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CHANGES IN RENAL AUTACOIDS IN AGED HUMAN HYPERTENSIVES

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The aging process determines several modifications of the kidney, that, however, do not provoke any dysfunction in normal conditions. But in the elderly — in the presence of stressful situations and particularly when adrenergic activation is present — the kidney is more vulnerable than in the young, and renal failure may arise. Variations typical of the aging kidney are accelerated when hypertension overlaps the physiological renal process, because both senescence and hypertension weight on the same structures, i. e. glomeruli. We studied renal hemodynamic adaptation capacity both in the healthy elderly and in patients affected by isolated systolic hypertension, in an acute experiment which requires the application of a mental stress-induced adrenergic activation. In hypertensive patients we have already demonstrated a total lack of renal adaptation capacity. In fact, while the elderly normotensives react with a prolonged and pronounced vasoconstriction, in those with isolated systolic hypertension, adrenergic activation induces a passive renal vasodilation and glomerular hyperfiltration. The anomalous adaptation capacity of renal hemodynamics is probably due to an impairment in the paracrine response of renal vasculature. Indeed in the hypertensive elderly, unlike in the normotensive one, no variations of autacoid production occur during the adrenergic activation. Following on from this, pattients affected by isolated systolic hypertension passively suffer the many hypertensive peaks which characterize their every day life. The altered renal autoregulation of the elderly with isolated systolic hypertension may explain the accelerated glomerulosclerosis and the greater incidence of renal damage and end-stage renal disease which characterize this condition. These aspects underline the primary role of the antihypertensive treatment of isolated systolic hypertension, not only for the prevention of cardiovascular mortality but also of renal damage and/or end-stage renal disease.

Key word: *kidney, isolated systolic hypertension, elderly, prostaglandins, endothelin.*

INTRODUCTION

Progressive decline of several functions is associated with aging. In spite of this, in older healthy adults, physiological capacity of many organs remains adequate for the normal activities of daily living. However, functional reserve declines and under conditions of stress the performance is reduced.

Age-dependent functional decline of the kidney is one of the most relevant and stems from glomerulosclerosis. Under normal conditions it does not provoke any dysfunction. However, when homeostatic balance in the elderly comes up against unusual events such as advanced dehydration or NSAID treatment, transient renal impairment may arise, even in the absence of disease. Hypertension greatly accelerates one of the most typical hallmarks of renal senescence, i.e. glomerulosclerosis, so that renal failure may occur above all in the medium-long term period.

Over the last few years, our group has directed its attention to the study of renal hemodynamic adaptation capacity, since, in both senescence and hypertension, renal vascular component is primarily involved. For this purpose, we developed an acute experimental model able to involve renal hemodynamics through an adrenergic activation applying in both to the healthy and hypertensive elderly. In this paper we shall review the results obtained and after we shall discuss the possible connections of the changes observed in this acute setting with chronic renal alterations and chronic renal failure occuring in the elderly hypertensive.

THE AGING KIDNEY

The principal anatomical modification of the aging kidney is a gradual renal mass reduction, caused by glomerulosclerosis, that affects primarily the cortex (1, 2).

Changes in renal function due to age are characterized by a decline of both renal plasma flow (RPF) and glomerular filtration rate (GFR). RPF falls from 600 ml/min/1.73 m^2 in the young adult to 300 ml/min/1.73 m^2 at the age of 80 (3, 4). Also GFR decreases from the age of thirty onwards (5). There is a progressive linear decline of creatinine clearance that proceeds at an approximate annual rate of 0.8 ml/min/1.73 m^2 in those over 30 (6). Lindeman *et al.* (7) in a longitudinal study confirmed these data in a selected population, in which elderly subjects affected by comorbid conditions were accurately excluded. Of interest was the fact that one third of these healthy elderly patients maintained the creatinine clearance in the normal range until advanced age. This suggests that the decrease in renal function with aging in healthy subjects may be modulated by racial, dietary, metabolic, hormonal or hemodynamic factors.

RPF decreases more than GFR with a consequent increase in filtration fraction (FF) (8). The increase in FF may be due to two different mechanisms: 1) hyperfiltration of the residual glomeruli for the greater constriction of the efferent arteriole in respect to the afferent one (9); 2) the relative increase of the medullary flow due to the reduction of RPF that is limited to the cortex (10, 11). Hyperfiltering condition of the aging kidney may accelerate glomerulosclerosis as it raises intraglomerular pressure (1).

In the healthy elderly conducting a normal life and despite the above-mentioned modifications, the aging kidney maintains its function until advanced age. However, the aging kidney becomes more vulnerable whenever a stressful situation occurs, especially in the presence of adrenergic activation (12). Indeed, in healthy elderly subjects, acute intense volume restriction or NSAID administration may give rise to acute renal failure (13). This is particularly relevant if disease is present, both acute (severe hypotension or hemorrhage), or chronic (cirrhosis or congestive heart failure). In this group of patients there is a marked decrease in effective circulating volume, which in turn leads to higher levels of circulating vasoconstrictive substances (catecholamines, angiotensin II and vasopressin). As a result of all these, renal circulation is critically dependent on the effect of vasodilatory prostaglandins which modulate excessive vasoconstriction. The importance of vasodilatory prostaglandins during adrenergic activation was experimentally demonstrated in 1977 by Terragno *et al.* (14). In the conscious dog at rest, renal prostaglandins did not contribute to RPF and their inhibition did not induce any change in renal vascular resistance or RPF. In contrast, in acutely stressed dogs, the withdrawal of prostaglandins resulted in a sharp increase in renal vascular resistance and decline in RPF. Therefore, this experiment clearly demonstrated that, under stress conditions, renal circulatory regulation relies largely upon prostaglandin production. All these considerations are particularly important when we consider that NSAID consumption in the elderly has increased dramatically in the past two decades (15).

New perspectives may arise in the field of NSAID-induced renal toxicity after the discovery and the characterization of cyclooxygenase (COX)-2 enzyme (16—18) and the subsequent development of COX-2 selective inhibitors (19—21). It was originally thought that COX was a single enzyme. Recently two COX insoforms were identified, COX-1 and COX-2. COX-1 is constitutively present through the body and generates prostaglandins which are responsible for normal homeostatic functions, while COX-2 is primarily produced in response to inflammation. The anti-inflammatory effects of classic, nonselective NSAIDs are mediated via the inhibition of COX-2, but the concomitant inhibition of COX-1 has deleterious side-effects on may organs, mainly the gastrointestinal tract and the kidney. The availability of COX-2 selective inhibitors as anti-inflammatory agents has substantially reduced gastric toxicity (20, 22). For what concerns renal toxicity, available data are less certain, because, unlike in the gastro-intestinal tract, also COX-2 seems to be constitutively present in the kidney (23). In fact, recent animal studies (24) demonstrated that selective COX-2 inhibitors reduced both RPF and sodium

excretion. On the other hand the few studies carried out in human showed that COX-2 selective inhibitors determined only acute sodium retention, without any modification of GFR, both in young and elderly subjects (25, 26). Therefore, even if selective COX-2 inhibitors seem to be less nephrotoxic than nonselective NSAIDs, the real advantage, in terms of nephrotoxicity of selective COX-2 inhibitors, has to be established by future studies. In this field comparative long-term studies are needed.

Vasodilating prostaglandins and the other vasoactive substances are critical for renal hemodynamics since they affect both afferent and efferent arteriolar tone and probably act in the autoregulation of the kidney. In 1951 Shipley (27) clearly described renal autoregulation in the dog. GFR and RPF remain constant in a wide range of mean blood pressure variations. This hemodynamic adaptation is possible thanks to two mechanisms: myogenic tone and tubuloglomerular feedback (TGF). Vasoactive paracrine substances probably modulate both these autoregulatory mechanisms through modifications in arteriolar and mesangial cell tone.

Our group, in an expressly designed acute experiment, elucidated the predominant role of autacoids in renal hemodynamics in the elderly. We studied renal humoral and hemodynamic modifications evoked by an adrenergic activation triggered off by mental stress (MS) in healthy women, both young and elderly (28). Experimental protocol included four periods of 30 minute each. Effective renal plasma flow (ERPF) and GFR were measured by radioistope clearances. In young healthy subjects MS provokes a limited vasoconstriction, while in the elderly the reduction of ERPF and the increase in FF and renal vascular resistance (RVR) is prolonged and more pronounced (*Fig. 1*). Despite this prolonged vasoconstruction, in the elderly, autoregulation is maintained as demonstrated by the constancy of GFR throughout the whole experimental period. These changes lead to a progressive increase in F. Therefore, autoregulation in the elderly is maintained at a cost of a further increase of intraglomerular pressure. These striking differences in hemodynamics are sustained by variations in stress-induced production of vasoactive substances. In the elderly, baseline excretion of vasodilating prostaglandins (PGE_2 and 6-keto-$PG_{1\alpha}$) and endothelin-1 is greater than in the young (*Tab. 1*). It is possible that these substances play a role in the hyperfiltering condition of the aging kidney. During adrenergic activation, the elderly had an increase in endothelin comparable to that in the young, but showed an inadequate increase in prostaglandins. Indeed, both PGE_2 and prostacyclin increased only during stress in the elderly, while in the young they increased also in the recovery periods. For this reason, in the elderly, vasodilating prostaglandins did not counterbalance the prolonged vasoconstrictive effect of endothelin-1 (*Tab. 1*), with a consequent long-lasting vasoconstriction (28).

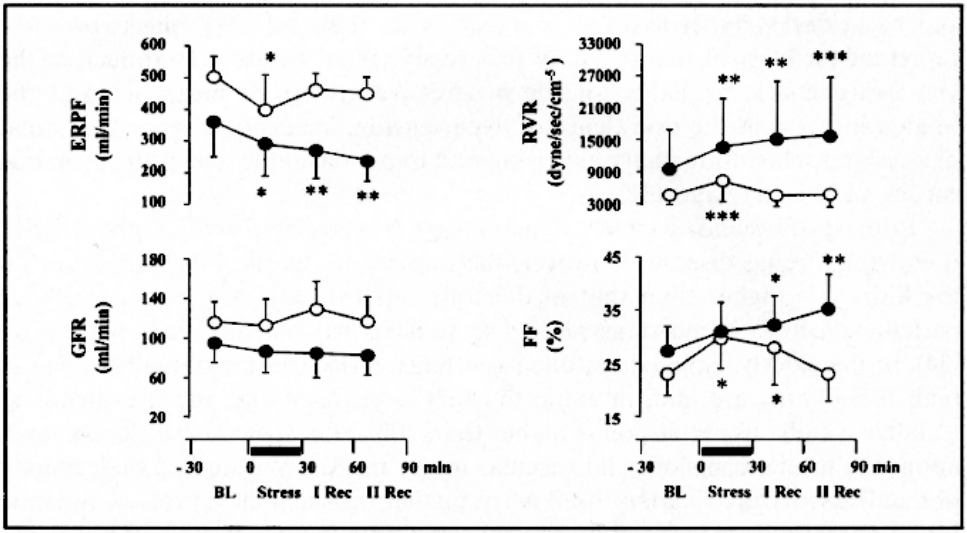

Fig. 1. Effects of mental stress on renal hemodynamics in normotensive young (○, n = 8) and elderly (●, n = 8) healthy subjects. ERPF: effective renal plasma flow; GFR: glomerular filtration rate; FF: filtration fraction; RVR: renal vascular resistance; BL: baseline; Rec. 1: first recovery period; Rec II: second recovery period. * = $p < 0.05$ versus baseline; ** = $p < 0.01$ versus baseline; *** = $p < 0.001$ versus baseline.

Table 1. Effects of mental stress on urinary autacoids in normotensive young and elderly subjects

		BL	Mental Stress	I Rec	II Rec
ET-1	Young	0.136±0.07	0.297±0.07 **	0.252±0.13 **	0.207±0.14
(fmol/ERPF)	Elderly	0.157±0.017	0.261±0.081 *	0.218±0.016 *	0.144±0.062
PGE_2	Young	5.1±2.3	12±3.5	20±4.5 **	23±5 ***
(pg/ERPF)	Elderly	46.8±15.3	72.3±11.5 *	40.5±17.5	35.6±11.5
b-keto-$PGF_{1\alpha}$	Young	12±0.1	15±6 **	18±8 **	15±4 **
(pg/ERPF)	Elderly	27.3±9.2	40.7±9.6 *	30.3±9.5	21±9
cGMP	Young	40.4±21.4	71.8±39.9 **	36.8±16.1	52.3±25.7
(pg/ERPF)	Elderly	26.4±10.0	41.9±13.4 *	36.5±18.7	33.2±15.1

Young, n = 8; elderly, n = 8. ET-1: urinary endothelin 1; PGE_2: urinary prostaglandin E_2; 6-Keto-$PGF_{1\alpha}$: urinary 6 Keto prostaglandin $F_{1\alpha}$; cGMP: urinary cyclic GMP. BL: baseline; Rec I: first recovery period; Rec II: second recovery period. * = $p < 0.05$ versus baseline; ** = $p < 0.01$ versus baseline; *** = $p < 0.001$ versus baseline.

RENAL FUNCTION AND ISOLATED SYSTOLIC HYPERTENSION IN THE ELDERLY

The damage to the kidney produced by high blood pressure develops in the same structures involved in age-related modifications (29, 30). Therefore, hypertension in the elderly is particularly harmful in respect to renal failure.

Indeed, elderly hypertensives, together with diabetic and black patients, represent the class at major risk of progressive renal failure (31). In fact, in the last two decades, probably for the progressive growth of mean age and the related increase in the prevalence of hypertension, incidence of end-stage renal disease and related mortality are rising and hypertension is one of the principal causes of this damage (32).

Both systolic and diastolic hypertension is associated with a greater risk o end-stage renal disease. However, the impact of systolic blood pressure on the kidney is higher than that of diastolic one (31, 33). Moreover, 12.5% of patients affected by end-stage renal disease have isolated systolic hypertension (34). In the elderly, isolated systolic hypertension (ISH) is the prevalent form of high blood pressure and, in subjects over 75 years of age, the prevalence of isolated systolic hypertension is higher than 70% (35). However, little is known about the mechanisms of renal vascular injury in ISH. We studied the capacity of renal vasculature to adapt itself when further transient elevations of systemic blood pressure were induced by mental stress, in patients affected with isolated systolic hypertension (36).

In baseline consitions, elderly subjects with ISH did not differ from normotensives in renal hemodynamics. Also urinary autocoids did not differ between the two groups except for PGE_2 excretion which was significantly less in the elderly with ISH than in normotensives (*Fig. 2*).

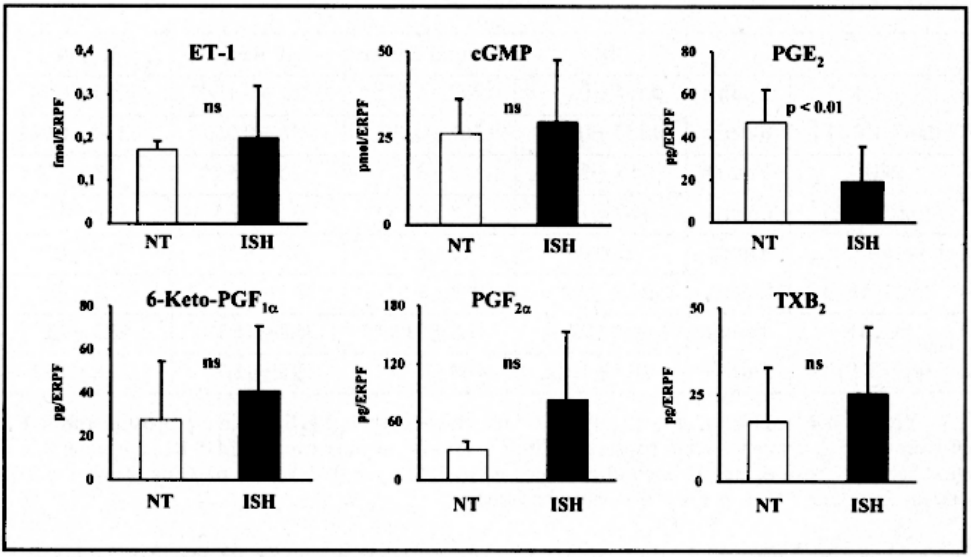

Fig. 2. Urinary autacoids in rest conditions (mean ± DS) in elderly normotensives (NT, n = 8) and elderly affected by isolated systolic hypertension (ISH, n = 8). ET-1: endothelin 1; cGMP: cyclic GMP; PGE_2, prostaglandin E_2; 6-Keto-$PGF_{1\alpha}$: 6-Keto-prostaglandin $F_{1\alpha}$; prostaglandin $F_{2\alpha}$; TXB_2: Thromboxane B_2.

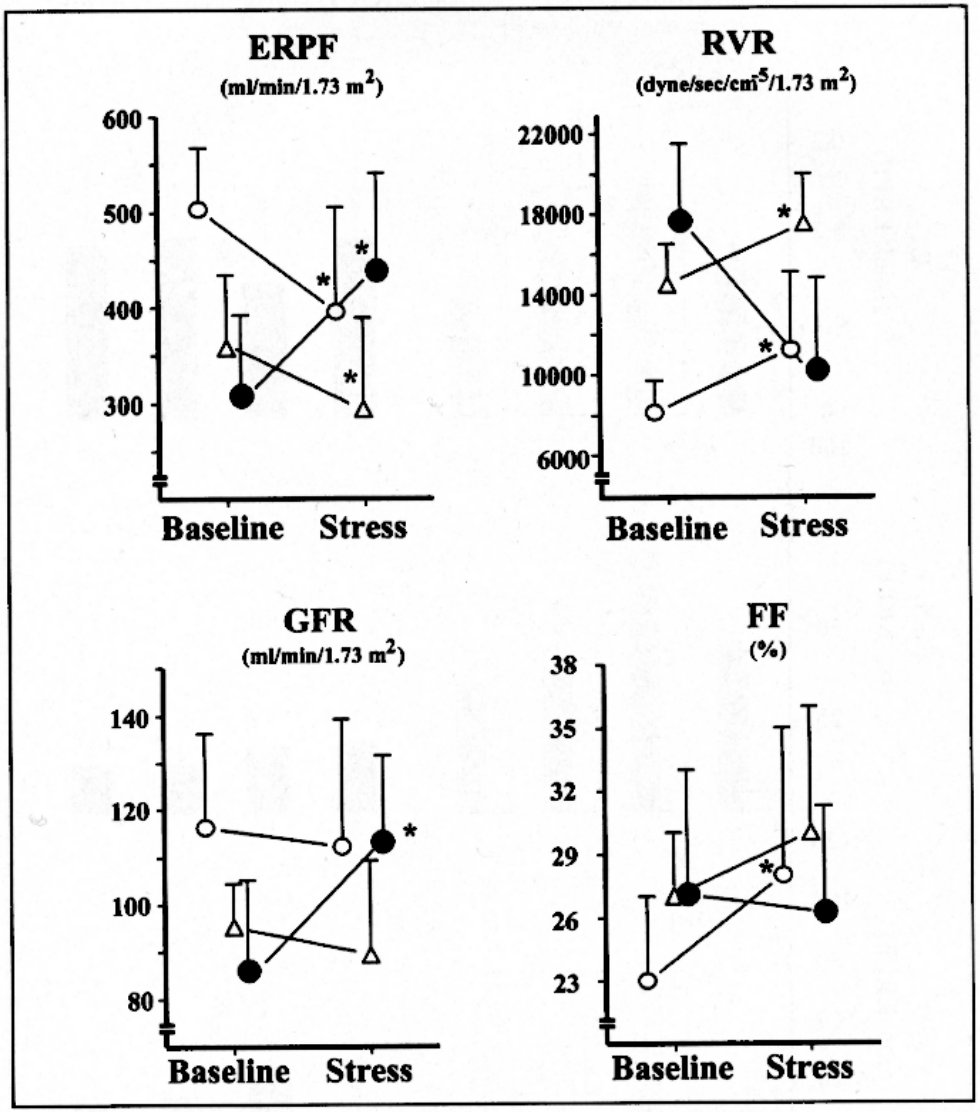

Fig. 3. Effects of mental stress on renal hemodynamics in normotensive young (○, n = 8) and elderly (▽, n = 8) healthy subjects and in elderly patients affected by isolated systolic hypertension (●, n = 8). ERPF: effective renal plasma flow; GFR: glomerular filtration rate; FF: filtration fraction; RVR: renal vascular resistance. * = $p < 0.05$ versus baseline.

During MS, while the absolute increase in systemic blood pressure was similar in both groups, renal hemodynamic response in the ISH group was greatly altered (36). In fact renal hemodynamics in the ISH group was characterized by a significant vasodilation during MS as demonstrated by an increase in ERPF and a reduction in vascular resistance (*Fig. 3*). In this group

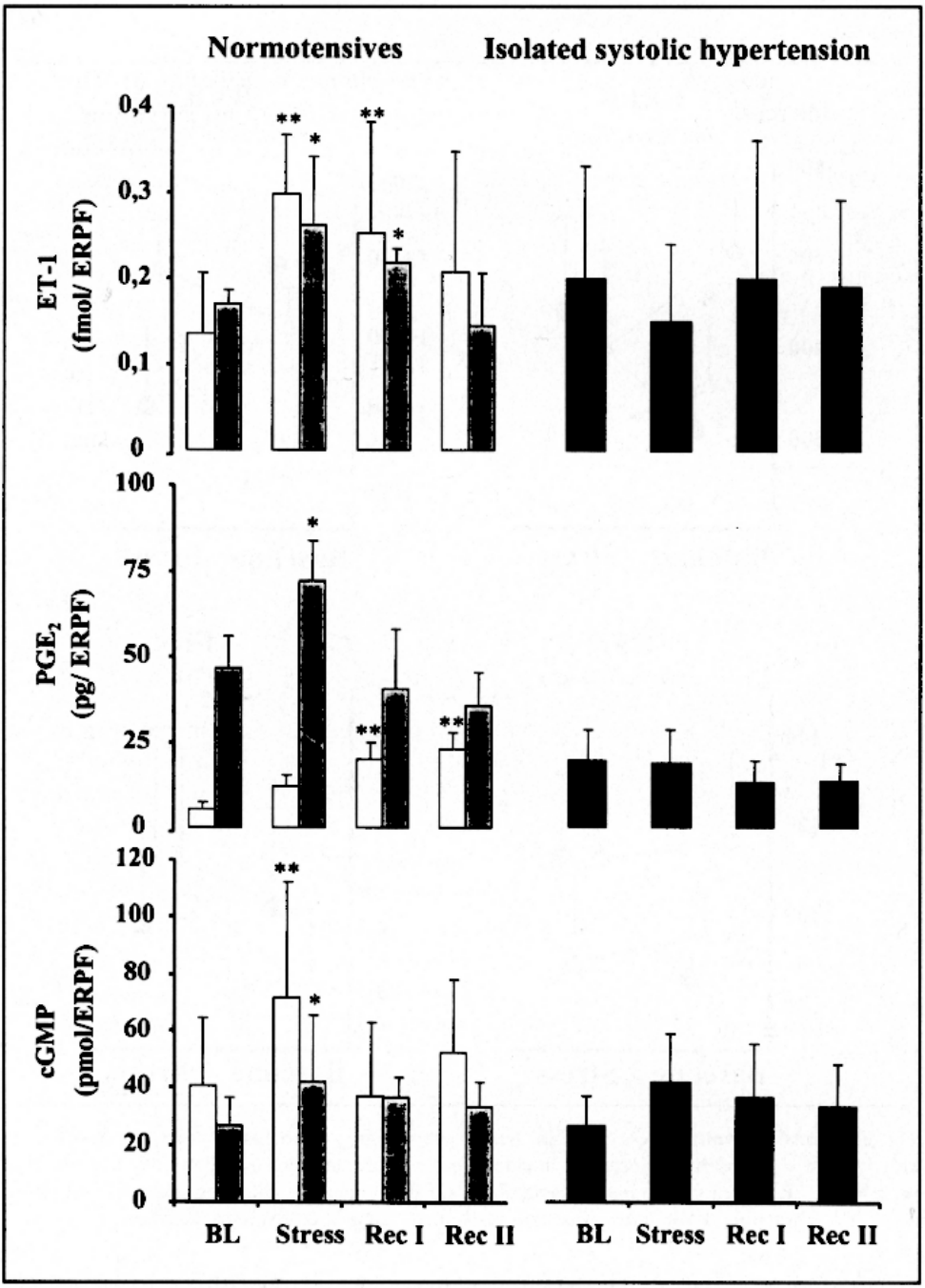

Fig. 4. Effects of mental stress on urinary excretion of endothelin-1 (ET-1), prostaglandin E_2 (PGE_2) and cGMP (cGMP) (mean ± SD) in elderly patients with ISH (n = 8, closed bar) and in normotensives young (n = 8, grey bar) and elderly healthy subjects (n = 8, open bar). ERPF: effective renal plasma flow; BL: baseline; Rec I: first recovery period; Rec II: second recovery period. * = $p < 0.05$ versus baseline; ** = $p < 0.01$ versus baseline.

GFR, too, increased during MS without any change in FF (*Fig. 3*). The ISH group, differently from the elderly normotensives, showed no variations in the production of the principal paracrine renal factors such as endothelin and prostaglandins (*Fig. 4*). This response is in sharp contrast with the physiological vasoconstriction described in both the young and the elderly (28). Therefore, in elderly hypertensives, the glomerulos passively suffers blood pressure increases being unable to modulate the tone of afferent and efferent arterioles and GFR is completely dependent on ERPF. The total lack of renal adaptation capacity makes renal glomeruli susceptibile to the many hypertensive peaks which characterize the everyday life of the elderly with ISH (37, 38). Van Dokkum *et al.* (39) demonstrated in the fawn-hooded hypertensive rats (FHH) that autoregulation is impaired before the development of glomerulosclerosis, so that the alterations in renal hemodynamics may be primarily involved in glomerulosclerosis and not only be the consequence of it. Therefore, the results from all these studies may contribute to the understanding of the mechanisms that make the ISH patients at high risk of developing end-stage renal disease (33, 34).

The vasodilation induced by a blood pressure increase not associated with any significant changes in the humoral response, may be related to the impairment of renal vascular endothelium of elderly hypertensive to react to adrenergic stimuli. A passive vasodilation in response to an increase in blood pressure has been previously demonstrated in Dahl salt-sensitive hypertensive rats (40). The passive vasodilation of elderly hypertensives may be explained by the lack of increase in endothelin observed in our experiments during the stimulus, in contrast to the normotensives where endothelin increase was preserved. Our data also indicate that renal vasculature of elderly hypertensives is unable to produce any vasoactive substance, including vasodilating prostaglandins. Recent studies by Alam *et al.* (41) showed that indomethacin administration did not alter systemic blood pressure in the elderly with ISH, while it increased blood pressure in normotensives. These data reinforce the hypothesis that in the elderly with isolated systolic hypertension, unlike in normotensives, the production of eicosanoids, in particular vasodilating prostaglandins, is so low that it is unable to exert any relevant modulation of vascular reactivity. Furthermore, these data show that prostaglandin vascular response may be altered also in systemic vasculature and not only in renal circulation, as hypothesized by our data.

The altered endothelial function and the associated arterial stiffness do not seem to be an unavoidable consequence of senescence and hypertension. It may be linked to the typical life-style of modern society, as demonstrated by some papers like that by Avolio *et al.* (42). The Authors carried out an epidemiological study in China. Subjects studied were represented by two ethnically similar groups — rural and urban — with low serum cholesterol and

equally low prevalence of atherosclerosis, but with a markedly different salt intake. When the two groups were compared at similar mean arterial pressure ranges, in the low salt intake rural group, aortic pulse wave velocity, that is an index of arterial stiffness, was consistently lower than in the high salt intake urban group. This may indicate that the difference in aortic distensibility between the two groups is independent of arterial pressure and strictly related to salt intake. Also the incidence of hypertension seems to be affected by nutritional factors. Indeed, the incidence of hypertension is lower in the rural community than in the urban one and, in the latter, the prevalence of ISH is higher than in systodiastolic hypertension (42). These data suggest that, in this Chinese urban community, similar factors might be responsible both for age-dependent increased prevalence of arterial stiffness and hypertension.

These results may also be in agreement with the view that lesions of arterial wall may precede the development of hypertension and/or partially account for acceleration of increased systolic arterial pressure. Subsequent experiments have strengthened this view (40, 43—45). In addition, Safar (46) hypothesized a possible role of endothelium dysfunction in the pathogenesis of isolated systolic hypertension. The lack of endothelium modulatory capacity, in fact, could be not the consequence but the cause of increase in arterial stiffness typical of isolated systolic hypertensives.

In conclusions, all these aspects underline the primary role of antihypertensive treatment in patients with isolated systolic hypertension, not only for the prevention of cardiovascular mortality, but also of renal damage and/or end-stage renal disease. In this kind of patients, as our data have suggested, hyperfiltration due to impaired renal autoregulation has a key role in renal damage. The normalization of vascular response should be a new target of antihypertensive treatment. Further studies should asses whether antihhypertensive drugs with different site of action (i.e. on afferent or efferent arteriole) have a different nephroprotective effect. Furthermore, lifestyle modifications, in particular changes in diet, may delay the arterial wall changes commonly ascribed to aging and retard the occurrence and the progression of high blood pressure.

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