Factors Associated With Glomerular Hyperfiltration in the Early Stage of Hypertension

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BACKGROUND
Glomerular hyperfiltration predicts development of nephropathy in hypertension but the factors responsible for increased glomerular filtration rate (GFR) are not well known. Aim of this study was to examine which clinical variables influence GFR in the early stage of hypertension.

METHODS
Participants were 1,106 young-to-middle-age hypertensive adults with creatinine clearance >60 ml/min/1.73 m². Clinic and ambulatory blood pressures (BPs) were measured and the difference between clinic and 24-h systolic BP was defined as the white-coat effect (WCE). In 606 participants, 24-h urinary epinephrine and norepinephrine were also measured. Glomerular hyperfiltration, defined as a GFR ≥150 ml/min/1.73 m², was present in 201 subjects.

RESULTS
Patients’ mean age was 33.1 ± 8.5 years and office BP was 146 ± 10.5/94 ± 5.0 mm Hg. In multivariable linear regression, significant predictors of GFR were younger age (P < 0.0001), male gender (P < 0.0001), 24-h systolic BP (P = 0.0001), body mass (P < 0.0001), WCE (P = 0.0001), log-epinephrine (P = 0.01), and coffee use (P < 0.01). In a logistic model, independent predictors of glomerular hyperfiltration were obesity (odds ratio, 95% confidence interval = 6.1, 3.8–9.8), male gender (2.9, 1.8–4.9), age <33 years (2.1, 1.5–3.1), ambulatory hypertension (2.0, 1.4–3.0), WCE >15 mm Hg (1.6, 1.1–2.3), heavy coffee use (2.0, 1.1–3.8), and epinephrine >25 mcg/24 h (1.9, 1.2–3.1).

CONCLUSIONS
The novel finding of this study is that hyper-reactivity to stress, as determined by urinary epinephrine level and WCE, and coffee use contribute to determining glomerular hyperfiltration in the early stage of hypertension. Our data may help to identify a subset of patients with glomerular hyperfiltration, who may be at increased risk of chronic kidney disease and may benefit from antihypertensive treatment.

Keywords: adrenergic; blood pressure; coffee; glomerular filtration rate; hypertension; sympathetic

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Arterial hypertension is a strong risk factor for the development of end-stage renal disease.¹ The early renal lesions in the hypertensive kidney include focal and segmental glomerulosclerosis.² Previous research indicates that increased glomerular filtration rate (GFR) may precede and hasten the development of glomerulosclerosis in hypertension,³–⁵ as observed in type 1 diabetes mellitus,⁶ suggesting that abnormal renal hemodynamics are early markers of hypertensive kidney dysfunction. However, the mechanisms that lead to glomerular hyperfiltration in hypertension are not well understood. Among patients in the initial stage of hypertension only a minority exhibit increased GFR⁴⁵ suggesting that in some hypertensive subjects the kidneys are more susceptible to the adverse effects of elevated blood pressure (BP).

In other words, for hyperfiltration to develop the concomitant action of a variety of pathogenetic factors is needed. Among these, male gender, young age, and increased body mass index (BMI) rank as major determinants of glomerular hyperfiltration both in diabetic and hypertensive patients.⁴⁶⁹ Recent research has shown that increased response to stress may also contribute to the initiation and/or exacerbation of renal dysfunction in hypertensive individuals.¹⁰ Increased adrenergic tone raises renal plasma flow and may lead to increased glomerular intracapillary pressure and hyperfiltration.¹¹ Among 505 young-to-middle-age hypertensive participants to the Hypertension and Ambulatory Recording Venetia Study (HARVEST) we previously observed that 20% of the patients had glomerular hyperfiltration (GFR ≥150 ml/min/1.73 m²) which implied an increased risk of developing microalbuminuria in subsequent years.⁴ The aim of the present study was to investigate factors associated with hyperfiltration in a larger sample of patients that included those previously studied, to assess more clearly relationships between elevated GFR and several clinical variables. In particular, we wanted to ascertain whether subjects with increased reactivity to stress were more susceptible to glomerular hyperfiltration than subjects with normal reactivity.
METHODS

Subjects. The study was carried out in 1,106 white subjects (798 men and 308 women) who took part in the HARVEST study. A detailed description of the sampling procedure and the study design has been published elsewhere.12–15 Patients with stage 1 hypertension (diastolic clinic BP between 90 and 99 mm Hg and/or systolic BP between 140 and 159 mm Hg at initial screening),16 aged 18–45 years and who never took any antihypertensive therapy, were eligible for the study. Patients with GFR <60 ml/min/1.73 m², diabetes mellitus, and urinary tract infection, were excluded.

Clinical examination. The health history included information regarding cardiovascular disease and drug intake and an interview about physical activity habits and current use of cigarettes, alcoholic beverages, and coffee consumption.12–14 Current smokers were those who reported smoking one or more cigarettes per day. Alcohol intake was calculated by summing the total number of milliliters of alcohol consumed as wine, beer, and spirits. Subjects were then categorized as nondrinkers (class 0), light drinkers (<50 g/day, class 1) and moderate to heavy drinkers (50 g or more of alcohol/day, class 2).12–14 Coffee consumption was defined according to the number of cups of Italian coffee drunk per day. Coffee users were divided into two categories of moderate drinkers (1–3 cups/day, class 1) or heavy drinkers (>3 cups/day, class 2). Physical activity was assessed using a standardized questionnaire. Subjects were categorized as sedentary (class 0) if they did not regularly perform any sports activity; mild exercisers (class 1) if they performed leisure physical activities, such as walking, gardening, yard working etc; and exercisers (classes 2 and 3) if they performed sports like running, jogging, cycling, swimming, soccer, tennis etc at least once a week during the previous 2 months. Within the exercisers, the subjects performed competitive sports (athletes, class 3) if they performed sports like running, jogging, cycling, swimming, soccer, tennis etc at least once a week during the previous 2 months. Within the exercisers, the subjects were separated into two categories of moderate drinkers (1–3 cups/day, class 1) or heavy drinkers (>3 cups/day, class 2).

Obesity was defined as a BMI ≥30 kg/m². GFR was estimated from creatinine clearance which was computed from creatinine excretion in a 24-h urine collection and a single measurement of serum creatinine, and the data were normalized by body surface area.4 Participants were defined as normofilterers or hyperfilterers according to whether their GFR was <150 ml/min/1.73 m² or ≥150 ml/min/1.73 m², respectively. This cut-off was chosen in accordance with the National Kidney Foundation Kidney Disease Quality Outcome Initiative suggestions for individuals of this age range17 and our previously published results.4 Other details on the methods used in the HARVEST study were reported elsewhere.12–15

Ambulatory BP monitoring. BP monitorings were obtained with the A&D TM-2420 model 7 (A&D, Tokyo, Japan) or with the ICR SpaceLabs 90207 (Spacelabs, Redmond, WA). The procedures used in the validation and the application of the devices were reported elsewhere.13 BP was measured every 10 min during waking hours (0600 to 2300) and every 30 min during the nighttime. BP measurements recorded during the ambulatory period were stored on a personal computer and screened for editing of artifactual values based on previously described criteria.13 Only recordings containing error measurements <20% were considered acceptable for evaluation. The arithmetic average of the edited pressures was used as the ambulatory measurement. Ambulatory hypertension was defined as a mean 24-h systolic BP ≥130 mm Hg. Nocturnal hypertension was defined as a mean nighttime systolic BP ≥120 mm Hg. The white coat-effect (WCE) was calculated as the difference between clinic systolic BP (mean of six readings) and average 24-h systolic BP.18,19

Twenty-four hour urine collection. The subjects were given verbal instructions on the collection of urine, which was performed during the 24-h BP recordings.4 All the collections were made in an unrestricted manner and no dietary restrictions were imposed. Immediately after completion, volumes were measured and aliquots of urine (10 ml) were taken from the 24-h collection and stored in glass tubes at −20°C. Thereafter, urine specimens were sent to the Coordinating Office in Padova. There the urinary albumin level was measured by a commercially available radioimmunoassay kit (H ALB kit-double antibody; Sclavo SpA, Cinisello Balsamo, Italy). Results were expressed as mg/24h and were transformed logarithmically. AER was available in 954 participants. In the 606 subjects enrolled in the centers of Padua, Vittorio Veneto, San Daniele del Friuli, Cremona, Rovigo, and Pordenone, participants were instructed to divide the urine after micturition using a graduated flask. To this end, patients were provided with two containers, one for catecholamines (containing 5 ml 50% HCl) and one for albumin. Urinary epinephrine and norepinephrine assessment was performed by a high-performance liquid chromatography method.20

Statistical analysis. The present cross-sectional analysis was performed on clinical variables collected within the first 2 weeks...
after enrollment. In particular, ambulatory BP monitoring and 24-h urinary collection for albumin and catecholamine assessment were performed after 2 weeks from the initial visit. Between-group differences were assessed with the ANOVA test for the variables normally distributed. Data were adjusted for age and sex by the use of linear regression analysis. \( \chi^2 \) analysis and Fisher’s exact test were used for the categorical variables. To study the linear relationship between GFR and other continuous variables, Pearson correlations test was used. Multivariate linear regression analysis was used to estimate the association of GFR with selected clinical variables (age, gender, family history for hypertension, BMI, lifestyle factors, 24-h systolic and diastolic BP, heart rate, WCE, log-epinephrine, and log-norepinephrine). To avoid multicollinearity when testing 24-hour urinary BP and systolic WCE simultaneously, the latter variable was centered before inclusion in the multivariable model. A general linear model procedure was used to evaluate independent associations of catecholamines with participant characteristics. The variables included in the general linear model models were age, gender, parental hypertension, obesity, lifestyle factors, 24-h systolic and diastolic BP, and heart rate. The influence of studied variables on hyperfiltration was tested by univariate and multivariate logistic regression analysis to estimate odds ratio and 95% confidence interval. In the logistic regressions, results were age, the WCE, and urinary epinephrine were dichotomized as 3-class variables, whereas physical activity was included either as a 2-class or a 4-class variable. A two-tailed probability value <0.05 was considered significant. For all statistical analyses, AER and urinary catecholamines were logarithmically (base 10) transformed owing to their skewed distribution. All analyses were performed using Statistica version 6 (Stat Soft, Tulsa, OK), Systat version 11 (SPSS, Evanston, IL), and MedCalc version 12 (MedCalc Software, Mariakerke, Belgium).

### RESULTS

#### Characteristics of the population

The main clinical characteristics of the study subjects divided according to whether they had normal filtration or hyperfiltration are reported in Table 2. Subjects with hyperfiltration (18.2%) were younger, heavier, and were more frequently male...
than normofiltering subjects and had a higher office and mean 24-h systolic BP. In addition, subjects with hyperfiltration had a greater systolic WCE than those with normal GFR. Urinary epinephrine, urinary norepinephrine (borderline significance) and AER were higher in hyperfilterers than normofilterers. Also, microalbuminuria was more common in the former than the latter. Smoking, alcohol use, and physical activity, irrespective of the classification used, did not differ according to GFR level. However, hyperfiltering subjects were more frequently coffee drinkers than normofilterers (borderline statistical significance). Coffee drinkers had a greater urinary epinephrine output than non-drinkers; epinephrine was 21.9 ± 15.5 mcg/24 h in abstainers, 25.3 ± 44.7 mcg/24 h in moderate drinkers, and 32.3 ± 38.8 mcg/24 h in heavy drinkers (P = 0.04). Other factors independently associated with epinephrine were male gender (P = 0.04) and 24-h systolic BP (P = 0.04). Variables independently associated with norepinephrine were obesity (P = 0.049) and 24-h systolic BP (P < 0.01).

Predictors of GFR

In simple correlation analysis GFR was positively correlated with BMI (r = 0.44, P < 0.001) and was negatively correlated with age (r = –0.28, P < 0.001). The positive correlations with clinic systolic BP (r = 0.12, P < 0.001), mean 24-h systolic BP (r = 0.13, P < 0.001), log-epinephrine (r = 0.11, n = 606, P = 0.01), and AER (r = 0.08, P = 0.01) were weaker and reached the level of statistical significance because of the large sample size. No correlation was found between GFR and norepinephrine (r = 0.05, P = 0.23). In a multivariable linear regression analysis performed in the whole population, significant predictors of GFR were male gender, coffee consumption, BMI, age, 24-h systolic BP, and the systolic WCE (Table 3). Average daytime systolic BP had a similar association with GFR (P < 0.001) to 24-h systolic BP, whereas average nighttime systolic BP had a weaker relationship (P = 0.045) and was not accepted by a model in which 24-h BP was also included. In the subset of 606 subjects who underwent catecholamine dosage, log-epinephrine was another independent associate of GFR. The coefficient of variation of daytime systolic BP was not associated with GFR in either univariate (P = 0.83) or multivariable (P = 0.18) regression. The actual GFR values in the participants grouped according to categorical predictors are presented in Table 1.

Predictors of hyperfiltration

In a logistic regression analysis which included parental hypertension, 24-h diastolic BP, 24-h heart rate, smoking, alcohol use, and physical activity, hyperfiltration was associated with male sex, younger age, obesity, 24-h ambulatory hypertension, coffee drinking, and increased WCE (Figure 1). When 24-h hypertension (n = 591) was replaced by nocturnal hypertension (n = 427), the association of ambulatory hypertension with hyperfiltration was no longer significant (P = 0.33). The relationship between coffee use and the risk of hyperfiltration was linear and reached the level of statistical significance for heavy drinkers. A significant interactive effect of obesity with ambulatory hypertension (P = 0.01) and young age (P = 0.01) was found on the risk of hyperfiltration. Among the 606 participants with catecholamine data, increased urinary epinephrine was another independent predictor of hyperfiltration (Figure 1). Coffee drinking was a significant independent predictor of hyperfiltration also in this subgroup (odds ratio, 95% confidence interval, 2.0, 1.6–3.3 for class 1, and 3.0, 1.3–6.7 for class 2). This relationship was slightly attenuated when log-epinephrine was included in the model (odds ratio, 95% confidence interval, 1.9, 1.1–3.4, for class 1, and 2.7, 1.2–6.1, for class 2). In the fully adjusted multivariable logistic model, microalbuminuria was associated with hyperfiltration with an odds ratio, 95% confidence interval, of 2.4, 1.2–4.6 (P = 0.01).

DISCUSSION

In this population of young-to-middle-age subjects in the early stage of hypertension, several clinical factors were associated with increased risk of glomerular hyperfiltration. Obesity, young age, male gender, and ambulatory hypertension were strong determinants of hyperfiltration confirming previous results obtained in diabetic populations or in subjects with metabolic disorders.22,23 Because of the age- and sex-related variability in GFR, there is no general consensus on how to define hyperfiltration. A noncorrected threshold may mask hyperfiltration at older ages and in women. However, the main purpose of our study was to explore the role played by other potential determinants of hyperfiltration in hypertension after adjustment for age, sex, and other possible confounders. A novel finding of this investigation is that increased WCE,
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Figure 1 | Odds ratios and 95% confidence interval for risk of hyperfiltration in 1,106 Hypertension and Ambulatory Recording Venetia study (HARVEST) participants. Result of multivariable logistic regression analyses. White-coat effect (WCE) indicates systolic blood pressure white-coat effect, reference category is WCE <15 mm Hg. Epinephrine indicates 24-h urinary epinephrine, reference category is epinephrine <25 mcg/24h. Coffee cups indicates daily consumption of cups of coffee, reference category is abstainers. Ambulant hypertension (HT) indicates 24-h ambulatory hypertension, reference category is 24-h systolic blood pressure <130 mm Hg. Reference category for age is age ≥33 years, for sex is female gender, and for obesity is body mass index <30 kg/m². For WCE, age, and urinary epinephrine (n = 606), binary categories were created based on the median value approximated to the nearest integer.

Elevated urinary epinephrine, and heavy coffee drinking were all independent determinants of hyperfiltration.

A large body of evidence has shown that type 1 diabetic subjects with glomerular hyperfiltration are at increased risk for albuminuria and the progression of diabetic nephropathy. Some studies suggest that this mechanism may be operative also in the early stage of hypertension. The present cross-sectional data show that microalbuminuria is more common in hypertensive subjects with hyperfiltration confirming our previous results and those by others. If sufficient evidence for hyperfiltration as a predictor of accelerated renal impairment in hypertension can be demonstrated, understanding the mechanisms that lead to increased GFR may help to identify a subset of patients likely to benefit from even earlier intervention than currently recommended.

The difference between clinic BP and ambulatory BP is currently taken as a surrogate measure of the WCE, thepressor response triggered by BP measured by the doctor in the office. Although its clinical significance has been questioned, an elevated WCE is considered a marker of hyper-reactivity to stressful situations. In the present study, a 60% higher risk of hyperfiltration was found in the subjects with WCE >15 mm Hg, suggesting that hyper-reactivity to psychological stress may favor the abnormal renal hemodynamic response that leads to hyperfiltration in hypertension. This hypothesis was supported also by the higher level of urinary epinephrine found in our hyperfiltrators, as the risk of hyperfiltration was almost doubled in the subjects with urinary epinephrine ≥25 mcg/24h. Epinephrine infusion in humans raises renal plasma flow and increases single nephron perfusion, which may lead to increased glomerular intracapillary pressure, hyperfiltration, and the triggering of the process that results in subsequent loss of GFR over time. Recently, Lambertucci et al found that the renal response to adrenergic activation induced by a mental stress was impaired. In these subjects the physiological glomerular vasconstriction, which prevents the transmission to the glomerulus of high BP during systemic adrenergic activation, was abolished, suggesting that in hypertension the glomerulus may be exposed to the injury caused by emotional stimuli in everyday life. The association of coffee consumption with increased GFR found in the present study may be also due to increased sympatho-adrenergic activity. Urinary epinephrine and norepinephrine and vanillylmandelic acid have been shown to increase after caffeine administration in humans. In agreement with our previous results, in the present study there was a linear relationship between coffee intake and urinary epinephrine output. When urinary epinephrine was included together with coffee category in the logistic model, the relationship between coffee use and hyperfiltration was slightly attenuated. Hence, it is possible that the influence of coffee on GFR is at least in part due to its effect on epinephrine release. In addition, coffee acutely raises BP and arterial stiffness and impairs endothelial dependent vasodilation which in turn may exert detrimental effects on glomerular hemodynamics.

In the present study, obesity was a strong determinant of hyperfiltration. A combined effect of overweight and hypertension on GFR was previously reported by ourselves and other investigators. The present data provide evidence for an interactive effect of obesity with 24-h BP on glomerular hemodynamics. Increased sympathetic activity has been proposed to explain the elevated GFR in obesity. In the present study obese subjects had higher level of urinary norepinephrine compared to the rest of the population but norepinephrine showed a weak relationship with hyperfiltration. This suggests that several other mechanisms such as hyperinsulinemia, hyperleptinemia, increased sodium intake, adipocytokines, and oxidative damage to lipids and proteins may explain the association of obesity with increased GFR. Although it is not a pre-requisite for intraglomerular hypertension, elevated systemic BP when present, is a well recognized cause of high renal plasma flow and raised glomerular hydraulic pressure. Indeed, in the present study an elevated 24-h BP load was an independent predictor of hyperfiltration. Daytime BP was a stronger predictor of GFR than nighttime BP supporting the hypothesis that glomerular hemodynamics may be influenced by BP fluctuations in response to everyday stimuli more than by a stable BP load. In addition, our results confirm the inverse relationship between GFR and age observed in previous epidemiologic studies as a consequence of the progressive fall in glomerular number throughout adult life.

Limitations
Some limitations in our study should be noted. First, the cross-sectional design of our study limits inferences on causality within the detected associations. Second, the study population consisted of young or middle-aged Caucasians with a low prevalence of obesity (9.2%), thus the results cannot be generalized to other age and ethnic groups or extrapolated...
to the general hypertensive population. Third, GFR was estimated from creatinine clearance which may overestimate true GFR values.\textsuperscript{34} However, our results were obtained in a large homogeneous sample of subjects without kidney disease and we used both continuous and categorical data as outcome variables. Finally, the link between hypertension and hyperfiltration may be explained by several other factors not measured in the present study. Activity of the renin–angiotensin system, atrial natriuretic peptide, prostaglandins, thromboxanes, and kinins among others have been proposed to contribute to alterations in glomerular hemodynamics.\textsuperscript{22,23} These limitations notwithstanding, strengths of this study are that our analyses offer data from a homogeneous population of subjects in the early stage of hypertension and that ambulatory monitoring was used to measure BP in all of the participants.

**Clinical implications**

In current clinical practice, detection of microalbuminuria is considered to be the earliest predictor of hypertensive nephropathy. The clinical significance of the events preceding microalbuminuria, particularly the hyperfiltration phase, is still controversial. The results of the present study indicate that hyperfiltration in hypertension is the result of a constellation of several concurrent factors. If sufficient evidence for hyperfiltration as a putative risk factor for accelerated renal impairment in hypertension will be provided, our data could help identify a subset of patients likely to benefit from even earlier intervention than currently recommended.

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