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Left Ventricular Hypertrophy and Diastolic Dysfunction: Their Relation to Coronary Heart Disease

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Summary. **Diastolic dysfunction is an early sign in the temporal sequence of ischemic events in coronary heart disease. The ischemic cascade, beginning with an oxygen demand supply imbalance and metabolic alterations, identifies diastolic disorders of the left ventricle (LV) as an early phenomenon, sometimes before systolic dysfunction, electrocardiographic changes, or chest pain occur. Although the physiology of diastolic function is complex, the factors contributing to diastolic disturbances can be differentiated into *intrinsic* and *extrinsic* LV abnormalities. Intrinsic mechanisms include (a) impaired LV relaxation, (b) the complex of LV hypertrophy, and (c) increased LV asynchrony. Myocardial hypertrophy leads to an increase of the myocardial mass/volume ratio, and the degree of hypertrophy is the main determinant of chamber stiffness. The main, if not unique, determinant of myocardial diastolic tissue distensibility is the structure and concentration of the collagen. Consequently, tissue stiffness is increased in coronary disease by reparative interstitial fibrosis or scar following myocardial infarction. In myocardial hypertrophy the LV collagen concentration is elevated due to reactive fibrosis. An increase in regional asynchrony of LV contraction and relaxation is a result of regional ischemia as well as of LV hypertrophy and tissue fibrosis. Factors extrinsic to the LV causing diastolic disorders include (a) increased central blood volume, which will increase left ventricular pressure without altering the LV pressure-volume relation, and (b) ventricular interaction mediated by pericardial restraint, which may cause a parallel upward shift of the diastolic LV pressure-volume relation. Improved insight into the mechanisms of LV relaxation and filling characteristics help in the treatment of LV diastolic dysfunction.**

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Coronary artery disease (CAD) is a major cause of mortality and morbidity in the industrialized world. There has been an increasing emphasis on the identification and early detection of factors that predispose to the development and the progression of CAD (Dzau and Braunwald, 1992). Elevated blood pressure has been well established as an independent risk factor for CAD (Martin et al., 1986), and the importance of left ventricular (LV) hypertrophy as a predictor of morbidity and mortality in hypertensive disease has been convincingly demonstrated (Levy et al., 1990). One of the early signs in the temporal sequence of ischemic events is diastolic dysfunction (Nesto et al., 1987). This review concentrates on the role of LV hypertrophy and diastolic dysfunction in the onset and development of CAD.

Ischemic Cascade

Myocardial ischemica results in a typical cascade of events in which the various markers can be hierarchically ranked in a time sequence (Heyndrickx et al., 1978). The flow heterogeneity, especially between subendocardial and subepicardial perfusion, precedes ischemia, followed by the metabolic changes, alterations in the LV diastolic relaxation, regional dyssynergy, and, mostly at a later stage, electrocardiographic changes, global LV dysfunction, and pain (Nesto et al., 1987).

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Diastolic (Dys)function and its Determinants

Left ventricular diastole is generally divided into four distinct phases: isovolumetric relaxation, rapid (early) LV filling, diastasis, and atrial systole (Nishimura et al., 1989a). Left ventricular relaxation and elastic recoil are predominant in early diastole. Passive chamber stiffness and atrial reserve are more important in the later stages of diastole (Fig. 1). A great variety of factors can influence LV diastolic performance at different times to different degrees (Störk, 1994). Although the physiology of diastolic function is complex, the factors contributing to diastolic disturbances can be differentiated into intrinsic and extrinsic LV abnormalities.

Intrinsic factors

Intrinsic mechanisms include (a) impaired LV relaxation, (b) LV hypertrophy including increased overall chamber stiffness as well as increased myocardial tissue stiffness, and (c) increased LV asynchrony (Litwin and Grossman, 1993).

Relaxation. Left ventricular relaxation proceeds as free ionized calcium is released from its binding site on troponin C, allowing the actin-myosin crossbridges to dissociate. The amount of calcium bound to the myofilaments at any given point in time depends on the affinity of troponin C for calcium and the concentration of free calcium in the cytoplasm. Cytoplasmic concentration, in turn, is regulated by the rate of calcium reuptake into the sarcoplasmic reticulum and extrusion of calcium from the cell by the sarcolemmal sodium-calcium exchanger and a sarcolemmal calcium pump. Sarcoplasmic calcium uptake is an energy-dependent process. Hence, any condition associated with decreased availability of high energy phosphates, such as *ischemia* or *hypoxia*, may impair myocardial relaxation (Morgan, 1991; Katz, 1992).

Invasive methods give a detailed insight into pressure and volume relations during diastole (Mirsky, 1984), but echocardiography has become an established tool for noninvasively assessing diastolic relaxation time and LV filling characteristics (Nishimura et al., 1989b). Impaired LV relaxation, that is, a delayed early diastolic pressure decay of the LV, results in a decrease of the early diastolic pressure gradient between the left atrium and LV (the driving force for LV inflow). This leads to a decrease in early mitral flow and subsequently a lowering of the early diastolic part, that is, the E wave, of the Doppler-derived mitral flow curve. In CAD a decreased early mitral inflow as a sign of LV diastolic dysfunction due to an impaired relaxation is most frequent (Fig. 2). A further decreased coronary flow in CAD patients, for example, induced by cigarette smoking, leads to an additional decrease of early mitral flow (Störk et al., 1991).

In contrast, administration of the calcium antagonist verapamil results in an improvement of the Doppler-derived LV filling curve. As cytoplasmic calcium concentrations were not measured, the interpretation that verapamil improved relaxation by reduction of cytoplasmic calcium remains hypothetical (Störk et al., 1992b; Fig. 2). Nonpharmacological stress-lowering measurements, which lead to decreased plasma concentrations of catecholamines, also have the potential to improve LV relaxation (Möckel et al., 1994).

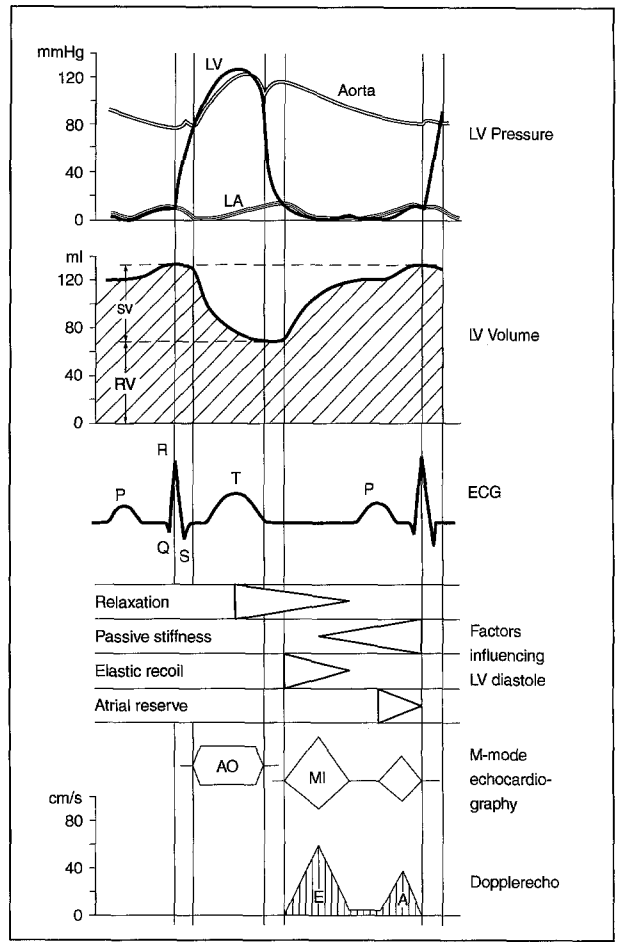

Fig. 1. *Left ventricular diastole and its determinants. In the upper part are shown the results of invasive measurements, and in the lower part are shown the echocardiographic recordings. LV, LA = left ventricle and atrium; AO, MI = aortic and mitral valve; E, A = E and A wave of the Doppler mitral flow.*

Although elevated early LV pressures as a result of impaired relaxation lead to a shift of mitral flow towards late diastole, we face a more complex situation when LV filling pressures, and in particular LV end-diastolic pressures, are markedly elevated. The increased atrial pressure augments the early LV filling fraction, resulting in a "pseudonormalization" of mitral flow (Appleton et al., 1988). In a Doppler exer-

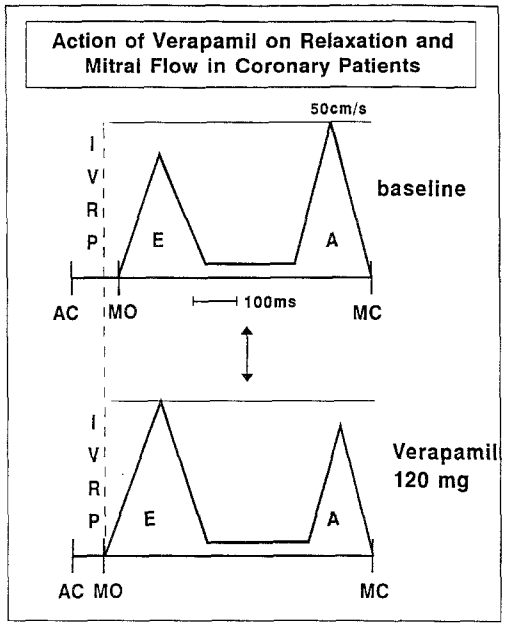

Fig. 2. *Action of verapamil on relaxation and mitral flow in coronary patients. AC = aortic closure; MO = mitral opening; MC = mitral closure; IVRP = isovolumetric relaxation phase; E = E wave; A = A wave (Doppler). The figure summarizes the results (median values) of a study published by Störk et al. (1992). Twenty-one CAD patients received 120 mg verapamil orally. Echocardiographic evaluation was done before and 60 minutes after administration of the drug. Intracellular calcium concentrations were not measured so that the extrapolation from the LV filling behavior to a verapamil-mediated effect on cytoplasmatic calcium remains hypothetical.*

cise study, elevated LV filling pressures during ischemia led to a normal LV filling pattern, with a high E wave and a low A wave (Völler et al., 1993).

Left ventricular hypertrophy. Elevated blood pressure is a risk factor for CAD, and LV hypertrophy is a predictor of morbidity and mortality in hypertensive disease (Martin et al., 1986; Levy et al., 1990). There are different methods to assess LV mass. Nuclear magnetic resonance imaging has been shown to be a very precise technique (Eichstädt et al., 1987). In the clinical routine, however, echocardiography is the method of choice for measuring LV mass and dimensions (Kücherer and Kübler, 1992; Störk, 1994).

Geometry of the LV. Chronic pressure overload leads to an increase of LV wall thickness relative to LV cavity volume. The elevated systemic vascular resistance (LV afterload) increases LV wall stress. Left ventricular hypertrophy with an increase of the LV mass-volume ratio is the response of the LV to reduce this wall stress. This results in an upward shift to the left of the diastolic pressure-volume curve, such that a given diastolic volume is associated with a greater pressure than the normal ventricle. In addition, the slope of the curve in the hypertrophied LV is steeper, so that any increment in volume (dV) is associated with an exaggerated increase in pressure (dP). Left ventricular chamber stiffness, or its reverse chamber compliance, is defined by analyzing the curvilinear diastolic pressure-volume relationship. The slope of a tangent, dP/dV, to this curvilinear relation defines the chamber stiffness at a given filling pressure. The chamber stiffness constant, k_1 or k_2, is derived from the slope of the linear relationship between dP/dV and pressure (Bonow and Udelson, 1992; Gaasch et al., 1985a).

Relaxation in LV hypertrophy. Active relaxation is impaired during LV hypertrophy. This may be due to an increase in oxygen demand by elevated muscle mass and a concomitant decrease in oxygen supply resulting from a frequent coexistence of large coronary obstruction and a decrease in the vasodilator capacity of coronary arterioles (Devereux and Roman, 1993).

Forms of hypertrophy. From a pathophysiological point of view, we have to distinguish different kinds of LV hypertrophy with different effects on LV diastolic function.

Adaptive hypertrophy. Chronic volume overload due to endurance training leads to the typical signs of the "athlete's heart." There is an increased heart size without any change in the mass-volume ratio, an *adaptive* hypertrophy. Consequently, early diastolic filling is not impaired in long-distance runners despite elevated LV mass. Additionally, a shift of mitral inflow towards late diastole, which can be seen in normal subjects after bicycle exercise, is not present in the "athlete's heart" (Möckel et al., 1992; Störk et al., 1992a).

Fibrosis and reactive hypertrophy. In the development of LV hypertrophy, the renin-angiotensin-aldosterone system plays an important role. Angiotensin II directly stimulates myocardial fibroblasts and thus augments the myocardial collagen content. The increased collagen concentration leads to an increase of intrinsic myocardial tissue stiffness, as assessed by the diastolic stress (σ)-strain (ϵ) relation. Thus, myocardial fibrosis results in an upward shift of the diastolic stress-strain relationship of the myocardial fiber. The myocardial or tissue stiffness constant can be derived from the slope of the linear relation between myocardial elastic stiffness ($d\sigma/d\epsilon$) and LV diastolic wall stress. The main, if not unique, determinant of the tissue stiffness constant is the collagen concentration (Brilla et al., 1990; Swynghedauw et al., 1992). In addition, LV diastolic function and coronary reserve could be directly impaired by interstitial fibrosis and

thickening of the medial layer of intramyocardial coronary arteries (Brilla et al., 1991).

Myocardial fibrosis following myocardial infarction may elevate filling pressures, but the degree of elevation is closely related to the intravascular volume status. Shifts in the diastolic pressure-volume relation reflect a loss of chamber compliance due to an increase in muscle stiffness. Increased amounts of extracellular matrix, specifically collagen, produce this permanent increase in muscle stiffness, which is central to the diastolic abnormalities in chronic CAD (Carroll et al., 1989).

Asynchrony. Left ventricular diastolic function is an active energy-consuming phenomenon governed by the interplay of several factors, such as intrinsic relaxation properties and loading conditions. Attention has been drawn to the role of spatial and temporal nonuniformity as a modulator of LV mechanics. (Brutsaert et al., 1984; Brutsaert, 1987; Gaasch et al., 1985b). Asynchrony plays an important role in both coronary and hypertensive heart disease (Betocchi et al., 1993; Nakashima et al., 1993).

Extrinsic factors

Factors *extrinsic* to the LV causing diastolic disorders include (a) increased central blood volume with high central venous pressure and augmented right ventricular filling, which in turn will increase left ventricular pressure without altering the LV pressure-volume relation; and (b) ventricular interaction mediated by pericardial restraint, which may cause a parallel upward shift of the diastolic LV pressure-volume relation (Litwin and Grossman, 1993).

Conclusions

Both LV hypertrophy and CAD are associated with impaired diastolic function, as can be assessed echocardiographically by a reduced early diastolic E wave (Nishimura et al., 1989a, 1989b; Störk et al., 1991, 1992b; Völler et al., 1993). The strong relationship between CAD and LV hypertrophy is mediated by three potentially independent but frequently interacting mechanisms: (i) increased total coronary flow demand due to elevated LV mass, (ii) the frequent coexistence of large coronary artery obstruction, and (iii) a decrease in the vasodilator capacity of coronary arterioles (Devereux et al., 1993). Both changes of inactivation/relaxation and of passive chamber stiffness may cause elevated LV diastolic pressures, resulting in an impaired LV filling. This impaired LV filling due to elevated diastolic pressures potentially leads to clinically apparent diastolic dysfunction, with eventually backward failure and pulmonary edema (Bonow, 1992; Litwin and Grossman, 1993).

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