

Update review

The influence of antihypertensive drug treatment on the prevention and regression of left ventricular hypertrophy

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Abstract

Left ventricular hypertrophy (LVH) has been recognized as an important cardiovascular risk factor. Hypertensive disease is the most frequent background of LVH and it is generally felt that anti-hypertensive treatment should not only lower blood pressure but also cause regression of LVH. In the present survey the patho-physiology of LVH, its measurements and animal models used to study LVH are briefly discussed. Subsequently, the effects of various drugs in animal models and in human hypertensives are reviewed. It has been shown repeatedly that various types of antihypertensive drugs show differential activities on the prevention or regression of LVH. It is not only the lowering of blood pressure which determines the anti-LVH activity, but also the interaction of drugs with neuro-endocrine mechanisms such as the renin-angiotensin-aldosterone system and the sympathetic nervous system. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introductory remarks

Left ventricular hypertrophy (LVH) was recognized as early as in the Framingham [1] study as an important cardiovascular risk factor. Since then much attention has been paid to LVH associated with hypertensive disease. Early animal experiments in the 1970s have shown that LVH can be prevented or brought to regression by a variety of antihypertensive drugs. The paper by Pegram et al., published in *Cardiovascular Research* in 1982 [2] has been quoted many times as representative of this type of research. Since then the subject has been studied intensively in animal models and subsequently in human patients, owing to the introduction of non-invasive techniques which allow the measurement of LVH.

The drug treatment of hypertension has been much refined since then, and it is generally felt that antihypertensive treatment should also be accompanied by the regression of LVH.

The present survey will be dealing both with results obtained since the 1980s in animal models and in human hypertensives.

2. Pathological left ventricular hypertrophy (LVH)

LVH has already been recognized as a strong, virtually independent risk factor in the well-known Framingham Study [1]. Various noxious sequelae of cardiovascular diseases and conditions such as coronary heart disease, stroke, congestive heart failure and sudden death are known to be aggravated by LVH [3].

LVH is the result of adaptation of the heart to chronic pressure or volume overload, and more recently neuro-endocrine activation processes have been recognized to play an important role as well [3,4].

In the general population *hypertension* is the most common cause of LVH. The geometrical characteristics of LVH may differ, also with respect to the increased risk of the aforementioned sequelae of cardiovascular diseases. Concentric hypertrophy is known to be associated with the highest risk and LVH with normal geometry with the lowest risk, whereas LVH with eccentric hypertrophy is associated with intermediate risk [4,5].

The question whether LVH should be considered as pathologic cannot be judged on morphological criteria only. For instance, the increased LV wall thickness in highly trained athletes is not necessarily pathologic and additional criteria (ECG in particular) are required to distinguish between an athlete's heart and a pathologically enlarged heart [6]. The hypertrophic heart as in hyper-

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trophic cardiomyopathy (HCM) is clearly a pathological condition with a strong genetic background, but not associated with a coexisting cardiac or systemic disease that could provoke LVH [7].

In the present survey the discussion will be limited to pathologic LVH associated with *hypertensive disease*.

At the cellular/molecular level various factors and mechanisms have been implied in the genesis and maintenance of LVH. Widely recognized growth factors are for instance the catecholamines (noradrenaline, adrenaline), angiotensin II, insulin, and the human growth hormone [8]. Much attention has been paid in addition to receptor changes (α - and β -adrenoceptors; angiotensin II (AT)-receptors, etc.) associated with LVH.

Taken together, pathological LVH is generally recognized as an important process, which is associated with significant structural, haemodynamic, and cellular changes. Since LVH is also recognized to indicate an unfavourable prognosis, it is not surprising that numerous therapeutic approaches have been pursued with the aim to induce regression of LVH and, hence, a reduction of cardiovascular risk.

2.1. Animal models

LVH has been studied in animal models from the 1970s onwards, in particular by R. Tarazi and E. Fröhlich and their co-workers [2,9,10]. Most hypertensive animals as used in various models of hypertension develop LVH, more or less parallel with the rise in blood pressure. Examples of such models are various types of hypertensive rats (in particular the spontaneously hypertensive rat=SHR) and rats, guinea pigs or ferrets subjected to aortic or pulmonary artery banding [11–13]. The original investigation by Pegram et al. [2] also used SHR. LVH can also be evoked by increasing cardiac afterload by means of infusions of noradrenaline or other vasoconstrictors, such as angiotensin II, or by the long term administration of β_1 -adrenoceptor agonists such as dobutamine [14,15].

The induction of LVH in animal models is not necessarily always accompanied by hypertension. Rapid pacing of dog hearts for several weeks or goat atria for 24 h induces LV hypertrophy and atrial remodelling, respectively, which is not accompanied by hypertension [16]. A well-known model of cardiomegaly without associated hypertension is offered by the cardiomyopathic Syrian hamster. The genetically determined cardiomyopathy in these animals is associated with congestive heart failure but not with high blood pressure [17].

For the sake of completeness we mention a rat model of *right* ventricular hypertrophy (RVH), accompanied by severe right heart failure. This condition of RVH was obtained by means of a single subcutaneous injection of monocrotaline, which after 4–6 weeks led to marked right ventricular and right atrial hypertrophy, pulmonary

oedema, increased pulmonary artery wall thickness, and renal hypertrophy [18].

Finally, myocardial infarction evoked in rats by coronary arterial ligation leads to concentric hypertrophy of the septum and the myocardial tissues of the heart cavities with a large increase in the thickness of the ventricular septum [19]. After 1–2 months following coronary ligation the aforementioned characteristics of hypertrophy are fully developed, but blood pressure has been lowered when compared with control animals.

The evaluation and quantification of cardiac hypertrophy and remodelling in experimental animals is clearly easier and more precise than in human patients, where only indirect techniques can be applied. In animal models the hearts can be removed, weighed, and then subjected to a variety of morphological and biochemical analyses, as already performed in the original study by Pegram et al. [2].

2.2. Receptor changes associated with LVH

Numerous data have been gathered with respect to possible changes in the characteristics of cardiac receptors, associated with pathological LVH. Such receptor changes may be of potential interest concerning the influence of drug treatment aiming at the regression of LVH.

Experimental data concerning changes in cardiac receptors are not clearly consistent, and rather different in the various experimental models which were investigated. With respect to cardiac β -adrenoceptors no major changes were found in the inotropic responses to various types of β -adrenoceptor agonists in moderately hypertrophied hearts of young SHR, but a gradual blunting of the responsiveness occurred in hearts with a much more severe LVH taken from animals subjected to aortic banding and from older SHR [20,21]. This blunting of the responsiveness of the β -adrenoceptor pathway appears to be rather secondary to post receptor events than the result of changes in the characteristics of the surface receptors.

In hypertrophied hearts from SHR and from rats subjected to aortic banding an impaired responsiveness to α_1 -receptor stimulation was also found, whereas there were no detectable changes in the characteristics of the surface receptors [22]. Only in animals with severe LVH the cardiac α_1 -receptor density was reduced, indicating that intracellular alterations will precede the changes at the surface receptor level. For review see [23].

Metabolic changes have also been observed in association with LVH. For review see [24].

3. LVH in patients: how to measure it

Over the years a few non-invasive methods have been introduced which are now accepted to offer valid criteria to

establish and quantify LVH in patients. We briefly mention these methods here.

Electrocardiography is not suitable for an *accurate* screening of LVH because it is much less sensitive than more modern methods such as ECHO-cardiography. However, once electrocardiographic LVH has been detected it has a high predictive value for morbidity and mortality. For this reason the ECG should not be discarded as a widely available and cheap technique for the clinical diagnosis of LVH. The same holds for chest X-ray pictures [25].

ECHO-cardiography has become the most widely used technique to diagnose and quantify LVH in patients [5,25].

M-mode echocardiography is well suited for estimating differences in left ventricular mass indices (LVMI) between groups of subjects, but it underestimates the prevalence of LVH [5,25].

Nuclear magnetic resonance imaging provides 'global' and more accurate information about left ventricular structure, but this technique is much more expensive than echocardiography [26,27].

4. The influence of drugs on LVH in animal models

In general terms the vast majority of antihypertensive drugs will cause regression of LVH in a variety of animal models, and there exists a large body of literature on this subject. Globally spoken drugs that lower blood pressure without causing a marked stimulation of either the sympathetic nervous system or the renin-angiotensin-aldosterone system (RAAS) can prevent LVH, or cause its regression in animal models. Accordingly, α - and β -adrenoceptor blockers, centrally acting antihypertensives that cause peripheral sympathoinhibition (α -methyl-DOPA, moxonidine, rilmenidine), ACE-inhibitors, calcium antagonists, and aldosterone antagonists have been shown to counteract LVH in animal models. The effect of thiazide diuretics is less convincing and subject to debate, probably as a result of the activation of the RAAS provoked by these agents. Classic potent vasodilators such as hydralazine may exacerbate LVH and they certainly do not prevent it, probably because of the activation of the sympathetic nervous system and the RAAS, provoked by such compounds.

It is difficult to compare the data in experimental animals with those obtained in human patients, for a variety of reasons:

1. in human studies the blood pressure differences between treatment and control conditions are much less than in animal models, where the degree of hypertension is clearly more severe than found in human hypertensives;
2. most of the animal data concern the *prevention* of LVH development, rather than the regression of established LVH which is usually studied clinically;

3. primary hypertension in humans has a much longer time scale than in animal models.

Without attempting completeness we will present a few relevant examples concerning the influence of various drugs on LVH in animal models.

4.1. Centrally acting antihypertensives

These agents were studied extensively with respect to the regression/prevention of LVH in animal models, in particular SHR, by the Tarazi Group as early as the 1970s [9,10].

Clonidine and α -methyl-DOPA (via its active metabolite α -methyl-noradrenaline) cause peripheral sympathoinhibition which is triggered by a central nervous mechanism located in the brain stem. α -Methylnoradrenaline is a selective stimulant of central α_2 -adrenoceptors, whereas clonidine stimulates both imidazoline (I_1)-receptors and α_2 -adrenoceptors [28].

In SHR both sympathoinhibitory agents significantly reduced the elevated blood pressure. However, α -methyl-DOPA prevented the development of LVH, whereas clonidine did not, as already discussed in the original publication by Pegram et al. [2]. In a later stage moxonidine and rilmenidine were developed as centrally acting anti-hypertensives. Both compounds trigger peripheral sympathoinhibition via the stimulation of imidazoline (I_1)-receptors in the brain, whereas they have much less affinity for the α_2 -adrenoceptor. Both I_1 -receptor stimulants are effective antihypertensives, in animal models and in patients. In SHR and other animal models of hypertension they counteract the development of LVH [29,30].

The experiments with the centrally acting drugs strongly suggest that sympathoinhibition is an important mechanism in the prevention and regression of LVH, although it has never been explained why clonidine is ineffective in this respect.

In this context it seems of interest to mention older experiments in rats with LVH caused by iron deficiency anaemia. This type of LVH could be suppressed by reserpine [31], which is known to depress sympathetic activity both via central nervous and peripheral mechanisms.

4.2. β -Adrenoceptor antagonists (β -blockers)

Several β -blockers have been shown to counteract the development of LVH in animal models of hypertension, and this activity of the β -blockers is beyond any doubt a class effect. As an example we mention here the effects of the β_1 -selective agent metoprolol. Several authors have demonstrated that prolonged therapy of SHR with an antihypertensive dose of metoprolol will suppress the development of LVH. In SHR metoprolol was shown to decrease wall thickness in response to the decreased

pressure load (antihypertensive action), whereas it did not change the LV internal radius. In SHR metoprolol treatment appeared to reduce the end-diastolic volume [32].

In a dog model, hypertension and LVH were induced by unilateral nephrectomy and the clipping of the contralateral renal artery. The animals were subsequently subjected to coronary occlusion in order to generate myocardial infarction. The hypertensive animals with LVH and a myocardial infarction showed a very high mortality [33].

Metoprolol treatment significantly reduced elevated blood pressure, LVH and the high mortality, whereas infarct size was also diminished. The authors presumed that the suppression of the aforementioned noxious phenomena by β -receptor blockade is not only explained by the antihypertensive action but also by electro-physiological effects of the drug [33].

The beneficial influence of β -blockers on LVH and its sequelae also substantiates the important role of the sympathetic nervous system and its transmitters in the genesis of LVH. Several authors have demonstrated the development of LVH as a result of the stimulation of cardiac β -adrenoceptors [14,15]. Alterations in the cardiac β -adrenoceptor-mediated signalling pathway associated with LVH and hypertensive heart disease have been recently reviewed in detail [34].

In hypertrophied hearts the inotropic response to β -adrenoceptor agonists is known to be blunted, probably as a result of lesions of the β -adrenoceptor system, both at the receptor level and within the signal transduction pathway.

4.3. α -Adrenoceptor antagonists (α -blockers)

Several α -adrenoceptor antagonists (α -blockers) have been shown to attenuate the development of LVH, associated with reduction of blood pressure in animal experiments. In this connection we mention the example of the α_1 -adrenoceptor antagonist bunazosin, which was studied in Dahl salt-sensitive rats [35].

Bunazosin was administered in a sub-antihypertensive dose, which did not influence the elevated blood pressure of these animals. However, LVH as characterized by the LV/body weight ratio and the LV tissue DNA content proved significantly lowered by the bunazosin treatment [35]. From these experiments the authors concluded that a sub-antihypertensive dose of bunazosin can inhibit the development of LVH without suppression of the pressure load, suggesting an important role of α_1 -adrenoceptors in the pathogenesis of LVH subsequent to the development of hypertension.

4.4. Direct acting vasodilators: hydralazine and minoxidil

Hydralazine and minoxidil are directly acting vasodilators, which develop their vasodilator effect without blunting

receptors or components of the sympathetic nervous system and the renin-angio-tensin-aldosterone system (RAAS). Although potent vasodilators they are no more used in the treatment of hypertension, since they cause reflex stimulation of the sympathetic system and probably also of the RAAS. Accordingly, they provoke reflex tachycardia, a rise in plasma noradrenaline and the retention of sodium and water.

Hydralazine and minoxidil have been studied in animal models of hypertension, associated with LVH, in particular in the SHR. It has been described repeatedly [2,36] that hydralazine in an antihypertensive dose does not prevent or attenuate LVH. Similar findings were obtained in transgenic (m REN 2) 27 rats with overexpression of the mouse renin 2^d gene. These animals have severe hypertension and cardiac hypertrophy [37].

Conversely, in several series of experiments it was observed that hydralazine exacerbates LVH, as reflected by an increased heart weight and media thickness [38]. Similar observations have been made with minoxidil [39].

The lack of beneficial effect on LVH or the possibility that it is worsened in spite of the antihypertensive action of such drugs may be explained by the aforementioned reflex activation of the sympathetic and renin-angiotensin-aldosterone systems.

4.5. Diuretics

Although established as effective antihypertensive agents since several decades, the influence of diuretic agents on LVH has not been studied intensively, and hardly any comparative studies with other antihypertensives have been performed. The general impression has been obtained that diuretics are but moderately or may be not effective with respect to the prevention and regression of LVH.

As an example we mention a study in SHR where both a thiazide diuretic (trichlormethiazide) and the loop diuretic furosemide have been compared [40]. When given in rather high doses a moderate reduction of LVH (and blood pressure) were achieved after 5 weeks of treatment. Both types of diuretics showed the same moderate efficacy on blood pressure and the prevention of LVH. The authors also investigated cardiac myosin isoforms and LVH-related gene expressions. Furosemide but not the thiazide diuretic significantly increased the proportion of cardiac V3 myosin of the SHR by enhancing the gene expression of the β -myosin heavy chain [40].

Conversely, trichlormethiazide but not furosemide suppressed the increased cardiac gene expression of skeletal α -actin. Accordingly, the effects on the gene expression of cardiac contractile proteins and collagen are significantly different among the two types of diuretics. The authors suggest that the two types of diuretics may have additional cardiac actions independent of their diuretic, antihypertensive and anti-LVH effects [40].

4.6. Calcium antagonists

Calcium antagonists (CA) are a rather heterogeneous group of anti-hypertensive and anti-anginal drugs. Nifedipine and other dihydro-pyridines are predominantly potent vasodilators, without a direct effect on the cardiac nodal tissues in therapeutic dosages. The rapidly and short acting drugs of this type, in particular the non-retarded nifedipine preparation provoke sympathetic activation and reflex tachycardia. Conversely, the more recently introduced dihydropyridines with a slow and long action (amlodipine, lacidipine, lercanidipine) do not alter heart rate. Verapamil and diltiazem are also vasodilators, but they reduce A-V conduction and heart rate as a result of their depressant effect on the nodal tissues. In spite of these discrepancies all three different categories of CA have been shown to prevent the development of LVH in various animal models of hypertension. We only mention a few examples here.

In SHR verapamil treatment for 45 weeks significantly reduced blood pressure, heart rate and the ratio of ventricular weight to body weight, as well as the collagen content of the heart [41].

Similarly, nifedipine treatment of SHR for 20 weeks caused a significant reduction of the LV muscle mass/body weight ratio and of the quotient of LV muscle mass and LV-end diastolic volume [42]. Accordingly, antihypertensive treatment with nifedipine can cause an already existing LVH in SHR to regress, in spite of the sympathetic activation associated with nifedipine administration. Numerous other studies, not to be mentioned here, have shown prevention or regression of LVH in SHR.

In non-hypertensive models of remodelling of the heart the suppressant effect of CA could be shown as well. For instance in dogs, electrical remodelling of the atrium during rapid atrial pacing was counteracted by verapamil [16].

Furthermore, amlodipine, one of the newer dihydropyridine-CA prevented progressive remodelling and a reduction of cardiac dysfunction in cardiomyopathic hamsters [43].

In conclusion, several types of CA in various models of cardiac hypertrophy appear to display antihypertrophic activity. In most models the reduction of high blood pressure is without any doubt a major factor. Explanations at the cellular level are difficult to offer, since the alterations in calcium handling in LVH and other types of remodelling are not consistent and subject to debate [13,19,44].

4.7. ACE-inhibitors

The ACE-inhibitors have been subjected to extensive studies with respect to their antiproliferative activity. Since the differences between the several ACE-inhibitors now available are very modest, it seems likely that the anti-

proliferative activity of the ACE-inhibitors is a class effect of these agents. Again we mention a few examples.

Accordingly, in SHR enalapril reduced elevated blood pressure and LV mass in association with a decreased total peripheral resistance, as well as a decreased coronary vascular resistance [45].

In another series of experiments in SHR enalapril induced regression of cardiac hypertrophy and also normalized the deranged pH regulator mechanisms associated with LVH [46]. Similarly, cilazapril treatment prevented the development of LVH and the decrease of coronary vascular reserve in the left and right ventricles of SHR [47]. Lisinopril was shown to reduce elevated blood pressure and LVH in SHR, whereas myocardial fibrosis was reversed, as a result of enhanced collagen degradation by activation of tissue matrix metalloproteinase 1 [48]. Diastolic stiffness in advanced hypertensive heart disease in SHR was improved. Systolic dysfunction of the left ventricle could be prevented.

The LVH in transplanted hearts of SHR was counteracted by perindopril, and the authors suggested that this effect depends on bradykinin [49].

In rats subjected to aortic banding quinapril was shown to prevent elevated blood pressure, LVH, and to reduce serum and cardiac ACE activities. Lower doses of quinapril neither reduced blood pressure nor LVH, although they reduced the cardiac ACE activity. It was concluded that elevated blood pressure (pressure overload) is a more important determinant than ACE activity in the genesis and maintenance of LVH [50].

Similar findings were obtained in SHR with trandolapril [51].

In a dog model, where LVH was induced by rapid pacing, fasinopril was shown to improve LV and myocyte geometry and function [16]. In cardiomyopathic hamsters enalapril was shown to prevent progressive remodelling and to reduce cardiac dysfunction [43].

In conclusion, the prevention and regression of LVH by various ACE-inhibitors has been demonstrated convincingly in several animal models.

4.8. Angiotensin (AT_1)-receptor antagonists

AT_1 -blockers have been introduced as effective anti-hypertensive agents, which appear to be very well tolerated. They may also be of value in the treatment of congestive heart failure. Data concerning their influence on the progression and regression of LVH are beginning to emerge.

Initially there existed some doubt whether the AT_1 -antagonists would be indeed effective as antihypertrophic agents, but more recent data may indicate that they display anti-LVH activity similar to that of the ACE-inhibitors. Again we briefly mention a few relevant examples.

In a dog model where LVH was induced by rapid cardiac pacing the AT_1 -blocker irbesartan proved less

effective than the ACE-inhibitor fosinopril [52]. Moreover, long term AT₁-receptor blockade in rats with aortic stenosis did not regress LVH [53]. However, in a detailed study in SHR losartan proved as effective as enalapril in counteracting LVH, provoked by hypertension [54], although the experimental AT₁-blocker L-158,809 did not diminish the severity of cardiomyopathy in Syrian cardiomyopathic hamsters [55].

More data will be required to obtain a convincing opinion concerning the possible role of AT₁-blockers in the suppression of LVH in experimental animals.

4.9. Endothelin receptor antagonists

Endothelin (in particular ET-1) is regarded as an autocrine/paracrine factor in the development of cardiac hypertrophy both in vivo and in vitro. For this reason endothelin receptor antagonists, which are now becoming available are subjected to investigation as potential anti-proliferative agents. New data are emerging, and we mention a single example.

The ET_A/ET_B receptor antagonist bosentan partially prevented LV dilatation and improved haemodynamics in rats with an MI, provoked by coronary ligation. This finding confirms that endothelin may play a role in LV remodelling after MI [56].

Further investigations concerning the possible role of ET antagonists as LVH agents are on the way.

5. Clinical data concerning the influence of drugs on LVH

The unfavourable effect of LVH on prognosis strongly suggests that regression of LVH by means of drug treatment and other measures is mandatory.

Numerous investigations have shown that LVH in hypertensives can be prevented or brought to regression by means of drug treatment and/or appropriate changes in life style, and some of those data will be discussed in the present survey.

However, conclusive evidence that LVH prevention or regression by means of treatment indeed improves prognosis with respect to the risks of hypertensive disease has so far not been published, although trials addressing this question are on the way.

Antihypertensive treatment as such usually leads to prevention or regression of LVH. However, the improved prognosis of treated hypertensives is primarily related to the reduction of blood pressure as such. In the individual patient in clinical practice there is no practical and reliable method available which allows proper judgement on the influence of treatment on LVH.

The TOMHS-Study has shown that appropriate life style changes as usual in antihypertensive treatment causes significant regression of LVH in patients with mild hyper-

tension (DBP 90–99 mm). Additional treatment with antihypertensives in these patients did not offer further regression of LVH [57].

A variety of antihypertensive drugs has been shown to cause regression of LVH in treated hypertensives.

As described for the animal models we will mention a few relevant examples and also discuss a meta analysis concerning the effect of drug treatment.

5.1. β -Blockers

Several β -blockers have been shown to cause regression of LVH in hypertensive patients. For instance, the β_1 -selective blockers bisoprolol and atenolol were shown to cause regression of LVH in hypertensive patients [58,59]. Bisoprolol was found to be similarly effective as the ACE-inhibitor enalapril. Similar findings were obtained with metoprolol [60]. It is very likely that this is a class effect of the β -blockers, involving β_1 -adrenoceptors.

5.2. Diuretics

No regression or little regression was found with diuretic mono-therapy [61], although these agents cause an acceptable reduction of elevated blood pressure.

5.3. Centrally acting antihypertensives

α -Methyl-DOPA and also clonidine were shown to cause regression of LVH in hypertensive patients [60]. Moxonidine has also been shown to cause regression of LVH in hypertensives [62]. The data concerning α -methyl-DOPA are on line with those described by Pegram et al. in the original publication [2]. However, Pegram et al. found no regression of LVH by the treatment with clonidine.

5.4. Calcium antagonists

Nitrendipine, a dihydropyridine calcium antagonist, was shown to cause regression of LVH in patients with hypertension and type II-diabetes (NIDDM) [63,64]. Comparable findings were obtained with several other dihydropyridines, such as nifedipine-GITS [65], felodipine [66], and isradipine [67]. Verapamil also caused LVH regression, whereas in a comparative study with several other drugs diltiazem did not.

5.5. Reserpine plus a thiazide diuretic

The rather old antihypertensive drug reserpine reduces blood pressure via both peripheral and central mechanisms. When combined with clopamide, a thiazide diuretic, 24 weeks of treatment of hypertensives led to a reduction of LVH and an improvement of haemodynamic parameters [68].

5.6. ACE-inhibitors

Numerous investigations have demonstrated the beneficial effect on LVH in hypertensives. As examples we mention captopril [69], fosinopril [70], lisinopril [71,72] and delapril [73]. This appears to be a class effect of the ACE-inhibitors. Furthermore, the inhibitory effect of ACE-inhibitors on remodelling of the heart in post-MI patients is also well established and probably an important mechanism in the secondary prevention in such patients.

5.7. Angiotensin II-receptor antagonists (AT_1 -blockers)

Several AT_1 -blockers have been shown to cause regression of LVH in hypertensive patients. As examples we mention losartan [74], and candesartan [75]. However, there has been one report on losartan causing an increase in left ventricular mass, in spite of a clear antihypertensive effect [76].

6. Comparative efficacy of various antihypertensive drugs

Several small comparative studies have been performed in order to find out which type of antihypertensive drug would be most effective in reducing LVH.

Because of discrepancies in methodology and low power of the studies it is difficult to decide which type of the drugs would be the most effective in reducing LVH. In spite of this limitation the following comparison of the activities has been proposed [77]:

ACE-inhibitors and calcium antagonists are most effective, whereas AT_1 -blockers probably display comparable activity, although the number of investigations on these newer drugs is limited so far. β -Blockers and even more so diuretics appear to be less effective than the above-mentioned newer classes of antihypertensives.

In a large study by the Veterans Affairs Cooperative Study Group on Antihypertensive Agents 6 different types of antihypertensives were compared as monotherapy in 1105 hypertensive men [78]. After achieving the goal diastolic blood pressure of 90 mm Hg during drug titration the patients entered a 1-year maintenance period. After this period LV mass and haemodynamic parameters were measured. The most effective reduction of LVH was obtained by captopril, atenolol and hydrochlorothiazide. However, efficacious antihypertensive treatment with diltiazem, clonidine or prazosin did not cause significant reductions of LVH. The authors concluded that antihypertensive drugs have disparate effects on LV mass independent of the magnitude of blood pressure reduction.

A recent *meta-analysis* of randomized double-blind trials [79] has shown that after a mean duration of treatment of 25 weeks, with approximately equi-effective antihypertensive doses of the drugs, LV mass decreased as

follows: ACE-inhibitors, -13%; Ca-antagonists, -9%; β -blockers; -6% diuretics; -7%.

7. Conclusion

LVH associated with hypertensive disease is widely recognized as an important risk factor. The desirability to prevent and induce regression of LVH by drug treatment is also widely understood, although the ultimate evidence that such treatment improves prognosis remains to be provided.

Since the early work in the 1970s, referred to in the Introduction of the present survey and emphasized in the original publication by Pegram et al. [2], animal models have been studied on a large scale and an impressive series of data has been obtained. More recently modern ECHO-techniques have allowed the investigation of LVH and the influence of drugs thereupon in human patients.

The impression is obtained that in animal models the vast majority of antihypertensive drugs will cause some degree of LVH-prevention or suppression (depending on the model used), where reduction of elevated blood pressure is a very important, but not the only factor.

It goes without saying that initial blood pressure values, the duration and intensity of treatment, as well as the degree of LVH are important determinants of LVH regression or prevention.

However, it has been recognized more and more that growth factors such as angiotensin II, catecholamines, and possibly insulin and human growth hormone are important factors in the development of LVH, which are influenced in a differential manner by the various categories of antihypertensive drugs. There is no doubt that angiotensin II is a very important factor, as demonstrated by the convincing antiproliferative effect of the ACE-inhibitors and the AT_1 -receptor antagonists. With respect to the AT_1 -receptor antagonists it may be speculated that the high concentrations of circulating angiotensin II associated with this treatment may contribute to the regression of LVH via the stimulation of the AT_2 -receptor [80]. Conversely, the weak or absent effect of diuretics on LVH might be attributed to the activation of the RAAS which is provoked by these agents. The sympathetic system is probably also important, as demonstrated by the anti-LVH activity of centrally acting anti-hypertensives such as α -methyl-DOPA [60] and moxonidine [62]. It is still difficult to understand why clonidine was ineffective in some animal models (see the original publication by Pegram et al. [2]). The moderate efficacy of the β -blockers with respect to LVH regression/prevention would indicate that the interaction of cardiac β -adrenoceptors with circulating catecholamines is probably not a very important factor in the development or regression of LVH.

In summary, since the publication of the paper by Pegram et al. in 1982 [2], LVH has been the subject of

intensive research, which has greatly deepened our insight into this phenomenon. Drug treatment appears to be feasible, although conclusive evidence that LVH regression would offer a better prognosis remains to be established. Pharmacological research has not only offered a better insight in the possibilities of drug treatment, but also greatly improved our knowledge of the pathophysiology of LVH.

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