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Surrogate Markers for Cardiovascular Disease

Functional Markers

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Endothelial Dysfunction

The endothelium constitutes the largest organ system in the body. "Endothelial function" refers to a multitude of physiological functions of the vascular endothelium that are achieved via secretion of diverse bioactive substances. This renders the endothelium an active participant in healthy homeostasis of the vascular wall that includes normal vasomotion, inhibition of platelet aggregation and thrombus generation, and maintenance of relative impermeability. Cardiovascular risk factors activate a number of pro-oxidative genes in the vascular wall resulting in generation of reactive oxygen species that ultimately promote endothelial release of transcriptional and growth factors, proinflammatory cytokines, chemoattractant substances, and adhesion molecules.¹⁻³ This complex cascade of events underlies the transition from normal endothelial function to endothelial dysfunction. One of the earliest manifestations of increased vascular oxidant stress is the reduced bioavailability of nitric oxide (NO) as a result of inhibition and uncoupling of endothelial NO synthase, the enzyme responsible for generation of NO, and from rapid catabolism of available NO by reactive oxygen species to peroxynitrite and hydrogen peroxide that can further amplify vascular oxidative stress. The resulting functional consequences include abnormal vasomotor activity, development of a procoagulant endothelial surface, inflammation, and, ultimately, plaque formation. Clinical measurements of endothelium-dependent vasodilation (NO-mediated process) by a variety of different techniques provide a marker of endothelial integrity.

Almost all conventional risk factors for atherosclerosis are associated with endothelial dysfunction. These include sedentary lifestyle and obesity, hypercholesterolemia, hypertension, diabetes, insulin resistance, smoking, and aging. The extent of endothelial dysfunction appears to correlate with the traditional risk factor "burden," thus implying that combined or repeated injury to the vascular endothelium results in greater dysfunction. Nevertheless, there is considerable heterogeneity in the magnitude of dysfunction observed in individuals with similar risk factor profiles.^{4,5} Novel risk factors such as infections, hyperhomocystinemia, genetic

heterogeneity, and the variable duration of exposure to individual risk factors presumably account for some of this observed variability. Moreover, evidence now suggests that endothelial function may be modulated not only by factors causing vascular injury but also by repair mechanisms, potentially mediated via circulating endothelial progenitor cells.⁶ Thus, the concept has been put forth that endothelial vasodilator function is a reflection of overall vascular health, or a barometer of the injury/repair inflicted by multiple environmental and genetic factors, and, therefore, could potentially serve as a useful diagnostic and prognostic tool in individual patients.

It is important to realize that the presence of a similar risk factor profile does not necessarily imply the presence of an equivalent degree of endothelial dysfunction. Thus, the observation that assessment of endothelial function can provide an independent prediction of future cardiovascular risk demonstrates not only the crucial pathophysiologic role of this entity to existing vascular disease but also how the disease is likely to progress with time.

Methodology

Invasive Measures

Invasive measures use intra-arterial infusion of specific endothelium-dependent vasodilators, most commonly acetylcholine, although methacholine, bradykinin, and substance P, or inhibitors of NO synthase, are also used. Acetylcholine stimulates NO synthase,⁴ but vasodilation in response to acetylcholine can be only partially abrogated by inhibitors of NO synthase, thus indicating the concomitant release of other endothelium-derived vasodilators such as prostacyclin and endothelium-derived hyperpolarizing factor.^{3,7} Using acetylcholine infusions, we now define normal or preserved endothelial function when coronary epicardial vessel dilation occurs, and endothelial dysfunction as when epicardial constriction is observed, the latter because the direct smooth muscle constrictor effects of acetylcholine in epicardial vessels override the dilator effects mediated by endothelium-dependent NO release.^{4,8} A similar phenomenon is also observed with stimuli that increase shear stress such as

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TABLE 1. Prediction of Future Cardiovascular Events by Measurements of Endothelial Function

Reference	N	Population	Follow-Up (mos)	Event Type	Number of Events	Other Independent Outcome Measures
Coronary circulation						
17	147	CAD	80	All	28	CAD, hypertension, NTG response
18	157	CAD, NCA	28	All	6	—
19	308	CAD, NCA	46	Major, all	56	Age, CAD, BMI
20	503	CAD, NCA	16	Stroke	7	Diabetes, MI, age
21	163	CAD, NCA	48	Acute, all	58	—
Peripheral circulation						
22	83	CAD, NCA	60	All	27	Sex, NTG response
23	276	CAD	54	All	91	Age
24	225	Hypertension	32	All	29	Mean 24-h BP
25	187	PAD	1	Major	45	Age, surgery, renal disease
26	199	PAD	14	Major	35	Age, surgery
27	131	PAD	23	All	39	ABI, stroke, hyperlipidemia
28	518	CAD	45	Deaths	21	—
29	152	CAD	34	All	22	Carotid IMT
30	200	ACS	30	Major	29	—
31	150	CHF	13	Death	17	—

ABI indicates ankle-brachial index; ACS, acute coronary syndromes; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; IMT, intima-media thickness; MI, myocardial infarction; NCA, normal coronary arteries; NTG, nitroglycerin; PAD, peripheral artery disease.

cardiac pacing, exercise, cold-pressor testing, or hyperemia. In other vascular beds such as the coronary microcirculation or the brachial or femoral circulations, a diminished dilator response is observed in the setting of endothelial dysfunction; constriction is rarely seen.^{3,9,10}

Indirect measurements of endothelial function use conductance vessel responses to external sympathetic stimuli such as exercise or cold-pressor testing. Sympathetic nervous system activation acts directly through adrenergic receptors and indirectly through the dilator response of blood vessels in response to an acute increase in blood flow secondary to increased myocardial oxygen demand. This stimulates NO release by shear-mediated activation of endothelial NO synthase, a phenomenon also termed flow-mediated dilation (FMD).^{10–12}

The response to endothelium-independent vasodilatory agents such as nitroglycerin or sodium nitroprusside, substances that donate NO directly to vascular smooth muscle cells, defines the vasodilatory properties of the blood vessels, independent of the endothelium, and thus serves as a control stimulus. Adenosine that causes vasodilation largely by stimulating specific receptors in the microcirculation is often used as a measure of endothelium-independent flow reserve in the coronary microcirculation. Although a small component of adenosine-mediated microcirculatory vasodilation is endothelium-dependent, the majority of flow-mediated epicardial vasodilation with adenosine is likely to be endothelium-dependent.

Noninvasive Measures

To overcome the constraints of arterial cannulation, noninvasive measurements have been developed using emerging technologies, including Doppler echocardiography, positron

emission tomography, and magnetic resonance imaging for the assessment of either the peripheral or the coronary vasculature. Ultrasound measurement of brachial artery reactivity is currently the best-validated technique.¹³ A high-frequency ultrasound transducer measures the extent of shear stress-mediated brachial arterial dilation after hyperemia resulting from a brief period of upper-arm occlusion that produces ischemia of the forearm muscle. Shear-mediated NO release causes brachial arterial dilation, and the magnitude of this vasodilator response, or flow-mediated vasodilation, is representative of endothelial function. Despite the frequent use of this technique in estimating endothelial function, the methodology is variable between centers and the technique is exquisitely operator-dependent. Other techniques that use measurement of microvascular dilation during hyperemia are being evaluated as potentially more feasible methods of estimating endothelial function.¹⁴

Evidence for Endothelial Dysfunction as a Predictor of Outcome

Coronary Endothelial Function

Several studies have now demonstrated that the extent of coronary vascular endothelial dysfunction is an independent reflection of the magnitude of future risk of adverse cardiovascular events (Table 1).^{15–31} In a study of 150 patients with normal or minimally diseased coronary arteries, the largest number of adverse events occurred in those in the lowest tertile of the coronary flow response after acetylcholine provocation, compared to those in the highest tertile.³² In another study, Schächinger et al¹⁷ enrolled 147 patients with normal coronary arteries or those with minimal disease after single-vessel angioplasty. Epicardial coronary arterial vascu-

lar function was assessed by using acetylcholine, cold-pressor testing, FMD, and after nitroglycerin. Endothelial dysfunction, identified in two-thirds of patients, was associated with a much higher incidence of cardiovascular events during follow-up. Interestingly, nitroglycerin-induced vasodilation was also decreased in those who had events. The value of cold-pressor testing in predicting future events was confirmed in a group of 130 patients with angiographically normal coronary arteries.³³ Patients with a vasodilator response had no events, whereas the majority of events occurred in those with severe constriction in response to cold-pressor testing during a 45-month follow-up period. Suwaidi et al¹⁸ enrolled 157 patients with insignificant coronary artery disease (CAD) and found that during a mean 28-month follow-up, the majority of adverse events occurred in those with a constrictor response in the microcirculation to acetylcholine. Importantly, the magnitude of atherosclerotic burden assessed by intravascular ultrasound bore no relationship to either endothelial function or outcome. Thus, the function of the coronary circulation, and not the structure, had greater prognostic value.

Results from 163 women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study have recently been reported.²¹ The cross-sectional area change with acetylcholine was an independent predictor of event-free survival during a median follow-up period of 48 months. There were 14 unpredictable cardiovascular events, including death, infarction, and stroke. The remaining events were revascularization procedures or recurrent angina. Nonsignificant trends were observed between the response to endothelium-independent vasodilators, nitroglycerin and adenosine, and outcome.

Combined, these studies demonstrate that coronary vascular dysfunction independently predicts adverse long-term prognosis, but the majority of "adverse events" were revascularization procedures. We therefore undertook a study to investigate whether the presence of coronary vascular endothelial dysfunction in patients with angiographically normal coronary arteries or those with CAD predicted a worse long-term outcome from unpredictable acute cardiovascular events, including death, myocardial infarction (MI), stroke, and unstable angina.¹⁹ In 308 patients (132 with and 176 without angiographic CAD), endothelial function was measured in the coronary microcirculation and in epicardial vessels after acetylcholine and sodium nitroprusside provocation, and cardiovascular events were monitored during a mean follow-up of 46.3 months. During this period, 35 patients (11.4%) experienced an acute ischemic event. Patients who exhibited epicardial constriction had a significantly greater incidence of acute ischemic events than those who dilated, a distinction that remained after multivariate adjustment and also after adjustment for the presence of CAD. Similarly, the prognosis was worse in those in the lowest tertile of acetylcholine response in the coronary microcirculation. When all cardiovascular events including revascularization were considered, events were more frequent in patients with epicardial constriction or decreased microvascular dilation with acetylcholine. Finally, endothelial dys-

function was a predictor of worse outcome in patients with and without CAD.

Thus, coronary endothelial dysfunction predicts acute ischemic events and outcomes such as need for coronary revascularization. Also, the prognostic value of endothelial dysfunction extends to patients with angiographically normal coronary arteries as well as to those with CAD. Finally, coronary resistance and conductance vascular function is predictive.

Peripheral Endothelial Function

Although intimal thickening is common in the brachial artery, obstructive atherosclerotic stenoses are rare, and a correlation exists between atherosclerosis in the human brachial and coronary arteries in younger adults.^{15,34} Studies also demonstrate a modest correlation between endothelial function in the coronary and brachial arteries, although coronary atherosclerosis weakens the correlation.^{5,35} Clinical outcome studies nevertheless have demonstrated the relevance of endothelial dysfunction in the brachial artery to prediction of future cardiovascular risk (Table 1).¹⁷⁻³¹

In a study of 73 patients with angina, those with impaired FMD (<10%) had greater rates of revascularization procedures, including bypass surgery and angioplasty, than those with preserved FMD (>10%) during a 5-year follow-up, a finding that remained significant after multivariate adjustment.²² Similar data were observed in a study when forearm microvascular endothelial dysfunction was measured in response to acetylcholine in 281 patients with stable angiographic CAD.²³ Over a mean 4.5-year follow-up, death, MI, ischemic stroke, and coronary revascularization procedures were significantly less frequent in those with preserved responses to acetylcholine compared with patients with decreased endothelial function. Vitamin C improved the blood flow response to acetylcholine in patients with and without events, although the effect was significantly greater in patients with an event during follow-up ($P < 0.001$), suggesting that oxidative stress was higher in those with increased risk.

Similar results were obtained in a study of 225 untreated hypertensive patients.²⁴ Outcomes during a mean 31.5-month follow-up included fatal and nonfatal MI, fatal and nonfatal stroke, transient ischemic attack, unstable angina, and coronary revascularization. The cumulative cardiovascular event rate in the group in the lowest tertile of vasodilation with acetylcholine was significantly higher. Gokce et al²⁶ measured brachial artery FMD in 187 patients scheduled for vascular surgery and noted that the frequency of adverse events (death, MI, unstable angina, ischemic ventricular fibrillation, or nonhemorrhagic stroke) assessed during the 30-day postsurgery period was higher in those with decreased FMD and that FMD was an independent predictor of outcome. After a 1.2-year follow-up of 199 patients with peripheral vascular disease, they reported a significantly higher preponderance of acute cardiovascular events, including death, MI, unstable angina, or stroke, in those with lower FMD compared with the upper tertile. The risk was 9-fold greater in those with FMD <8.1%.²⁵

Whether mortality rate can be predicted by endothelial function assessment was addressed in a preliminary study. A

higher cardiovascular and noncardiovascular mortality rate was observed in those within the lowest tertile of flow-mediated vasodilation of the brachial artery in 518 patients with CAD.²⁸

The additive value of endothelial function assessment to structural measurement of atherosclerotic disease burden has been demonstrated in 2 recent studies. In a population of 131 patients with peripheral vascular disease followed-up for \approx 2 years, FMD and ankle-brachial index were both independent predictors of outcome such that patients below the medians for both parameters had 13-fold higher relative risk compared with those above the medians.²⁷ Patients with abnormality in a single parameter had intermediate risk. In another study of 152 patients with CAD, carotid atherosclerosis was measured as intima-media thickness of the common carotid artery using ultrasound, together with FMD. There was no correlation between intima-media thickness and FMD. Both the structural (plaque burden) and FMD were independent predictors of outcome that included revascularization during a 34-month follow-up, with low FMD predicting worse outcome irrespective of plaque burden.²⁹

The value of endothelial function measured as the vasodilator response of the forearm microcirculation to acetylcholine in patients presenting with acute coronary syndromes was reported recently. In 200 patients tested within 5 days of presentation, the only independent predictor of cardiovascular events, including death, MI, and stroke, over a 2.5-year follow-up period was the response to acetylcholine. This remained an independent predictor after adjustment for troponin and CRP levels.³⁰

In 150 patients with congestive heart failure, FMD was an independent predictor of mortality at 13 months.³¹ Additional studies have demonstrated that ischemic stroke occurred more frequently in patients with endothelial dysfunction,²⁰ and hypertension developed during follow-up only in subjects who had endothelial dysfunction.

Can Change in Endothelial Function Be Used as a Surrogate for Change in Cardiovascular Risk?

Although several studies described have demonstrated the predictive value of endothelial dysfunction, few were designed to examine whether improvement in vascular endothelial function will be predictive of improved long-term outlook and vice versa. A recent report from Modena et al³⁶ has shed some light on this issue. In a study involving 400 postmenopausal women with hypertension, brachial artery FMD was measured before and 6 months after normalization of blood pressure (BP). There was an improvement of FMD by $>10\%$ in almost two-thirds of subjects. Event rates were 7-fold higher in those in whom FMD improved by $<10\%$ compared with those who had improvement $>10\%$. Although preliminary, this study provides support for the concept that endothelial function may be considered a "target" for cardiovascular therapy in which reversibility of dysfunction will be indicative of improvement in risk.

Unresolved Issues, Controversies, and Future Directions

Extending implications of these studies to the general population is tempered by the realization that they have been

conducted in selected high-risk populations, in relatively small numbers, and using multiple end points including revascularization procedures. Data are lacking on its prognostic value in very low-risk populations. There is therefore an urgent need for prospective trials in specific populations to assess the true incremental value of endothelial function assessment to conventional methodologies available for risk assessment, including some of the newer markers of inflammation and oxidative stress. Evaluation of these somewhat cumbersome technologies needed to perform these assessments and their cost/benefit potential also needs to be explored and simpler technologies that could be more widely applicable need to be evaluated.

Although there is convincing evidence that endothelial function predicts future outcome, evidence that such a measure can be a surrogate marker for assessing a changing risk profile after therapeutic interventions is available from a single study thus far. This is a crucial issue because although aspirin,³⁷ angiotensin-converting enzyme inhibitors,³⁸ and statins³⁹ improve endothelial function and reduce cardiovascular morbidity and mortality,^{40–42} antioxidants (in some studies⁴³) and hormone replacement therapy,⁴⁴ at least during acute administration, also improve endothelial function but have either neutral^{42,45} or negative⁴⁶ effects on clinical outcomes. Thus, studies designed to correlate improvement in endothelial function with improvement in outcome are needed to convince us that normalization of function with repeated measurements is an appropriate strategy in management of patients with endothelial dysfunction.

Conclusions

Endothelium-dependent vasomotor function in the coronary and/or brachial arteries predicts long-term cardiovascular risk, including acute cardiac and cerebrovascular events, and development of hypertension. This finding is consistent regardless of the method used to assess endothelial function and it supports the pivotal biologic role of the vascular endothelium as a modulator and mediator of vascular disease. This evidence is now extending to populations with acute coronary syndromes, heart failure, peripheral arterial disease, and hypertension.

Blood Pressure

Pathophysiology

Mean BP is the product of cardiac output and peripheral vascular resistance. Pulsatile pressure is also dependent on large and small artery compliance, a reduction of which contributes to a progressive increase in systolic pressure with aging. The distribution of systolic and diastolic pressure in the population is continuous, and there is no natural cut-point that distinguishes elevated pressures from normal pressures.⁴⁷ High BP is traditionally defined as a systolic pressure >140 mm Hg or a diastolic pressure >90 mm Hg. Because cardiac output is generally normal in those with high pressures, the physiological abnormality appears to be a reduction in caliber of the arteriolar resistance arteries and/or a reduction in compliance of the larger arteries. The overall prevalence of high BP in adults ages 18 to 74 years is 21.1% in the US.⁴⁸ The prevalence increases with age, exceeding 50%

(54%) in those aged 60 to 69 and involving two-thirds of those older than 70 to 80 years.⁴⁹

Hypertension is a leading risk factor for atherosclerotic disease. The main manifestations are ischemic heart disease, stroke, heart failure, and end-stage renal disease (ESRD).^{50,51} Elevated systolic BP is the leading contributor worldwide, exceeding the contribution of tobacco, high serum cholesterol, and overweight.⁵²

Methodology

Because variation in BP is large, the diagnosis of hypertension demands repeated measurements—at least 3 measurements over 3 months in patients with modest pressure elevation.⁵³ The average of these measurements may best characterize the pressure in a given patient. Furthermore, because of diurnal variation, measurements of pressure ideally should be performed at a similar time of day or averaged from measurements at different times.

Target Levels

In high-risk patients, such as those with diabetes mellitus and patients with renal injury, goal or target BP values have shifted down to lower levels over the past decade. These are reviewed in detail. Current recommendations for such patients suggest a systolic BP <130 mm Hg and a diastolic pressure <80 mm Hg.⁵⁴

Systolic Blood Pressure, Diastolic Blood Pressure, and Pulse Pressure

Until recent years, the major therapeutic focus has been on diastolic BP,^{55,56} which was thought to be a better guide to arteriolar resistance. Growing evidence now exists that systolic BP and pulse pressure might contain more information on natural history to shift our therapeutic aims and strategies. Indeed, systolic BP appears to be a better predictor of morbid events than diastolic BP.⁵⁷ As an index of cardiovascular risk, both systolic and pulse pressure have emerged as major risk factors.^{58–64}

Blood Pressure Measurement in the Clinic/Office Versus at Home

In 61 prospective clinical trials included in a recent meta-analysis, BP was measured in a physician's office or analogous clinical setting.⁶⁵ However, the large spontaneous fluctuation in BP and the transient elevation some patients show in BP measurement (ie, "white coat hypertension") lessens the predictive value of office BP for cardiovascular events. Remarkably, 20% to 30% of patients with mildly elevated BP in the office prove to have "white coat" hypertension and may not require drug treatment.^{66–69} Given that a diagnosis of hypertension carries a commitment to lifetime drug therapy, the usefulness of ruling out "white coat" hypertension is obvious. Moreover, some individuals with high BP show the normal BP decrease during sleep at night and others do not. Both phenomena are relevant to clinical practice, and the additional information would refine the surrogate end point.

An approach with important clinical indications is provided by the wide availability of instruments that allow patients to measure their BP at home. The average of multiple BP readings obtained throughout a 24-hour interval correlates

better with end-organ involvement and with cardiovascular events than does the average of a few BP measurements obtained in a limited number of office visits.^{62,63,69–73}

Home BP monitoring can be an attractive alternative to the more expensive technology needed for ambulatory BP monitoring. Oscillometric monitors are reasonably accurate, easy to use, and have memory to store the readings.⁷⁴ Reimbursement for ambulatory BP monitoring is now available from many third-party payers and government agencies, and the cost of oscillometric BP monitors has decreased sharply.

Blood Pressure Measurement at Rest Versus After Provocation

In the 1 million patients who participated in 61 prospective studies mentioned, BP was measured at rest.⁶⁵ Blood pressure is labile in response to unseen stimuli, and many emotional or physical situations also result in an increase in BP.⁵⁶ Most recommendations on BP measurement have involved these sources of fluctuation to provide an index of "BP at rest."⁵⁵

The possibility exists, however, that there is more information in the BP response to provocation than there is in BP at rest. One of the earliest attempts to standardize a stimulus involved immersing a hand in ice water, the "cold-pressor test." After 30 to 40 years of studies, Pickering⁵⁶ concluded the maneuver provided no useful information.

There has been a resurgence of interest in the area of provocation provided by exercise as opposed to cold. The initial stimulus was probably provided by the widespread use of exercise as a provocation for CAD. Arterial BP is routinely monitored during such studies, and an increase in BP is common. The rationale for interest in exercise, moreover, is similar to that for ambulatory and home BP monitoring. Blood pressure during rest is labile and easily influenced by external factors such as noise. When the circulation is challenged by a large increase in cardiac output as it is during exercise, it is argued that "true hypertension" might be unveiled. In several careful, long-term studies in a substantial number of subjects, exercise-induced BP increases predicted future cardiovascular events.^{75–78} The power of the exercise-induced BP increase was so great that in a multivariate analysis, it canceled the contribution of casual BP.⁷⁶

Evidence for Blood Pressure as a Surrogate Risk Marker

The evidence that BP is linearly related to the risk of morbid cardiovascular events is remarkably robust.⁶⁵ Similarly, there is unambiguous evidence that pharmacotherapy that reduces BP in hypertensive patients is associated with a reduction in the risk of morbid events. Nonetheless, it is clear that cardiovascular morbid events (MI, stroke, heart failure, renal failure) occur in individuals who are not identified as having hypertension, so BP may not be a sensitive surrogate for atherosclerotic or atherothrombotic disease. Furthermore, elevated BP has been observed in many patients who do not experience adverse events during long lifetimes. Thus, BP cannot serve as a specific marker for the disease by predicting individual risk, but it does serve as an important population risk marker.

The relation between BP and cardiovascular risk is not only strong but also continuous, independent, and highly predictive of risk for adults of all ages up to 89 years.⁶⁵ Risk increases from BP levels of 115/75 mm Hg, and there is no level at which the risk suddenly increases. Adjustment for the contribution to risk of cholesterol, high-density lipoprotein (HDL), diabetes mellitus, and cigarette smoking does not alter the risk associated with BP.⁶⁵ In the analysis of the 61 prospective observational studies, each increase of 20 mm Hg in systolic BP was associated with a 2-fold increase in risk of death from stroke and ischemic heart disease.⁶⁵ The relation between BP and stroke is more pronounced than that with ischemic heart disease and other vascular events.

Although elevated BP is an independent risk factor, there is clear evidence that it also is associated with risk clustering (ie, with increased levels of other risk factors including lipid abnormalities and impaired glucose tolerance).⁷⁹ Risk increases as the level and number of risk factors increases.^{80–82} This is especially evident in the case of the metabolic syndrome, which includes impaired glucose tolerance (blood glucose >6.1 mmol/L) or type 2 diabetes mellitus, high BP (systolic BP >140 mm Hg), obesity (body mass index >29 kg/m²), an increase in serum triglycerides (>1.73 mmol/L [>150 mg/dL]), a low level of HDL (<1.03 mmol/L [<40 mg/dL]), and microalbuminuria (>30 mg/24 hours).⁸³ These syndromes have led to substantial interest in the possibility that beyond BP reduction, specific classes of agents may provide a risk reduction that exceeds that associated with the decrease in BP.⁵⁴

It is conceptually useful to examine the issue of absolute and relative risks. Absolute risk involves the number of subjects in whom disease presents over a time interval divided by the number of disease-free subjects at the beginning of that time interval.^{84,85} Relative risk is a ratio defined by dividing the absolute risk in a comparison group with the risk in a specified subset—often associated with a specific risk factor or the effect of treatment. Absolute risk tends to be low in young people, even in the presence of multiple risk factors, and absolute risk tends to be high in old people even if the risk factor levels are moderate.⁸⁴

Evidence That Blood Pressure Tracks Regression/Is a Guide to Therapeutic Efficacy

Randomized trials have shown that reducing BP can quickly reduce risk. More circumstantial evidence suggests an even greater reduction in risk is likely with more prolonged treatment, beyond 4 to 5 years.⁶⁵ These relationships raise the interesting possibility that treatment of those presently labeled “normotensive” could be useful.⁶⁵ Currently, arterial hypertension is defined as a systolic BP >140 mm Hg and/or a diastolic BP >90 mm Hg.^{50,51} There is substantial current interest in BP goals as low as 130 mm Hg systolic and 80 mm Hg diastolic in patients at high risk, such as those with diabetes mellitus or evidence of renal injury.⁵⁴

Unresolved Issues/Controversies

Because the risk and benefit appear to be linear, the absolute BP level at which treatment should be instituted remains controversial and is more dependent on other factors that

influence risk than on the pressure alone. Recent guidelines that emphasize BPs >120/80 mm Hg as a risk (“prehypertension”) reflect the evolving views⁵⁴ and remain controversial. The choice of what phase of the pulsatile pressure to focus on and on what conditions (rest or stress) that should exist at the time of measurement remains uncertain as attempts are made to improve the sensitivity and specificity of pressure as a surrogate marker for cardiovascular disease (CVD).

Future Directions

As abundant as information on therapeutic efficacy is, we are not much closer to identifying the responsible pathogenic factors in individual patients than we were 4 decades ago. The value of BP as a marker for risk and as a target for therapy in large population studies does not address its inadequate precision in monitoring individual patients. More precision in methodology and better means of separating high-risk from low-risk individuals are necessary to make BP a more useful tool in clinical practice. Whether the ultimate screening tool will be resting pressure, stress-induced pressure, or some additional measure of vascular health to augment data from the pressure readings will require further study.

Conclusions

Blood pressure is a well-established risk marker and its therapeutic reduction in those with high BP is a guide to therapeutic benefit.

Arterial Compliance, Elasticity, or Stiffness

Functional and structural changes in the artery wall precede and accompany atherosclerosis and its obstructive and thrombotic events. These changes should alter the volume increment that occurs in the arterial bed during the systolic pressure increase with each cardiac cycle. A variety of techniques developed in recent years provide quantitation of these pathophysiologic changes in the arterial wall. Because aging produces changes similar to those observed in atherosclerosis, all methods for evaluation must be corrected for age and, perhaps, gender.⁸⁶ Thus, to serve as a useful surrogate for disease progression, the method must provide insight into disease presence independent of age. Furthermore, if arterial wall compliance, elasticity, or stiffness is to serve as a valuable surrogate for efficacy of therapy, it should be tracked with disease progression and regression.

Pathophysiology

In evaluating currently available methods, an important distinction must be made among large conduit arteries, smaller more distal arteries and branch points that are the site of pulse wave reflections, and arterioles that determine resistance to flow. Stiffening of the aorta and large conduit arteries accelerates pulse wave velocity and increases pulse pressure (increased systolic, decreased diastolic pressure).⁸⁷ Stiffening of the reflecting sites will alter the timing and decay rate of reflections that alter the contour of the pressure wave.⁸⁸ Some methods focus on the large conduit arteries, some on the smaller reflecting sites, and others provide information on both or on a mixture of the 2. Stiffening or

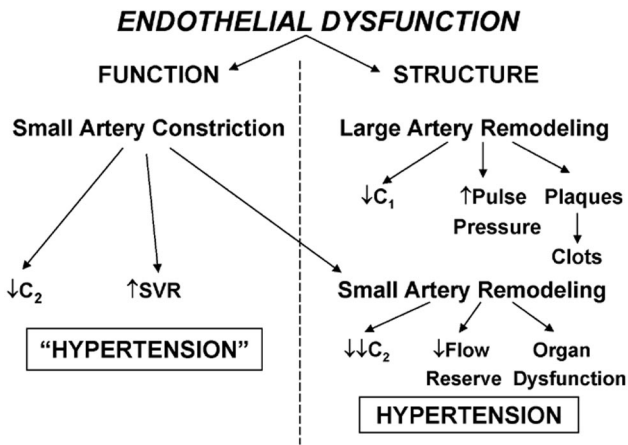


Figure 1. Role of endothelial dysfunction on small and large arteries. Functional effect is predominantly on small arteries. Structural effects of dysfunction occur later and affect the large and small arteries. Functional abnormalities may raise blood pressure, often within the normotensive range. This so-called hypertension may be complicated by structural changes that further reduce small artery compliance and subsequently large artery compliance and lead to atherothrombotic complications. C1 indicates large artery compliance or elasticity; C2, small artery compliance or elasticity; SVR, systemic vascular resistance

caliber decrease in the resistance arteries causes an increase in mean arterial pressure.

The mechanism of changes in compliance also differs markedly in the large and small arteries. The wall of the aorta and large arteries is composed of varying amounts of elastin and collagen that are the main determinants of the functional behavior of these arteries. The collagen in these arteries renders their compliance or distensibility pressure-dependent (ie, they become stiffer as transmural pressure increases because of progressive engagement of the stiff collagen fibers).⁸⁹ Altered structure with aging and disease, not altered smooth muscle function, is the major mechanism of chronic stiffening.⁸⁶ In medium-sized conduit arteries (eg, brachial, radial), vascular smooth muscle function begins to play a role in caliber and compliance. Flow-mediated release of endothelial NO can be monitored by a change in caliber of the brachial artery as a guide to endothelial function.⁹⁰

In the microcirculation, however, the caliber and compliance of arteries that constitute reflecting sites or that serve as sites of vascular resistance are critically dependent on smooth muscle tone. NO released from the endothelium penetrates the full layer of these thin-walled arteries and plays an important role in determining their tone and stiffness.⁹¹ Structural changes may ultimately contribute to functional changes (eg, smooth muscle concentric remodeling, cellular and collagen infiltration), but reduced functional effects of vasoactive substances released from the endothelium serve as an early marker for the atherosclerotic process⁹² (Figure 1). To the extent that these changes influence the tone of the thin-walled arterioles, an increase in BP and a decrease in small artery compliance may be manifestations of the process.

Methodology

The terms compliance, elasticity, and stiffness are used interchangeably, although their physical definitions are somewhat different. All these terms relate to volume or dimensional change in the artery in response to a transmural pressure change ($\Delta V/\Delta P$, or $\Delta D/\Delta P$). The term distensibility is different, however, because it refers to a fractional change in caliber in relation to the original caliber ($\Delta D/\Delta P/P_0$). Thus, if an artery dilates or enlarges, distensibility may be reduced but compliance maintained.⁹³

Another major methodological distinction is between local and systemic measurements. Ultrasound can image conduit arteries and monitor their caliber change during the cardiac cycle. Such a measurement provides data on that specific arterial segment. Ideally, pressure would be measured simultaneously at the same site to provide an accurate pressure/volume relationship for the imaged artery. Unfortunately, however, pressure is rarely measured in humans at the site of dimensional measurement, because it would require puncturing the imaged artery. Consequently, pressure usually is measured noninvasively by an upper arm cuff technique using either an auscultatory or an oscillometric method that cannot quantitate the local pressure. Methods such as pulse wave analysis provide data on a systemic pressure signal that can be used with various models to define systemic arterial compliance characteristics. These pulse waves could be recorded invasively, but noninvasive transducers on the radial artery provide almost identical data.⁸⁶ Although these methods provide a more global assessment of the circulation, they suffer from the inability to localize the findings to a specific vascular site.

Many methods have been used to gain clinical insight into the pressure/volume relationship of various segments of the arterial system. These are described.

Pulse Pressure

The pressure difference between diastole and systole provides a crude guide to stiffness of the large conduit arteries.^{87,94} However, a number of other physiological factors also influence pulse pressure. Usefulness of the pulse pressure measurement is dependent on its providing an estimate of the pressure/volume relationship in the conduit arteries. The volume increment during systole is determined by stroke volume and systolic runoff. Calculation of the ratio of pulse pressure to stroke volume should improve the usefulness of the measurement,⁹⁵ but because systolic runoff cannot be quantified, the calculation remains a crude guide. Aortic insufficiency and arteriovenous fistulae will invalidate the method. Furthermore, because the conduit arteries display a nonlinear pressure/volume relationship, pulse pressure will be directly related to the mean arterial pressure. Lowering BP will reduce pulse pressure without necessarily exerting a direct effect on the arterial wall.

Pulse Wave Velocity

The velocity of the pulse wave as it traverses the arterial tree is critically dependent on characteristics of the conduit artery wall. The Moens-Korteweg equation defines the determinants of pulse wave velocity, which is directly related to wall stiffness (elastic modulus) and inversely related to vessel

caliber.⁹⁶ Because remodeling of the conduit artery with aging and disease is usually accompanied by an increase in artery caliber, the expected increase in pulse wave velocity as the wall stiffens may be counterbalanced by a slowing associated with the volume increase. These processes of wall and caliber changes may differ in the upper and lower extremities, thus the influence of age or disease on pulse wave velocity is also dependent on the site of measurement. As with pulse pressure, nonlinearity of the pressure/volume relationship mandates that apparent stiffness of the artery wall will be directly related to pressure. Thus, pressure reduction will slow pulse wave velocity without any direct effect on the artery wall stiffness or structure. Pulse wave velocity is usually assessed by the delay in upstroke between a proximal and distal sensor, usually a Doppler probe placed directly over the artery, divided by the distance traversed, usually measured with a tape measure. Central pulse wave velocity is measured from the carotid artery to the femoral artery, whereas more peripheral velocity is assessed from the carotid to the brachial or radial arteries and the femoral to the dorsalis pedis or posterior tibial arteries.

Pulse Wave Contour Analysis

The shape of the arterial pressure wave is critically influenced by the structure and function of the large and small arteries. Its shape is also strikingly altered as the pulse wave travels from the root of the aorta to the more distal arterial sites of measurement.⁹⁷ The systolic pressure peak is augmented distally, the dicrotic notch is altered, and the diastolic decay may change. In simplest terms, the contour of the pulse wave is dependent on the incident wave generated by left ventricular stroke volume, the reflected waves or oscillations that originate at arterial branch points and in the microcirculation, viscosity of the blood, and the structure and tone of various segments of the arterial vasculature.⁹⁸

Methods for analysis of the wave contour have involved evaluation of both systole and diastole. Shape of the systolic wave is dependent on the velocity of left ventricular ejection and the impedance to ejection. In addition, pressure reflection from the more distal vasculature produces a reflected wave that accounts in part for a dicrotic wave in diastole but also may augment the pressure in late systole. The magnitude of this wave and the timing of its appearance will influence the pressure in late systole.⁹⁹ An augmentation of central pressure in late systole has been identified with aging and with vascular disease, probably as a consequence of both an alteration in the artery wall at the reflecting sites and a more rapid transit back to the root of the aorta because of an increased pulse wave velocity. Clinical methodology to identify this late systolic augmentation has involved the recording of a peripheral pressure and use of a mathematical transfer function in an effort to replicate the central pressure waveform.¹⁰⁰ The reliability of this transfer function in a wide variety of individuals has been criticized.^{101,102}

The pressure wave reflection is not a single wave but an oscillation in the system that creates a decaying sinusoidal wave detectable throughout diastole. Analysis of the diastolic pressure decay has involved the use of a Windkessel model of the circulation.¹⁰³ This model depicts the arterial vasculature

as a hydraulic filter converting pulsatile flow from the left ventricle into steady flow in the capillary bed. The principle of the model is that the arterial tree is loaded in systole by the stroke volume and that after aortic valve closure, the diastolic pressure contour is a function of resistance, compliance, and inertance of an isolated arterial system. The site of measurement therefore is theoretically unimportant, because the system is closed and the pressure is transmitted within the system. The local differences in contour relate only to initial conditions that are not model-dependent.¹⁰³ The simplest Windkessel model includes a resistor and single capacitor (compliance) in parallel. This model can provide a single value for arterial compliance based on the slope of pressure decay in diastole. This simple model disregards reflected waves and cannot evaluate the influence of these oscillations on the slope of pressure decay. A more complicated model is the modified Windkessel, which incorporates a second compliance in parallel with the first. The model defines this second compliance as more distal and influencing predominantly the frequency and decay rate of the oscillatory pressure waves originating at reflecting sites in the smaller arteries.¹⁰³ The modified Windkessel thus identifies separately the total systemic large artery compliance (C_1) and the small artery compliance or elasticity (C_2). The nonlinear pressure/volume relationship of the large arteries renders the C_1 sensitive to pressure, as are all measurements relating to compliance of the large conduit arteries. In contrast, the C_2 appears to be largely independent of pressure so that its change can be more clearly attributed to an effect directly on the structure or function of the artery wall.¹⁰⁴ Application of this modified Windkessel model to evaluation of the arterial vasculature has been simplified by computer analysis incorporated in a noninvasive device that is currently marketed for clinical use.

Ultrasound Visualization

Accessible arteries (eg, carotid, brachial, radial, femoral) can be visualized by ultrasound to define wall thickness, wall function, and caliber.¹⁰⁵ Measurement precision is dependent on the transducer characteristics and the skill of the ultrasonographer in visualizing a true cross-section of the artery undergoing study. The carotid and brachial sites have provided information on wall thickness and systolic expansion.⁹³ Translation of systolic caliber change into an assessment of stiffness is dependent on the accuracy of a simultaneous pressure measurement usually made indirectly at another site.

Indirect Pressure/Volume Relationship

Attempts to define the pressure/volume relationship of arteries without their visualization have spawned a number of methods usually applied to single arteries. The brachial artery has been used most frequently. Cuff occlusion of the artery followed by gradual release leads to pulsatile changes in the volume of the artery that are transmitted into the overlying cuff as a pressure signal.¹⁰⁶ This pulsatility becomes maximal when the cuff pressure is at mean arterial pressure. The magnitude of the pressure (volume) signal is a crude guide to the compliance of the underlying artery. Because the artery underlying the cuff is only occluded distally; however, the length of the segment contributing to pulsatile volume changes may be quite variable.¹⁰⁷ The magnitude of pulsatil-

ity may then relate to the compliance of the wall and the length of the segment compressed.

Biopsy

Small arteries may be assessed directly by biopsy. The technique of buttocks biopsy popularized by Mulvany¹⁰⁸ has provided a wealth of data on 200- μ arteries, including wall thickness, wall/lumen ratio, and compliance characteristics.^{109,110} Remodeling of these arteries with a reduction of lumen size and increased wall thickness has been demonstrated in hypertension, perhaps as a consequence of endothelial dysfunction.¹⁰⁹

Evidence That Arterial Compliance, Elasticity, or Stiffness Are Markers for Disease

Endothelial dysfunction and alterations in function and structure of the underlying arterial wall are the earliest changes in aging and atherosclerosis. Because these changes are detectable earlier in small arterioles and microvasculature than in large conduit arteries, assessment of small artery function and structure is essential. Pulse wave analysis focusing on the diastolic decay and the oscillatory or reflective function of the distal vasculature (C_2) is an effective means of identifying abnormal small arteries. The numerical result (in mL/mm Hg \times 100) is age- and gender-dependent.⁸⁶ This age and gender dependence indicates that small arteries stiffen with age and that women have fewer or smaller arteries than men. Values for C_2 cannot distinguish functional from structural changes in the vasculature and cannot separate aging changes from atherosclerotic changes, although both may place the patient at risk for a vascular event.

Large artery stiffening occurs later than small artery stiffening and may be detected by a variety of instruments. Large artery elasticity (C_1) is reduced and pulse wave velocity may be increased, particularly in the aorta and lower extremities.¹¹¹ Brachial artery compliance may be reduced and the pulse pressure increased.¹¹² Augmentation index will be increased because of the rapid velocity of the reflected pulse wave's return to the aortic root.⁹⁹ A relationship between large artery stiffness and cardiovascular events has been explored with studies of pulse pressure, pulse wave velocity, and pulse contour analysis. Large artery stiffening as manifested by an increased pulse pressure has been identified as a "risk factor" for cardiovascular events.⁶⁰ This terminology is unfortunate, because unlike such risk factors as cholesterol, it is better viewed as a manifestation of advanced vascular disease that makes it "predictive" of events. It is a "risk marker" rather than a "risk factor."¹¹³ Pulse wave velocity has also been identified as an independent predictor of coronary and cardiovascular events.^{114–116}

Small artery stiffness or compliance should be an earlier marker for disease, because it is uniquely sensitive to NO.^{117,118} In an assessment of 419 screened patients, reduced small artery elasticity (C_2) assessed by pulse contour analysis was a significant predictor of cardiovascular events independent of aging.¹¹⁹ These preliminary observations need independent validation in larger patient populations with longer follow-up times.

Based on the evidence that detectable vascular disease should precede complications of atherosclerosis by a considerable number of years, a case could be made that aggressive intervention on cholesterol or BP should be confined to individuals with evidence of early vascular disease. Such an approach, which needs validation, might greatly enhance the effectiveness of interventions by avoiding treatment in patients not at risk for premature vascular events.

Evidence That Arterial Compliance, Elasticity, or Stiffness Track Regression Are Guides to Therapeutic Efficacy

The focus in managing hypertension has in recent years changed more toward artery protection than to BP control alone.¹²⁰ Recent trials suggest that BP reduction is not the sole determinant of artery protection. In particular, drugs such as angiotensin-converting enzyme inhibitors⁴¹ and angiotensin receptor blockers (ARBs)¹²¹ exert benefits beyond BP control. Furthermore, lipid reduction with statin drugs reduces morbid events without much if any BP-lowering.^{122,123} These benefits may be mediated at least in part by an improvement in endothelial dysfunction.³⁸ Therefore, pulse wave analysis might provide evidence for drug-induced small artery relaxation (increased C_2) and favorable structural effects. Sequential biopsy studies have already demonstrated an improvement in wall/lumen ratio in small arteries.^{124,125}

Unresolved Issues/Controversies

The multitude of methods used to measure "arterial stiffness" has generated confusion in the clinical literature. All agree that age stiffens at least some of the vasculature. Most studies support the concept that stiffening, whether assumed functionally or measured structurally, is associated with a higher risk of vascular morbid events. The data on individual vascular segments and on the relative sensitivity and specificity of differing methodologies remain controversial.

Yet to be confirmed is the reliability of changes in arterial stiffness as a guide to therapeutic efficacy. Time is a critical issue. Functional changes in response to a therapy might appear quickly, but structural reversal that influences arterial stiffness may be delayed. Documentation of the time-course of these effects and their relationship to morbid events requires long-term studies in large numbers of patients, preferably using multiple methods that will allow assessment of sensitivity and specificity.

Future Directions

Recognition that the disease we aim to treat is in the artery wall has stressed the need for monitoring techniques to identify effective treatments in trials and to track individual patients for the natural history of their disease and the efficacy of interventions. Although data using existing technologies are still limited in scope and follow-up, pulse wave analysis is particularly attractive because of its simplicity and apparent sensitivity. Pulse wave velocity also is relatively simple, but its confinement to the aorta and large conduit arteries limits its application to identifying structural changes in the large arteries.

Reproducibility and freedom from extraneous influences are critical to the application of methods for monitoring. Blood pressure measurement itself is neither reliably reproducible nor free from extraneous influences. Nonetheless, BP has served in population studies as a guide to cardiovascular risk. Its use in individuals, however, usually is buttressed by repeated measurements, either in the office or at home, by exclusion of outlying measurements, and by awareness of environmental conditions at the time of measurement. Assessment of the mechanical properties of the small and large arteries has the potential to be far more sensitive and specific for detecting CVD and the response to drug therapy than the BP alone. Early experience with vascular measurement techniques, including diastolic waveform analysis, has been encouraging, but as with BP some variability must be accepted and interpreted. The value of diastolic waveform analysis in sequential monitoring of patients is now being evaluated in several large-scale trials, including the National Heart, Lung, and Blood Institute's MESA study. Such data should help to establish the adequacy of this and other techniques to improve the early detection and to monitor management of CVD.

Conclusions

Measurements of arterial stiffness provide useful information regarding the health of the arterial vasculature. Large artery stiffness, as assessed by pulse pressure and pulse wave velocity, is age-dependent and reflects structural alterations in the conduit arteries that are accelerated by hypertension and atherosclerosis. Small artery stiffness, as assessed by pulse contour analysis, is also age-dependent but reflects function (endothelial NO-dependent) and structural changes. Methodology is now available to use arterial stiffness as a marker for premature disease and to track changes in stiffness as a guide to progression of disease and the impact of therapy.

Microalbuminuria and Proteinuria

The appearance of trace amounts of albumin (microalbuminuria, 30 to 300 mg/d) and larger amounts (frank proteinuria, >1 g/d) are associated with an increased risk for renal failure, heart disease, stroke, and cardiovascular mortality.^{126–135} The MONITORING Trends and Determinants of CARDIOVASCULAR Diseases (MONICA) study investigators established in 2782 Danish participants that albuminuria was a potent predictor for the development of ischemic heart disease, independent of other traditional risk factors such as male gender, hypertension, lipids, advancing age, and obesity.¹²⁶ The overall impact of albuminuria in the MONICA study was that the untoward cardiovascular effect associated with conventional risk factors was more than doubled in subjects with microalbuminuria. The level of urinary protein excretion better-refines cardiovascular risk and predicts cardiovascular mortality in subjects with diabetes.^{128–134} Miettinen et al¹²⁷ found an association between amount of urinary protein excretion and risk of stroke and lower extremity amputation in a cohort of subjects that was independent of diabetes status and traditional risk factors.

Pathophysiology

Although the mechanism whereby proteinuria confers increased cardiovascular risk has not been fully elucidated, there are a number of plausible explanations. It is possible that increased urinary protein excretion may adversely affect traditional risk factors or is a harbinger of coclustering of traditional risk factors. In several trials, subjects with albuminuria were more likely to be smokers, have elevated BP, have dyslipidemia,^{126–128} and demonstrate features of the metabolic syndrome, including salt sensitivity and insulin resistance. Alternatively, there is compelling evidence that urinary protein is a marker of impaired endothelial function not only in the glomerulus but also throughout the vascular tree.¹³⁶ This rather appealing hypothesis suggests that proteinuria may be a marker of widespread vascular damage, endothelial dysfunction, enhancing atherogenesis, or, perhaps, it may be itself a marker of CVD. Moreover, the appearance or disappearance of urinary protein may track progression/regression of atherosclerosis. Thus, it is possible that proteinuria completely captures the association between impaired vascular function and progression to cardiovascular events and thereby would serve as an important surrogate marker for progression to CVD. This particular marker is appealing in that it is easily measured and relatively inexpensive, heralding its potentially broad use for cardiovascular risk assessment and as an important marker for monitoring the adequacy of specific interventions.

Methodology

Approximately 40% of urinary protein consists of albumin, which is normally filtered to a small degree. Qualitative screening for urinary protein is achieved with high sensitivity (80%) by dipstick techniques (eg, Albustix) when values exceed 200 mg/L, whereas rapid qualitative latex agglutination tests are sensitive to measures as low as 20 mg/L. Dipstick tests are relatively insensitive to initial increases in glomerular permeability, thereby limiting their usefulness for replacing direct measures of proteinuria. Direct urinary protein excretion can be quantified by radioimmunoassay, immunochemical, and other techniques, and may be affected by plasma albumin concentrations. For this reason, albumin excretion is best expressed as a function of creatinine or as a clearance. Timed 24-hour urine collection has been the gold standard for quantifying urinary protein excretion but is limited by poor compliance and a cumbersome collection technique. Modifications to the 24-hour collection to include shorter collection time (12- or 4-hour collection after a standard water load or first morning void) have yielded to the simplicity of measuring a spot protein/creatinine ratio. The correlation between spot and 24-hour collection ranges between 0.62 and 0.92, but there are a paucity of data to characterize the precision or bias in these measures. Ultimately, the spot protein/creatinine ratio provides an approximation of the level of proteinuria. The exact level usually is not required for clinical decision-making.¹³⁷

Evidence That Microalbuminuria and Proteinuria Are Surrogate Risk Markers

A strong and consistent association between proteinuria and renal disease has been demonstrated in both diabetic and

nondiabetic patients, in subjects with or without hypertension, and in multi-ethnic populations.^{127,129,132,135} A plethora of secondary end point data from clinical trials facilitate the exploration of proteinuria as a surrogate marker of renal disease and, indirectly, as a marker of cardiac morbidity and mortality data in subjects with chronic kidney disease.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL),¹³⁸ the Irbesartan Diabetic Nephropathy Trial (IDNT),¹³⁹ and the African American Study of Kidney Disease and Hypertension (AASK)¹³⁵ are hypertension intervention trials that demonstrate the predictive power of proteinuria on renal end points. Moreover, the design of these trials sought to determine whether specific renoprotective drug regimens could confer benefit beyond their ability to control BP. Consistently, these intervention trials made serial measures of urinary protein to assess the adequacy of urinary protein excretion for predicting dialysis, transplantation, significant decline in renal function, or death. The results provide overwhelming support for the risk prediction of the level of proteinuria at study entry for renal end points. Moreover, in the RENAAL trial, the residual level of proteinuria 6 months after intervention predicted an excess risk of ESRD. Of relevance to the hypothesis that proteinuria may serve as a surrogate for cardiovascular events, RENAAL, IDNT, and AASK tested the benefits of blocking the renin-angiotensin system (RAS) compared with equivalent levels of BP control without RAS blockade. Proteinuria was reduced better with RAS-blocking regimens than with regimens that did not contain RAS blockade. Moreover, RAS blockade was better at reducing renal clinical end points, thereby lending strong support to the role of proteinuria as a surrogate for renal function. Based on these results, clinicians fully embrace proteinuria as an important surrogate for renal disease. The amelioration of proteinuria is a primary clinical strategy for treating patients with diabetic and nondiabetic chronic kidney disease. The American Diabetes Association and the National Kidney Foundation recommend angiotensin-converting enzyme inhibitors or ARBs as preferred therapy for diabetic subjects with chronic kidney disease.¹³⁷

Considerably less data directly assess the role of proteinuria as a surrogate marker for diffuse atherothrombosis and cardiovascular events. While the trials in patients with chronic kidney disease were able to determine the role of proteinuria in predicting risk of subsequent renal events, they were underpowered for correlating the benefit of reducing proteinuria for nonrenal cardiovascular events. Moreover, cursory data available from the renal trials yield inconsistent findings. In the RENAAL trial, the ARB regimen was superior for preventing incident diabetes and heart failure, thus suggesting that the intervention targeting reduction in proteinuria was best able to reduce subsequent cardiovascular events. However, in the IDNT trial, whereas treatment with an ARB improved proteinuria and renal outcomes, it was the regimen containing the calcium-channel blocker amlodipine that tended to improve nonrenal cardiovascular events.¹³⁹ Important to the issue of proteinuria as a surrogate marker of CVD, the use of amlodipine in this trial was associated with worsening proteinuria, creating dissociation between protein-

uria, renal protection, and cardiovascular risk reduction. The relatively low number of cardiovascular events in the IDNT trial, the limited usefulness of post hoc analyses for clinical decision-making, and the differences in BP between the study arms are factors that limit the ability of the IDNT trial to adequately test the usefulness of proteinuria as a surrogate marker for atherothrombosis and CVD.

The usefulness of proteinuria as a surrogate marker for cardiovascular events can be assessed indirectly from examining recent clinical trials in hypertension that test putative superiority of various monotherapy strategies for reducing cardiovascular events.^{41,121,140–142} If RAS blockade were a superior strategy for cardiovascular risk reduction, it would demonstrate that a regimen that reduces proteinuria also retards CVD progression. This notion is clearly supported by the Heart Outcomes Prevention Evaluation Study (HOPE), in which subjects at high risk for future cardiovascular events had a 22% risk reduction with the RAS blocker ramipril when compared with placebo.⁴¹ Further support for the hypothesis that RAS blockade, and indirectly a regimen that reduces proteinuria, improves cardiovascular outcomes is contributed by the Losartan Intervention For Endpoint Reduction Study (LIFE), in which high-risk subjects with left ventricular hypertrophy achieved a 13% risk reduction in cardiovascular events from the RAS blocker losartan when compared with a β -blocker-based regimen.¹²¹ However, the majority of trials that compare RAS blockade to other strategies (eg, calcium-channel blockers, diuretics, β -blockers, α -blockers) for cardiovascular risk reduction demonstrate the benefits of lowering BP rather than the superiority of any particular drug class in cardiovascular risk reduction.¹⁴³ Thus, although RAS blockade is clearly a superior strategy for reducing proteinuria and reducing the incidence of ESRD, not enough evidence exists to extend the renal benefits diffusely to the cardiovascular system. The inability to demonstrate that interventions designed to reduce proteinuria also confer cardiovascular risk reduction is a limitation of the study design of the trials available for review. The trials focused on renal end points had too few nonrenal cardiovascular events on which to draw any meaningful conclusions, whereas trials that focused on cardiovascular end points frequently failed to obtain serial measures of proteinuria. Thus, proteinuria remains a viable and important marker of cardiovascular risk; however, additional trials with the appropriate study design and power are necessary to fully elucidate the potential of proteinuria as a surrogate marker for atherothrombosis and CVD.

Evidence That Microalbuminuria and Proteinuria Are Guides to Therapeutic Efficacy

Whereas the level of proteinuria is a powerful predictor of subsequent progression to renal failure, improvement in proteinuria is not tightly correlated with improvement in renal function. In the AASK trial,¹³⁵ although treatment with ramipril was associated with slowing the progression to ESRD at all levels of baseline proteinuria, amlodipine was associated with better preservation of glomerular filtration rate than was ramipril in subjects with small amounts of proteinuria (<300 mg/d). The improvement in glomerular

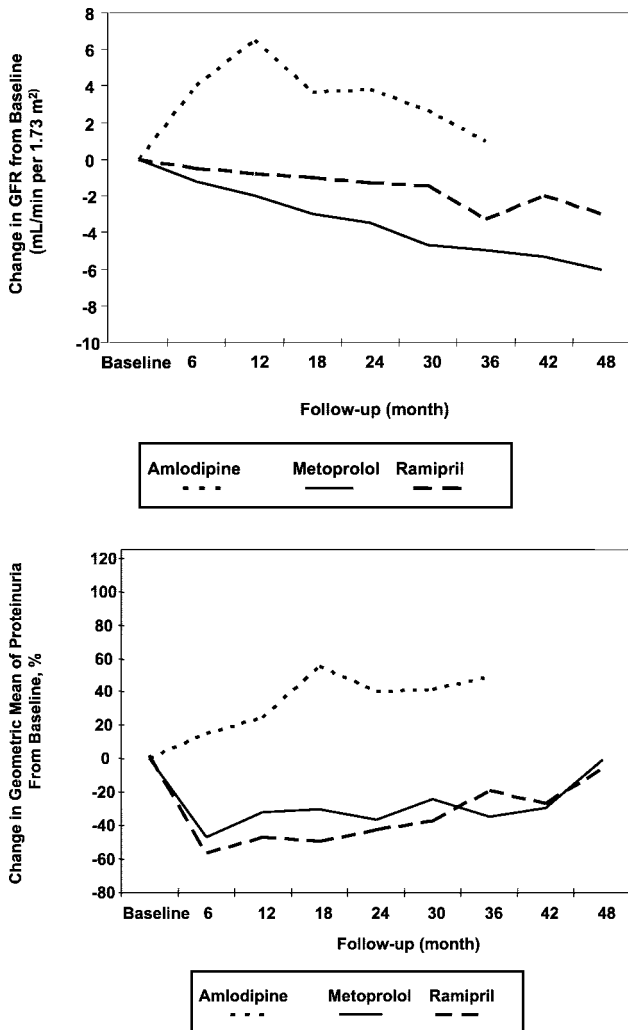


Figure 2. Change in renal function over time (top) was not associated with change in urinary albumin (bottom) in 1075 participants in the African American Study of Kidney Disease and Hypertension (AASK).¹⁴⁴ Amlodipine (dashed line) was associated with an increase in proteinuria and renal function. Thus, proteinuria was not a surrogate for renal events in the AASK trial. Metoprolol indicated by solid line; ramipril, broken line.

filtration rate associated with amlodipine occurred within the first few months of this trial, representing the ability of amlodipine to cause an acute vasodilatory response, improving renal blood flow and glomerular filtration rate primarily by a hemodynamic mechanism. However, in AASK participants with >300 mg/d of proteinuria, amlodipine accelerated the decline in renal function, necessitating the early termination of the amlodipine arm. Thus, in AASK, it is possible that the relationship between baseline proteinuria and improvement in renal outcomes could in part have reflected a greater vasodilatation reserve (amlodipine) and reduction in proteinuria (ramipril) (Figure 2).¹⁴⁴

In a patient-level meta-analysis, statistical adjustment for proteinuria indicates that treatment of renal insufficiency with RAS blockade yields a residual beneficial effect slowing progression to ESRD beyond improving proteinuria and lowering BP.¹⁴⁵ This suggests that benefits of RAS blockade are not completely explained by reduction in proteinuria. The

lack of clarity between improvement in proteinuria and improvement in renal function has led to hesitancy in accepting proteinuria as a surrogate marker for renal end points by the Food and Drug Administration. It appears that the Food and Drug Administration will consider conferring provisional approval of agents that retard proteinuria pending the results of outcome trials that measure traditional end points.

Unresolved Issues, Controversies, and Future Directions

An intervention trial designed at determining the adequacy of proteinuria as a surrogate marker for CVD is an unmet need and represents an opportunity for future trials.

The Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE) seeks to determine whether valsartan is better able to reduce cardiac events in subjects with hypertension and high risk for CVD when compared with amlodipine. The essential hypothesis of this trial is that RAS blockade will reduce proteinuria, improve endothelial dysfunction, and ameliorate angiotensin-II-mediated untoward vascular effects.¹⁴⁶ The beneficial effect of valsartan over amlodipine for the reduction in proteinuria has been demonstrated in the MicroAlbuminuria Reduction with VALsartan (MARVAL) trial.¹⁴⁷ The VALUE trial investigators obtained baseline measures of proteinuria and creatinine and will therefore contribute important new information to the association between proteinuria, renal function, and cardiovascular events when the trial ends in late 2003.

The usefulness of proteinuria as a surrogate marker of CVD is currently being directly assessed in the National Institutes of Health-funded Chronic Renal Insufficiency Cohort study (CRIC). The long-term follow-up of the 3000 subjects with renal insufficiency from hypertension and/or diabetes began in May 2003. Proteinuria is being quantified and measured serially along with other markers (eg, circulating markers of inflammation, coronary calcium scores, cardiac echo) and will be correlated to cardiovascular events. Surrogate markers for CVD, including proteinuria, are also being studied in 900 black subjects with hypertensive nephropathy in the AASK cohort trial. The long-term follow-up in these cohort studies will help determine the predictive power of proteinuria compared with other surrogate markers; however, because the cohort studies are not intervention trials, any associations that are uncovered will not fully determine whether proteinuria could emerge as a surrogate for atherothrombotic events (eg, stroke, MI, and cardiovascular mortality).

Conclusions

Urinary albumin is a sensitive and specific measure that can be easily applied in the clinical setting. Urinary albumin, whether in the microalbuminuria range (30 to 300 mg/d) or frank proteinuria (≥ 1 g), is an important marker for vascular disease of the kidney, heart, and brain. The presence of albuminuria confers cross-sectional and longitudinal CVD risk. The risk prediction of proteinuria is supported by clinical trial data in which interventions that reduce proteinuria also reduce risk for the development of ESRD. Although the

TABLE 2. Clinical Applicability of Potential Surrogate Functional Markers for Cardiovascular Disease

	Methodology Available/ Convenient	Methodology Standardized	Sensitivity/ Specificity for Disease	Identifies Severity of Disease	Tracks With Treatment of Disease
Endothelial dysfunction	+	+	++	++	+
Blood pressure	+++	++	+	++	+++
Arterial stiffness	++	+	++	++	+
Albuminuria	++	++	++	++	++
Ankle-brachial index	+++	+++	+	++	?
Serum collagen marker	+	+	?	?	?

predictive power of proteinuria is compelling, reduction in proteinuria neither adequately predicts improvement in cardiovascular outcomes nor completely captures the association between proteinuria and CVD and thereby fails as a true surrogate end point. Therefore, although proteinuria may not replace the collection of hard cardiovascular end points, it remains an important clinical target for determining the optimal strategy for target organ protection.

Other Functional Surrogate Markers

As noted, other putative functional markers are discussed briefly. A summary of the usefulness of all functional surrogates is shown in Table 2.

Ankle-Brachial Systolic Pressure Index

The Doppler pressure gradient from the brachial artery to the foot is used to identify plaque obstruction to blood flow to the lower extremities. It has been identified to serve as a useful marker in elderly or diabetic individuals for asymptomatic peripheral vascular disease.¹⁴⁸ As a marker for advanced obstructive disease, an unlikely marker for a favorable effect of therapy, and an insensitive guide to the presence of atherosclerotic disease in asymptomatic younger individuals, it probably cannot serve as a valuable surrogate marker for screening purposes.

B-Type Natriuretic Peptide

The plasma level of this cardiac hormone has emerged as a remarkably sensitive and specific guide to the presence of heart failure in symptomatic patients and to left ventricular dysfunction in asymptomatic subjects. The concentration is a powerful determinant of adverse outcome in heart failure¹⁴⁹ and appears also to correlate with a favorable therapeutic effect on outcome.¹⁵⁰ As such, plasma B-type natriuretic peptide may ultimately prove to be a reliable surrogate marker for the severity of left ventricular remodeling and perhaps a sensitive and specific marker for the progression of cardiac disease in ischemic and nonischemic forms of cardiomyopathy.¹⁵¹ Because plasma B-type natriuretic peptide should be normal except in the presence of advanced left ventricular dysfunction, its use as a surrogate for atherothrombotic disease will likely be limited.

Composite Disease Markers

Because none of the surrogate markers discussed in this section provides highly sensitive and specific recognition of progressive CVD, an attractive strategy has been to use a combination of these evaluations to better-define the presence of early disease. This approach requires a scoring system for the biological detection of early disease, much like the Framingham risk score has evolved as a measure of the statistical risk of disease. One such scoring system of 10 individual tests has been advocated.¹⁵² Long-term data in large numbers of patients are required to confirm the usefulness of such a composite score and the added value of individual tests performed.

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