

# Prognostic Significance of Endothelial Dysfunction in Hypertensive Patients

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**Background**—Forearm endothelial dysfunction, characterized by an impaired vasodilating response to acetylcholine (ACh), may be associated with several cardiovascular risk factors, including essential hypertension. Although the prognostic value of coronary endothelial dysfunction has been demonstrated, that of forearm endothelial dysfunction is still unknown.

**Methods and Results**—Endothelium-dependent and -independent vasodilation was investigated in 225 never-treated hypertensive patients (age, 35 to 54 years) by intra-arterial infusion of increasing doses of ACh and sodium nitroprusside. Patients were divided into tertiles on the basis of their increase in ACh-stimulated forearm blood flow (FBF) from basal: group 1, from 30% to 184%; group 2, from 185% to 333%; and group 3, from 339% to 760% increase from basal. During a mean follow-up of 31.5 of months (range, 4 to 84 months), there were 29 major adverse events at the cardiac (n=19), cerebrovascular (n=9), or peripheral vascular (n=1) level. Events included myocardial infarction, angina, coronary revascularization procedures, stroke, transient cerebral ischemic attack, and aortoiliac occlusive disease. Event rate per 100 patient-years was 8.17, 4.34, and 2.02 in the first, second, and third tertiles of peak percent increase in FBF during ACh infusion. The excess risk associated with an FBF increase in the first tertile was significant (relative risk, 2.084; 95% CI, 1.25 to 3.48;  $P=0.0049$ ) after controlling for individual risk markers, including 24-hour ambulatory blood pressure.

**Conclusions**—Our data suggest that forearm endothelial dysfunction is a marker of future cardiovascular events in patients with essential hypertension. (*Circulation*. 2001;104:191-196.)

**Key Words:** endothelium ■ cardiovascular diseases ■ hypertension

Many experimental and clinical studies have shown a strong link between atherosclerosis and cardiovascular risk.<sup>1-5</sup> Atherosclerosis is a progressive process that initially involves endothelial dysfunction and accumulation and peroxidation of intimal lipids, followed by release of inflammatory cells and growth factors, resulting in vascular smooth muscle cell (VSMC) proliferation and collagen matrix production.<sup>6-8</sup> The normal endothelium—an autocrine, paracrine, and endocrine organ—plays a key role in regulating vascular tone, thrombogenesis, lipid breakdown, inflammation, and vessel growth.<sup>9-11</sup> There is growing evidence that endothelial dysfunction may influence the progression of atherosclerotic lesions.<sup>8,11,12</sup>

Traditional risk factors such as hypertension,<sup>13-15</sup> cigarette smoking,<sup>16</sup> diabetes,<sup>17</sup> age,<sup>18</sup> and hypercholesterolemia<sup>19</sup> induce coronary and brachial artery endothelial dysfunction owing to decreased bioavailability of nitric oxide (NO). A dysfunctioning endothelium may lose its ability to exert its

protective effect on the vascular system by reducing its antiatherosclerotic and antithrombotic actions and thus playing a key pathophysiological role in the development and progression of the atherosclerotic process.

Endothelial function is most commonly measured as the vasodilating response to physical or pharmacological stimuli such as shear stress, acetylcholine (ACh), bradykinin, thrombin, substance P, and serotonin.<sup>11</sup> Each agonist acts through a cellular membrane receptor, with signal transduction operating through G proteins. In this way, it has recently been demonstrated that depressed coronary endothelial function in humans may be associated with myocardial ischemia.<sup>20,21</sup> Furthermore, cholesterol-lowering agents significantly improve outcomes in secondary<sup>3-5</sup> and primary<sup>22</sup> prevention, and it has been speculated that these beneficial effects may be mediated, at least in part, by an improvement in endothelial dysfunction. More recently, it has been shown that coronary endothelial vasodilator dysfunction predicts long-term ath-

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erosclerotic disease progression and cardiovascular events rate.<sup>23,24</sup> Thus, coronary endothelial vasoreactivity may provide diagnostic and prognostic information in patients at risk for coronary artery disease (CAD). At present, however, no data exist on the prognostic significance of forearm endothelial dysfunction evaluated by strain-gauge plethysmography.

On the basis of these observations, the aim of this study was to evaluate prospectively the outcomes in initially untreated and uncomplicated hypertensive patients with forearm endothelial dysfunction.

## Methods

### Study Population

A total of 225 outpatients at Catanzaro University Hospital, 106 men and 119 women 35 to 54 years of age (mean±SD, 46.4±5.3 years) with well-documented history of essential hypertension and complete follow-up data who were enrolled between March 1992 and April 2000, are included in the present analysis. All patients were white and underwent physical examination and review of their medical histories. Causes of secondary hypertension were excluded by clinical and biochemical tests. At the time of vascular evaluation, none of the patients had a history or clinical evidence of angina, myocardial infarction (MI), valvular heart disease, diabetes, hyperlipidemia, peripheral vascular disease, coagulopathy, or any disease predisposing them to vasculitis or Raynaud's phenomenon. The following risk factors for atherosclerosis were assessed at the time of the first evaluation: glucose, cholesterol, triglycerides, smoking, and a positive family history of CAD. Body mass index ranged between 24.0 and 28.0 kg/m<sup>2</sup>. All participants had never been treated with antihypertensive drugs.

The local ethics committee approved the study, and all participants gave written, informed consent for all procedures.

### Blood Pressure Measurements

A physician measured blood pressure (BP) 3 times using a mercury sphygmomanometer with the patient seated for ≥5 minutes, and the mean of the last 2 measurements was used. Hypertension was defined as systolic BP ≥160 mm Hg, diastolic BP ≥95 mm Hg, or both.

Ambulatory BP monitoring was obtained with A&D TM 2420 and A&D TM 2421 (Takeda) recorders. Recordings were taken every 10 minutes during the day (from 7 AM to 11 PM) and every 20 minutes during the night (from 11 PM to 7 AM). The patients were invited to observe these periods of rest and activity closely.

### Vascular Function

All studies were performed at 9 AM after subjects had fasted overnight, with the subjects lying supine in a quiet, air-conditioned room (22°C to 24°C); the protocol previously described by Panza et al<sup>13</sup> and subsequently used by our group<sup>15,25,26</sup> was employed for the present study. Subjects were requested to refrain from smoking ≥4 hours before starting the examination. All patients underwent measurement of forearm blood flow (FBF) and BP during intra-arterial infusion of saline, ACh, and sodium nitroprusside (SNP) at increasing doses. All participants rested 30 minutes after artery cannulation to reach a stable baseline before data collection; measurements of FBF and vascular resistance (VR), expressed in units, were repeated every 5 minutes until stable. Endothelium-dependent and -independent vasodilation was assessed by a dose-response curve to intra-arterial ACh infusions (7.5, 15, and 30 μg · mL<sup>-1</sup> · min<sup>-1</sup>, each for 5 minutes) and SNP infusions (0.8, 1.6, and 3.2 μg · mL<sup>-1</sup> · min<sup>-1</sup>, each for 5 minutes), respectively. The sequence of administration of ACh and SNP was randomized to avoid any bias related to the order of drug infusion. The drug infusion rate, adjusted for forearm volume of each subject, was 1 mL/min.

### Follow-Up and Cardiovascular Events

Follow-up included periodic control visits in the outpatient clinic of our university hospital for most patients. To improve long-term follow-up, a questionnaire was also mailed to family physicians. All patients were treated with the purpose of reducing clinic BP to <140/90 mm Hg through standard lifestyle and pharmacological treatment. Antihypertensive agents included diuretics, β-blockers, ACE inhibitors, calcium channel blockers, angiotensin II receptor antagonists, and α<sub>1</sub>-blockers alone or in various associations. Contact with family physicians and telephone interviews were periodically undertaken to assess the incidence of major cardiovascular events. All information regarding potential cardiovascular events was validated by source data, including hospital record forms, death certificates, and other available original documents.

The following cardiovascular events were assessed during long-term follow-up: fatal and nonfatal MI, fatal and nonfatal stroke, transient cerebral ischemic attack (TIA), unstable angina, coronary revascularization procedures (bypass surgery or angioplasty), and symptomatic aortoiliac occlusive disease documented with angiography. MI was defined as an increase in creatine kinase exceeding 2-fold the upper limit and new ST elevation ≥2 leads. Unstable angina was defined by typical chest pain associated with ischemic ECG changes and successively documented by provocative tests (treadmill exercise test or/and stress echocardiography, myocardial scintigraphy, or coronary angiography). TIA was defined by physician diagnosis of any sudden focal neurological deficit that cleared completely in <24 hours.

Most patients were referred periodically to our university hospital for clinical and BP control and other diagnostic procedures.

### Drugs

ACh (Sigma) was obtained from commercially available sources and freshly diluted to the desired concentration by the addition of saline. SNP (Malesci) was diluted in 5% glucose solution immediately before each infusion and protected from light with aluminum foil.

### Statistical Analysis

Standard descriptive and comparative analyses were undertaken. Events rate is reported as the number of events per 100 patient-years based on the ratio of the number of events observed to the total number of patient-years of exposure up to the terminating event or censor. For the patients without events, the date of censor was that of the last contact with the patient. For patients who experienced multiple events, survival analysis was restricted to the first event. Survival curves were estimated by use of the Kaplan-Meier product-limit method and compared by using the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated by use of the stepwise Cox semiparametric regression model. The assumption of linearity for the Cox model was tested through visual inspection, and no violation of proportional hazards was found. We tested the following variables: age, sex, body mass index, triglycerides, serum cholesterol, smoking habits (previous or current smokers or never smoked), and clinic and ambulatory BP. FBF was tested either as a continuous variable or by tertiles. Significant differences were assumed to be at *P*<0.05. All group data are reported as mean±SD.

## Results

### Study Population

Intra-arterial infusion of ACh caused a dose-dependent and significant increase in FBF and decrease in forearm VR. The FBF increments from basal at the 3 incremental doses of ACh were 1.9±1.9 mL · 100 mL<sup>-1</sup> tissue · min<sup>-1</sup> (55%), 3.0±1.9 mL · 100 mL<sup>-1</sup> tissue · min<sup>-1</sup> (142%), and 10.8±6.3 mL · 100 mL<sup>-1</sup> tissue · min<sup>-1</sup> (293%). At the highest dose of ACh (30 μg/min), FBF increased to 14.6±9.0 mL · 100 mL<sup>-1</sup> tissue · min<sup>-1</sup>, and VR decreased to 10.1±5.0 U. Intra-arterial infusion of ACh caused no changes in BP or heart rate values.

**TABLE 1. Subject Characteristics by Tertiles of Peak Percent Increase in FBF During ACh Infusions**

Data	All (n=225)	First Tertile (n=75)	Second Tertile (n=75)	Third Tertile (n=75)	P
Sex, M/F	106/119	46/29	37/38	23/52	0.0001
Age, y	46.4±5.3	47.1±5.8	46.0±5.2	46.1±5.1	0.384
Women in postmenopausal/HRT	40/2	12/0	12/1	16/1	0.615
BMI, kg/m <sup>2</sup>	26.0±1.0	26.2±1.1	26.1±0.9	25.9±1.2	0.222
Current smoker, %	24.0	26.6	24.0	21.3	0.746
Total cholesterol, mmol/L	4.8±0.4	4.9±0.4	4.9±0.5	4.8±0.5	0.323
Triglycerides, mmol/L	1.31±0.2	1.33±0.2	1.33±0.2	1.30±0.2	0.571
Fasting glucose, mmol/L	5.05±0.5	5.1±0.6	5.0±0.5	5.0±0.5	0.420
BP, mm Hg					
Clinic systolic	158±13	160±12	158±14	156±13	0.173
Clinic diastolic	95±7	96±8	95±8	94±7	0.283
Clinic mean	116±8	117±8	116±9	115±7	0.138
24-h Systolic	148±9	150±9	149±9	148±8	0.371
24-h Diastolic	89±7	90±6	89±8	88±8	0.256
ACh-stimulated FBF, % increase	293±176	125±42	249±41	503±123	0.0001
ACh-stimulated VR, U	10.1±5	15.1±4.8	9.1±2.2	6.02±2.1	0.0001
SNP-stimulated FBF, % increase	350±90	346±89	345±90	358±90	0.614
SNP-stimulated VR, U	7.5±2.3	7.8±2.8	7.4±2.3	7.2±1.9	0.287

HRT indicates hormone replacement therapy; BMI, body mass index.

The peak percent increase on FBF during ACh infusion was considered both as a continuous variable and according to specific tertiles: from a 30% to 184% increase from basal (first tertile), from a 185% to 333% increase from basal (second tertile), and from a 339% to 760% increase from basal (third tertile).

During SNP infusion, a significant increase in FBF and a decrease in forearm VR were observed, but no significant differences were found between tertiles. Peak increases in FBF in the 3 tertiles were 346±89%, 345±90%, and 358±90%, respectively (*P*=0.614 by ANOVA); the increases in VR were 7.8±2.8, 7.4±2.3, and 7.2±1.9 (*P*=0.287 by ANOVA).

Table 1 reports the clinical, humoral, and hemodynamic characteristics of the study population by tertiles of ACh-stimulated FBF. In the total population, the baseline clinic and ambulatory BP values were 158/95±13/7 and 148/89±9/7 mm Hg. After 6 months and 1 year of treatment, the clinic BP values decreased to 140/87±12/8 and 136/84±10/

9 mm Hg, respectively. The BP reduction was similar in the 3 tertiles. Finally, the different treatment strategy in the study population, divided by ACh tertiles, is reported in Table 2.

### Outcome Events

During a mean follow-up period of 31.5±23.9 months (range, 4 to 84 months), there were 29 new cardiovascular morbid events (4.9 events per 100 patient-years) at the cardiac (n=19), cerebrovascular (n=9), or peripheral vascular (n=1) level, as reported in Table 3. In particular, there were 6 patients with MI (1 fatal), 10 with unstable angina pectoris, 3 with coronary revascularization procedures, 7 with stroke (1 fatal), 2 with transient cerebral ischemia, and 1 with new-onset aortoiliac occlusive disease. Indications for the revascularization procedures were put forward by physicians not involved in this study.

As reported in Figure 1, the rate of total (fatal plus nonfatal) cardiovascular events (per 100 patient-years) was 8.17, 4.34, and 2.02 in the first, second, and third tertiles of

**TABLE 2. Antihypertensive Drugs in the Study Population by Tertiles of ACh-Stimulated FBF**

	First Tertile (n=75), n	Second Tertile (n=75), n	Third Tertile (n=75), n	P
ACE inhibitors	22	19	17	0.772
Angiotensin II receptor antagonists	3	4	3	0.909
α <sub>1</sub> -Blockers	2	2	3	0.871
β-Blockers	6	5	6	0.947
Calcium channel blockers	11	14	12	0.851
Diuretics	3	2	3	0.880
Associations	28	29	31	0.945

**TABLE 3. Cardiovascular Events in the Study Population by Tertiles of ACh-Stimulated FBF**

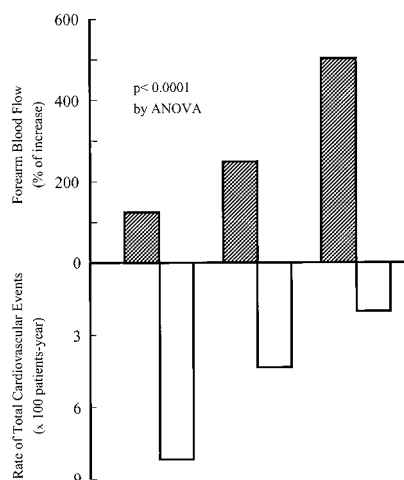
	First Tertile (n=75), n	Second Tertile (n=75), n	Third Tertile (n=75), n
Acute MI	4	1	
Fatal	1		
Stroke	3	2	1
Fatal	1		
Unstable angina	5	3	2
Coronary revascularization procedures	2	1	
Transient cerebral ischemia		1	1
Aortoiliac occlusive disease	1		

peak percent increase in FBF during ACh infusion. Event-free survival curves in the 3 tertiles of FBF are graphically reported in Figure 2. The cumulative cardiovascular events rate in the first tertile was 57.2% at 7 years compared with a cumulative rate of 14.4% in the third tertile ( $P=0.0012$ , log-rank test). Differences across tertiles remained significant ( $P=0.0166$ ) after exclusion of soft cardiovascular events (TIA, unstable angina, coronary revascularization procedures, and aortoiliac occlusive disease).

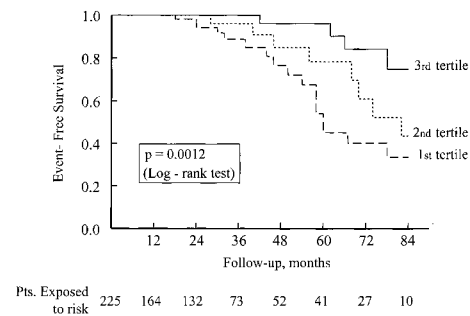
Finally, when we divided the study population in the SNP subgroups, the rate of total cardiovascular events (per 100 patient-years) was 4.3, 5.9, and 4.5 in the first, second, and third tertiles of peak percent increase in FBF (log-rank=1.664,  $P=0.44$ ).

### Multivariate Analysis

To identify the effect of endothelial dysfunction and the classic risk factors for atherosclerosis as independent predictors of cardiovascular events, we performed a multivariate Cox regression analysis. As shown in Table 4, the only independent predictors of cardiovascular events were mean 24-hour ambulatory BP and the peak percent increase in FBF. In the first tertile of peak percent increase in FBF, event risk



**Figure 1.** Rate of total (fatal and nonfatal) cardiovascular events and mean values of percent increase in ACh-stimulated FBF in 3 tertiles.



**Figure 2.** Kaplan-Meier analysis. Event-free survival curves in hypertensive patients (pts) were subdivided into tertiles of FBF.

was about twice that in the third tertile (adjusted hazard ratio, 2.084; 95% CI, 1.249 to 3.477;  $P=0.0049$ ). When the peak percent increase in FBF entered the equation as a continuous variable, results did not change (adjusted hazard ratio for every 1% increase in FBF, 0.994; 95% CI, 0.991 to 0.998;  $P=0.0014$ ). A marked risk gradient for adverse cardiovascular events was noted across the tertiles of FBF after adjustment for other covariates.

### Discussion

This study shows for the first time that forearm endothelial dysfunction is a marker for future cardiovascular morbid events in initially untreated and uncomplicated subjects with essential hypertension. This relation, statistically significant and clinically consistent, persisted after adjustment for established risk factors for atherosclerosis. Results did not change when FBF changes were analyzed as a continuous variable or divided by tertiles. We used the tertiles partition because currently there is no agreed-on definition of normal FBF change.

Our data are in agreement with those recently reported by Suwaidi et al<sup>23</sup> and Schächinger et al,<sup>24</sup> who demonstrated a link between endothelial coronary dysfunction and subsequent cardiovascular events. The basic mechanisms by which forearm endothelial dysfunction may predispose to subsequent cardiovascular morbid events are largely unknown. The reduced NO bioavailability that characterizes the endothelial dysfunction may induce important steps in the appearance and progression of the atherosclerotic lesions, including monocyte and leukocyte adhesion and platelet-vessel wall interaction.<sup>6-8,27</sup> NO also reduces vascular tone, decreases endothelial permeability,<sup>28</sup> and inhibits VSMC migration and proliferation in vitro and in vivo.<sup>6-8</sup> Thus, a persistent decrease in NO availability might represent a pivotal basic

**TABLE 4. Independent Predictors of Cardiovascular Morbid Events (Cox Model)**

Variable	Adjusted Hazard Ratio (95% CI)	P
24-h Mean BP	1.100 (1.045-1.158)	0.0002
FBF		
Tertile 1 vs 2	1.027 (0.570-1.851)	0.9270
Tertile 1 vs 3	2.084 (1.249-3.477)	0.0049

mechanisms predisposing to clinical adverse events associated to human atherosclerosis.

### Hypertension, Endothelial Function, and Atherosclerosis

An abnormal endothelial function has been implicated in the pathophysiology of essential hypertension.<sup>12–14</sup> Endothelial cells produce some potent vasoactive substances such as the vasodilator molecule NO and the vasoconstrictor peptide endothelin-1. Reduction of NO synthesis and/or its increased inactivation by oxygen free radicals may account for the increased VR in hypertensive patients and contribute to clinical consequences of this condition such as vascular and cardiac hypertrophy, CAD, and stroke. The mechanisms underlying reduced NO availability in human essential hypertension are almost certainly multifactorial; however, there is substantial evidence that NO bioavailability is reduced because of oxidative inactivation by excessive production of superoxide anions.<sup>12,29</sup> In the vascular wall, an increase in oxidative stress is thought to modify several important physiological functions. Regulation of vascular tone and blood flow, increased platelet and monocyte adhesion to the endothelium, and control of cellular growth are strongly influenced by reactive oxygen species. These phenomena ultimately modulate vessel diameter and remodeling and formation of atherosclerotic lesions.<sup>6–8,27,28</sup> These vascular abnormalities that induce structural and mechanical changes may offer important insights into the development and progression of vasculature-initiated end-organ damage in cardiovascular diseases. Thus, a depressed endothelium-dependent vasodilation may be considered an earlier modification, present in essential hypertension and other cardiovascular risk factors, that may promote and develop the coronary and extracoronary atherosclerotic process by stimulating the proliferation of VSMCs and fibroblasts. Finally, chronic endothelial dysfunction often may be associated with an erosion and/or rupture of the atherosclerotic plaque that promotes plaque instability and acute vascular syndromes.<sup>8</sup>

### Evaluation of End Points in Hypertension

The benefits of antihypertensive treatment in decreasing both cerebrovascular and cardiac events have been substantiated by meta-analyses of major randomized outcome trials.<sup>30–32</sup> Cardiovascular mortality, MI, and stroke remain undisputed hard end points in intervention trials. However, intermediate end points are frequently used as substitutes for the hard end points. These intermediate or substitute end points are sometimes referred to as surrogate end points, and it is reasonable to consider BP itself the chief validated surrogate marker of cardiovascular outcome in hypertensive patients. Nevertheless, event-based trials of antihypertensive therapy did not determine whether pharmacological treatment influences the development and progression of the atherosclerotic process.

The coronary and extracoronary endothelium of hypertensive patients has depressed ability to induce vascular relaxation because of an impaired response or increased inactivation of NO. Endothelial dysfunction may thus play a key role in myocardial, cerebral, and renal complications of hypertensive status. In this context, our data suggest a direct link

between endothelial dysfunction and hypertensive vascular complications. Our findings imply that ACh-stimulated vasodilation could be considered a surrogate end point for assessing the time course of atherosclerosis and its clinical consequences. This concept may be reinforced by our previously published findings demonstrating a strong and significant relationship between echocardiographic cardiac mass and endothelial dysfunction.<sup>25</sup> In fact, both cardiac hypertrophy and depressed ACh-stimulated vasodilation in hypertensive patients may be considered indicative of an increased risk for subsequent cardiovascular events. Finally, the demonstration that hypertension-associated endothelial dysfunction<sup>26,33</sup> and cardiac hypertrophy<sup>34,35</sup> may be reversed by a pharmacological treatment may represent a new target for therapeutic intervention in essential hypertension.

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