Haemodynamic evaluation of diastolic abnormalities in hypertrophic cardiomyopathy

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Summary: Haemodynamic studies suggest that an important abnormality in diastolic relaxation is characteristic of advanced hypertrophic cardiomyopathy. Current evidence supports the concept that cytosolic Ca^{++} overload is the pathophysiological basis for this impaired relaxation, and may in turn represent impaired membrane Ca^{++} pumping activity.

Diastolic abnormalities can alter the haemodynamic relationship between ventricular pressure and volume during chamber filling. The classic method of examining ventricular diastolic function is the diastolic pressure-volume plot (Figure 1). As seen in the left ventricular (LV) diastolic pressure-volume plot from the normal heart, LV diastolic pressure increases during ventricular filling, but the increase is not linearly proportional to volume. Changes in ventricular compliance or distensibility alter the relation between diastolic pressure and volume. As seen in Figure 1, increased LV diastolic pressure can result from either an increase in chamber volume (A → B), or an increase in chamber stiffness, with a higher diastolic pressure needed to fill the ventricle to the same chamber volume (A → C).

Altered diastolic distensibility of the left ventricle

Figure 1 Diastolic pressure-volume relations for the left ventricle (LV) in the normal heart and in a heart with increased LV diastolic stiffness (decreased distensibility or compliance). See text for details.

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can result from a variety of processes. Two important determinants of LV diastolic chamber distensibility are listed in Table I. In hypertrophic cardiomyopathy (HCM), increased wall thickness contributes to altered LV diastolic distensibility, and accounts for some of the elevation in LV filling pressure seen in this condition. In addition, there may be some increase in collagen concentration and fibrosis in advanced cases, which would also increase passive diastolic chamber stiffness. Active elasticity of the LV chamber in diastole probably reflects diastolic cross-bridge cycling (Stern *et al.*, 1983), and is present to a slight degree in normal cardiac muscle. However, substantial impairment of the relaxation process (including reversible and irreversible forms of contracture) may occur in a variety of settings, including hypoxia, ischaemia and calcium overload (Serizawa *et al.*, 1981; Nayler *et al.*, 1979; McLaurin *et al.*, 1981; Lorell *et al.*, 1981; Momomura *et al.*, 1984; Carroll *et al.*, 1983; Bourdillon *et al.*, 1983; Henry *et al.*, 1977; Bourdillon & Poole-Wilson, 1981).

Several years ago, we had the opportunity to study a patient with severe hypertrophic cardiomyopathy (non-obstructive type) who had a history of orthopnoea and increasingly severe dyspnoea on exertion

Table I Two important determinants of LV chamber distensibility

1.	Passive elasticity of chamber:
(a) Thickness of ventricular wall
(b) Composition of ventricular wall (i.e., muscle, fibrous tissue, amyloid, etc.)
2.	Active elasticity of chamber (residual diastolic interaction between contractile elements):
(a) Incomplete relaxation, diastolic tone, contracture

Figure 2 Abnormal left ventricular (LV) diastolic pressure waveform in a patient with advanced non-obstructive hypertrophic cardiomyopathy. Also shown are aortic (Ao) pressure and rate of rise of LV pressure, dp/dt . See text for details.

(Lorell *et al.*, 1980). This 54 year old woman had an echocardiogram that showed marked asymmetric hypertrophy with an interventricular septum of 25 mm in thickness and a posterior LV wall thickness of 12 mm. Cardiac catheterization showed marked increases in LV filling pressure, with pulmonary capillary wedge pressure of 32 mm Hg and LV end-diastolic pressure 40 mm Hg, while cardiac index was decreased at 2.0 litres/min/m². A remarkable finding was the abnormal appearance of the LV pressure waveform in diastole (Figure 2), which was consistently present despite repositioning of the LV catheter and measurement of pressure with a micromanometer tracing. We knew of the work from Germany (Kaltenbach *et al.*, 1979; Hanrath *et al.*, 1980) and from Bethesda (Rosing *et al.*, 1981) supporting the value of the calcium antagonist verapamil in patients with hypertrophic cardiomyopathy, and we wondered whether the abnormal LV diastolic waveform in our

patient represented slow and incomplete myocardial relaxation due to diastolic calcium overload. Accordingly, we administered nifedipine sublingually to this patient. The result was a substantial improvement in the LV diastolic pressure waveform with a reduction in filling pressure (Figure 3). This improvement occurred with no change in LV diastolic volume, so that the LV diastolic pressure-volume relationship shifted downward, indicating increased distensibility. Subsequent studies in a large number of patients with hypertrophic cardiomyopathy have supported the finding of beneficial effect of calcium-channel blockade on diastolic relaxation (Lorell *et al.*, 1982; Paulus *et al.*, 1983).

What is the mechanism for the impaired LV relaxation in patients with hypertrophic cardiomyopathy? Evidence is accumulating to suggest that intracellular calcium overload may be playing a crucial role in the pathophysiology of hypertrophic cardiomyopathy (Morgan & Morgan, 1985; Lorell & Barry, 1984). The

Figure 3 Improvement in abnormal diastolic relaxation following administration of a calcium blocking agent, nifedipine, to the patient illustrated in Figure 2. Reprinted from Lorell *et al.* (1980) with permission. See text for details.

disorder may be associated with a cellular defect in calcium metabolism, characterized perhaps by increased membrane permeability to calcium. Ordinarily, the myocardial cell defends its internal milieu against calcium overload by means of membrane pumps both on the external or sarcolemmal membrane, and the internal membrane of the sarcoplasmic reticulum (SR). The sarcolemmal calcium pumps are ATP-dependent and extrude Ca^{++} from the cell against an enormous concentration gradient. Normally, the cytosolic Ca^{++} concentration is 10^{-7}M in diastole, whereas the Ca^{++} concentration of interstitial fluid is approximately 10^{-3}M . The SR calcium pump also consumes ATP as it sequesters Ca^{++} within the confines of SR vesicles, again acting against a high concentration gradient. Membrane 'leakiness' and/or defective Ca^{++} pump activity could lead to cytosolic Ca^{++} overload. At first, this might result in increased inotropy, and it is noteworthy that in its early stages hypertrophic cardiomyopathy is characterized by abnormally high ventricular ejection fraction and dp/dt . Increased contractility would be expected to eventuate in hypertrophy (Grossman *et al.*, 1983) which might be asymmetric if the cellular defect involved myocardial tissue only in one region. Once hypertrophy became advanced, subendocardial ischaemia

would be expected to develop, as is common in a variety of conditions associated with marked LV hypertrophy (e.g. severe aortic stenosis). Ischaemia would further depress SR function with a resultant impairment in diastolic relaxation (Nayler *et al.*, 1979; Lorell & Barry, 1984; Grossman & Barry, 1980). As diastolic relaxation became impaired, systolic function would also deteriorate (Lorell & Barry, 1984) since there would be a smaller fraction of quiescent cross-bridges available for systolic activation. This is only a hypothesis, and much work will need to be done to ascertain the fundamental defect in hypertrophic cardiomyopathy. However, Morgan and co-workers (1985) have obtained preliminary results on a study of intracellular calcium transients, measured with the photoluminescent protein aequorin, in cardiac muscle removed at surgery from patients with IHSS undergoing myomectomy. These data suggest that the intracellular rise in free Ca^{++} occurs rapidly and normally in myocytes from patients with hypertrophic cardiomyopathy, but the decline in free Ca^{++} following activation is slow and prolonged, and correlates with a slow decline in muscle tension measured simultaneously. Whether this represents SR dysfunction or some other defect in these myocytes will require further study.

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