Target Organ Damage in Hypertension: Pathophysiology and Implications for Drug Therapy

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Abstract: Hypertension is a well known risk factor for cardiovascular and cerebrovascular events such as heart attacks and strokes. In addition, it is associated with earlier changes in organ systems in the body, such as left ventricular hypertrophy (LVH), proteinuria and renal failure, retinopathy and vascular dementia which are grouped under the term "target organ damage"(TOD).

There are many processes involved in the pathogenesis of TOD and these include endothelial activation, platelet activation, increased thrombogenesis, changes in the renin aldosterone angiotensin system (RAAS), and collagen turnover. All these changes work hand in hand and lead to the production of hypertensive TOD. In this review, we aim to provide an overview of the recent advances in pathophysiology of hypertensive TOD, and examine how these changes lead to the production of TOD. A better understanding of these pathogenic processes would help us better devise treatment strategies in preventing the dreaded complications associated with hypertension.

Key Words: Hypertension, target organ damage, endothelial activation, platelet activation.

INTRODUCTION

Hypertension is a common ailment, with a prevalence of around 15 to 20% in persons over the age of 40 [1]. This proportion rises with increasing age and also varies in different ethnic groups, with higher prevalence rates in African Americans and Hispanics [2, 3]. Its importance as a risk factor of cardiovascular disease is undisputed, being associated with a higher incidence of myocardial infarction and stroke [4, 5]. As early as the 1970s, the significance of hypertension in the pathogenesis of atherothrombotic stroke was established, and newer studies continue to confirm the benefit achieved with blood pressure reduction.

The high blood pressure that is associated with hypertension can also affect specific organ groups leading to the term "target organ damage" (TOD), which in addition to the atherosclerotic vascular diseases mentioned above, include renal failure, retinopathy, vascular dementia and left ventricular hypertrophy. Apart from blood pressure per se many pathophysiological processes may contribute to the development of hypertensive TOD.

For example, hypertension is associated with abnormalities in coagulation, platelets and the endothelium, leading to a prothrombotic or hypercoagulable state [6]. The latter may explain why despite the blood vessels being exposed to high pressures, the main complications of hypertension, that is, heart attacks and strokes, are thrombotic rather than haemorrhagic, the so called 'thrombotic paradox of hypertension' (the Birmingham thrombotic paradox) [7]. Furthermore, thrombogenesis is intimately related to atherogenesis and angiogenesis in vascular disease (the "Birmingham vascular triangle") and indeed, abnormalities of all 3 processes are found in hypertension [8]. In addition there are other changes involving the renin-angiotensin-aldosterone system (RAAS), metalloproteinases, natriuretic peptides, etc, which could all influence the pathogenesis of the above mentioned TOD.

In this review, we aim to provide an overview of the recent advances in pathophysiology of hypertensive TOD, and briefly examine how these changes lead to the production of TOD. A better understanding of these processes would help us better devise treatment strategies in preventing the dreaded complications associated with hypertension.

SEARCH STRATEGY

We performed a comprehensive literature search by using electronic bibliographic databases (i.e. MEDLINE, EMBASE, DARE, COCHRANE DATABASE), scanning reference lists from included articles and hand searching abstracts from national and international cardiovascular meetings. For the search, we had used the terms "hypertension", "target organ damage", "left ventricular hypertrophy" and "hypertensive retinopathy". The searches were limited to studies on humans and those published in English. Bibliographies of all selected articles and review articles were reviewed for other relevant articles. Finally, the supplements of major journals were hand searched to identify relevant abstracts that had not been published as peer reviewed articles. Where necessary, study authors were contacted to obtain further data.

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LEFT VENTRICULAR HYPERTROPHY AND LEFT VENTRICULAR DYSFUNCTION

Left ventricular hypertrophy (LVH) is a common finding in hypertensives. LVH is predominantly related to the duration of hypertension and the levels of blood pressures that the patient has [9, 10].

The mechanisms involved here include a general hypertrophy of the muscles in response to contracting against a high arterial pressure. In the initial stages, LVH is therefore a compensatory process that represents an adaptation to increased ventricular wall stress; however, LVH is also the first step in the development of overt clinical disease. For example, data from the Framingham study has shown that patients with more severe hypertension tend to have thicker ventricles, demonstrating a direct link between the blood pressure and the muscle thickness [10]. In addition studies have shown regression of LVH with treatment of the high blood pressure, confirming the 'cause and effect' relationship [11].

Data from the Framingham study were the first to demonstrate conclusively a relationship between LVH and future prognosis [12]. A large number of studies have since also shown a direct relationship between LVH at baseline examination and the risk of subsequent morbid or mortal events in clinical or epidemiological populations [13-18]. Indeed, subjects with LVH have a 2 to 4 fold higher rates of cardiovascular complications independent from other risk factors such as hypercholesterolemia, age and blood pressure measured in the clinic [19]. Table **1** summarises examples of the different studies on prognosis and LVH, updating the systematic review by Vakili *et al.* [20].

Concentric hypertrophy appears to carry the highest risk and eccentric hypertrophy an intermediate risk [19, 21]. The reason for this difference in prognosis for the different geometric patterns is not certain. The eccentric pattern of LV mass distribution is considered to reflect normal mass to volume distribution, whilst the concentric pattern is more suggestive of a response to volume or pressure overload. This pattern is associated with severe haemodynamic and structural abnormalities and therefore represents a more unfavourable pattern [21, 22].

LVH can also lead to increased mortality and morbidity by other mechanisms including an increased risk of arrhythmias, diastolic dysfunction, decreased contractility and impaired coronary reserve [23]. In addition to the prognostic implications of LVH, studies have also shown that left ventricular diastolic dysfunction in hypertensives (often a result of LVH) can also predict worse outcome in these patients [24].

Regression of LVH with treatment appears to decrease the chance of cardiovascular morbidity and mortality, and improved left ventricular diastolic function [25-28]. Verdecchia *et al.* [29] published a meta-analysis of various trials studying the effect of LVH regression during the treatment

Table 1. Examples of Studies Investigating the Effect of Left Ventricular Hypertrophy (LVH) on Cardiovascular Prognosis

Authors	Patient population	Findings
Okin *et al.* [13]	8854 hypertensive patients with ECG evidence of LVH who were treated in a blinded manner with atenolol or losartan based regimens	Increased CV death- HR 2.26, 95% CI 1.78 to 2.86, fatal/nonfatal MI -HR 2.16, 95% CI 1.67 to 2.80), fatal/nonfatal stroke (HR 1.76, 95% CI 1.39 to 2.21), and the composite CV end point (HR 1.99, 95% CI 1.70 to 2.33)
Schillaci [178]	1970 hypertensive patients without prevalent cardiovascular disease, but ECG evidence of LVH were followed for up to 9.1 years (mean 4.7 years).	Risk of developing CV disease in patients with ECG findings of LV strain was hazard ratio 4.00, 95% CI 2.09-7.65; P < 0.001
Tsang [179]	Study of predictive value of baseline echocardiography in a general population	LVH by echo was a significant predictor of coronary events
Novelli *et al.* [180]	148 patients with gestational hypertension	LVH was associated with increased risk of maternal and fetal outcomes (HR 3.65, 95% CI-1.3-10.2, p=0.014
Ghanem [181]	Cross sectional study on 115 diabetic and hypertensive patients-	Increased risk of cardiovascular mortality, heart failure, atrial fibrillation and stroke
Verdecchia [182]	1033 hyperensive subjects with no previous vascular disease followed up for 4 years	LVH increased risk of cardiovascalur events RR 2.08, 95%CI 1.22-3.57; For every 39gm/m2 incrase in LV mass, there was a 40% increase in the risk of an event
Sundstrom [183]	475 men above the age of 70 followed up for 5 years	Echo diagnosis of LVH predicted increase total mortality (RR 1.44, 95%CI 1.09-1.92) and cardiovascular mortality (RR2.38, 95%CI1.52-3.73); ECG diagnosis of LVH (Cornell score) also predicted increased total mortality (RR2.89, 95%CI 1.41-5.96)
Vakili [20]	Meta analysis of previous studies (20 studies with 48,545 participants)	Mean risk ratio of 2.3 for all studies with a range from 1.5 to 3.5 for total mortality in hypertensive patients with LVH

LVH- Left ventricular hypertrophy, ECG- Electrocardiogram, CV- Cardiovascular, HR- Hazard ratio, CI- confidence interval, RR- relative risk.

of hypertension, and the effect of prognosis, they concluded that patients who fail to achieve LVH regression or in whom LVH developed during treatment of hypertension are more likely to suffer morbid events than those in whom LVH regressed or never developed. However, there may be other factors such as ethnicity which may affect this benefit [30].

Different anti-hypertensives appear to have different effects on LVH regression [31], as has indeed been demonstrated by the LIFE study [32] and in a metanalysis by Klingbeil *et al.* [33]. In the latter metaanalysis, 80 trials with 146 active treatment arms (n = 3767 patients) and 17 placebo arms (n = 346 patients) were identified. After adjusting for treatment duration and change in diastolic blood pressure, there was a significant difference (P = 0.004) among the different medication classes. The use of angiotensin II receptor antagonists decreased left ventricular mass index (LVMI) decreased by 13%. There was a reduction in LVMI by 11% with calcium antagonists, 10% with ACE inhibitors, 8% with diuretics and by 6% with beta-blockers. In pairwise comparisons, angiotensin II receptor antagonists, calcium antagonists, and ACE inhibitors were more effective at reducing left ventricular mass compared to beta-blockers.

Other factors are also associated with variations in the incidence of LVH. For example, Toprak *et al.* [34] studied the 24 hour blood pressure patterns in 35 non diabetic renal transplant recipients and correlated these findings with the presence or absence of LVH. They demonstrated that the absence of a nocturnal fall in blood pressure (non dipper status) is associated with a higher incidence of LVH. Jokinitty *et al.* [35] followed up 65 male patients with newly diagnosed hypertension, for 10 years. All their patients had echocardiography at baseline and again on follow up. Of all the variables they studied, pulse pressure most significantly predicted the incidence of LVH on follow up. This is important as pulse pressure does reflect the elasticity of the blood vessels [36], and perhaps suggests that the same mechanisms that cause vessel inelasticity and thickening are responsible for LVH.

The role of dietary salt in the pathogenesis of LVH was first described by Schmeider *et al.* [37, 38] in 1988. Since then ot, hers have also confirmed this association [39-41]. It has been suggested that increased sodium intake increases the preload and thereby increases LVH. Salt excess has also been suggested to work *via* the renin-angiotensin-aldosterone pathway, and *via* the sympathetic nervous system [40, 42]. Indeed, there have also been studies demonstrating regression of LVH with salt restriction [43]. A low salt di*et al*so improves the LVH regression by antihypertensive agents [44].

HYPERTENSIVE RETINOPATHY

Hypertensive retinopathy are commonly seen in the eyes of patients with long standing uncontrolled hypertension [45]. These changes occur in the retina, optic nerve head and choroidal circulation. The changes in the retina (hypertensive retinopathy) are the most widespread early changes that are seen and that have been described. There are many classifications for these changes, including the well-established Keith-Wagener-Barker classification and the Scheie classification. However, it is now thought that these classifications do not correlate well with the severity of hypertension and progression, and new simpler two-grade classification of non malignant *vs.* malignant retinopathy was proposed [46]. A similar classification has been suggested to encourage the utilisation of the eye as a hypertensive target organ for risk stratification and therapeutic decision making [47].

Under normal circumstances, the retinal vasculature is initially protected from increases in BP by metabolic and myogenic mechanisms. The retinal vessels have the ability to maintain a constant blood flow despite changes in perfusion pressures, by either vasodilation or vasoconstriction. Endothelial derived molecules, ie endothelins, thromboxane A2, prostaglandins and nitric oxide all play a role in the autoregulation. Breakdown of this autoregulation occurs with changes in the perfusion pressure beyond a critical range. Alteration in the endothelial function (see below) in hypertension could contribute to the failure of autoregulation. In chronic stages of hypertension, diffuse arteriolar narrowing will be apparent because of the localized areas of spasm of the arterial wall. This would then lead on to other changes such as oedema and fibrosis [48]. In malignant hypertension, the changes seen include papiloedema, hard and soft exudates which are due to severe vasospasm of the vessels in response to the high pressures (as seen in malignant hypertension), leading to necrosis and focal leakage from the precapillary arterioles that lie deep in the retina.

COGNITIVE IMPAIRMENT/VASCULAR DEMENTIA

The inverse association between blood pressure and cognitive impairment has been demonstrated in a number of epidemiological and treatment studies.

The Framingham Heart Study was one of the first to demonstrate that attention and memory measures are inversely related to blood pressure levels and duration of hypertension [49]. A large study from Uppsala, Sweden, where 999 men were observed from ages 50 to 70 confirmed the effects of a high baseline blood pressure on future development of cognitive impairment [50]. Among these subjects, a high diastolic blood pressure at baseline predicted later impairment of cognitive function. Other factors that predicted cognitive impairment were non-dipping of blood pressure, insulin resistance, and diabetes mellitus. Similar findings were obtained from the Honolulu Asia Aging study [51] and the Atherosclerosis Risk In Communities' study [52].

The mechanisms involved in cognitive impairment/ vascular dementia secondary to hypertension are not certain. Hypertension is a risk factor for atherosclerosis, stroke or cerebral infarction, which in turn may cause cognitive decline. In the absence of an overt cerebrovascular accident or stroke, cognitive impairment may be a result of occlusion of microvasculature. Patients with hypertension also have smaller volumes of thalamic nuclei, larger volumes of cerebrospinal fluid in the cerebellum and temporal lobes and performed worse on language and memory tests than non hypertensives [53]. In addition, autopsy studies have demonstrated a relationship between elevated systolic blood pressure and impaired cognitive function with low brain weight and greater numbers of neurofibrillary tangles in the cortex

and hippocampus [51]. Hypertension may also cause demyelination of the white matter and the consequent cognitive decline [54].

The Systolic Hypertension in Europe Study (Syst Eur) was one of the first studies to demonstrate a protective effect of antihypertensive therapy on the development of cognitive impairment [55]. Similar findings have been demonstrated in the population-based Rotterdam study [56] and the Medical Research Council treatment trial of hypertension in Older adults [57].

More recently, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) also showed that treatment with perindopril an Angiotensin converting enzyme inhibitor resulted in a non significant risk reduction for dementia of 12% overall, but a significant reduction of 34% in patients with prior stroke [58]. The study on Cognition and Prognosis in the Elderly (SCOPE) demonstrated that patients on Candesartan, an Angiotensin receptor blocker, had a significantly slower decline in cognitive function [59]. Antihypertensive therapy has also been shown to reduce the incidence of what mater changes on MRI [60].

HYPERTENSIVE RENAL DISEASE

Renal disease has an important relationship with hypertension in that it could be either a cause or an effect of hypertension. It is epidemiologicaly more common to see renal failure leading on to hypertension, but the converse is controversial [61-63], except in malignant hypertension, where progressive deterioration of renal function has been demonstrated [64].

The mechanisms involved here are similar to those seen above for the retinal disease. Here as well, the glomerular vessels autoregulate the blood flow by vasoconstriction or vasodilatation depending on the perfusion pressures, to keep the actual perfusion at the glomerulus constant. Prolonged high perfusion pressures can lead to significant vasoconstriction, which can then cause localised damage to the glomeruli. This can cause necrosis of the glomeruli leading to microalbuminuria, which could lead to significant proteinuria if the disease is not treated [65]. Renal failure in the absence of the malignant phase could also be an effect of atherosclerosis affecting the renal arteries, leading to under perfusion.

In one study of kidneys of accident victims, the kidneys of hypertensive patients had almost half the number of glomeruli per kidney as compared to kidneys from aged matched normotensive subjects [66]. However, others have suggested that it might be the decreased glomerular number at birth that is the primary feature, and this leads to hyperperfusion of each nephron and thereby leading to glomerular sclerosis and thus, hypertension [67].

In a cohort of young patients with essential hypertension who are not diabetic, Redon *et al.* [68] were not able to demonstrate any specific risk factor for the development of microalbuminuria. However, those patients who were treated with an ACE-inhibitor tended to have lower rates of development. Those who did progress to microalbuminuria did have a higher blood glucose level and higher uric acid levels – nonetheless, age, sex, body mass blood pressures, other biochemical parameters or even the presence (or absence) of LVH did not appear to influence this.

As with LVH, microalbuminuria has also been shown to correlate with future cardiovascular events [69-71]. The reversal of microalbuminuria with the strict treatment of hypertension has been shown to improve cardiovascular events [72, 73].

MOLECULAR MECHANISMS INVOLVED

The hemodynamic burden of an increased blood pressure causes systemic changes as seen above. As also seen above, changes in one organ (i.e. LVH or microalbuminuria) can reflect changes in other organs or a predisposition to changes in other organs. There are many changes involved in the pathogenesis of these changes, and no single factor can be singled out to be responsible for the changes in that particular organ. The changes are a sum total of different changes, with some changes being more predominant in some organs than the other.

THE ENDOTHELIUM

The changes in the endothelium in hypertension are widespread and well established. This activated endothelium causes increased production of procoagulant and inflammatory agents and is associated with a shift of the actions of the endothelium toward reduced vasodilation, a proinflammatory state, and prothrombic properties [74]. With constant exposure to this high pressure flow, and as a result of the inflammatory mediators and the effects of the neutrophils and platelets that have got adhered to the endothelium, it then starts to become dysfunctional. This “dysfunctional” or “damaged” or “activated” endothelium then sets up a vicious cycle whereby the blood pressure tends to remain elevated due to changes in the NO and endothelin bioavailability.

It is likely that the initial triggering factor could be anything ranging from age [75], diabetes, hyperlipidaemia [76], smoking [77] or a familial predisposition [78] or just the raised blood pressure itself.

As a result of endothelial activation and dysfunction, there is a decrease in basal NO activity [79, 80]. Endothelium dependent vasodilatation in response to acetylcholine is also impaired in these patients both in the forearm circulation [81-84] as well as in the coronary vascular bed [85]. Other changes that are seen include increased oxidative stress [86, 87], elevated endothelins (in patients with coexisting renal failure) [88] and increase in levels of serum angiotensin converting enzyme (ACE) [89].

Many of these changes are interrelated, especially since angiotensin II (AII) that is produced by the increased levels of ACE stimulates generation of oxide ions by increasing the expression of the NADPH oxidase gene and increasing the activity of NADPH oxidase [90]. Furthermore, AII also increases the production of endothelin in the blood vessel wall, which exerts vasoconstriction and induces proliferation of the vascular smooth muscle [91].

Levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI), both produced by the endothelium, have been shown to be higher in hypertensives than

non hypertensive patients [92-94].They are found to reflect impaired fibrinolysis and correlate with endothelial dysfunction in these patients. These changes are said to be important in the pathogenesis of the complications of hypertension [95].

Significance of Endothelial Dysfunction in Hypertension

Endothelial dysfunction is associated with different cardiovascular risk factors such as aging [75, 96, 97], postmenopausal status [98], hypercholesterolemia [76, 99], diabetes mellitus [100, 101], smoking [77, 102], hyperhomocysteinemia [103] and hypertension. It is also detectable in the presence of coronary atherosclerosis [104]. Combination of these risk factors has been shown to lead to further deterioration of the endothelial dependant vasodilatation [75, 76, 98].

This is especially important as changes in NO also have effects on platelet aggregation [105], smooth muscle proliferation [106] and migration [107], as well as monocyte adhesion [108] and adhesion molecule expression [109], that play an important role in the genesis of thrombosis and atherosclerotic plaque. Therefore, endothelial dysfunction is now considered a relevant mechanism that promotes atherosclerosis and thrombosis. Indeed, it has shown that in hypertensives impaired forearm response to ACh is correlated to intimal medial thickening in carotid arteries, which is an index of atherosclerotic vascular damage [110].

Recently, it has been shown that levels of endothelial damage in hypertensive patients are related to the presence or absence of TOD [111] as well as to cardiovascular risk [112] and prognosis [113]. Conceivably, endothelial function can also be used as an intermediary end point in the treatment of hypertension [114].

PLATELETS

Platelets from patients with hypertension differ morphologically and biochemically from those in normotensive subjects (Table **2**) and it is well accepted that platelets from patients with hypertension are in a state of activation [115].

Platelets get activated in hypertension due to a variety of reasons. These include the increased shear force that platelets are exposed to neuroendocrine factors, such as increase in angiotensin II levels and catecholamines [116, 117], as well as endothelial dysfunction.

Increased shear force has also been shown to increase the number of platelet microparticles [118] and these could lead to further platelet activation. These microparticles are released from platelets during activation. They have procoagulant effects, and may promote platelet adhesion to the vessel wall, as well as thrombin generation. Platelet microparticles also contain platelet GP Ib, IIb, and IIIa, P-selectin, and thrombospondin, it is possible that due to the presence of these glycoproteins, they could first bind to the sub-endothelial matrix, and act as a substrate for further platelet binding. These microparticles therefore set up a kind of a vicious cycle, which leads to further platelet activation.

Endothelial activation (discussed above) plays an important role in platelet activation. Such endothelial activation/dysfunction leads to decreased production of nitric oxide (NO) and bradykinins, which are important inhibitors of platelet activation. Finally, an increase in whole blood viscosity caused by an elevated haematocrit as well as decreased deformability of red blood cells occasionally seen in hypertensive patients may also contribute to activating platelets [119].

Table 2. Changes of Platelets in Patients with Hypertension

1) Morphological changes
a. Increased volume
b. Change in shape
c. Increased turnover
d. Decreased life span
2) Biochemical changes
a. Increased intracellular free calcium
b. Decreased calmodulin levels
c. Increased sensitivity to catecholamines
d. Higher density of adrenoceptors
e. Decreased levels of intracellular catecholamines and serotonin
f. Decreased ability to take up monoamines, including serotonin
3) Functional changes
a. Increased aggregability to agonists such as collagen and ADP
b. Increased adhesiveness to molecules such as vitronectin and fibrin
c. Increased spontaneous aggregation
d. Increased expression of membrane markers, such as P selectin
e. Increased release of soluble markers from granules, such as beta thromboglobulin

It should be noted that other co-morbidities, such as atrial fibrillation, diabetes and congestive heart failure are more common in hypertensive patients, and are known to activate platelets [120, 121]. Conceivably, some consider that the atherosclerotic lesions that are seen with hypertensive patients could act as a nidus for further platelet activation [116].

THROMBOGENESIS

Many changes in the coagulation and fibrinolytic pathways of hypertensive patients have been documented. These changes suggest increase in coagulability, and impaired fibrinolysis. For example, activity of (tPA), and levels of plasminogen activator inhibitor (PAI) antigen have been shown to be higher in hypertensives than non hypertensive patients [92-94, 122-124]. The Framingham offspring study [125] had also demonstrated a relationship between increasing blood pressure and impaired fibrinolysis in patients without known cardiovascular disease or without risk factors for cardiovascular disease (thus removing any confounding factors), after adjusting for age, sex, and body mass index. Plasma viscosity was also positively correlated with both systolic and diastolic blood pressure in these patients.

However, a large cohort study, the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study [126], involving 1558 subjects

had different results. They found that only in men, the diastolic blood pressure predicted a low tPA activity and high PAI activity. A high PAI activity correlated with systolic blood pressure in both men and women. However, on excluding patients with a history of myocardial infarction, stroke, diabetes or women with HRT, these relationships were no longer significant. Body mass index (BMI) and hypertriglyceridemia were the strongest predictors of PAI-1 and tPA activity in these patients.

Fibrin D-dimer, an index of fibrin turnover and thrombogenesis, have also been shown to be raised in hypertensives [127]. Plasma fibrin D-dimer levels are predictive of both arterial thrombotic events [128] and postoperative thrombosis [129]. Lip *et al.* [127]further showed a correlation between increased fibrinogen levels and left ventricular hypertrophy (LVH) which is a known independent predictor of cardiovascular events (see above).

CHANGES IN MATRIX METALLOPROTEINASES

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endoproteinases with the combined ability to degrade all the components of extra-cellular matrix at a physiological pH [130]. More than 20 MMPs have been cloned and characterized, and classified into five main groups according to structural similarities and substrate affinities (Table **3**). Tissue inhibitors of these MMPs (TIMPs) have also been described and they tend to keep the action of MMPs under check [131]. Imbalances between the levels of TIMPs and MMPs could therefore lead to changes in the extra-cellular matrix.

Table 3. Classification of the Matrix Metalloproteinases

1) Interstitial collagenases- MMP 1 and 8
2) Gelatinases- MMP 2 and 9
3) Stromelysins – MMP 3 and 10
4) Membrane type (MT) subgroup of six MMPs (MT-1-MMP to MT6-MMP)
5) A Heterogenous subgroup- MMP 7,12, 19 and 20

In addition to their action on the extra cellular matrix, the MMPs and TIMPS also have interactions with the coagulation cascade [132], and affect angiogenesis and cell morphology [133]. Depending on their substrate (growth factors or their receptors, extracellular matrix components, and angiogenic factors), MMP activation results in the generation of proangiogenic or antiangiogenic factors [134, 135]. MMPs are therefore not simply proangiogenic as was previously thought. The effects on angiogenesis are especially important in the context of target organ damage in hypertension. Extra cellular matrix molecules such as thrombospondin-1 and 2 and proteolytic fragments of matrix molecules such as endostatin, can exert anti angiogenic effects by inhibiting endothelial cell proliferation, migration and tube formation. In contrast other matrix molecules promote endothelial cell growth and morphogenesis and stabilize nascent blood vessels [136].

Clinical studies have also shown that serum levels of MMP-1 (a collagenase) are decreased along with an increase in TIMP-1 in hypertension [137]. Indeed it has also been suggested that elevated TIMP-1 levels may be useful as a non invasive marker of left ventricular diastolic dysfunction and fibrosis [138]. Concentrations of MMP-2 and 9 (gelatinises) have been reported as either decreased or unchanged in hypertensive patients as compared to normotensive controls [139, 140]. Correlations of levels of MMP and TIMPs have also been demonstrated in hypertensives with the presence or absence of microalbuminuria and a prothrombotic state [141, 142]. Recent clinical studies have shown that the levels of MMPs are altered in hypertension and that these correlate with cardiovascular risk and improve with treatment of hypertension [143]. The levels of MMP-9 and TIMP-1 also correlate with diastolic function both in hypertensives and correlate with levels of LVH [144].

It has been shown that MMP-2 can cleave big endothelin-1 (ET-1) to a novel form of ET-1that is a potent vasoconstrictor [145]. Similarly, MMP-2 and MMP-9 can cleave big ET-1 to generate another molecule ET-1 [1-32] which is thought to alter the interactions between neutrophils and endothelium and could affect the structure of the extra cellular matrix locally [146]. ET-1 [1-32] could also cause cardiac fibrosis by acting on the ET-A receptor [147, 148].

Transforming growth factor-β (TGF-β) is a potent inducer of systemic fibrosis by up to regulating collagen type-I and type III mRNA [149]. Various substances are thought to increase the synthesis of TGF-β such as Angiotensin II, noradrenalin and chronic NO inhibition, all of which are seen in hypertension. High levels of this cytokine have been demonstrated in cardiac, renal and arterial fibrosis [149, 150].

CHANGES IN ANGIOTENSIN-II

The RAAS plays a very important role in the maintenance of a normal blood pressure. As seen above, the endothelial dysfunction that occurs in hypertension can lead to alterations in the RAAS. Alterations in the RAAS in turn can lead to severe vascular changes [151, 152].

Angiotensin-II (Ang-II) is a trophic factor of vascular muscle *in-vitro* [153, 154]. *In-vivo*, however, it is difficult to distinguish between changes in the vascular wall due to the raised blood pressure or that due to the administered Ang-II. By the co-administration of Ang-II and hydralazine to rats, the effect of the raised blood pressure can be circumvented [155]. These studies have demonstrated that Ang-II leads to increased protein and glycosaminoglycan synthesis in both the arterial and venous vascular muscle which is independent of the blood pressure [156, 157].

Ang-II is also a potent vasoconstrictor and could theoretically increase the levels of relative tissue hypoxia that may be seen in some vascular beds (such as the glomerular and retinal circulations) in hypertension. This could therefore lead to alterations in angiogenesis and fibrosis and necrosis as a result. In addition Ang-II plays an important role in the initiation of the atherogenesis, progression of the atheromatous plaque and is also a potent platelet activator [158].

Thus, in hypertension that is related to a high angiotensin-II/high renin state, levels of Ang-II could contribute to the increased vascular thickness and stiffness that is seen in hypertensives. This is especially important, as it has been shown that high plasma renin activity in hypertensive patients is associated with increased risk for coronary events and stroke.

ALTERED ANGIOGENESIS

Altered angiogenesis in hypertension has been well documented. The microcirculation is important in regulation of peripheral vascular tone and it is altered in hypertension [159, 160]. It has been demonstrated that in essential hypertension, there is small vessel rarefaction and an absence of angiogenesis [161]. The exact mechanism of this is not known. However, it has been suggested that vessel wall thickening and a response of the muscular wall of the vessels to increased flow and blood pressures causes this rarefaction [162, 163]. This vascoconstriction of the peripheral vessels causes increased peripheral resistance which then perpetuates the increased blood pressure and sets up a vicious cycle [164]. Endothelial dysfuntion, as discussed above, also occurs with decrease in NO, leading to further peripheral vasoconstriction. The pulse pressure, mean arterial pressure and the pressure wave, along with the cardiac output also affect the microcirculation [165, 166].

Recent studies have shown increase in plasma levels of VEGF, and angiopoietins in hypertensives [167]. These levels correlate well with cardiovascular risk [168] and improve with treatment [168, 169]. It has been suggested that the increase in the angiogenic factors are a compensatory mechanism as a result of tissue hypoxia due to the rarefaction of the microcirculation [169].

OVERVIEW

As seen above, many pathogenetic mechanisms are at work in hypertension. Most of these changes are inter-related (Fig. **1**). The endothelial dysfunction and platelet activation lead to changes including increase in Angiotensin –II levels, which in turn leads to smooth muscle proliferation and collagen deposition by altering levels of MMPs and TGF-β. These changes are responsible for the microvascular disease such as retinopathy and nephropathy and could also influence LVH. The increase in thrombogenesis, impaired fibrinolysis and platelet activation could be responsible for the

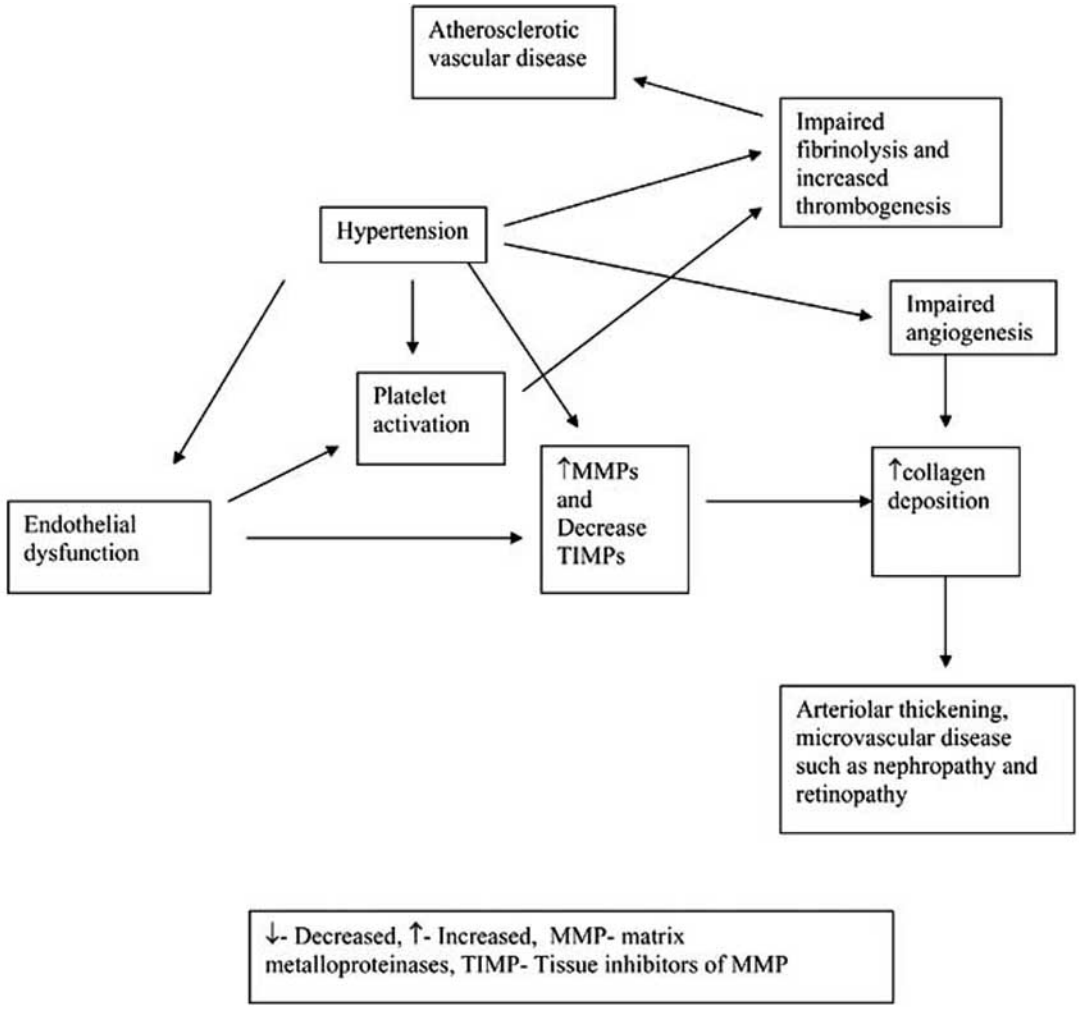

Fig. (1). Complex interrelationships between different processes in the pathogenesis of TOD in hypertension.

macrovascular diseases such as strokes and peripheral vascular disease, whilst all the changes together could result in increased atherogenesis.

The main aim in the management of a patient with hypertension is the prevention of cardiovascular and cerebrovascular complications. The importance of good blood pressure control towards this end cannot be over emphasised [170]. The medical literature is full of studies demonstrating the clinical benefits of good blood pressure control in preventing cardiovascular and cerebrovascular end points, irrespective of the agent used. Recent studies also show that it is the ambulatory blood pressure control over 24 hours that gives a better indication of the patients risk of cardiovascular end points rather than the office blood pressure readings [171-173].

Different studies demonstrate the benefits of one class of antihypertensive drug over the other. Recent examples include the LIFE study [174], ALLHAT [175] and ASCOT. However, all trials show the benefit of treatment as compared to placebo. Perhaps some group of drugs may have benefits over and above their blood pressure lowering effects. The ACE-inhibitors are the prime example of this, as they act on the RAAS and other systems, such as angiogenesis, extracellular matrix turnover and coagulation-fibrinolysis.

Angiotensin receptor blockers (ARBs) also have effects which may not be as pronounced as the ACE-I due to different modes of action, despite their action on the RAAS. This could be due to the added effect of the ACE-I on bradykinins which is not seen with the ARBs. The ARBs have been shown to have anti platelet effects through their effects on nitric oxide. In contrast, calcium channel blockers (CCBs) appear to have predominant effects on platelets rather than on the endothelium [115]. It is beyond the scope of this overview to cover detailed effects of each of these different agents and more specific reviews on the topic are available [115, 176].

The role of aspirin in high risk hypertensives is also important, in view of the levels of platelet activation that is seen. A recent Cochrane review [177] concluded that aspirin be used only in secondary prevention in hypertension patients rather than in primary prevention, as the benefits obtained with the use of aspirin are offset by the increased bleeding risks.

CONCLUSION

In patients with hypertension, many physiological and biological changes take place. The main changes include activation of the endothelium and platelets, as well as changes in the extracellular matrix. Along with these changes, there are also changes in the coagulation and fibrinolysis pathways and in angiogenesis. Importantly, the majority of these changes are interlinked. For example, the activated endothelium leads to platelet activation, and changes in the coagulation and fibrinolysis pathways. These changes in turn can lead to macrovascular and microvascular changes.

The changes in angiogenesis could be due to the increased vascular thickening, and vascular vasoconstriction as compensation to the increased perfusion pressures. The changes in angiogenesis could lead to altered MMP levels which could then cause altered extra cellular matrix in different organs and can lead to worsening of conditions such as left ventricular hypertrophy, renal nephrosclerosis etc.

An understanding of the different pathophysiological mechanisms involved in the causation of TOD in hypertension is important, as this would help us devise means of reducing catastrophic complications of hypertension. Whilst the use of anti-hypertensive agents has been shown convincingly to reduce cardiovascular and cerebrovascular complications, and that they reverse (for example) endothelial and platelet activation in hypertension, but a direct correlation between the improvement in endothelial and platelet activation and a decrease in cardiovascular endpoints has not been shown. Similarly, despite the presence of these abnormalities in hypertension, specific modalities to modulate the MMP and TIMP systems or the angiogenic pathways are lacking, as are clinical trials.More studies are needed to fully understand the different mechanisms involved in the pathogenesis of target organ damage in hypertension, and in devising strategies to prevent them.

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