Vasodilator therapy of dilated cardiomyopathy

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Summary: Vasoconstriction increases impedance to ventricular ejection and impairs the performance of the dilated myopathic heart. Vasodilator drug therapy by reducing vascular resistance, increasing vascular compliance and increasing vascular capacitance improves cardiac function and relieves the signs and symptoms of congestive heart failure. Earlier intervention in an attempt to alter the natural history of cardiomyopathy should be studied.

The performance of the dilated failing left ventricle is critically dependent upon aortic impedance, which consists of arterial vascular resistance and compliance (Cohn, 1973). The magnitude of effect of impedance changes on performance of the severely failing heart was made clear more than 12 years ago by the observation that sodium nitroprusside, a smooth muscle relaxant that lowers resistance and increases compliance of the arterial vasculature, can produce a striking rise in stroke volume and cardiac output and a marked fall in cardiac filling pressure in patients with dilated cardiomyopathy (Guiha *et al.*, 1974).

Subsequent studies have provided new insights into the mechanisms that may alter the peripheral circulation in heart failure and thereby increase impedance to left ventricular ejection. Activation of the sympathetic nervous system has been demonstrated by observing high plasma noradrenaline in resting supine patients with congestive heart failure (Levine *et al.*, 1982). Similarly, many patients with heart failure exhibit high plasma renin activity indicative of heightened activity of the renin-angiotensin-aldosterone system (Curtiss *et al.*, 1978). A third neurohumoral system, the antidiuretic hormone-vasopressin system, also appears to be activated in heart failure as demonstrated by high levels of arginine vasopressin (Goldsmith *et al.*, 1983). The role of each of these neurohumoral vasoconstrictor systems in supporting the high impedance to left ventricular ejection in heart failure is not known. Nonetheless, since each of these hormonal systems may directly alter systemic vascular resistance and compliance it is appropriate to consider therapeutic interventions that may produce vasodilatation by directly interfering with one or more of these neurohumoral vasoconstrictor mechanisms.

Five pharmacological approaches to vasodilatation may thus be utilized to improve left ventricular

function in patients with dilated cardiomyopathy: (1) interference with the sympathetic nervous system through α -adrenoceptor blockade, blockade of noradrenaline release at the sympathetic nerve ending, blockade of noradrenaline release in the synaptic cleft, or interference with sympathetic nerve traffic through central inhibitory mechanisms; (2) interference with the renin-angiotensin system most commonly with the use of a converting enzyme inhibitor; (3) interference with the action of arginine vasopressin through the use of a vasopressin analogue; (4) calcium antagonists that may dilate both small and large arteries but also may have a deleterious direct effect on myocardial contractility; and (5) vasodilator drugs that work directly on vascular smooth muscle to reduce resistance in the smaller vasculature and/or increase compliance in the more proximal arterial bed.

The acute haemodynamic response to drugs in all five of the above categories is quite favourable in patients with dilated cardiomyopathy. Cardiac output and stroke volume usually rise and the cardiac filling pressure usually falls, particularly in response to a drug which has a venodilator effect and consequently increases venous capacitance. Heart rate usually does not increase reflexly in these patients with heart failure, and if mitral regurgitation had been present before administration of the drug the regurgitant volume will decrease as a result of the vasodilator effect (Chatterjee *et al.*, 1973). A mild to moderate fall in arterial pressure usually will occur in response to vasodilator therapy of heart failure, but the magnitude of this fall in blood pressure varies considerably dependent both on the specific patient being treated and on the drug being utilized. For example, the converting enzyme inhibitors tend to produce a greater fall in arterial pressure than do drugs such as hydralazine (Levine *et al.*, 1980).

The effect of vasodilator drugs on symptoms and exercise tolerance in patients with dilated car-

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diomyopathy is more difficult to demonstrate than their effects on haemodynamics. Nonetheless, several trials carried on over a period of weeks have demonstrated that patients taking digitalis and diuretics and given in addition a vasodilator drug exhibit an improvement in exercise tolerance and a reduction in symptomatology when compared to patients given a placebo in a double-blind fashion. This improvement has been demonstrated with converting enzyme inhibitors and with nitrates (Captopril Multicenter Research Group, 1983; Franciosa *et al.*, 1978). The improvement has been less clear cut in trials using hydralazine or prazosin.

Despite the striking haemodynamic response to vasodilator drugs and the trend for symptomatic and functional improvement certain other manifestations of heart failure appear to be less dramatically altered. Left ventricular ejection fraction, a quantitative assessment of left ventricular function, is not reliably increased in response to therapy even though the stroke volume and cardiac output increase. Ventricular arrhythmias, which are a very common manifestation of severe heart failure, also do not appear to be strikingly reduced in response to vasodilator therapy. Most importantly, a high mortality is noted in patients treated with vasodilator drugs (Cohn *et al.*, 1984). Whether this high mortality is the same or somewhat less than mortality in similar patients not treated with such a vasodilator regimen has not yet been clearly demonstrated. Nonetheless, the observations make it clear that vasodilator therapy introduced in patients with advanced congestive heart failure does not have a profoundly favourable effect on the shortened life expectancy of this syndrome.

Studies over the last dozen years have therefore

made it clear that the symptomatology and haemodynamic abnormality in patients with dilated cardiomyopathy cannot be attributed exclusively to the myocardial process. Changes in the peripheral vasculature apparently induced in part by a neurohumoral response to the impaired left ventricular function appear to play an important role in the disturbed ventricular performance. The so-called end-stage cardiomyopathy need not necessarily be viewed as a terminal state of myocardial dysfunction incompatible with life but rather as a complex interaction between the heart and the peripheral circulation that results in circulatory embarrassment. Interventions that could abort or reverse the myocardial process or improve muscle function despite the myocardial process must take precedence in devising an appropriate form of therapy. But interventions aimed specifically at the peripheral circulation to alter resistance, impedance and capacitance may have a remarkably beneficial effect on the performance of the heart without directly affecting the myocardium itself. Interventions aimed at interfering with the neurohumoral mechanisms that appear to contribute to this peripheral vascular response may be the most promising approach to correcting the imbalance between impedance and cardiac function that contribute to the disability in this syndrome. Further studies are needed to evaluate the efficacy of earlier intervention with neurohumoral blockers or vasodilator drugs. Further studies also are needed to evaluate the relative merit of the various pharmacological agents that affect haemodynamic improvement in this syndrome. Finally, studies of a larger scale and longer duration need to be carried out to determine what, if any, therapy can alter the poor prognosis in this syndrome.

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