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## Impaired Tissue Perfusion

### A Pathology Common to Hypertension, Obesity, and Diabetes Mellitus

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The microcirculation is generally taken to include the smallest arteries, the arterioles, capillaries, and venules.<sup>1,2</sup> Exchange of gases, nutrients, and metabolites between the blood and tissues occurs almost exclusively in the microcirculation, and adequate perfusion via the microcirculatory network is essential for the integrity of tissue and organ function. Our aim in the present article is to bring together recent clinical and experimental research indicating that inadequate perfusion may underlie much of the tissue and organ dysfunction associated with chronic conditions including hypertension, obesity, and diabetes mellitus. Given the high level of research activity in this field, our review can be neither systematic nor comprehensive. We apologize to the many authors whose important contributions are not acknowledged here; additional references are given in a Data Supplement on the journal's Web site.

#### Regulation of Tissue Perfusion by the Microcirculation

In addition to providing the large surface area needed for blood-tissue exchange, the microcirculation largely controls the perfusion of tissues in response to varying metabolic requirements. Large and medium-sized arteries and veins offer relatively little resistance to the flow of blood, and work pioneered by DeLano and colleagues<sup>3</sup> showed that some 70% to 90% of the systemic arterial pressure is delivered to the microcirculation, where the main resistance to flow is offered. The microcirculation, therefore, largely determines local and overall peripheral resistance. The precapillary elements of the microcirculation also protect the fragile capillaries from the potentially damaging pressures that occur in the larger arteries.

#### Tissue Perfusion in Hypertension

An abrupt increase in pressure brings about a rapid and reversible vasoconstriction of small resistance vessels due to

their inherent myogenic tone.<sup>4</sup> Prolonged elevations of pressure can cause a range of more lasting changes in the microcirculation, 2 of which, remodeling of small arteries and arterioles and rarefaction of arterioles and capillaries, will be considered briefly below.

#### Small Artery and Arteriolar Remodeling

Small arteries and arterioles, with pronounced myogenic responses, react to acutely increased pressure with a reduction in luminal diameter produced by smooth muscle contraction. If the high pressure is prolonged, the luminal narrowing may be maintained by a form of remodeling in which the vessel wall components are rearranged without growth, known as eutrophic inward remodeling.<sup>2</sup> These more permanent structural changes, characterized by an increase in wall:lumen ratio, displace the initial active vasoconstriction, and myogenic responses return to normal.<sup>5</sup>

Numerous cellular processes may be involved in remodeling. Animal and human studies have shown that increased production of reactive oxygen species (ROS), particularly by NAD(P)H oxidases, and inflammatory reactions, characterized by attachment and migration of leukocytes, mediated in part by the I- $\kappa$ B/nuclear factor- $\kappa$ B system, are central to many of the adverse changes seen in the microcirculation and may offer potential targets for therapeutic intervention.<sup>6</sup> Extracellular matrix alterations and increased levels of apoptosis accompany the increase in wall:lumen ratios in animal models.<sup>7</sup> Angiotensin II plays an important role in many of these processes,<sup>8</sup> stimulating NAD(P)H oxidase and production of ROS, activating nuclear factor- $\kappa$ B, and increasing expression of inflammatory mediators and adhesion molecules.

#### Microvascular Rarefaction

Microvascular rarefaction, the reduced number or combined length of small vessels in a given volume of tissue, has been

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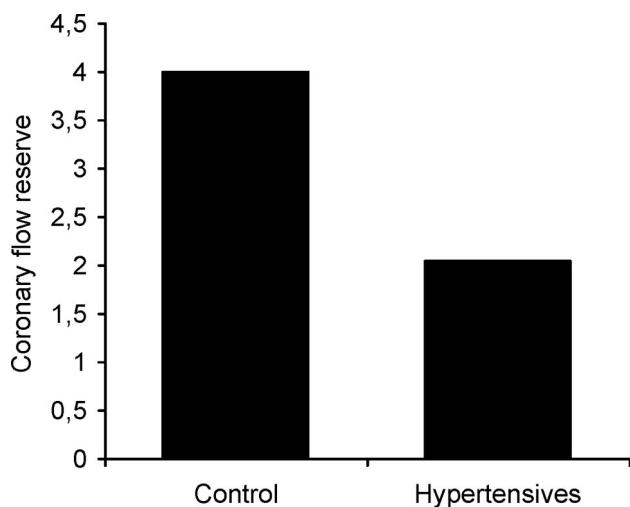
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**Figure 2.** Coronary flow reserve in normal control subjects and uncomplicated hypertensive patients, measured by positron emission tomography. Adapted from Mourad et al.<sup>29</sup>

Measures of coronary flow reserve are somewhat nonspecific: A low reserve may be due to a high basal value, a low maximal value, or both. Numerous structural and functional factors affecting basal and maximal coronary flow have been identified in the absence of coronary artery stenosis. Camici and Crea<sup>27</sup> reviewed the complexity of the assessment of coronary microvascular dysfunction.

In healthy young individuals, coronary flow reserve is  $>3$ , and it may be close to 6 in trained athletes. Numerous studies have concluded that coronary flow reserve is reduced in hypertension, including borderline hypertension,<sup>28–31</sup> with values ranging from 1.7 to 2.9 (Figure 2), and that it is inversely related to systolic blood pressure (Figure 3).<sup>31</sup> Most studies have shown that basal myocardial blood flow is elevated and maximal flow is reduced in hypertension. Increased basal blood flow is probably related to the increased myocardial workload in hypertension; the difference between hypertensive and normotensive individuals disappears if the basal blood flow is adjusted for heart rate and blood pressure.<sup>31</sup> Reduced maximal blood flow is probably related mainly to structural abnormalities in the coronary microcirculation, although functional factors, including endothelial dysfunction, may also contribute.<sup>30</sup>

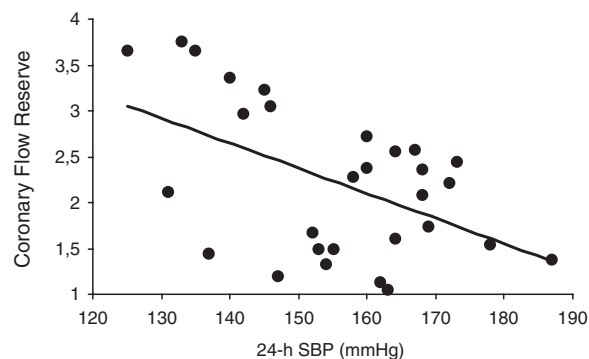
### **Blood Rheology**

An additional factor that influences local tissue perfusion is blood rheology. The apparent viscosity of blood depends on several factors, including hematocrit, red blood cell deformability and aggregation, and leukocyte activation. Many of these factors are influenced by inflammatory mediators and ROS, and reduced blood fluidity can significantly impair tissue perfusion.<sup>32</sup> Intravenous injection of blood from SHR causes an increase in blood pressure in normal rats, in part due to the high incidence of circulating leukocytes with pseudopods, which hinder passage through capillaries.<sup>33</sup>

## **Tissue Perfusion in Diabetes, Obesity, and Other Risk Factors**

### **Diabetes Mellitus**

Small arteries in diabetic subjects, whether hypertensive or normotensive, exhibit severe hypertrophic remodeling,<sup>34</sup> and



**Figure 3.** Inverse relationship between coronary flow reserve and median 24-hour systolic blood pressure (SBP) in hypertensive patients. Adapted from Olsen et al.<sup>31</sup>

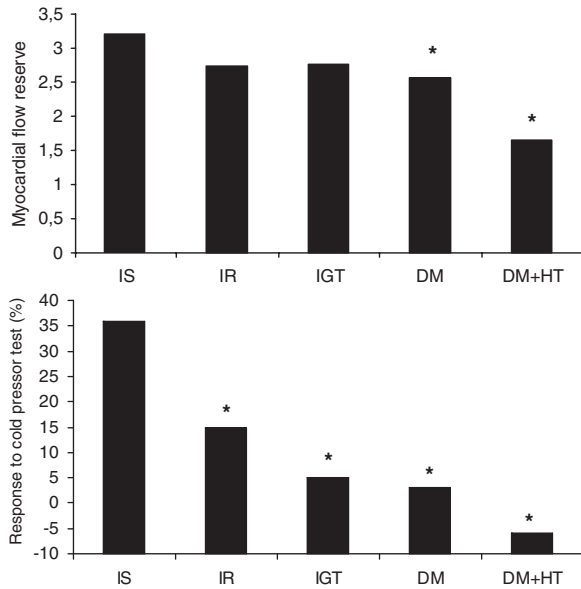
histological analysis of skeletal muscle biopsy samples reveals capillary rarefaction in subjects with type 2 diabetes.<sup>35</sup> Histological capillary density is inversely related to fasting plasma glucose and fasting insulin levels and positively related to insulin sensitivity in nondiabetic individuals.<sup>36</sup> Microvascular permeability to large molecules such as albumin is increased in diabetes, a process that is linked to hyperglycemia and ROS.<sup>37</sup>

Several studies have shown impaired coronary flow reserve in diabetic individuals in the absence of coronary artery stenosis.<sup>38–41</sup> In people with type 2 diabetes, coronary flow reserve is inversely related to hemoglobin A<sub>1c</sub> and fasting plasma glucose levels,<sup>39</sup> which suggests that chronic hyperglycemia is a key factor. The impairment in coronary flow reserve is more severe in diabetic patients with retinopathy than in those without and is worse in those with advanced rather than mild retinopathy.<sup>38</sup> An inverse relation between hyperemic myocardial blood flow and fasting insulin level has also been found among healthy, nonobese individuals, which suggests that even mild insulin resistance is associated with impaired coronary flow reserve.<sup>42</sup>

The decreased myocardial perfusion in diabetes is due primarily to reduced maximal myocardial blood flow. It is possible to gain information on the mechanisms underlying this reduction by comparing the hyperemia provoked by the cold pressor test (predominantly endothelium dependent) with that induced by adenosine or dipyridamole (predominantly endothelium independent) in individuals with various degrees of glucose metabolic dysfunction.<sup>40</sup> There is a progressive decrease in endothelium-dependent myocardial hyperemia from the earliest stages of the insulin resistance cascade to overt diabetes; however, endothelium-independent vasodilation, which reflects structural microvascular changes, was significantly reduced only in those with overt diabetes (Figure 4). Thus, there appears to be a progression from functional microvascular disturbance to one that includes structural changes with increasing severity of metabolic dysfunction, reminiscent of the progression noted during hypertension.

### **Cause and Effect in Diabetes**

There is considerable evidence to suggest that insulin resistance and hyperglycemia, acting via oxidative stress, inflammation, and advanced glycation end products, can induce



**Figure 4.** Myocardial blood flow reserve (top) and myocardial endothelium-dependent dilation (bottom) in individuals who are insulin sensitive (IS), insulin resistant (IR), who have impaired glucose tolerance (IGT), diabetes mellitus (DM), and diabetes mellitus and hypertension (DM+HT). \*Significantly different from IS group. Adapted from Prior et al.<sup>40</sup>

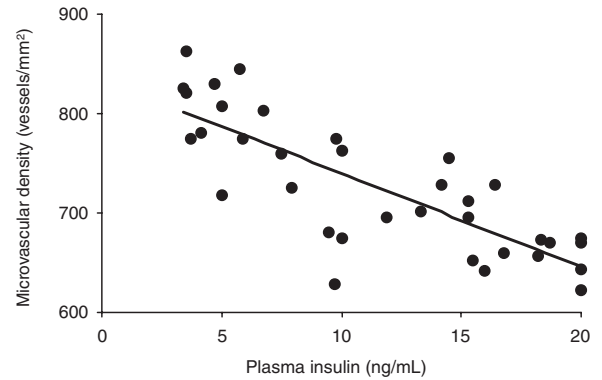
microvascular abnormality.<sup>6</sup> However, inflammation may also be important in the development of insulin resistance,<sup>43</sup> and impaired microvascular perfusion may itself play a role in the pathogenesis of diabetes. Capillary recruitment is an important mechanism by which insulin promotes uptake of glucose from the blood.<sup>44</sup> Capillary rarefaction and impaired recruitment may, therefore, reduce glucose uptake and contribute to insulin resistance.

It is possible to envisage a vicious circle of progressive microvascular dysfunction that contributes to and is exacerbated by worsening insulin resistance. Such a circle might be analogous to that involving microvascular dysfunction and elevated peripheral resistance proposed in the development of hypertension.<sup>1</sup> Reduction in inflammation and improvement in tissue perfusion may become important therapeutic targets in the prevention of disease progression and complications in diabetes.

**Obesity**

In humans, coronary flow reserve is significantly lower in obese than in nonobese subjects,<sup>45</sup> and capillary recruitment is reduced in nondiabetic obese individuals compared with lean control subjects.<sup>26</sup> Even in a sample of healthy children (11 to 14 years of age), microvascular function was negatively correlated with adiposity.<sup>46</sup> Thus, obesity appears to have an independent effect on microvascular function.

Understanding of the microvascular abnormalities associated with obesity has been enhanced by studies in the obese Zucker rat (OZR), in which a defective leptin receptor gene causes excessive food intake and leads to obesity, type 2 diabetes, and hypertension. OZR show microvascular remodeling and rarefaction in skeletal muscle before any elevation of blood pressure has occurred, and rarefaction is not pre-



**Figure 5.** Inverse relationship between skeletal muscle microvascular density and fasting plasma insulin concentration in obese Zucker rats. Adapted from Frisbee.<sup>47</sup>

vented if the increase in blood pressure is prevented by treatment with hydralazine.<sup>47</sup> Rarefaction in this situation, therefore, is not a consequence of hypertension. However, microvascular density is inversely related to fasting plasma insulin (Figure 5).<sup>47</sup>

Several mechanisms have been identified by which excessive adiposity could cause microvascular abnormalities. First, in OZR, oxidative stress and reduced NO availability are important mechanisms in the development of microvascular rarefaction.<sup>48</sup> Second, excess adiposity is associated with a chronic state of vascular inflammation, with increased levels of proinflammatory cytokines. In particular, production of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), largely from nonfat cells in adipose tissue, is markedly increased in obesity.<sup>49</sup> Serum TNF- $\alpha$  levels in healthy adults are negatively correlated with skin capillary recruitment and insulin sensitivity.<sup>50</sup> Deposits of fat around arterioles may be involved in local TNF- $\alpha$  signaling, resulting in impaired perfusion and insulin resistance.<sup>51</sup> Third, increased fat mass leads to prolonged elevation of free fatty acid levels in the blood, which can impair capillary recruitment.<sup>52</sup>

In the human coronary microcirculation, endothelium-dependent vasodilation is impaired in both overweight and obese individuals, but endothelium-independent vasodilation is reduced significantly only in obese subjects.<sup>45</sup> Thus, in obesity, as in hypertension and diabetes, it appears that an early functional microvascular impairment can progress to involve more permanent, structural abnormality.

**Other Risk Factors**

**Age**

Coronary flow reserve decreases progressively with age in subjects without coronary artery disease,<sup>53</sup> from approximately 4 at 30 years to 3 at 65 years of age, largely due to increased basal myocardial blood flow.

**Smoking**

Tobacco smoking acutely impairs capillary recruitment, and thus hyperemic blood flow increases in skin<sup>54</sup> and coronary flow reserve is reduced in established smokers.<sup>55</sup> Coronary flow reserve in smokers can be improved by administration of antioxidant vitamin C,<sup>55</sup> which suggests that smoking-related oxidative stress is an important mechanism.

**Dyslipidemia**

Individuals with hypercholesterolemia without coronary artery disease have reduced coronary flow reserve, and coronary flow reserve is inversely correlated with LDL cholesterol.<sup>56</sup> A reduction in coronary flow reserve can be detected in healthy young men (mean age 31 years) with familial hypercholesterolemia,<sup>57</sup> which suggests that microvascular abnormality is detectable early in the atherosclerotic process.

**Overall Risk Score**

Given the relationships between individual cardiovascular risk factors with measures of microvascular status, it is not surprising that the overall Framingham risk score is inversely correlated with skin capillary recruitment,<sup>58</sup> maximal skin capillary density,<sup>9</sup> and coronary flow reserve.<sup>53</sup>

**Target-Organ Damage, Complications, and Prognosis**

Microvascular abnormalities that lead to impaired tissue perfusion appear to represent a generalized condition that affects multiple tissues and organs. For example, in hypertension, coronary flow reserve is correlated with the media:lumen ratios of small arteries in biopsies of subcutaneous fat.<sup>59</sup> Dilatation of venules in the retina independently predicts progression of cerebral small-vessel disease,<sup>60</sup> and in diabetes, reduced coronary flow reserve predicts the occurrence of retinopathy.<sup>61</sup>

Impaired tissue perfusion may be involved in target-organ damage and complications that involve several vascular beds. For the coronary microcirculation, an obvious example associated with both hypertension and diabetes is the occurrence of myocardial ischemia and angina in the presence of angiographically normal epicardial coronary arteries, also known as cardiac syndrome X. Impaired myocardial perfusion may also be an important factor in the development of hypertensive heart failure and may lead to localized ischemia and disturbed patterns of electrical activity that constitute a substrate for serious arrhythmias.<sup>62</sup> In the case of renal disease, glomerular and peritubular capillary rarefaction has been noted in different animal models and in human progressive renal disease, and it precedes the development of impaired perfusion and chronic hypoxia.<sup>63</sup> It has been suggested that hypoxia may be the common factor linking many forms of progressive renal disease.<sup>64</sup>

Microvascular abnormality is also a predictor of prognosis. In hypertensive patients, the media:lumen ratio of peripheral small arteries is a strong independent predictor of cardiovascular events.<sup>65,66</sup> Among individuals with normal or minimally diseased coronary arteries, reduced coronary flow reserve is an independent predictor of cardiovascular events within the next decade.<sup>67</sup> Finally, in patients with chest pain and angiographically normal arteries, coronary flow reserve <3 is associated with a 6-fold increase in all-cause mortality risk compared with coronary flow reserve >3 during 8.5 years of follow-up.<sup>68</sup>

**Effects of Treatment on Perfusion****Hypertension**

It has been confirmed recently in hypertensive patients that effective antihypertensive therapy can reverse both functional

and structural rarefaction of skin capillaries.<sup>9</sup> Several years ago, literature reviews concluded that antihypertensive agents that act mainly by vasodilation are effective in improving microvascular structure, whereas agents that act mainly by reducing cardiac output are not effective.<sup>1,69</sup> Recent work has confirmed this view and highlighted the antioxidative and antiinflammatory actions of some agents.

 **$\beta$ -Blockers**

$\beta$ -Blockers act primarily by reducing cardiac output and are not effective in improving microvascular structure and function in SHR or in hypertensive or hypertensive and diabetic patients.<sup>1,70</sup> It would be expected that  $\beta$ -blocker therapy might improve coronary flow reserve by lowering basal myocardial blood flow owing to reduced cardiac work; however, 1 year of treatment with atenolol had no net effect on coronary flow reserve owing to reductions in both basal and maximal myocardial blood flow.<sup>30</sup> Interestingly, nebivolol, a  $\beta_1$ -blocker with a  $\beta_3$ -adrenoceptor agonist effect and vasodilatory properties, improved coronary flow reserve and maximal coronary blood flow in hypertensive patients.<sup>71</sup>

**Diuretics**

Hydrochlorothiazide therapy has no beneficial effect,<sup>1</sup> but chlorthalidone<sup>72</sup> improves minimal forearm vascular resistance (an indirect measure of microvascular structure) in hypertensive patients. Indapamide prevented hypertrophic remodeling of cerebral arterioles in SHR.<sup>73</sup>

**Calcium Antagonists**

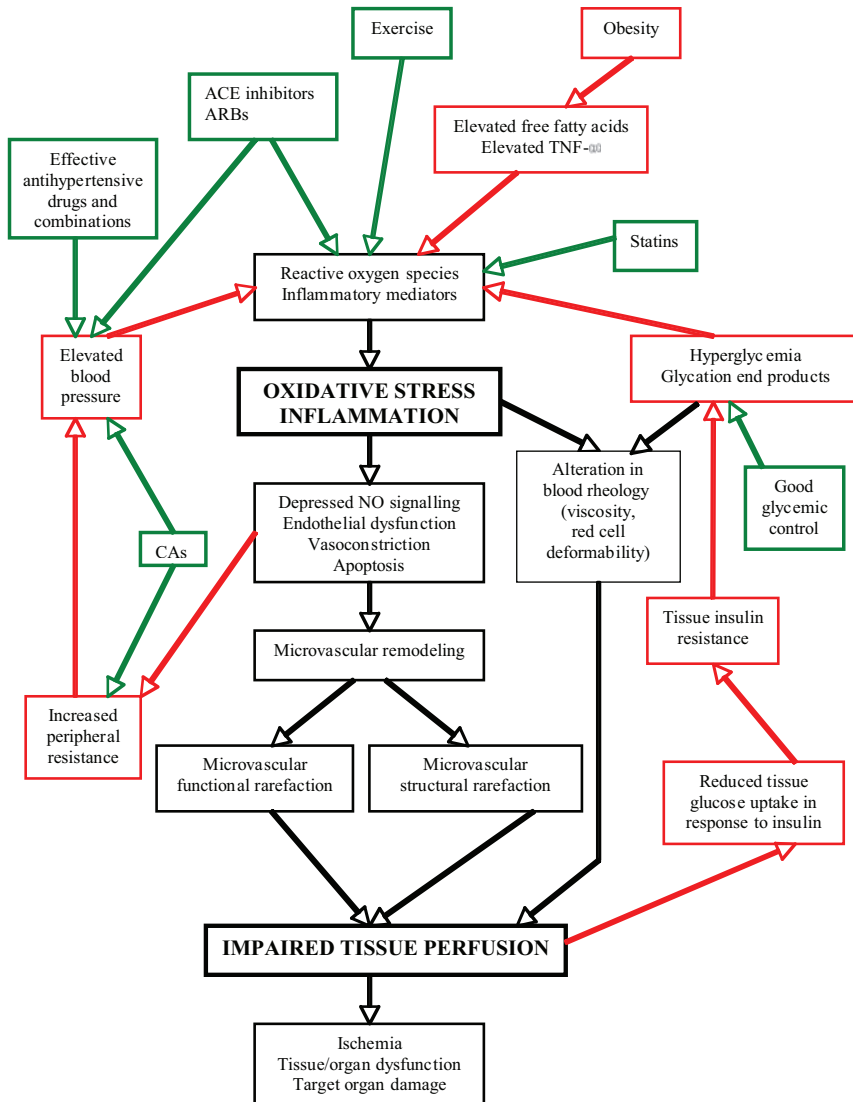
Calcium antagonists inhibit vascular smooth muscle contraction to produce vasodilation and generally improve microvascular structure, including reducing the media:lumen ratio of resistance arteries.<sup>1</sup> Benidipine and amlodipine improve myocardial capillary density and coronary flow reserve in rat models of experimental hypertension.<sup>74,75</sup>

**ACE Inhibitors and Angiotensin Receptor Blockers**

Angiotensin II is not only a vasoconstrictor but also promotes the generation of ROS and inflammatory mediators that are implicated in many of the adverse changes in microvascular structure and function. There is a substantial body of evidence showing that agents that inhibit the renin-angiotensin system, particularly ACE inhibitors, improve microvascular structure and function.<sup>1</sup> ACE inhibition has been shown to improve microvascular structure in SHR and hypertensive patients<sup>76</sup> and resistance arterial structure in hypertensive patients and in hypertensive individuals with type 2 diabetes.<sup>77</sup>

Microvascular improvement has also been reported with angiotensin receptor blockers in SHR, hypertensive subjects, and diabetic hypertensive patients<sup>70,77</sup>; however, it has been demonstrated that long-term ACE inhibitor treatment in stroke-prone SHR increases myocardial capillary density by a bradykinin-dependent mechanism.<sup>76</sup> In contrast, long-term AT<sub>1</sub>-receptor blockade failed to alter cardiac capillary density, possibly because of stimulation of AT<sub>2</sub>-receptor-mediated antigrowth actions on coronary endothelial cells.

ACE inhibition also improves coronary flow reserve in hypertensive patients with and without left ventricular hypertrophy.<sup>28,30</sup> In 2 studies, 1 in dogs with experimental dilated cardiomyopathy<sup>78</sup> and 1 in hypertensive patients with left



**Figure 6.** Summary of the hypothetical pathogenic sequence that leads to impaired tissue perfusion. Deleterious influences in red, beneficial influences in green. ARB indicates angiotensin-receptor blocker; CA, calcium antagonist.

ventricular hypertrophy,<sup>28</sup> an ACE inhibitor was compared directly with an angiotensin receptor blocker. Significant improvements in coronary flow reserve were seen with the ACE inhibitor but not the angiotensin receptor blocker, consistent with the importance of bradykinin-mediated mechanisms. It is possible that these differences are related to the blood pressure-independent reduction in risk of coronary heart disease reported recently for ACE inhibitors but not angiotensin receptor blockers.<sup>79</sup>

**Combination Therapy**

Many hypertensive patients require more than 1 drug to achieve blood pressure targets. The combination whose effects on tissue perfusion have been studied most extensively is a low-dose combination of the ACE inhibitor perindopril and the diuretic indapamide. This combination improves myocardial capillary density in renovascular hypertensive rats<sup>80</sup> and stroke-prone SHR<sup>81</sup> and enhances neovascularization, capillary density, and perfusion in response to experimental hypoperfusion and ischemia in rat skeletal muscle.<sup>82</sup> In each of these studies, the beneficial effect of the combination was greater than with either component alone.

This combination also improves coronary flow reserve in hypertensive patients, reducing basal and increasing maximal myocardial blood flows.<sup>29</sup>

**Statins**

In addition to their well-documented effects on blood lipids, statins also have antiinflammatory actions. Statin therapy that has no effect on blood pressure reduces the media:lumen ratio of small resistance arteries in genetically hypertensive rats<sup>83</sup> and normalizes microvascular density in renovascular hypertensive pigs.<sup>84</sup>

**Diabetes, Obesity, and Hypercholesterolemia**

Optimal hypoglycemic therapy improves coronary flow reserve in patients with poorly controlled type 2 diabetes.<sup>85</sup> Agents that reduce oxidative stress and inflammation are also of benefit to the microcirculation in diabetes. The ACE inhibitor perindopril reduced systemic inflammation and oxidative stress in normotensive patients with type 2 diabetes,<sup>86</sup> and treatment with an ACE inhibitor, but not an ARB, increased coronary flow reserve in individuals with type 2 diabetes.<sup>41</sup>

In OZR, the perindopril/indapamide combination increased myocardial capillary density and prevented renal tubulointerstitial damage.<sup>87,88</sup> Interestingly, this antihypertensive combination also improved insulin sensitivity.<sup>87</sup> In nondiabetic patients with hypercholesterolemia, 8 to 12 months of simvastatin therapy increased coronary flow reserve.<sup>89</sup>

Lifestyle changes can also improve tissue perfusion. Regular exercise reduces levels of proinflammatory mediators, including TNF- $\alpha$ ,<sup>90</sup> and increases skeletal muscle capillary density in OZR and human subjects.<sup>91,92</sup>

### Conclusions

The research reviewed in this article suggests that impaired tissue perfusion due to abnormality of the microvascular system is common among the conventional cardiovascular risk factors, including hypertension, diabetes, obesity, and dyslipidemia. Microvascular changes are hallmarks of the long-term complications of hypertension and diabetes; however, it is now clear that microvascular changes occur very early in these conditions and may be important in their pathogenesis and progression. It is noteworthy that microvascular changes that result from 1 risk factor could predispose to other risk factors. Microvascular rarefaction due to hypertension may directly reduce skeletal muscle uptake of glucose, resulting in reduced insulin sensitivity. Similarly, excessive adiposity that causes microvascular changes increases peripheral vascular resistance and consequently tends to increase blood pressure.

There is increasing awareness that hypertension, insulin resistance, obesity, and dyslipidemia often cluster within individuals, producing the "metabolic syndrome" that is highly prevalent in industrialized countries and is associated with substantially increased overall and cardiovascular mortality. Target-organ damage may be increased to a greater extent than expected from each component of the syndrome considered separately.<sup>93</sup> Among the different components of the metabolic syndrome, high blood pressure appears to make the greatest single contribution to the overall increase in risk.<sup>94</sup> In Figure 6, we summarize the main hypothetical pathogenic sequence that leads to impaired tissue perfusion and the possible influence of antihypertensive, antidiabetic, and cholesterol-lowering drugs and strategies.

Many of these microvascular changes can be reduced, prevented, or reversed with appropriate pharmacological treatment and lifestyle modifications. In addition to ensuring that all relevant risk factors are considered and, if necessary, treated, it may be important to use drugs and combinations that have beneficial effects on microvascular structure and tissue perfusion. With early, appropriate, and adequate use of such treatments, it may be possible to actually achieve the risk reductions that should be possible theoretically.

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