic ventricular compliance into series and parallel components is artificial, it is conceptually useful in understanding the relative contributions of cardiomyocytes and interstitial matrix to ventricular compliance. The series component of ventricular compliance can be modeled as, for example, springs of dramatically different constants (e.g. myocytes and matrix) arranged in an alternating manner. Subjected to a stretching force, the springs of lower coefficient (myocytes) stretch essentially to their limit with minimal change in the length of the higher constant spring (matrix). At the length limit of myocytes, the compliance of this component of the series increases abruptly, and further stretching of the system is resisted by the constant of the "stiffer" spring (matrix).

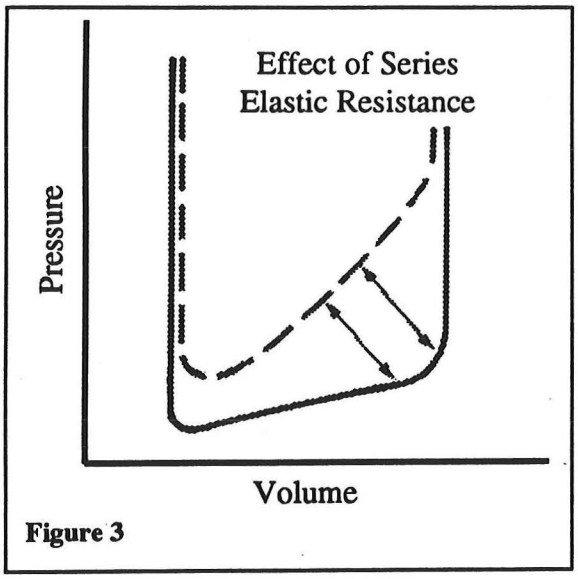

Figure 3

Stretching of normal relaxed ventricular myocytes to "optimal" (Frank-Starling) length occurs at a low spring constant, resulting in a very gradual slope to the ventricular pressure volume curve in mid-diastole. As ventricular volume approaches full distention, however, increasing resistance arises from interstitial matrix, producing an increasing slope to the pressure-volume curve (Figure 3).

Physiologically, the consequence of the series elastic component is slope of the pressure-volume relationship as a function of volume. Increased in series elastic resistance can arise from ventricular dilation, incomplete ventricular relaxation (e.g. ischemia), dyshomogeneity in ventricular stretching (e.g. regional infarction) or an increase in interstitial matrix mass (myocardial fibrosis). In each case, the manifestation is an increase in the slope of the mid- and late-diastolic portion of the ventricular pressure volume relationship.

Parallel elastic resistance

In addition to contributing to series elastic resistance, interstitial connective tissue also provides resistance to ventricular distention in parallel with that arising from ventricular myocytes. Similar effects arise from infiltrative diseases of the myocardium. In the setting of myocyte hypertrophy, elastic resistance may be increased throughout mid-diastole as a result of either incomplete relaxation or simply increased elastic properties of hypertrophied myocytes. In each of these cases, the change in physiology can be modeled as springs of differing constant arranged in parallel, and *the effect is to mediate an upward displacement of the ventricular pressure volume relationship* (Figure 4).

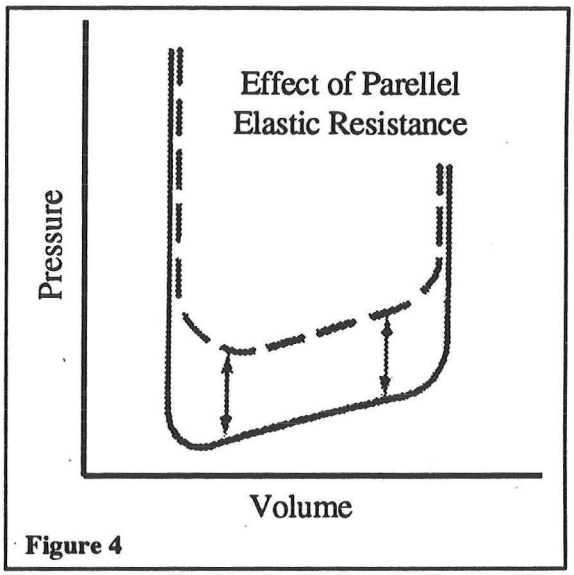

Figure 4

Physiologically, alterations in ventricular compliance resulting from interstitial matrix reflect series and parallel effects combined to varying degree, and the components are often impossible to separate. The extent to which abnormal ventricular compliance reflects increased series vs. parallel resistance, however, may have a significant impact on the clinical course and response to therapy in patients with congestive heart failure. *In contrast to parallel resistance, increases in series elastic resistance result in greater volume sensitivity, i.e. a tendency for LVEDP/PCWP to vary sharply with small changes in volume status* (compare Figures 3 and 4).

Pericardial constraint

Contrary to common perception, the normal human pericardium constrains right ventricular (and right atrial) volume – i.e. the compliance of the normal right ventricle would allow expansion of RV end-diastolic dimension beyond that observed in humans with an intact pericardium. It is the fall in pericardial pressure with inspiration that is largely responsible for the normal respiratory increase in right ventricular filling (Shebetai 1988). Under normal circumstances, however, this effect is minimal, as the pericardium is on the flat portion of a pressure-volume relationship similar in shape to that shown above of the left ventricle. Even with ventricular dilation, gradual expansion of pericardial volume right-shifts this pressure-volume relationship and the constraining effect of the pericardium is minimal (Janicki 1990).

More acute or extreme increases in ventricular volume, however, can distend the pericardium to the steeper portion of its compliance curve, precipitating a condition termed ventricular interaction or interdependence – in which increases in the volume of one ventricle occur at the expense of reduced volume of the contralateral ventricle (Atherton 1997 and see below). The initial clinical manifestation of ventricular interdependence is an accentuation of the normal respiratory-phasic variation in

ventricular filling (paradox). In the extreme, ventricular interdependence is the mechanism underlying the syndrome associated with constrictive pericardial disease (discussed below).

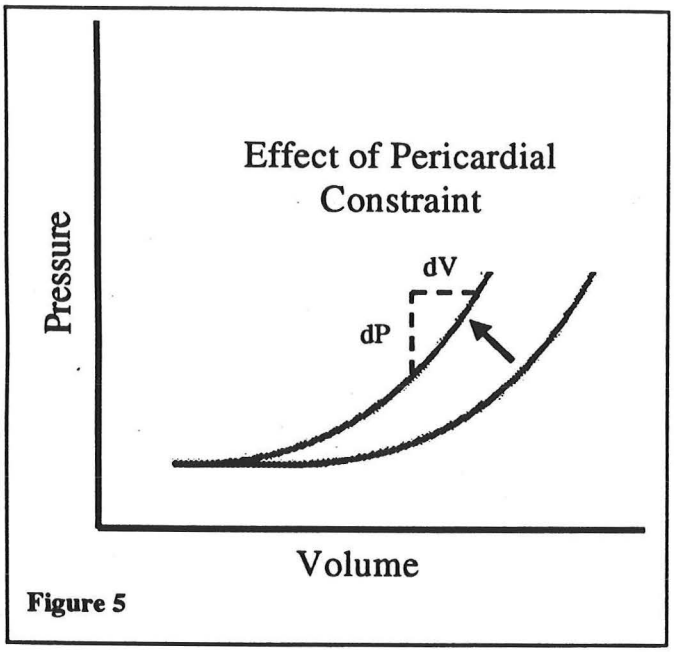

Figure 5

Hemodynamically, the effect of pericardial constraint is to produce an essentially discontinuous left ventricular pressure-volume relationship. At volumes below nominal pericardial volume, ventricular filling is governed by the intrinsic ventricular compliance curve. At or above nominal pericardial volume, however, further ventricular filling is resisted by (steep) pericardial compliance (Figure 5). This is reflected in rapid but abbreviated early ventricular filling (increased E wave velocity, shortened E deceleration time), and diminished mid-diastolic filling (Atherton 1998, Dauterman 1995). Qualitatively, these changes resemble those of an increase in the series elastic component of resistance to ventricular filling – accounting for the similarity in ventricular filling patterns observed in restrictive cardiomyopathies and constrictive pericarditis.

Ventricular interdependence and interaction

Right ventricular filling significantly impacts left ventricular filling via two mechanisms. The first of these - interdependence in the presence of pericardial constraint as discussed above – is encountered in the settings of constrictive pericardial disease or substantial/rapid increases in ventricular volumes (e.g. severe DCM, acute valvular regurgitation, acquired intracardiac shunt, right ventricular infarction).

The second mechanism by which ventricular interaction may impair left ventricular filling occurs in the settings of right ventricular pressure loading/hypertrophy or decompensated right ventricular failure. Under these conditions, the normal convexity of the interventricular septum becomes flattened or reversed, and "stretching" of the septal wall is resisted by pathologically elevated right ventricular diastolic pressure.

This has two effects on left ventricular filling. First, early diastolic filling can be compromised by displacement of the septum "into" the left ventricular chamber by higher early diastolic right ventricular pressures. Second, and probably more importantly, virtual volume lost from the left ventricular chamber by the change in septal curvature results in an effective rightward shift of the left ventricular pressure-volume relationship in mid-diastole. The volume displaced by the septal deformation requires that for constant left ventricular volume, the radius of the left ventricular free wall is increased - essentially the left ventricular free wall is "stretched" (Figure 7). This increases series and parallel elastic resistance to left ventricular filling as the free wall is moved upward and rightward on its compliance curve.

Late diastolic filling

Atrial contraction

Under normal physiologic conditions, atrial contraction is estimated to contribute ~15% to left ventricular filling. This contribution, however, varies widely with atrial pressure, atrial contractility (and the existence of organized atrial contraction), pre-atrial systolic ventricular volume, the slope of the ventricular compliance curve at pre-atrial systolic volume, and the relative timing of atrial and ventricular systole (AV delay) (Holt 1994). Important impairment of late ventricular filling arises from the loss of effective atrial systole associated with dysrhythmia, and with a steep slope of the ventricular pressure-volume relationship at pre-atrial systolic volume.

Diagnosis and Evaluation of Impaired Ventricular Filling

Echocardiography

Two-dimensional echocardiography can provide a qualitative impression of the pattern of ventricular filling, particularly in the setting of constrictive pericardial disease or advanced restrictive cardiomyopathy, in which very rapid early ventricular filling abruptly ends. More sensitive and specific information, however, is available from Doppler analysis of transmitral flow. Figure 6 shows a schematic representation of the transmitral flow velocity profile in a normal heart. On this diagram, E represents early diastolic filling, A represents late ventricular filling associated with atrial systole, and DT is the E wave deceleration time measured in msec. In the normal heart, early diastolic filling predominates. Peak E wave flow velocity is >60 cm/sec, the E/A (peak flow velocity) ratio is >1 (mean in a young population 1.9+/-0.6), and E wave deceleration time is >130 msec

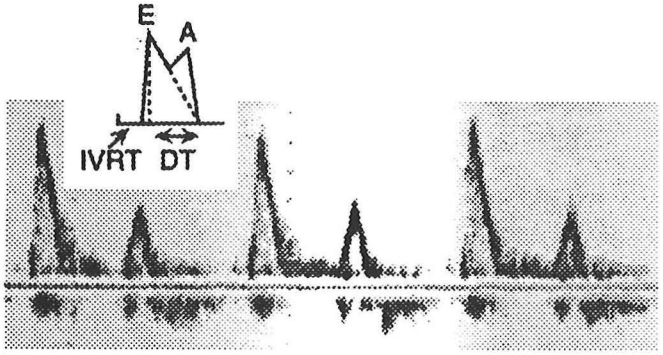

Figure 6

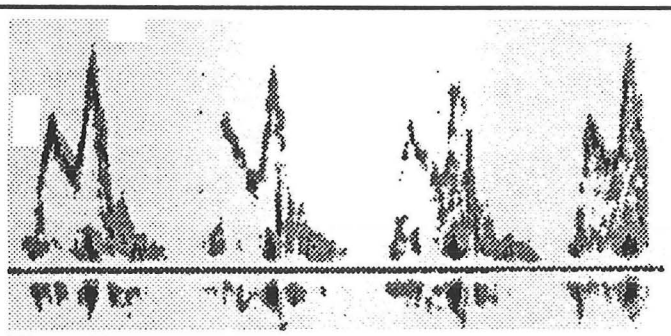
Figure 7a

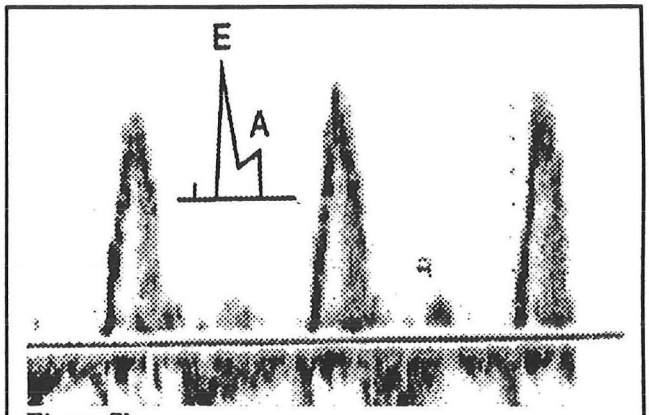

Figure 7b

(mean 180 +/-20). Impaired ventricular relaxation results in a decrease in peak E wave velocity, a reversal of the normal E/A ratio, and a prolongation of E wave deceleration time (Figure 7A). In contrast, impaired mid-diastolic filling (e.g. restrictive or constrictive physiology) results in an increase in peak E wave velocity and a shortening of E wave deceleration time (Figure 7B).

Additional information concerning diastolic filling can be derived from the pattern of pulmonary venous blood flow, generally assessed during transesophageal echocardiography. Figure 8 shows the normal pattern of pulmonary venous blood flow. The S wave represents rapid atrial inflow during

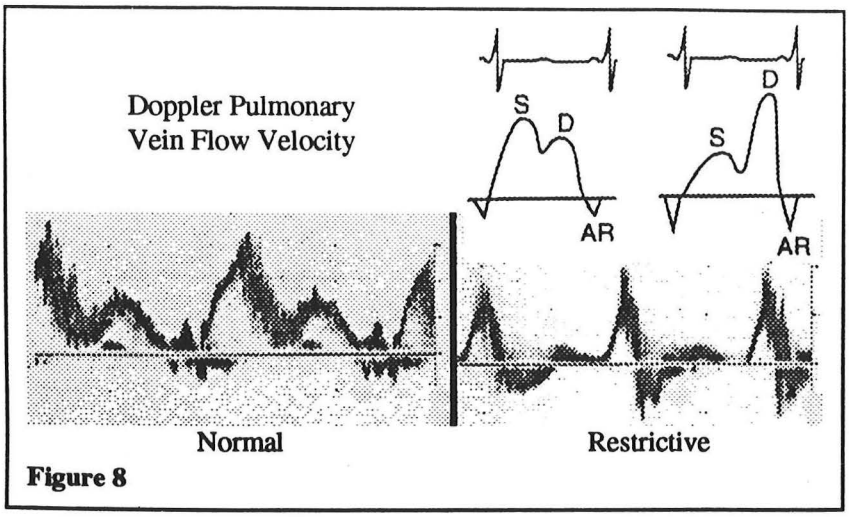

Figure 8

ventricular systole, the D wave atrial inflow after mitral valve opening, and AR the reversal of pulmonary venous flow during atrial systole. The magnitude of the pulmonary venous S wave provides a qualitative estimate of LVEDP, as increased atrial afterload impairs atrial emptying during atrial systole. As a result, atrial filling during ventricular systole is reduced – generally with a corresponding increase in atrial filling after mitral valve opening (reversed S/D ratio). Parenthetically, a similar pattern in hepatic venous flow can be used as an index of right ventricular filling.

Other Imaging Modalities

Left ventricular filling can also be assessed by ventricular imaging modalities – radionucleide angiography (Arrighi 1995), gated cardiac magnetic resonance imaging (Hoff 1994) and gated electron beam computerized axial tomography. Of these, radionucleide angiography is most commonly employed. Essentially, left ventricular filling is assessed by the absolute and fractional rates of increase in ventricular activity (directly related to volume) – measures tailored to assess the rate of early ventricular filling. The most commonly employed measures are peak filling rate (in diastolic volumes/sec) and the fraction of ventricular filling occurring in the first 1/3 of diastole. Impaired ventricular relaxation reduces both peak filling rate and the fractional filling in the first 1/3 of diastole. These approaches are less sensitive in the detection and assessment of impaired mid-diastolic ventricular filling.

Hemodynamic Assessment of Impaired Ventricular Filling

While in theory, left ventricular pressure-volume loops can be measured at the time of cardiac catheterization, practically this is rarely done outside investigative protocols. High resolution ventricular angiograms (rapid frame rate) are necessary, and injection of contrast inherently alters ventricular pressure. Pulmonary capillary wedge pressure (left atrial pressure) and left ventricular pressure tracings are readily obtained.

Ventricular relaxation can be assessed from the rate of fall in intraventricular pressure. Ventricular pressure decay during the relaxation follows an approximately exponential curve that can be characterized by the peak rate of fall of intraventricular pressure (–dP/dT, Figure 9), and/or from the time constant for the decay in intraventricular pressure given by $P_v = (P_o e^{-t/\tau} + P_b.)$. The latter provides a more precise index of relaxation than the time to diastasis (roughly equal left atrial and ventricular pressures).

Mid- and late diastolic filling are less readily assessed by invasive hemodynamic measurements, although LVEDP is a rough surrogate for the slope of the terminal ventricular compliance curve.

Invasive measurements of left ventricular pressure are useful in identifying restrictive/constrictive abnormalities of ventricular filling. Figure 10 shows the "dip and plateau"

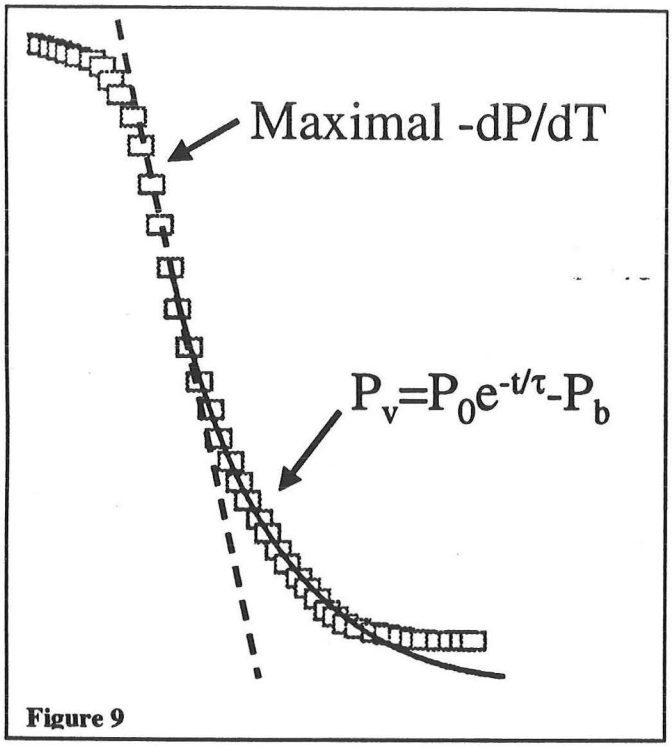

Figure 9

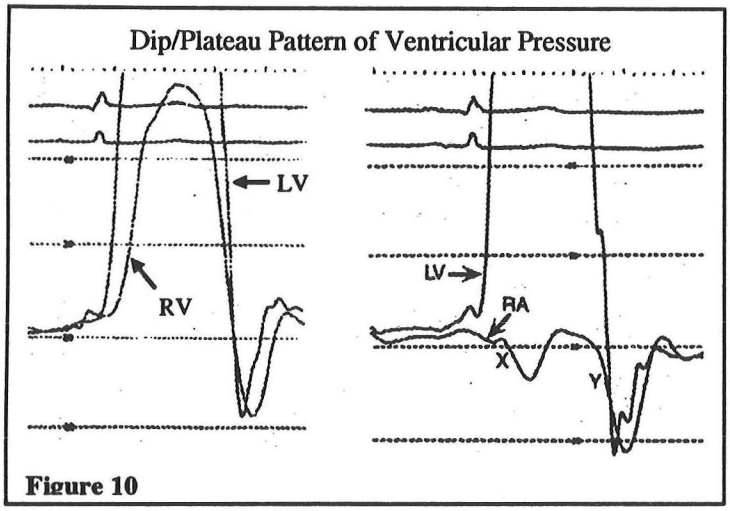

Figure 10

pattern of intraventricular pressure, and the rapid X and Y descents in the left atrial pressure that characterize restrictive/constrictive physiology.

Patterns of Impared Ventricular Filling in Dilated Cardiomyopathy

Four distinct patterns of ventricular filling have been observed in patients with dilated cardiomyopathy (Ohno 1994, Cohen 1996, Vitarelli 1998). They represent a continuum from normal ventricular filling to severely impaired diastolic function - in essence, these patterns represent stages in the evolution of diastolic filling abnormalities. Changes in pattern in both directions are observed in response to progression or regression of the disease process, therapy and loading conditions.

The first pattern is normal – early ventricular filling predominates, and is reflected in a normal peak E wave velocity, E/A ratio > 1 and normal deceleration time on Doppler assessment of transmitral flow. With delayed left ventricular relaxation (pattern II), early ventricular filling declines (peak E velocity < 60, E/A < 1, deceleration time increases). The third pattern of ventricular filling is termed psuedonormal, as increased left atrial pressure overcomes impaired ventricular relaxation and restores early ventricular filling toward normal, albeit at the expense of significantly increased LVEDP and PCWP. The fourth pattern is "restrictive". High left atrial pressure and perhaps enhanced elastic recoil of a progressively "fibrotic" ventricle result in very rapid but abbreviated early ventricular filling. Peak E velocity and E/A ratio are increased, but deceleration time shortens as series and parallel elastic forces resist ventricular distention. A wave velocity is reduced by poor terminal ventricular compliance. This restrictive filling pattern identifies patients with DCM with a poor prognosis (Pinamonti 1993, Xie 1994, Rihal 1994, Koilpillai 1996 and as discussed above).

Special Cases of Impaired Ventricular Filling

Hypertrophic Cardiomyopathy

Abnormal diastolic filling is a nearly universal component of the syndrome of hypertrophic cardiomyopathy, and may dominate the clinical presentation. Impairment of both early and mid-diastolic

filling may be observed, but the former predominates. Pak (1997) examined active and passive (preload) pressure-volume relations in patients with HCM, and demonstrated a marked discordance – dynamic impairment to filling greatly exceeded passive ventricular stiffness – consistent with a dominant defect in ventricular relaxation. Izawa (1997) further demonstrated that the normal enhancement of ventricular relaxation rate with exercise is blunted in patients with HCM.

Diminished re-uptake of calcium into the sarcoplasmic reticulum has been demonstrated in patients with HCM in association with delayed relaxation (Wigle 1985). This is potentially exacerbated by the increased systolic load, resulting in an excess burden of cytosolic free calcium (Morgan 1991). Peak ventricular relaxation rate (-dP/dT) is generally reduced, and time to peak E wave velocity prolonged. Impairment of early ventricular filling is reflected in a decreased E/A ratio, often dramatic by virtue of a marked increase in the contribution of atrial systole to ventricular filling (Appleton 1988). Prolongation of ventricular systole (hypercontractile state, ventricular outflow obstruction and elastic recoil and inertial resistance to ejection) may result in dyshomogeneity in repolarization, further exacerbating "relaxation failure" (Inoue 1991). Observations in the transgenic mouse model of αMHC403/+ HCM suggest abnormal energetics (reduced phosphocreatine/Pi ratio), suggesting one possible mechanism for slowed calcium re-uptake (Spindler 1998).

Several components contribute to impaired mid-diastolic filling in HCM. Increased myocardial mass increases viscoelastic and inertial resistance to filling, intrinsic muscle stiffness is increased by mass and by disorganization in myofibrillar structure, and an increase in interstitial connective tissue contributes to increased serial and parallel elastic resistance to ventricular filling. The net effect is an upward and leftward shift in the pressure-volume relationship (Gaasch 1976). On rare occasions, the increase in stiffness may be the dominant abnormality, producing a restrictive pattern ventricular filling defect, in which high atrial pressure results in rapid, abbreviated early diastolic filling (Wigle 1995).

Restrictive Cardiomyopathy vs. Constrictive Pericarditis

The hallmarks of a restrictive filling pattern – rapid, abbreviated early diastolic filling and diminished filling with atrial systole – and the Doppler echocardiographic manifestations – high E wave velocity, E/A ratio, decreased deceleration time and diminished A wave - have been described previously. Similar hemodynamic alterations characterize pericardial constriction. As described previously, the principal hemodynamic distinction between these similar impairments to ventricular filling is ventricular interdependence in the setting of constriction.

To summarize again, interdependence simply implies a competition between the right and left ventricles for space within the pericardium. Beyond a restrictive filling pattern, the principal hemodynamic manifestations are equalization of diastolic intrapericardial pressures, a rapid and steep decline in early left ventricular diastolic pressure and an abrupt increase in left ventricular pressure when ventricular volume encounters pericardial constraint (dip and plateau or square root pattern).

A similar pattern characterizes restrictive cardiomyopathy. Hemodynamic findings that assist in distinguishing restriction/constriction include in the former an LVEDP generally 5 mmHg > RVEDP, an RV systolic pressure <50 mmHg and an RVEDP > 1/3 RVSP. The patterns of constrictive and restrictive disease, however, may overlap.

Doppler transmitral flow velocities show distinguishing characteristics – a marked respiratory-phasic change in the cardiac filling in characterizes constriction. Because, in the setting of constriction, the atria and ventricles are isolated from changes in intrathoracic pressure (by the thickened pericardium) while the pulmonary (and to a lesser degree systemic) venous drainage is not, inspiration reduces the pulmonary vein to left atrium pressure gradient and reduces filling, This can be seen by Doppler

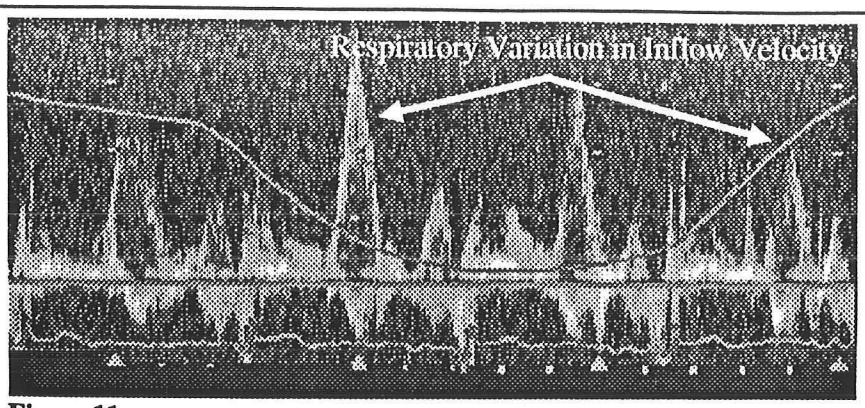

Figure 11

echocardiographic measurement of pulmonary venous flow. In restriction, systolic atrial filling is reduced throughout the respiratory cycle (blunted S/D ratio). In constriction, the S/D ratio is generally normal, but with inspiration, both S and D velocity are dramatically reduced. Similar changes in the filling of the ventricles are observed. Early ventricular filling manifest as E wave velocity, is reduced with the onset of inspiration, resulting in a respiratory-phasic variation in E velocity (Hatle 1989). Diagnostically, respiratory variation in E velocity >25% suggests constriction (Figure 11). A similar respiratory-phasic pattern in tricuspid inflow occurs, but is frequently less prominent. In some patients with constrictive physiology, respiratory variation is masked by marked elevation in atrial pressures (Oh 1997). In this event, diagnostic respiratory variation can be unmasked by preload reduction.

Recently, careful hemodynamic recordings using micromanometer tip catheters have confirmed these echocardiographic findings in constrictive pericardial disease. Specifically, a respiratory-phasic change in the PCWP to minimal early diastolic LV pressure > 5 mmHg (hemodynamic demonstration of isolation of the ventricles from intrathoracic pressure changes during respiration) has been reported to be 90% sensitive and >80% specific for the diagnosis of pericardial constriction (Hurrell 1996).

Imaging of a thickened pericardium (>3-3.5 mm) lends support to the diagnosis of constriction. Gated MR imaging is particularly useful (sensitivity/specificity >90%, Hartnell 1996), but one recent report suggests that pericardial thickness > 3mm on transesophageal echocardiography is similarly sensitive (>90%, Ling 1997). Finally, imaging techniques may allow characterization of the rate of left ventricular diastolic expansion. Using MRI and Doppler tissue imaging, expansion of the left ventricle in its longitudinal axis has been reported to distinguish between patients with constrictive (more rapid) and restrictive physiology (Garcia 1996).

Mechanisms Underlying Impaired Ventricular Filling

Luisitropic dysfunction

As discussed previously, there is evidence for diminished re-uptake of calcium in both hypertensive cardiomyopathy and familial HCM (Flesch 1997, Wigle 1985). Several potential mechanisms – reduced SERCA expression (Flesch 1997), reduced phosphorylation of regulatory proteins (Morgan 1991), abnormalities in myocardial energetics (Spindler 1998) - have some experimental support. Neither the proximate stimulus precipitating, nor the signaling cascades mediating any of these abnormalities have been defined at a molecular level, and thus therapeutic interventions remain empiric.

Cardiac interstitial matrix

Impaired ventricular filling in the setting of idiopathic or ischemic cardiomyopathy is associated with an increase in interstitial collagen. The course of ventricular fibrosis depends upon the appearance,

disappearance, persistence or increase in the population of myofibroblasts [myoFb] (Weber 1997). Myofibroblasts are phenotypically transformed fibroblasts that both produce procollagen types I and III and are contractile via expression of α-smooth muscle actin (Vracko 1991, Campbell 1995, Bishop 1994). Transformation of fibroblasts appears to be initiated by TGF-β, produced both by myoFb (and by monocytic cells, Desmouliere 1993) in response to, amoung others, angiotensin II (Casscells 1990). Human cardiac myofibroblasts in culture increase collagen expression in response to angiotensin II and aldosterone (Weber 1995), and human myocardium obtained at transplantation from DCM shows ~2-fold greater collagen concentration than normal myocardium (Gunja-Smith 1997).

Collagen is continuously synthesized and degraded, and tissue collagen content reflects a balance between these processes. Collagen is degraded by matrix metalloproteinases [MMPs], most importantly MMP1 (collagenase) and MMP9 (stromelysin). The activity of MMPs is tightly regulated. They are secreted from myoFb as inactive zymogens, activated by proteolytic cleavage (e.g. by plasmin), and are subject to inhibition by tissue inhibitors of metalloproteinases [TIMPs], also produced by myoFb. Most MMP in myocardium is in latent form (inactive zymogen or complexed to TIMPs) (Tyagi 1996).

In animal models of congestive heart failure, there is increased collagen turnover (Bishop 1998). The hearts of cardiomyopathic Syrian hamsters overexpress mRNAs encoding collagen types I and III and accumulate interstitial collagen. Both can be blocked by administration of AT1 receptor blockade (Dixon 1997). Similarly, the hearts of SHR rats demonstrate accumulation of interstitial collagen, which can be blocked by ACE inhibitor therapy. Human DCM myocardium obtained at transplantation has been reported to show ~2-fold greater collagen concentration than normal myocardium, increased mRNA encoding MMP1 (Tyagi 1996), and MMP1 and 2 activity (Gunja-Smith 1996). There is conflicting data on TIMP expression in the setting of cardiomyopathy (Gunja-Smith 1996, Thomas 1998).

The collagen synthesis/degradation equilibrium is modulated in response to several identified effectors, most importantly angiotensin II and aldosterone. An increase in circulating AII activity in animal renal ischemia models is associated with diffusely increased mRNA for types I and III collagen and myocardial collagen accumulation (Brilla 1994, Zhou 1996, Chapman 1990). In SHR rats, overexpression of MMP1 and accumulation of interstitial collagen are blocked by ACE inhibitors. Evidence suggests that local production of angiotensin II in the myocardium is also important. Angiotensinogen is expressed in heart by myoFb and cardiac myocytes (Sawa 1992). While there is no convincing evidence that renin is expressed in the heart, cathepsins D and G are expressed and catalyze cleavage of angiotensinogen to angiotensin I.

Angiotensin converting enzyme is expressed in heart at sites of high collagen turnover (Yamada 1991). AII binding to the AT1 receptor on myoFb induces expression of collagen, MMPs and TIMPs (Katawa 1995, Filip 1986). In injured hearts, ACE continues to be expressed by myoFb, rather than being downregulated as with pulmonary endothelial ACE in the presence of AII.

Circulating aldosterone also appears to effect collagen turnover in the heart. While increasing synthesis of collagen, aldosterone decreases expression of collagenase (MMP1) (Weber 1995), thus favoring collagen accumulation. In animal models of cardiomyopathy, aldosterone receptor antagonists attenuate collagen accumulation (Weber 1995), suggesting a significant pathophysiologic role for aldosterone in the development and progression of myocardial fibrosis.

Bradykinin may also play a role in modulating collagen turnover in the heart. ACE also functions as a kininase II, and may modulate bradykinin concentration in heart (Weber 1997). There is some evidence that bradykinin receptor blockade may attenuate collagen accumulation in experimental models of myocardial infarction.

In addition to synthesizing procollagen, MyoFb are contractile in response to AII, ET1, PGE2 and 5HT (Katawa 1995, Filip 1986). Intracoronary administration of ACE inhibitors to hypertensive patients causes rapid fall in LVEDP, probably reflecting relaxation of myoFb (Haber 1994).

There is evidence of accelerated collagen turnover in human heart failure. Plasma levels of N-terminal procollagen III peptide and type I collagen C-telopeptide increase in parallel with the severity of heart failure, and with the collagen content of hearts explanted at transplantation (Klappacher 1995). In addition, serum N-terminal procollagen III peptide is elevated in patients with hypertension, and correlates directly with plasma renin activity and inversely with peak transmitral E flow velocity (Diez 1995). In vitro stretch of cultured fibroblasts induces MMP expression (Tyagi 1998), suggesting that collagen turnover may be directly load sensitive. Finally, inhibition of MMP-1 activity by administration of a small molecule inhibitor blocks progression of heart failure in SHR-HF rats (Peterson 1997).

In aggregate, these observations suggest that activation of both the systemic and local RAAS systems recruits a population of synthetic and contractile myofibroblasts, stimulates procollagen synthesis, and accelerates collagen turnover. A clear understanding of the factors that push this process toward myocardial fibrosis and increased ventricular "stiffness" or toward dilated cardiomyopathy (also associated with enhanced collagen turnover) is lacking, but some evidence suggests aldosterone and bradykinin may play significant roles. Contractile activity of myofibroblasts may also contribute significantly to decreasing myocardial compliance.

Implications of Impaired Ventricular Filling in Therapy of CHF

The treatment of patients with diastolic heart failure is controversial, and studies to date involve limited numbers of patients (Vasan 1995, Ruzumna 1996). There are few published clinical trials, and those that exist have generally not stratified patients on the basis of the mechanism of impaired ventricular filling.

It has been suggested based on studies of patients with hypertrophic cardiomyopathy that β-adrenergic receptor antagonists and rate-limiting calcium channel antagonists may be efficacious in the setting of impaired ventricular relaxation, but evidence supporting this extension is lacking. Even less information is available concerning therapy of patients with a restrictive impairment of ventricular filling.

Barbier (1996) investigated whether the structural characteristics of the left ventricle may influence the acute effects of captopril in patients with untreated hypertensive or idiopathic cardiomyopathy. In hypertensive patients, early mitral inflow increased, while in patients with DCM, late mitral flow improved. Philiban and colleagues (1997) examined the efficacy of ACE inhibitor therapy on outcome in patients with CHF and preserved left ventricular systolic function in comparison to patients with LV contractile dysfunction. 763 hospital survivors who had measurement of systolic function were identified from among a series of consecutive patients with CHF admitted to 10 community hospitals. They were prospectively followed-up for 6 months. Outcomes were stratified by ACE inhibitor use among those with preserved (LVEF > 0.40) or depressed systolic function. ACE inhibitor therapy was associated with a similar trend for a lower risk of death and readmission in each group, suggesting that ACE inhibition may benefit the course of CHF with preserved LV systolic function. Less favorable results were reported by Lang (1995) who observed no improvement in peak filling rate, peak transmitral flow velocity or E/A ratio in 12 patients with "diastolic heart failure" treated with lisinopril.

In a report published in 1995, Eric Eichhorn and colleagues from this institution described studies intended to identify patients who will have systolic and/or diastolic improvement on beta-blocker therapy for heart failure. They retrospectively examined pre-treatment characteristics of 24 patients subsequently treated with metoprolol. They observed that the degree of improvement in diastolic function was related to the initial severity of diastolic impairment. Patients with the highest LVEDP and most prolonged isovolumic relaxation at baseline responded best to β-adrenergic receptor antagonist therapy. Similar results have been reported by Andersson (1996) in 77 patients with a restrictive left ventricular filling pattern treated with metoprolol, in whom E wave deceleration time improved on therapy. Conflicting results have been presented by Quaife (1996), who observed no improvement in radionuclide parameters – peak filling rate and time to peak filling – in 36 patients treated with cavedilol.

In very small trials, infusions of brain naturetic peptide (Clarkson 1996) and exercise training (in patients with an impaired relaxation pattern, Belardini 1995) have been observed to improve exercise PCWP and peak early transmitral flow velocity respectively, but effects on clinical outcome were not described.

In light of the available clinical data and recent insights into molecular mechanisms that may play an important role in the pathophysiology of impaired ventricular filling, the following summarizes one (my) perception of the current state of knowledge:

1. The common perception that diastolic dysfunction should be treated with rate limiting calcium channel antagonists rests on thin evidence. While some evidence supports the use of negative inotropic agents in the setting of familial hypertrophic cardiomyopathy, evidence of improvement in "diastolic function" is limited. There is one small trial providing evidence of a benefit in patients with hypertensive cardiomyopathy and an impaired ventricular relaxation pattern on transmitral Doppler echocardiography. There is no specific evidence supporting their use in patients with impaired ventricular filling characterized by a restrictive pattern of transmitral flow. The most supportive evidence from animal studies is the recent observation that calcium channel antagonists may inhibit the myocardial fibrosis in response to infused angiotensin II or aldosterone.

2. The data on beta-adrenergic receptor antagonists is incomplete, but generally appears more favorable. At least some patients treated with chronic beta-blocker therapy demonstrate improvement in ventricular filling parameters. As improvement in diastolic filling parameters with β-blocker therapy is delayed, it seems likely that this occurs for reasons other than an acute effect on myocardial relaxation.

3. Conventional wisdom that diruesis or preload reduction with nitrates, while relieving pulmonary congestion, reduces cardiac output by "backing down the Frank-Starling curve" oversimplifies the truth as it applies to patients with impaired ventricular filling. The observations that ventricular interdependence/interaction may accompany a restrictive ventricular filling pattern and that preload reduction can relieve this interdependence suggest that aggressive preload reduction in the setting of severely decompensated CHF may beneficially affect cardiac output in selected patients.

4. Antagonists of the RAAS system – either ACEI or AII receptor antagonists – beneficially affect two processes involved in impairing ventricular filling. Acutely these agents promote relaxation of myofibroblasts and may improve ventricular filling. Chronically, these agents antagonize the signaling cascade responsible for the accumulation of myofibroblasts in the heart, reduce collagen synthesis and restore impaired collagen degradation. At the present time, RAAS antagonism

should probably be viewed as the most promising of available therapies for patients with impaired ventricular filling.

5. There is experimental evidence to suggest that blockade of aldosterone function may have a salutary effect on ventricular fibrosis, but clinical trials to date (RALES) do not provide evidence of improved clinical outcome.

6. Manipulation of other signaling pathways – bradykinin, PGE2, BNP, ANF, NO (positively) and ET1, TGFβ (negatively), or of potential effectors of the phenotypic transformation of myofibroblasts have not been investigated even in animal models. This remains an area of basic investigation.

Summary and Conclusions

Impaired ventricular filling is an important determinant of prognosis in patients with the syndrome of congestive heart failure, and may be the principal determinant of functional status. Excluding obstruction to ventricular inflow in mitral stenosis, atrial dysrhythmia and constrictive pericarditis, impaired filling occurs in two broad (potentially coexisting) forms:

1. impaired ventricular relaxation, manifested as reduced rate of early diastolic filling and resulting in most cases from delayed re-uptake of calcium into the sarcoplasmic reticulum. This may reflect deficient expression of SERCA, disordered regulation of SERCA and/or myofibrillar calcium affinity, or disordered myocardial energetics.
2. elastic resistance to ventricular distension, manifested as abbreviated early ventricular filling and reduced mid- and late-diastolic compliance. This may be due to viscoelastic properties of hypertrophied myocardium, an increase in myocardial collagen content and/or active contraction of cardiac myofibroblasts. Angiotensin II - both circulating and produced locally in the heart, and aldosterone appear to play important pathophysiologic roles, and their effects may be mediated in part through TGF-β. Ultimately, the result is a restrictive filling pattern, in some cases complicated by ventricular interdependence.

Doppler echocardiography is the most informative modality for the evaluation of ventricular filling, supplemented in some cases by invasive hemodynamic measurements and/or one of several ventricular imaging techniques. Clinical trials to date provide little guidance in management. Beta-adrenergic receptor antagonists and calcium channel antagonists may beneficially alter ventricular relaxation, but the data in support of the latter, at least, is very limited. ACE inhibitors and AT1 receptor antagonists appear to favorably effect myocardial fibrosis in experimental models, and favorable effects have been observed in some limited clinical trials. Ventricular interdependence is more common than generally appreciated, and has important implications for management. Both the clinical management of patients and future clinical trials must be guided by attention to the specific physiology underlying impaired ventricular filling.

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