HYPERTENSION AND HEART FAILURE

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Epidemiology

At the present time a persistent increase in morbidity and mortality associated with congestive heart failure (CHF) has been observed and heart failure remains a common cause of premature death [1].

Hypertension is the most important modifiable risk factor for heart failure [2] and increases the risk for heart failure in all age groups. It has been calculated that in subjects aged 40 years or older with increased blood pressure (≥ 140 and/or 90 mm Hg) the lifetime risk of developing heart failure is double than that of subjects with blood pressure lower than 140/90 mm Hg. For CHF occurring in the absence of myocardial infarction it has been calculated that lifetime risk is 1 in 9 for men and 1 in 6 for women, which indicates that the risk of CHF is largely attributable to hypertension. In the Framingham Study update in 2003 only 25% of patients with heart failure suffered a myocardial infarction and about 75% of patients had a history of arterial hypertension; a significant association was observed between systolic and/or pulse pressure and the incidence of heart failure [3]. Night-time blood pressure appears to convey additional risk for CHF beyond office blood pressure measurements and other established risk factors, as shown in a cohort of uncomplicated elderly men from Sweden [4].

In patients with an acute myocardial infarction the diagnosis of hypertension antecedent to the acute coronary event increases the risk of heart failure, interacting with age, neurohormonal activation and early left ventricle remodelling [5].

Despite the well-recognised beneficial effect of antihypertensive treatment on systolic heart failure, a persistent increase in morbidity and mortality associated with CHF has been observed in recent years [6, 7]. This phenomenon may also represent the consequence of diastolic dysfunction (i.e. impairment in ventricular relaxation and filling). In fact, approximately half of the patients with overt congestive heart failure may display normal ejection fraction and marked impairment in diastolic function [6] (Table 1).

Mechanisms

Hypertension can lead directly to the development of CHF by several mechanisms, alone or in combination, such as haemodynamic load, decreased intrinsic myocardial contractility, adverse chamber remodelling and left ventricular hypertrophy, coronary microvascular disease with impaired coronary haemodynamics and ventricular fibrosis. In fact, in the presence of a chronic pressure overload a parallel addition of sarcomeres takes place with an increase in myocite width, which in turn increases wall thickness and the development of concentric remodelling or hypertrophy [7]. Myocite hypertrophy is also associated with apoptosis, collagen deposition and ventricular fibrosis. A variety of hormones, including angiotensin II and aldosterone, cytokines such as TGF-β_1 and growth factors such as insulin-like growth factor have profibrotic effects and favour perivascular and interstitial fibrosis.

Myocite degeneration, cell death and replacement or reparative fibrosis lead to irreversible myocardial damage.

In addition, hypertension is a major risk factor for epicardial coronary artery atherosclerosis and coronary artery disease, which in turn represents another important risk factor for heart failure [8].

Clinical manifestations

As expected, asymptomatic systolic and diastolic dysfunction are more prevalent than symptomatic disease [9]. In many hypertensive patients, left ventricle chamber performance is often normal in resting conditions, although an abnormal ejection fraction response to exercise may be observed, particularly in those with concentric hypertrophy or with eccentric hypertrophy and obesity. The use of a more physiological midwall mechanics index (midwall fractional shortening) has shown that left ventricular midwall function is commonly reduced at rest in about 15–20% of hypertensive patients. Asymptomatic left ventricle chamber dysfunction (as evaluated by ejection fraction) may also be identified in about 3–4% of hypertensive patients and is associated with a higher risk of cardiovascular events.

Many patients are diagnosed with the onset of typical symptoms for heart failure, including dyspnoea at rest or with exertion, consequent to elevated pulmonary capillary pressure and pulmonary congestion [10]. Patients with diastolic dysfunction do not tolerate tachycardia and rapid changes in blood pressure. The occurrence of atrial fibrillation may cause a reduction in cardiac output and the development of pulmonary congestion.

In hypertensive patients regression of left ventricular hypertrophy (LVH) is associated with an improvement in midwall systolic function, diastolic relaxation and filling parameters and with a reduced incidence of new onset atrial fibrillation. More importantly, it has been shown that regression of LVH improves cardiovascular prognosis and, in particular, decreases the incidence of heart failure, as shown by the HOPE [11] and LIFE [12, 13] studies.

Diagnosis

A low-cost electrocardiogram is commonly used to evaluate the presence of LVH and/or of arrhythmias. An echocardiography is more sensible for the detection of increased left ventricular mass and can give information on left ventricular geometry and systolic chamber or midwall performance. A Doppler echocardiography with an analysis of transmitral flow combined with pulmonary vein flow may be used to define diastolic dysfunction. Other new echocardiographic technologies, such as tissue Doppler imaging, are less load-dependent and may increase diagnostic accuracy of diastolic dysfunction [14].

Another tool for the diagnosis of heart failure is the measurement of plasma brain natriuretic peptide (BNP). The increase in left ventricular stress activates the transcription and release of BNP, which can be measured in the plasma of patients with systolic and/or diastolic dysfunction; the elevation in plasma BNP levels cannot, however, discriminate systolic from diastolic dysfunction. It has been demonstrated that in patients with preserved systolic chamber function and symptoms of heart failure, a plasma level of BNP > 57 pg/ml has a positive predictive value of 100% for diastolic abnormalities as identified by echocardiography.

Treatment

Most of the earlier randomised clinical trials evaluating the efficacy of antihypertensive drugs have been associated with significant prevention of systolic cardiac failure, thereby increasing patient survival [15]. The efficacy of antihypertensive therapy supports the important contribution of persistently elevated blood pressure to the onset and progression of CHF [16]. In the UKPDS study a significant reduction in heart failure rate was associated with a progressive decrease in blood pressure (12% decrease in the incidence of heart failure for a 10 mm Hg decrease in systolic blood pressure) [17].

However, the metanalysis of the results of major interventional randomised trials conducted in hypertensive patients has shown that reduction in the incidence of CHF is related not only to the degree of blood pressure reduction but also to the class of drug used [18].

Table 1. Characteristics of patients with systolic or diastolic heart failure

Characteristic	Diastolic heart failure	Systolic heart failure
Age	Frequently elderly	All ages, typically 50–70 yr
Sex	Frequently female	More often male
Left ventricular ejection fraction	Preserved or normal, approximately 40% or higher	Depressed approximately 40% or lower
Left ventricular cavity size	Usually normal, often with concentric left ventricular hypertrophy	Usually dilated
Left ventricular hypertrophy on electrocardiogram	Usually present	Sometimes present
Chest radiography	Congestion with or without cardiomegaly	Congestion and cardiomegaly
Gallop rhythm present	Fourth heart sound	Third heart sound

Table 2. Effects of angiotensin-converting enzyme (ACEI) inhibitors, calcium antagonists and angiotensin II receptor blockers vs. Placebo and blood pressure-lowering regimens based on different drug classes on the risk of heart failure. Modified from Arch Intern Med 2005 (ref. 18)

	Class of drug	Comparison	Relative risk (95% confidence intervals)
No DM	ACEI	Placebo	0.78 (0.62–0.98)
DM	ACEI	Placebo	0.88 (0.67–1.16)
Overall	**ACEI**	**Placebo**	**0.82 (0.69–0.98)**
No DM	CCB	Placebo	1.07 (0.43–2.62)
DM	CCB	Placebo	1.29 (0.97–1.72)
Overall	**CCB**	**Placebo**	**0.99 (0.53–1.86)**
No DM	ACEI	D/BB	1.09 (0.95–1.25)
DM	ACEI	D/BB	0.94 (0.55–1.59)
Overall	**ACEI**	**D/BB**	**1.07 (0.96–1.20)**
No DM	CCB	D/BB	1.33 (1.16–1.52)
DM	CCB	D/BB	1.09 (1.01–1.61)
Overall	**CCB**	**D/BB**	**1.09 (1.01–1.61)**
No DM	ACEI	CCB	0.86 (0.73–1.01)
DM	ACEI	CCB	0.92 (0.67–1.27)
Overall	**ACEI**	**CCB**	**0.84 (0.75–0.95)**
No DM	ARB	Other	1.13 (0.87–1.46)
DM	ARB	Other	0.70 (0.59–0.83)
Overall	**ARB**	**Other**	**0.79 (0.66–0.95)***

*Indicates that there is a difference in the effectiveness of the treatment regimen between patients with and without diabetes that is fairly unlikely to have occurred by chance alone; DM: diabetes mellitus; ACEI: angiotensin--converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BB: beta-blocker; CCB: calcium channel blocker; D: diuretic

Diuretics and beta-blockers were comparable to angiotensin-converting enzyme (ACE) inhibitors in preventing the development of heart failure, and results for diuretics, beta-blockers and ACE inhibitors showed them to be more effective than calcium antagonists [18]. Angiotensin II receptor blockers (ARBs) have been demonstrated to be more effective than diuretics, beta-blockers and calcium-antagonists in reducing the incidence of heart failure in hypertensive diabetic patients with renal disease (RENAAL, IDNT) or LVH (LIFE) [19] (Table 2).

On the other hand, in the ALLHAT study [20], symptoms of heart failure increased in patients randomised to treatment with the ACE-inhibitor or with the calcium-antagonist, possibly because previous therapy, including a diuretic, was withdrawn at inclusion; in addition, despite significant differences in the incidence of heart failure, heart failure mortality did not differ between treatment arms with different antihypertensive drugs.

In the VALUE study [21] heart failure incidence was significantly lower in patients receiving valsartan in comparison with those treated with amlodipine only after 3 years of treatment. In hypertensive patients with coronary artery disease the control of blood pressure seems to be particularly relevant in the prevention of heart failure. The ACTION study [22] has shown that nifedipine GITS may reduce the number of new-onset heart failure in all patients (–29%) and to a greater extent in the hypertensive subgroup (–38%).

The goal of antihypertensive treatment for the prevention of heart failure should be not only the control of blood pressure but also the regression of LVH, coronary epicardial artery atherosclerosis and small-vessel structural alterations, in addition to an improvement in ventricular fibrosis. ACE inhibitors and ARBs seem more effective in favouring the regression of LVH and structural changes of small vessels. They may also have a favourable effect in the reversal of myocardial fibrosis [23].

Only a few studies have evaluated the effect of blood pressure reduction in patients with heart failure because of the lack of systematic recordings of arterial pressure. The SOLVD study [24] has clearly shown a beneficial effect of treatment with ACE-inhibitors in comparison with a placebo in hypertensive patients, super-imposable to that obtained in normotensive subjects.

Specific treatment of hypertension in heart failure may depend on the type of heart failure, whether systolic or diastolic. In systolic dysfunction the aim of antihypertensive treatment is the reduction of preload and afterload, improvement of left ventricular function and control of symptoms and signs of pulmonary and systemic congestion. In diastolic dysfunction the main task is the lowering of blood pressure and a reduction in heart rate together with control fluid homeostasis and myocardial ischaemia. The CHARM (Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity) study [25] has shown that in patients with diastolic dysfunction (Preserved group) treated with candesartan, the hospitalisation rate for heart failure was significantly lower in comparison with patients treated with a placebo, while differences in cardiovascular mortality did not reach the level of statistical significance. Another study (I-Preserve) will evaluate the effect of an ARB (irbesartan) in patients with diastolic dysfunction.

The Joint National Committee VII guidelines [26] state that a decrease in blood pressure is beneficial for all patients with heart failure. Although target blood pressure values are not clearly defined, systolic blood pressure values between 110 and 130 mm Hg are associated with an increased benefit.

The European hypertension guidelines recommend the treatment of hypertension in patients with heart failure, which is frequently associated with coronary heart disease and atrial fibrillation, and further suggest following the heart failure guidelines by introducing blood pressure-lowering drugs that simultaneously deal with the concomitant diseases [27, 28]. The drugs of choice are ACE inhibitors, ARBs, diuretics, beta-blockers and aldosterone receptor antagonists. Alpha-blockers and calcium antagonists may be needed in combination with other drugs in order to achieve the target blood pressure, which is a stable value < 130/80 mm Hg.

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