

# Current Concepts in Hypertension

## Editor's Comments

The last issue of this series of *Current Concepts in Hypertension* was devoted to a fuller definition of the problem of high risk hypertension as viewed through the lens of endothelial dysfunction and the exaggerated vasoreactivity caused by hypercholesterolemia, insulin resistance, smoking, and other risk factors. This issue of *Current Concepts* focuses on the pattern of abnormal capillary circulation in hypertension and related syndromes such as heart failure and insulin resistance.

The articles included in this issue were written by prominent investigators who are defining fundamental abnormalities of tissue perfusion in hypertension. When cardiac output is low, as in congestive heart failure, the obligatory tissue hypoperfusion yields a pattern of organ dysfunction, summarized by LeJemtel, that is similar to that present in diabetes, as detailed by Sowers. The reversible functional regulation of the microcirculatory anatomy by the renin-angiotensin-aldosterone system is presented by Andrew Green and Richard Roman, who describe capillary abnormalities of the renal microcirculation that cause glomerulosclerosis. How these observations relate to the apparent superiority of drugs that counteract renin and angiotensin as "target organ protectors" remains to be elucidated, however.

These minireviews are intended to paint a picture of linkages in the syndrome of essential hypertension rather than describe isolated events. It seems appropriate to use the format provided by this vehicle to provoke further thought in the field. In this way, we may begin to put back together the fragmented pieces of the puzzle that define the far-reaching syndrome of essential hypertension.

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## The Microcirculation in Hypertension: An Overview

The microcirculation, principally represented by capillary perfusion, is one of the last frontiers to be investigated in the syndrome of essential hypertension. Abnormalities of the microcirculation, once thought to be a secondary phenomenon related to tissue hyperperfusion, are now considered by several leading experts to be primary abnormalities in essential hypertension's pathogenesis.

*"... insulin resistance may result from capillary flow heterogeneity because hypoperfused cells do not receive enough oxygen or substrate to function normally."*

*"Pressure damage in hyperperfused capillaries may play an insidious role in perpetuating heterogeneous flow..."*

Speculation from a number of European and American laboratories now suggests the syndrome of insulin resistance is partly caused by an exaggerated degree of heterogeneous capillary circulation. In this model, there is underperfusion in some capillaries and overperfusion in others. The resulting heterogeneous flow can cause a net diminution of organ performance and lead to linked metabolic abnormalities. For example, insulin resistance may result from capillary flow heterogeneity because hypoperfused cells do not receive enough oxygen or substrate to function normally. These cells alter their metabolic pathways accordingly, contributing to an overall phenotypic pattern of insulin resistance.

Pressure damage in hyperperfused capillaries may play an insidious role in perpetuating heterogeneous flow, with the consequence of reduced capillary surface area. Sullivan and others have demonstrated capillary hemorrhages occur in young humans with high cardiac output syndromes and a family history of hypertension prior to development of sustained hypertension.<sup>1</sup> These lesions are identical to those seen in glomerular capillary hypertension and focal glomerulosclerosis. Because they predate sustained hypertension, they may be pathogenetically related to development of elevated systemic blood pressure and, later, also consequences of the process!

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## Skeletal Muscular Microcirculation in Heart Failure

The functional capacity of patients with congestive heart failure (CHF) due to depressed left ventricular (LV) systolic function is extremely variable. Some patients are bedridden while others can exercise nearly as much as healthy subjects of similar age.<sup>1</sup> Such apparent discordance between the severity of LV dysfunction and functional capacity became less bewildering when it was recognized that, in patients with severe CHF, peak functional capacity is primarily limited by a fixed capacity of the skeletal muscle vasculature to dilate and not by LV performance.<sup>2</sup>

Abnormalities of the skeletal muscle vasculature have been documented at both arteriolar and microvascular levels in patients with CHF. Zelis et al were the first to demonstrate abnormal responses of the forearm vasculature to various dilating stimuli in patients with CHF.<sup>3</sup> Subsequently, similar findings were reported in the lower limb vasculature by Wilson et al.<sup>4</sup> Interestingly, Jondeau and others found peak hyperemic response of the calf vasculature was depressed at a time when the forearm peak hyperemic response was still normal.<sup>5</sup> The regional and temporal nature of the vascular abnormalities in patients with CHF suggests local factors such as deconditioning may play a greater role in their genesis than systemic factors such as heightened activity of the sympathetic and renin-angiotensin-aldosterone system.

Disturbances of peripheral microvascular function have also been reported in patients with CHF.<sup>6</sup> These disturbances affect delivery of substrates to meet the metabolic demands and prevent accumulation of toxic metabolites. The extent of the microcirculatory disturbances appear to parallel the severity of the syndrome in patients with CHF. The mechanisms that mediate the disturbances of the microcirculation are poorly understood in patients with CHF. Structural changes of the basal membrane have been reported.<sup>7</sup> However these structural changes do not correlate with the severity of the syndrome and, thus, their relevance to the pathophysiology of CHF is unclear. Functional rather than structural changes are more likely to be responsible for disturbances of the skeletal muscle vasculature. Activation of the sympathetic nervous system and renin-angiotensin-aldosterone system may

contribute to microvascular dysfunction. In addition, local mechanisms that appear to be important at the arteriolar level are also likely to play a predominant role at the microvascular level.

Impaired vascular endothelial function, which is probably due to physical deconditioning, has been well documented in large vessels and resistance arterioles of patients with CHF.<sup>8</sup> Endothelial dysfunction at the arteriolar level directly promotes microvascular dysfunction by increasing arteriolar diameter. As arteriolar diameter becomes smaller, capillary patency decreases, with a reduced capacity for substrate delivery and toxins' removal.<sup>9</sup> Prevention of microvascular abnormalities by angiotensin converting enzyme inhibition, which has been reported in the skeletal muscles of rats with large myocardial infarction, probably results from enhanced vascular endothelial function induced by converting enzyme inhibition.<sup>10</sup> Similarly, physical training is likely to beneficially impact microvascular dysfunction by enhancing arteriolar endothelium dependent dilatation and, thereby, capillary patency in patients with severe CHF.

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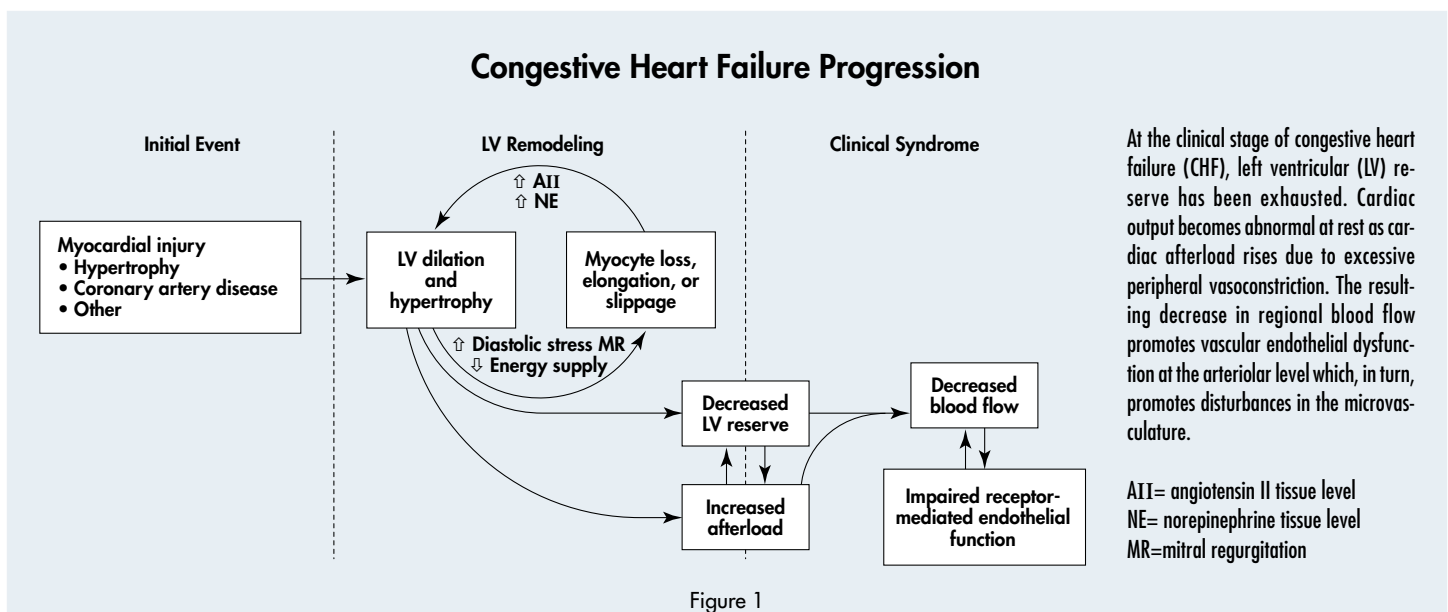


Figure 1

## Microangiopathy in Diabetes

Damage to the microvasculature underlies major complications of diabetes mellitus including nephropathy, retinopathy, neuropathy, and cardiovascular disease.<sup>1-6</sup> Hyperglycemia and other metabolic and hemodynamic abnormalities associated with diabetes may promote microangiopathy through action exerted on endothelial cells and vascular smooth muscle cells. One of the major factors involved in diabetes-related angiopathy appears to be that of altered vascular nitric oxide (NO) biology.<sup>1-3</sup> In states of diabetes in animals and man, hyperglycemia appears to reduce vascular release or biological activity of NO. Exposure of endothelial cells to elevated glucose concentration results in activation of the diacylglycerol-protein kinase C pathway, the polyol pathway, and nonenzymatic glycosylation—all processes that may contribute to reduced vascular NO production and activity (Table 1).

Additionally, hyperglycemia alters endothelial cell matrix production, which may contribute to the generalized basement membrane thickening that occurs in diabetes mellitus. Hyperglycemia enhances endothelial collagen IV and fibronectin production and increases the activity of enzymes involved in collagen synthesis. Diabetes is also associated with increased expression of adhesion molecules such as vascular cellular and intercellular adhesion molecules and endothelial procoagulant activity (that is, increased production of plasminogen activator I, factor VIII, von Willebrand's factor) and reduced anticoagulant factors (fibrinolytic activator and antithrombin III). Additionally, there are many coexistent metabolic abnormalities (Table 2) in diabetes that contribute to diabetes-related microangiopathy.

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*“... diabetes may promote microangiopathy through action exerted on endothelial cells and vascular smooth muscle cells”*

*“In states of diabetes in animals and man, hyperglycemia appears to reduce vascular release or biological activity of nitric oxide.”*

*“... hyperglycemia alters endothelial cell matrix production, which may contribute to the generalized basement membrane thickening.”*

*“Diabetes is also associated with increased expression of adhesion molecules...”*

### Alterations in Vascular Endothelium Associated with Diabetes Mellitus

1	Elevated plasma levels of von Willebrand's factor
2	Elevated expression, synthesis, and plasma levels of endothelin-1
3	Diminished prostacyclin release
4	Decreased release of endothelium-derived relaxing factor (NO) and reduced responsiveness to NO
5	Impaired fibrinolytic activity
6	Increased endothelial cell procoagulant activity
7	Increased endothelial cell surface thrombomodulin
8	Impaired plasmin degradation of glycosylated fibrin
9	Increased levels of advanced glycosylated end products
10	Increased expression of adhesion molecules

Table 1

### Metabolic Abnormalities Seen in Diabetes Mellitus

1	Elevated plasma levels of low and very low density lipoproteins and lipoprotein a
2	Decreased plasma high density lipoproteins cholesterol
3	Increased lipoprotein oxidation
4	Increased lipoprotein glycation
5	Increased small, dense low density lipoproteins cholesterol products
6	Decreased lipoprotein lipase activity
7	Increased fibrinogen and plasminogen activation inhibitor (PAI-1)
8	Decreased plasminogen activator and fibrinolytic activity
9	Increased insulin and proinsulin levels

Table 2

## Renal Hemodynamics and Glomerular and Vascular Injury in Hypertension

Elevated renal vascular tone is a central feature of essential hypertension. Moreover, the kidney is a primary target for end-stage organ damage. Depending on the experimental model and duration of hypertension, there are structural changes that occur in the renal microcirculation, varying degrees of glomerular injury leading to proteinuria and, in some cases, end-stage renal disease. The characteristic structural changes in the renal microcirculation include hypertrophy of the smooth muscle layer and narrowing of the lumen in preglomerular arterioles that leads to an increase in the wall to lumen ratio of the vessel. The glomerular injury can be ischemic, characterized by small and shrunken glomeruli with collapse of capillary loops (glomerulonecrosis), or a progressive proliferative injury characterized by hypertrophy of the glomeruli and increased deposition of a mesangial matrix material positive for *p*-aminosalicylic acid that eventually fills in and collapses capillary loops (glomerulosclerosis).

Whether abnormal control of renal vascular tone plays a primary role in the development of hypertension or only contributes to maintenance of the disease once glomerular and vascular injury occurs is a complex issue that is still unresolved and an area of intense investigation.<sup>1</sup> As summarized in Figure 2, elevated renal vascular tone has been identified early in the development of experimental models of hypertension. The rise in renal vascular resistance in many experimental models can be due to mechanical occlusion of the renal artery or aorta, removal of a renal mass, or administration of angiotensin II or other vasoconstrictors. Similarly, numerous investigators have reported renal vascular resistance and reactivity is altered early in the development of hypertension in spontaneously hypertensive, Dahl salt-sensitive, and Lyon hypertensive rats. The elevated renal vascular resistance is thought to diminish transmission of pressure to the renal microcirculation (either in the renal cortex or medulla) and reset the pressure natriuresis relationship so the kidney requires a higher perfusion pressure to excrete the same amount of sodium and water as normotensive animals. After hypertension develops there are further structural changes in the preglomerular arterioles and there is also endothelial dysfunction which further increases renal vascular resistance and often contributes to a more severe and progressive form of hypertension.

Glomerular damage occurs in the maintenance stage of hypertension. In angiotensin II models of hypertension and in the spontaneously hypertensive rat, which are characterized by elevated preglomerular vascular tone and elevated myogenic and tubuloglomerular feedback autoregulatory responses, the elevated pressure is not transmitted to the glomeruli. In these models the glomerular injury develops slowly and is usually characterized by ischemic collapse of capillary loops. In contrast, in low-renin, salt-sensitive models of hypertension such as the Dahl S rat, reduced renal mass and Doca-salt models, there is rapid development of severe, progressive glomerulosclerosis. Glomerular capillary pressures are elevated and there is glomerular hypertrophy and filling in of capillary loops with mesangial matrix material.

Clearly, the etiology and pathology of glomerular injury varies in different experimental animal models of hypertension and it is likely that, as we begin to dissect different genetic causes of human essential hypertension, we will better understand the susceptibility to glomerular injury in its various forms. The different mechanisms involved in various ge-

netic subtypes of human essential hypertension may some day help explain why black hypertensive patients are 16 times more likely to develop end-stage renal disease than white hypertensive patients.<sup>2,3</sup>

One of the new and hopeful concepts that has emerged from work in animal models in the last 2 years is that structural changes in the renal vasculature and glomerulus that accompany hypertension are potentially reversible with some forms of treatment. For example Frolich reported angiotensin-converting enzyme inhibitors or high-arginine diets given to old spontaneously hypertensive rats with advanced glomerulosclerosis reduced proteinuria, reversed hypertrophy of the vascular wall, and improved the appearance of the glomerulus and perfusion of glomerular capillaries.<sup>4</sup> These beneficial effects were not simply due to the antihypertensive actions of these drugs since other equally effective treatments such as thiazides or triple therapy had no beneficial effects on glomerular or vascular injury. Similarly, our laboratory has recently reported that HMG-CoA inhibitors can lower arterial pressure, reverse hypertrophy of preglomerular vasculature, and/or improve glomerular injury in both spontaneously hypertensive and Dahl salt-sensitive rats.<sup>5,6</sup> Clearly, similar work in various human hypertensive populations is necessary. The possibility that structural changes in the renal vasculature and glomerular injury might be prevented and even reversed by certain therapeutic treatment regimes is one of the most exciting and promising developments in the hypertension field to emerge in recent memory.

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### Altered Renal Hemodynamics in Hypertension

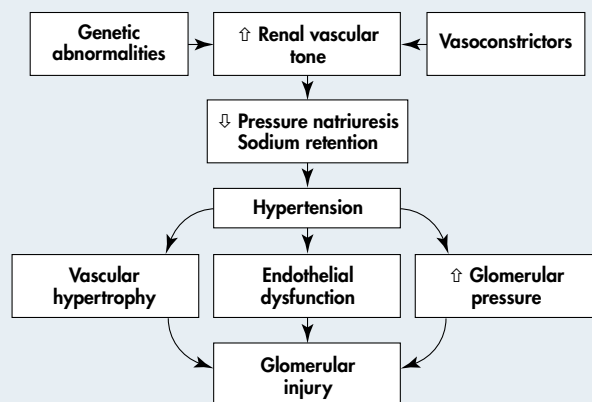


Figure 2

# Microvascular Remodeling in Hypertension: A Role for the Renin-Angiotensin-Aldosterone System

The development of hypertension has been shown to be accompanied by rarefaction (reduction in microvascular density) of arterioles and capillaries in both animal models and in human studies.<sup>1,2</sup> While many studies have examined the effects of antihypertensive therapy on cardiac hypertrophy, coronary reserve, and large vessel structure, the question of whether changes in microvascular structure induced by hypertension can be restored by normalizing arterial pressure has yet to be answered.

In several different animal models of hypertension, the renin-angiotensin-aldosterone system is suppressed, resulting in low circulating levels of plasma renin activity (PRA) and angiotensin II (AII). In these models a consistent reduction of microvessel density is found, implicating renin-angiotensin system (RAS) suppression as a component of microvascular rarefaction (Fig. 3).<sup>3,4</sup> Furthermore, we have shown normotensive animals fed a high sodium diet and with suppressed PRA exhibit reduced microvascular density, which can be blocked by AII infusion.<sup>5</sup> Others have also demonstrated that blockade of the renin-angiotensin-aldosterone system by captopril administration can inhibit both large and small vessel growth.

We tested the hypothesis that normalization of blood pressure in a low renin hypertension model by dietary salt restriction would reverse microvascular rarefaction. Nine-week-old Sprague-Dawley rats with reduced renal mass (RRM) were placed on a low (LS) or high sodium (HS) diet for 4 or 8 weeks or a combination of 4 weeks of HS followed by 4 weeks of LS. Blood pressure was directly measured during development of the hypertension and its reversal. PRA, angiotensin converting enzyme (ACE) activity, and AII concentration were measured throughout the experiment. The cremaster and hindlimb muscles were removed and microvascular density determined by quantitative stereology. Four weeks of HS increased blood pressure ( $152 \pm 7$  mm Hg) and reduced microvessel density (13.7%). RRM hypertension was rapidly reversed after the rats were returned to an LS diet ( $124 \pm 7$  mm Hg after 3 days) and reduced microvascular density was completely returned to baseline. After 4 weeks of HS, circulating PRA and AII fell by 94% and 82%, respectively. Plasma ACE activity increased after 2 weeks of HS but returned to baseline after 4 weeks of LS (Fig. 4).

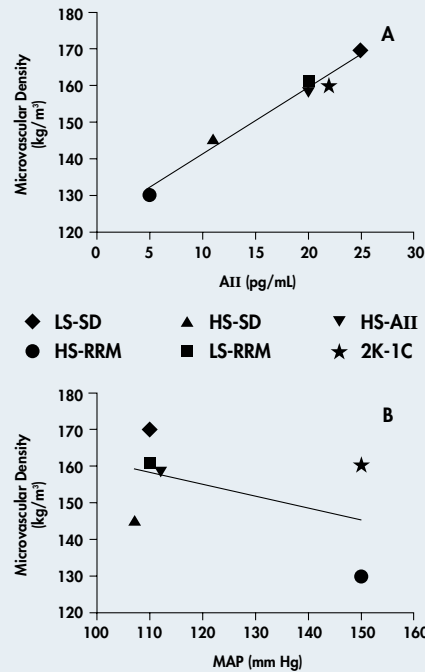
This study demonstrates microvascular density is reduced in RRM rats following exposure to HS diet, associated with a fall in circulating PRA and AII levels. Microvascular density can be returned to normal levels following reactivation of the circulating renin-angiotensin-aldosterone system, providing further evidence for the hypothesis that modulation of the renin-angiotensin-aldosterone system is important in regulating microvascular structure.

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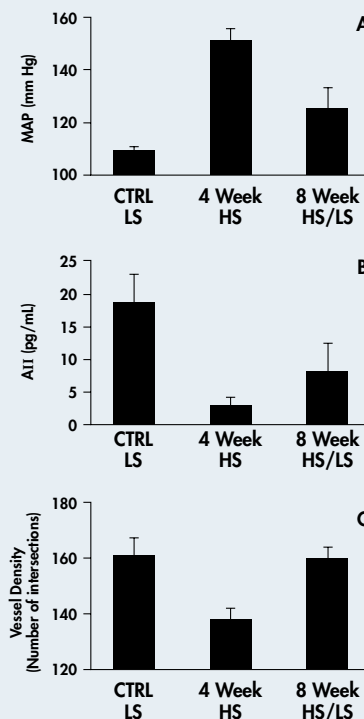
## Microvascular Density Correlates with AII Concentration but not MAP



Comparison of the correlation of microvascular density with plasma AII concentration (A) and mean arterial pressure (MAP) (B) in several normal and hypertensive animal models. Microvascular density correlates well with AII plasma concentration but not with MAP. LS-SD: low sodium Sprague-Dawley rat, HS-SD: high sodium Sprague-Dawley rat, HS-AII: high sodium fed AII infused rat, HS-RRM: high sodium fed reduced renal mass hypertensive rat, LS-RRM: low sodium fed reduced renal mass rat, 2K-1C: 2 kidney 1 clip hypertensive rat.

Figure 3

## Reversibility of Rarefaction



Blood pressure was rapidly elevated in RRM rats following an HS diet and returned to control by normalization of sodium intake (A). Reciprocal changes in plasma AII were associated with rarefaction and subsequent regrowth of microvessels (B, C).

Figure 4

# ASH American Society of Hypertension

The American Society of Hypertension (ASH) is the largest US organization dedicated exclusively to hypertension and related cardiovascular disease. ASH was founded in 1985 by Dr. John Laragh and 16 other world-famous clinicians and scientists in an effort to evaluate the vast accumulation of data on hypertension and to provide a separate forum for those involved in the study or management of high blood pressure. The mission of the Society became "to organize and conduct educational activities designed to promote and encourage the development, advancement, and exchange of scientific information in all aspects of research, diagnosis, and treatment of hypertension, and related cardiovascular diseases."

Today, the Society boasts a membership of over 3,000 strong with 95% of its members holding an MD, PhD, or other advanced degree. The Society continues to fulfill its mission by annual meetings that provide registrants with the rare opportunity to exchange information and ideas with more than 2,500 fellow scientists from around the world. Highlights of the meeting include state-of-the-art lectures by renowned faculty, plenary sessions, original communications, poster presentations, technical and scientific exhibits, and provocative special symposia.

In addition, the Society publishes the prestigious *American Journal of Hypertension*, a monthly publication containing the latest information in both basic science and clinical research.

Membership in ASH is open to all those who have undertaken and accomplished meritorious original scientific investigation in the field of hypertension and/or related cardiovascular disease, those involved in the diagnosis and treatment of hypertension and related cardiovascular disease, and those with a demonstrated serious interest in the field. Among the benefits of ASH membership are association and interaction with clinicians and scientists who are world leaders in the field, a subscription to the *American Journal of Hypertension* and all its supplements, a listing in the ASH Member Directory used for patient referral, and a savings of 50% or more on registration fees for the annual scientific meeting.

The American Society of Hypertension sponsors three award programs annually. The first award program focuses on the area of ongoing research training in the field of hypertension for young clinicians planning a career in academic medicine. Another recognizes and rewards three scientists who have carried out a significant body of work in the field of hypertension or related cardiovascular diseases. The last award program recognizes and rewards five young physicians, currently residents or fellows, who have a demonstrated interest in the study of hypertension or who plan a career change into the field.

For further information on ASH membership, awards programs, future meeting dates or to add your name to the ASH mailing list, contact:

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