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EDITORIAL COMMENT

PATHOPHYSIOLOGIC ARGUMENTS FOR VASODILATORS IN CARDIAC FAILURE

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The primary mechanism of heart failure is dysfunction of the myocardium, which cannot be directly influenced by vasodilators. Vasodilators can, however, change the working environment of the failing heart. This report will deal with three main mechanisms, which secondarily characterize the clinical syndrome of heart failure, and which may be favorably affected by vasodilator therapy. These mechanisms are an inadequate vasoconstriction, reduced stroke volume due to afterload mismatch, and congestive symptoms due to increased cardiac preload.

Vascular resistance increases in heart failure due to activation of several compensatory neurohumoral systems [1–3]. This compensatory vasoconstriction is beneficial, if cardiac output is reduced by other causes than primary myocardial failure; it may be beneficial even in the early stages of heart failure. In severe myocardial failure, however, vasoconstriction leads to a reduction of stroke volume and reduces myocardial efficiency by afterload mismatch [4, 7]. This in turn increases the ventricular volume, thereby progressively utilizing the Starling reserve. The increased preload produces congestive symptoms, so-called backward failure.

Vasoconstriction in heart failure is caused by different synergistic mechanisms (Figure 1). The most prominent role in this process is played by increased sympathetic activity [2, 8] and activation of the renin-angiotensin system [9, 10]. In some patients with heart failure, but by no means in all of them, plasma vasopressin levels are also increased [2]. The pathophysiologic role of atrial natriuretic factor (ANF) in heart failure is as yet not fully understood [11]. Its plasma level is usually increased, tending to counteract the vasoconstriction [12]. It is questionable, however, whether ANF is adequately increased in chronic heart failure. The fluid and salt retention usually present in heart failure leads to an increased vessel wall stiffness. Presently available vasodilators interact with the first two of these mechanisms or have a direct effect on the vascular smooth muscle. As yet, the last three mechanisms cannot be specifically influenced by drug therapy.

What are the causes for the increase of sympathetic activity in heart failure? The tonic restraint on sympathetic activity from cardiopulmonary as well as arterial baroreceptors is reduced due to baroreflex dysfunction. With progression of the disease, peripheral hypoperfusion occurs, which via peripheral chemoreceptors further increases sympathetic activity. The increased sympathetic activity leads to generalized vasoconstriction and redistribution of regional blood flow. Renal perfusion, especially, is decreased, which induces fluid retention, and direct stimulation of tubular-receptors increases reabsorption of Na^+. Stimulation of the juxtaglomerular beta-receptors increases the secretion of renin, which gives rise to a positive feedback with the sympathetic system.

The renin-angiotensin system is activated directly by sympathetic stimulation as mentioned above, and by reduced renal perfusion. The increased renin activity lends to vasoconstriction mediated by angiotensin

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1.) increased sympathetic activity
2.) Renin-Angiotensin system
3.) increased plasma vasopressin
4.) Atrial natriuretic peptide ?
5.) increased vessel wall stiffness

Fig. 1. Vasoconstriction mechanisms in CHF.

II. It further increases sympathetic activity, mainly by a central nervous effect and by facilitation of peripheral noradrenaline-release via presynaptic AII-receptors. Whether increased noradrenaline synthesis and inhibition of sodium reuptake are pathophysiologically important, remains to be determined. Finally, heightened renin activity stimulates the secretion of aldosterone, thus inducing water and sodium retention.

Of special importance are the positive feedback mechanisms connecting the sympathetic and renin systems, which may lead to progressive vasoconstriction. From a pathophysiologic point of view it seems reasonable, therefore, to use catecholamine antagonists and converting enzyme blockers as the vasodilator therapy of choice in heart failure.

The role of plasma vasopressin in the clinical syndrome of heart failure is less clear. Vasopressin is increased only in some patients, and its increase is by far less dramatic than that of sympathetic and renin activities. Dysfunction of both arterial and cardiopulmonary baroreflexes may contribute to a rise in vasopressin. Unlike normal conditions, vasopressin does not correlate with plasma osmolarity in heart failure. This suggests that the osmoreceptors lose their ability to sufficiently control vasopressin release. Angiotensin II can facilitate the release of vasopressin, but vasopressin levels do not correlate well with plasma renin activity. One might also speculate that decreased hepatic and renal clearance contributes to vasopressin increase, but elevated levels of vasopressin have also been observed in heart failure patients, demonstrating normal hepatic and renal function.

Whatever the reason, studies with a selective antagonist of vasopressin indicated that this peptide may contribute to vasoconstriction and fluid retention in some patients with heart failure [2].

All these neurohumoral mechanisms contribute to a vicious circle connecting myocardial function with peripheral vascular resistance (Figure 2). Myocardial dysfunction, by decreasing cardiac output, compensatorily increases vascular resistance and blood volume. The resulting increase in aortic impedance in turn leads to progressive myocardial dysfunction. The goal of vasodilator therapy is to interrupt this originally beneficial but eventually adverse regulatory system.

What is the promise of vasodilator therapy for the failing myocardium? Let us first look at the relations between cardiac afterload and stroke volume.

It is well known that stroke volume is dependent on afterload even in the intact heart (Figure 3). The steeper the slope of the correlation between afterload and stroke volume, the more severely the heart fails. In

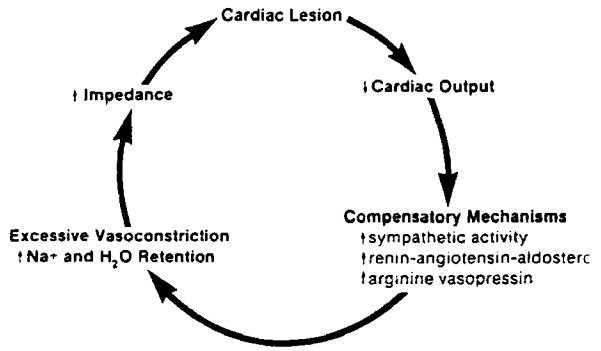

Fig. 2. Vicious circle connecting cardiac failure with inadequate vasoconstriction. [Reproduced from [18] by courtesy of Am J Cardiol.]

an intact heart, an increase in outflow resistance results in hypertension without significantly affecting cardiac output, since by compensatory activation of the Starling reserve and by increased contractility stroke volume is held constant. These compensatory mechanisms, however, are partly or fully utilized in the failing heart.

What effects can we expect from a reduction in outflow resistance on ventricular mechanical performance in cardiac failure? Figure 4 demonstrates the left ventricular working conditions in a patient with aortic stenosis before and after valve replacement. The reduction of outflow resistance allows a significant increase in stroke volume, which leads to an impressive decrease of systolic wall stress. Before operation, wall stress remained high during the whole systole. The increase in myocardial efficiency allows a shift to the left on the Starling curve, thereby secondarily reducing not only afterload but also preload. The same changes can be observed, for example, in patients with dilative cardiomyopathy after treatment with arterial vasodilators.

Since, as demonstrated by this example, pre- and afterload are not independent determinants of myocardial performance, arterial vasodilatation does not selectively mean reduction of afterload.

Why should we attempt to reduce preload directly in the failing heart? In the normal heart, a positive correlation exists between preload and cardiac output. Usually, this correlation is depicted as the Starling curve. The slope of the Starling curve progressively flattens in heart failure, but it remains positive as far as the ventricular filling pressure does not grossly exceed the upper limit of normal (figure 5). On the other hand, increases in preload cause congestive symptoms,

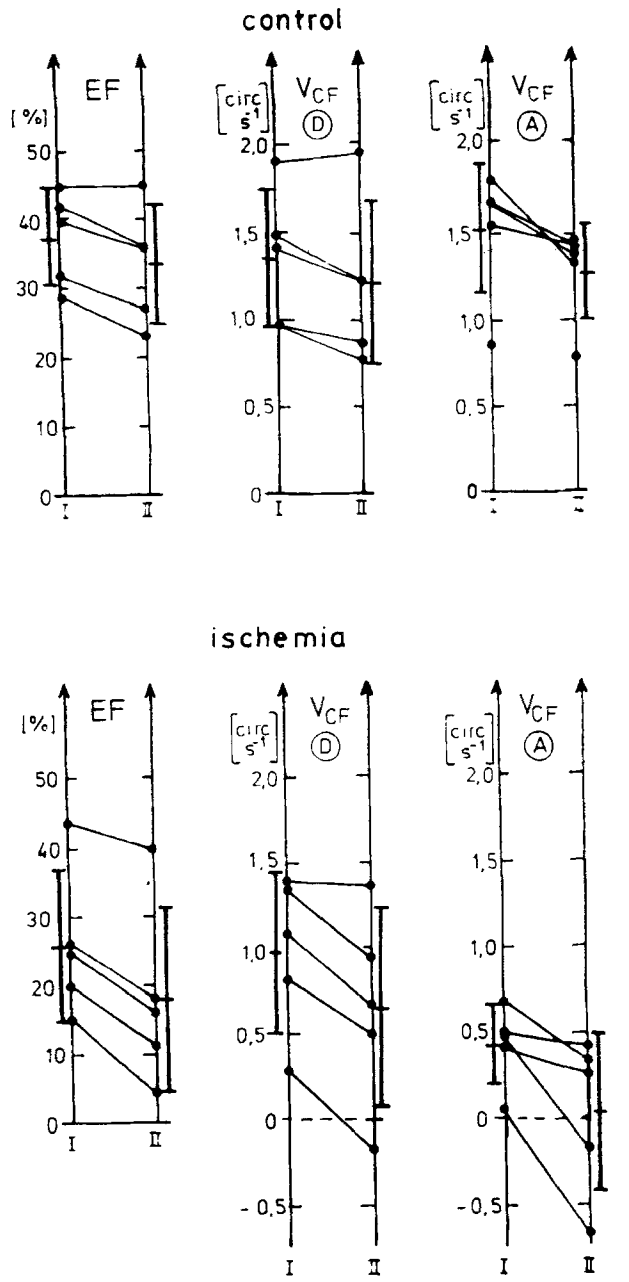

Fig. 3. In this dog experiment, ejection fraction and myocardial fiber shortening were determined in two successive beats; in the second beat aortic pressure was increased by 15 mmHg. Ejection fraction and fiber shortening are significantly reduced, as expected. The reduction of both is more pronounced after the ventricle has been made ischemic by coronary artery occlusion (lower part of figure). Note that myocardial fiber shortening is nearly abolished in the ischemic part of the ventricle by increased afterload. Mean and standard deviation (SD) of three experiments are given.

the so-called backward failure, which may be the predominant clinical feature of heart failure. These symptoms can be promptly relieved by reducing venous return with venodilators. Decreased venous return invariably reduces cardiac output in the intact heart. If, however, the Starling reserve has been fully utilized, venodilatation affects cardiac output minimally or not at all. From this is can be concluded that the effect of venodilation is best and its potential risk is minimal in patients with the highest prevailing ventricular filling pressures.

The flattened Starling curve of the failing heart can be explained by simple geometrical considerations. If one looks at the resting pressure-volume curve of the ventricle (Figure 6), it becomes clear that the higher the ventricular filling pressure, the smaller are the changes of volume with a given change in pressure. Moreover, myocardial fiber length, which finally regulates cardiac performance in the Starling mechanism, is proportional to the third root of ventricular volume. Therefore, in an enlarged ventricle with elevated filling pressures even substantial decreases of the filling pressure do not significantly affect the stroke volume.

In summary, there are three main arguments in favor of a vasodilator therapy of heart failure.

1. Adverse vasoconstrictor mechanisms are counteracted, thereby interrupting a vicious circle leading to further myocardial damage.
2. Stroke volume is strongly dependent on the outflow resistance in the failing heart. Therefore, a reduction of outflow resistance by arterial vasodilators promises to increase cardiac output. The increase in myocardial efficiency allows a shift on the Starling curve to the left, thereby also reducing preload.
3. Reduction of pathologically increased ventricular filling pressures by venodilators improves congestive symptoms without significantly affecting cardiac output.

It may be questioned, however, which of these arguments hold true in the clinical situation of heart failure. The arguments discussed above cannot be wrong, since in all acute trials of vasodilator therapy in heart failure the expected hemodynamic improvements in fact occurred. However, these pathophysiological considerations do not explain all about vasodilator therapy in cardiac failure. Besides other open questions, it is not clear why the clinical improvement of heart failure patients on chronic vasodilator therapy does not correlate closely with the hemodynamic changes. In a recent study by Massie and co-workers [13], heart failure patients on captopril were divided

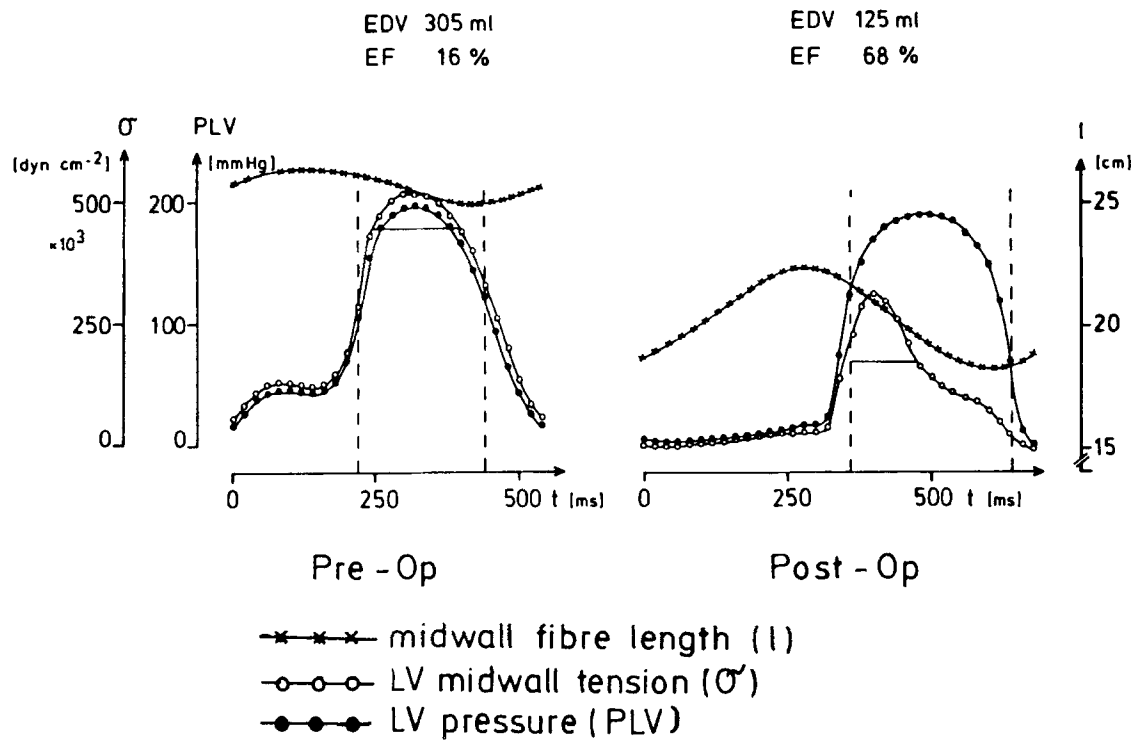

Fig. 4. Left ventricular pressure, volume, and myocardial wall tension in a patient with aortic stenosis before (left) and after valve replacement (right). For explanations see text.

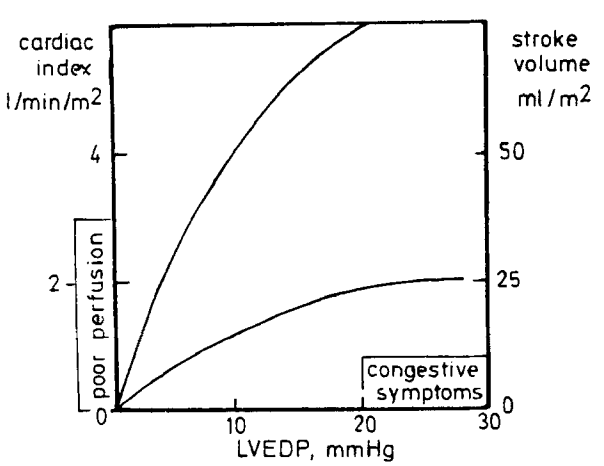

Fig. 5. Starling curves of the intact (upper curve) and failing ventricle. In the failing heart, cardiac output is affected only minimally by reductions of cardiac preload, since the slope of the curve is flattened. Therefore, a reduction of preload relieves congestive symptoms in heart failure without reducing forward flow, as far as preload is pathologically elevated.

into clinical responders and nonresponders. Surprisingly, the hemodynamic changes after captopril were not different in both groups. The fall in peripheral resistance and hence the increase in cardiac output were even more pronounced in the clinical nonresponders. Therefore, other factors besides easily measured hemodynamic effects seem to play a significant role, especially in chronic therapy.

Contrary to the considerations given in this report, *purely arterial vasodilators have proved to be clinically ineffective in heart failure,* even though they improved left ventricular performance. In a placebo-controlled study of minoxidil in cardiac failure, Franciosa and co-workers [14] observed an increase in cardiac output and improved ventricular performance after minoxidil. However, the clinical course of the patients on minoxidil was worse than in the placebo group. The total number of clinical events, especially worsened heart failure and increased diuretic dosage, was higher in the treatment group. Agostoni et al. [15] observed an increase in exercise tolerance of patients with CHF after treatment with captopril, but not with nifedipine, despite similar reductions in afterload with

both drugs. Barjon et al. [16] reported that seven out of ten patients with heart failure treated with the calcium antagonist nisoldipine developed pulmonary edema, though peripheral resistance decreased and stroke volume index increased. They concluded that nisoldipine leads to deterioration in the clinical state of patients with heart failure by further activation of the sympathetic and renin-angiotensin systems in spite of its hemodynamically beneficial effects.

In an own study we investigated the effect of different vasodilators on the carotid baroreflex [17]. Carotid baroreceptor stimulation was performed by neck suction, which reflexly lowers heart rate and blood pressure. ACE-inhibitors increased the reflex bradycardia without affecting the fall in blood pressure. ISDN selectively increased the reflex hypotension. In contrast, the arterial dilator, nifedipine, had no effect on carotid baroreflex sensitivity.

Whatever this means for vasodilator therapy of heart failure, *the arterial baroreflexes are an important mechanism in the counterregulatory vasoconstriction.* Different influences of vasodilators on cardiovascular reflexes may, therefore, modulate the clinical response to therapy.

Thus, from a pathophysiologic point of view we are left with more questions than answers concerning vasodilator therapy of cardiac failure.

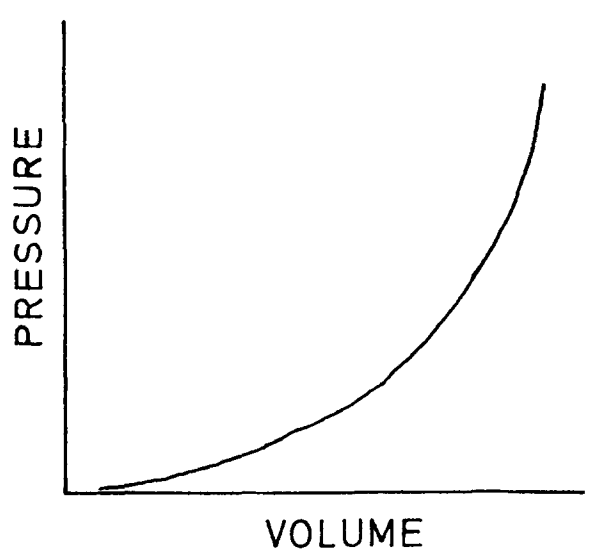

Fig. 6. Resting pressure-volume curve of the left ventricle. For a given change in filling pressure, the change in volume is less in the enla ' ventricle of a failing heart than under normal conditions

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