Factors Involved in the Pathogenesis of Hypertensive Cardiovascular Hypertrophy
A Review

Björn Dahlöf
Department of Medicine, Östra Hospital, Göteborg

Summary

All tissues can rapidly adapt their structural design whenever prolonged changes of load/activity occur within the limits characteristic of each tissue. This structural adaptation, however, is modified by various genetic and trophic influences. When antihypertensive therapy is considered in the hypertensive patient, such changes are usually well established and the cardiovascular system is structurally adapted to maintain a higher pressure than normal.

Increased blood pressure and afterload cannot solely explain the development of cardiac hypertrophy. Permissive actions from the sympathetic nervous system and the circulating angiotensin II are likely, but conflicting results still exist. There is evidence for a functional renin-angiotensin system in the heart, which may be involved in the genesis of left ventricular hypertrophy. Also, a soluble factor in the hypertrophied myocardium that stimulates protein synthesis may play a key role in modulation of myocardial structure during development or regression of myocardial hypertrophy in hypertension.

Hypertrophy of both the large and smaller arterial vessels has been shown to follow the same general pattern of development and regression as in the heart. The vascular hypertrophy (predominantly of the media in the arterioles) can be considered as the ultimate structural factor behind the progression of hypertension independent of the initiating factor. A vicious circle with the increased resistance as the key factor can be identified. There are at least 3 possible initiating factors: a small rise in arterial pressure, an abnormal or reinforced response to pressure, or trophic/mitogenic stimuli acting directly on the vascular smooth muscle cell.

The ultimate goal in the treatment of high blood pressure is to reduce hypertension-related morbidity and mortality. Normalisation of structural cardiovascular changes is also important and easier to evaluate in the individual. Understanding of the pathogenesis of structural adaptation may help in the selection of the best treatment.

Whenever sustained changes of activity and/or load occur it is common for all tissues of the body to adapt their structural design, a process which is often modified by various 'trophic' and genetic influences. Examples of this are the hypertrophic response of skeletal muscle to different training loads and to the use of drugs such as anabolic steroids, as well as the muscle atrophy seen after prolonged inactivity. The cardiovascular system is no exception to this rule. As will be discussed below, its structure can be considerably affected by prolonged changes in demand by the tissue supplied, by changes in the haemodynamic load, and also by various neurohormonal influences. Changes in car-
diovascular structure are relevant mainly because of their haemodynamic consequences, e.g. to what extent they affect cardiac work, blood pressure, nutritional supply, vascular resistance etc.

Bright (1836) reported on an association between 'hardness of the pulse' and aortic wall thickening and cardiac hypertrophy. Chanutin and Barksdale (1933) were the first to actually demonstrate that experimental induction of systemic hypertension, in a renoprival model, could produce hypertrophy of the left ventricular myocardial fibres. The increases in heart weight and fibre diameters were directly related to the arterial pressure. However, it was not until Folkow’s work in 1956 that the functional consequences of these structural cardiovascular changes in hypertension were seriously considered.

Whatever the initiating mechanism behind the rise in blood pressure (BP) and irrespective of the way hypertension develops, the common denominator for all kinds of hypertension is structural changes in the heart and vessels (Folkow 1978, 1982) which are of profound importance for the pathogenesis of hypertension (Lever 1986). Furthermore, the development of left ventricular hypertrophy (LVH) constitutes a considerable risk for both morbidity and mortality in hypertension (Carr et al. 1985; Frohlich 1987; Kannel 1983; Kannel et al. 1969, 1970; Messerli et al. 1983). In the Framingham study LVH (defined from ECG criteria) in hypertensive patients was associated with a higher incidence of stroke and heart failure, and also with increased incidence of coronary heart disease independent of BP level (Kannel 1969, 1970). Although the connection between an increased incidence of ventricular premature beats and sudden death remains controversial, it has been documented that patients with LVH have both increased ventricular premature contractions (Messerli et al. 1983) and a greater risk of sudden death (Kannel 1983) than those with a normal myocardium.

At any given level of BP, patients with LVH have a worse prognosis than those without, and since most of the risk evaluation of LVH so far has been made using ECG and not echocardiography (Carr et al. 1985), these risks have probably been underestimated. There are several possible underlying reasons as to why cardiac hypertrophy should lead to increased risk, including accelerated atherogenesis, myocardial fibrosis, coronary arterial insufficiency and a predisposition to congestive heart failure, cardiac dysrhythmias and sudden death (Frohlich 1987).

The structural changes of the cardiovascular system in hypertension have long been thought to be almost exclusively due to the increased load induced by pressure itself (Grossman et al. 1975), but results from several experimental studies have shown that there is a clear dissociation between changes in pressure load and effect on structural changes in vessels and heart (Dahlof 1987; Ruskoaho 1984). Various other factors also relevant for the development of cardiovascular hypertrophy have been discussed: sympathetic influences, the renin-angiotensin system, growth hormone and insulin among others.

This paper will briefly discuss the mechanisms behind the structural adaptation of the cardiovascular system which takes place in all hypertensive patients, will put these structural changes in perspective with the pathogenesis of hypertension, and will consider the implications for therapy.

1. Haemodynamics

In established hypertension, the increased BP is determined by an increase in total peripheral vascular resistance while cardiac output is normal or somewhat reduced (Folkow 1982; Freis 1960; Lund-Johansen 1967; Pickering 1968). The raised peripheral resistance appears to be distributed between all organs of the body (Brody & Zimmerman 1976; London et al. 1984) mostly in precapillary resistance vessels proximal to vessels which have a diameter of 10 μm (Bohlen 1983; Zweifach et al. 1981).

There are well-defined haemodynamic changes that occur during the course of primary hypertension (Julius & Conway 1968; Korner & Fletcher 1977; Lund-Johansen 1980). In mild borderline hypertension, about half of the patients have a raised cardiac index and a normal total peripheral