Microalbuminuria and Transcapillary Albumin Leakage in Essential Hypertension

Roberto Pedrinelli, Giuseppe Penno, Giulia Dell’Omo, Simona Bandinelli, Davide Giorgi, Vitantonio Di Bello, Renzo Navalesi, Mario Mariani

Abstract—Microalbuminuria (an increased urinary albumin excretion that is not detectable by the usual dipstick methods for macroproteinuria) predicts cardiovascular events in essential hypertensive patients. A possible reason for this behavior is that albumin leaks through exaggeratedly permeant glomeruli exposed to the damaging impact of subclinical atherogenesis. To evaluate this possibility, the transcapillary escape rate of albumin (TER alb, the 1-hour decline rate of intravenous 125I-albumin), a parameter that estimates the integrity of systemic capillary permeability, albuminuria, blood pressure, echocardiographic left ventricular mass, lipids, and body mass index were measured in 73 uncomplicated, glucose-tolerant men with essential hypertension and normal renal function; 53 were normoalbuminuric, and 20 were microalbuminuric. Twenty-one normotensive age-matched male subjects were the controls. TER alb was higher in hypertensives, a behavior explained in part by a positive correlation with blood pressure values, although body mass index, lipids, and left ventricular mass showed no association. Transcapillary albumin leakage values did not differ between normoalbuminuric and microalbuminuric patients and were unrelated to albuminuria. Blood pressure, particularly systolic, and cardiac mass were higher in microalbuminuric patients in whom albuminuria correlated with both cardiovascular variables and indicated the influence of the hemodynamic load on urinary albumin levels. Thus, TER alb, a parameter influenced by the permeability surface area product for macromolecules and the filtration power across the vascular wall, is altered in essential hypertensives. However, this abnormality is dissociated from the amount of albuminuria, which is contrary to the hypothesis that a higher albumin excretion reflects a greater degree of systemic microvascular damage in essential hypertension. (Hypertension. 1999;34:491-495.)

Key Words: albuminuria ■ hypertension, essential ■ cardiac mass ■ blood pressure ■ capillary permeability

Microalbuminuria (ie, an abnormal urinary albumin excretion [UAE] in a range not detectable by the usual dipstick methods for urinary protein) is associated with a greater incidence of cardiovascular events in hypertensive patients1–3 and predicts all-cause and coronary disease morbidity and mortality independently from other cardiovascular risk factors in nondiabetic populations.4–7 However, the reasons why a renal parameter behaves as a marker of atherosclerotic cardiovascular disease in hypertension remain obscure. One concept postulates that more albumin leaks through exaggeratedly permeant glomeruli that reflect the systemic damaging impact of subclinical atherogenesis,8 a process characterized by a diffuse involvement of the entire vascular system.9 This hypothesis, which was originally formulated to account for the higher cardiovascular morbidity rate in diabetic patients,8 may also apply to essential hypertensive patients,10 but no information is available on this issue at this time.

To bridge the gap, we studied the behavior of the transcapillary escape rate of albumin (TER alb, the fraction of the intravascular mass of albumin passing through the vascular bed per unit time), a parameter determined by the permeability surface area product for macromolecules and the filtration power across the vascular wall and that estimates the integrity of the systemic capillary network.11 TER alb was evaluated in relation to UAE and other cardiovascular and metabolic variables in a group of uncomplicated essential hypertensive patients, who were or were not microalbuminuric.

Methods

Subjects
The hypertensive sample included 73 eligible stage 1 to 3 essential hypertensive male patients consecutively screened in our center. Eligibility required casual blood pressure (BP) values >140/90 mm Hg while on no treatment, normal oral glucose tolerance (2-hour post–oral glucose load <7.8 mmol/L [140 mg/dL]), serum creatinine <110 μmol/L (1.2 mg/dL), total serum cholesterol <7.8 mmol/L (300 mg/dL), normal urinary sediment, no urinary tract infection, body mass index (BMI) <30 kg/m², and no evidence (ejection fraction >50%) or history of myocardial infarction, congestive heart failure, or cerebrovascular disease. Renal ultrasound scan showed normal-sized kidneys, although routine clinical and hematological examinations excluded other secondary forms of hypertension. No patient had ever been on lipid-lowering drugs.
Fifty-one patients were newly diagnosed, and the remaining 22 patients were evaluated after a 4-week washout period. Twenty-one men with normal physical examination, routine blood and urinary tests, BP, ECG, abdominal echograms, and ankle/brachial index were the controls. Data collection was completed in 2 weeks.

According to institutional guidelines, subjects were aware of the investigational nature of the study and agreed to participate. The study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the local ethical committee.

### Experimental Procedures

$^{125}$I-labeled human serum albumin (6 to 8 μCi [222 to 296 kBq]; SARI-125 A-2, SORIN Biomedica) was bolus injected after the patient had a 30-minute rest in the sitting position, and blood was withdrawn from the contralateral arm every 5 minutes during the hour after the injection, as described. Radioactivity was measured (Cobra 5000 γ-counter; Packard) in duplicate in whole blood samples centrifuged for 10 minutes at 3000g for 40 minutes. Hematocrit (Coulter Counter 55; Coulter Electronics) was determined in each sample by micromethod (intra-assay variation coefficient, 1.5±0.4%, SD) without any consistent change, which indicated a stable plasma volume throughout the 1-hour period of sampling. Baseline serum albumin was measured by immunonephelometry (Behring Laser Nephelometer System, Behring; intra-assay variation coefficient, 5.2%) immediately before tracer injection. Labeling was obtained by electrolytic technique, a procedure that does not alter the biological behavior of albumin in vivo. Radioactive tracer batches were eluted from free $^{125}$I through passage in Sephadex G 25 mol/L columns (Column PD-10; Pharmacia), a purification step that reduces free $^{125}$I content in the injected dose to <1%; repeatability studies had also shown a mean 8.3% intrasubject variation coefficient of $\text{TER}_{\text{ab}}$ determination.

At variance with the original studies performed in the morning after overnight fasts, we decided for technical reasons to run these studies between 2 and 4 PM after the subjects underwent a 4-hour fast, with no tea, coffee, alcohol, or tobacco since early morning. The influence of this protocol modification was studied in 5 normal men (age, 28±3 years) in whom measurements were obtained in both experimental conditions at 1-week intervals. $\text{TER}_{\text{ab}}$ determinations averaged $7.6±0.8%/\text{h}$ in the early afternoon versus $5.6±0.6%/\text{h}$ in the morning sessions ($P<0.03$ by paired t test). The latter figure was comparable to our previous results obtained in normal controls studied under the same experimental conditions ($5.16±1.09%/\text{h}$).

UAE was measured by nephelometry (Behring; limit of detection, 0.1 mg/dL; interassay variation coefficient, 3.5%) on overnight samples collected from 8 PM to 8 AM during 3 consecutive days. Wall thickness and chamber volumes were determined by monodimensional and bidimensional echocardiograms (Hewlett Packard Sonos 1000) with 2.5- and 3.5-MHz transducers. BP was measured through an automated oscillometric device (SpaceLabs 90207, SpaceLabs) every 8 minutes throughout a 2-hour interval during the $\text{TER}_{\text{ab}}$ procedure. Anthropometric measurements (height and weight) were performed after each participant had removed his shoes and upper garments. Blood samples were obtained between 8 and 9 AM after an overnight fasting and 15 minutes of supine rest. Total cholesterol, HDL cholesterol, and triglycerides were assessed by enzymatic colorimetric techniques (Boehringer-Mannheim). Serum and urine creatinine levels were assayed by standard colorimetric methods.

### Data Analysis

Plasma $^{125}$I-labeled albumin concentration (cpm/mL) was plotted on a semilogarithmic scale, and the transcapillary escape rate (%/h) was calculated from the monoexponential disappearance rate constant of the $^{125}$I curve from 10 to 60 minutes. Only linear regression values with a correlation coefficient of ≥0.85 were accepted. UAE (μg/min) was the average of 3 consecutive overnight collections (median variation coefficient of the triplets, 22%; range, 0.5% to 127%). Microalbuminuria was defined as a value between 15 and 150 μg/min; 2 patients with UAE of 162 and 190 μg/min were included in the analysis. BP values were the arithmetic mean of ≥12 readings after artifact editing. Plasma volume (mL/1.73 m$^3$) was determined by extrapolation to zero time of the disappearance curve corrected for the injected dose of tracer obtained by weighing the syringes before and after the injection. BMI (body weight/squared surface area), creatinine clearance, and LDL cholesterol [total cholesterol−(HDL cholesterol+triglyceride/5)] were derived from standard formulas. Left ventricular mass (Penn convention) was corrected for body surface area to derive the left ventricular mass index (LVMI) (g/m$^2$).

### Statistical Analysis

Log transformation was applied to raw data not distributed normally. Descriptive statistics were expressed as mean±SD or median (range) for skewed data. Differences among means were tested by 1-way ANOVA, and a multiple range test was used to evaluate differences between means. Intraindividual association of variables was tested by Pearson’s correlation coefficients. Statistical significance was set at $P<0.05$. Calculations were performed by the use of Statgraphics Plus (release 1997, Manugistic Inc).

### Results

UAE averaged 6 μg/min (range, 2 to 14 μg/min) in the controls (n=21). Of 73 hypertensives, 53 were normoalbu-
minuric and microalbuminuric patients (Figure 1). Among the continuous variables listed in Tables 1 and 2, only systolic (r = 0.5), diastolic (r = 0.25, P < 0.01; n = 94) and LVMI (r = 0.28, P < 0.006; n = 94).

Discussion

Dissociation Between Albuminuria and Transcapillary Albumin Leakage

The lack of any association with TER_{alb}, a parameter that estimates the integrity of systemic capillary permeability, does not support the view of an augmented urinary albumin leak as a marker of systemic microvascular disturbance in uncomplicated essential hypertensives. This negative conclusion is the same as that drawn from studying TER_{alb} behavior in nondiabetic subjects, either normotensive or hypertensive, with fully developed atherosclerotic disease. On the other hand, the hemodynamic load appeared to be a more important determinant of albuminuria in this study as well as in previous studies of microalbuminuric patients characterized by higher BP (see Reference 18 for a review) that, if transmitted to renal glomeruli, might increase glomerular ultrafiltration of albumin. However, this possibility, which is supported by results of clinical trials in which acute increments in systemic perfusion pressure caused consensual UAE changes, is not consistent with the renal hemodynamic pattern that emerged from studies in essential hypertensive subjects with microalbuminuria. Furthermore, accruing epidemiological evidence shows pressure-independent links between albuminuria and vascular disease. Thus, incompletely explored nonhemodynamic factors may contribute to increase UAE, even though exaggerated capillary permeability (present data and Reference 17), accelerated Na^+-H^+ exchange rate, and hyperinsulinemia did not explain that phenomenon in essential hypertension in our previous experience.

It was important to be able to reproduce the TER_{alb} values previously reported by us in normal subjects because this indicates the validity of the radioiodinated tracer. Therefore, nontechnical reasons, eg, circadian rhythms or accelerated lymph flow, may explain the slightly higher normal TER_{alb} measured in the early afternoon after only 4 hours of abstinence from food. These considerations are to be remembered when our data are compared with those obtained by

**TABLE 2.** BP and Cardiac Parameters in Controls and Essential Hypertensive Patients Categorized According to UAE Levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=21)</th>
<th>Normoalbuminurics (n=53)</th>
<th>Microalbuminurics (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124±8</td>
<td>148±12†</td>
<td>158±11‡</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>77±7</td>
<td>92±11†</td>
<td>96±9†</td>
</tr>
<tr>
<td>Septum, cm</td>
<td>1.0±0.1</td>
<td>1.17±0.1†</td>
<td>1.23±0.1†</td>
</tr>
<tr>
<td>Posterior wall, cm</td>
<td>1±0.09</td>
<td>1.05±0.1*</td>
<td>1.11±0.1*</td>
</tr>
<tr>
<td>End-diastolic diameter, cm</td>
<td>4.9±0.3</td>
<td>4.9±0.4</td>
<td>4.9±0.4</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>106±18</td>
<td>124±27†</td>
<td>137±19†‡</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.01, †P<0.001 vs controls.

‡P<0.05, §P<0.01, normoalbuminurics vs microalbuminurics.
other investigators performing the technique under conditions of more prolonged fasting. Still, this discrepancy does not invalidate the present conclusions because the same strictly standardized protocol was applied to both patients and controls. It is also relevant to highlight the contrast between our data and those obtained in diabetes,11,12,27 a difference probably explained by the peculiar characteristics of that disease, as well as in acute infections28 and high altitude ascent,29 stressful conditions that differ markedly from stable, uncomplicated mild-moderate essential hypertension. Other, albeit somewhat more speculative, possibilities can also be hypothesized. Similar to the explanation put forward for the lack of differences in TER alb between patients with diabetic and incipient nephropathy,27 a ceiling may exist for the transcapillary albumin escape rate11 that hypertension per se might maximally accelerate, thus obscuring any further vascular leak associated with microalbuminuria. This hypothesis is supported by in vitro models that predict marked increases in macromolecular transport even when the capillary wall is only minimally altered,10 but the relevance of this model to the human situation is unknown. Type of previous antihypertensive medication31 or the length of treatment might have affected the transcapillary leakage of albumin, although this is an unlikely possibility because the majority of our patients had never been treated and the others were studied after an appropriate drug withdrawal period. It might even be speculated whether increased albuminuria in the presence of abnormal glomerular permselectivity might be obscured by compensation of other renal control mechanisms, such as modulation of afferent and efferent arteriolar tone, and mesangial cell contractility modifications that may change surface filtration area.32 Confounding from circadian variability in UAE might also play some role, because albuminuria and TER alb were measured at different times of the day, but our data cannot provide data in favor of or against any of the above possibilities. As a final point, ex post facto calculation of statistical power showed that our sample size (53 normoalbuminuric versus 20 microalbuminuric patients) had the statistical power to exclude safely (β<0.20) differences in TER alb $\approx 1.9%/h$. Figures lower than that limit could not be identified safely, a limitation to be taken into account.

**Transcapillary Albumin Leakage in Essential Hypertension**

Our results confirm33 the influence of systemic BP levels, more the systolic than the diastolic component in this particular sample, on TER alb, a parameter influenced by the permeability surface area product for macromolecules and the filtration power across the vascular wall. Hypertension may increase capillary pressure,34 and acute elevation in systemic perfusion pressure may accelerate hyperfiltration,35 although other data are not consistent with this hypothesis.36 On the other hand, the correlation with BP did not explain the largest part of TER alb variability, which suggested the influence of additional factors on the abnormal vascular albumin permeation. Both larger surface capillary area in which most of the albumin exchange takes place,11 and plasma volume expansion17 might play a role, but the capillary network seems rarefied in hypertension,38 although plasma volume was normal in our patients. Increased permeability of vascular endothelium, perhaps in the context of the endothelial dysfunction described in some hypertensive patients,39 is also to be taken into account. However, it is impossible to be more specific because transcapillary macromolecular transport is a complex phenomenon, and hypertension might damage each of several different pathways, such as diffusion through endothelial cell membranes, passage via intercellular junctions, transendothelial channels of organs and tissues with highly different permeability, and surface area products.40

In conclusion, systemic capillary permeability is altered in essential hypertensives, but this abnormality is not reflected by proportionate changes in albuminuria, in contrast to the hypothesis that the augmented urinary albumin leak through

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**Figure 2.** Greater BP and LVMI (mean±SD) in essential hypertensives with microalbuminuria (n=20) vs normoalbuminuric patients (n=53). Data of age- and sex-matched controls are also reported (n=21). For statistics, see Table 2. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

**Figure 3.** Absence of a relationship between TER alb and UAE (log scale). The plot identifies control subjects (●, n=21) and normoalbuminuric (○, n=53) and microalbuminuric (●, n=20) hypertensive patients. The correlation coefficient was 0.06; n=94.
the glomerular capillaries reflects a greater perturbation of systemic microvascular permeability in chronic essential hypertension.

Acknowledgments

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