

Congestive Heart Failure

Increased renal formation of thromboxane A₂ and prostaglandin F_{2α} in heart failure

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Renal formation of the vasoconstrictor prostaglandins thromboxane A₂ (TXA₂) and prostaglandin F_{2α} (PGF_{2α}) was investigated in 25 patients with cardiac failure, divided into New York Heart Association functional classes I to IV, and in eight healthy control subjects. Plasma renin activity (PRA) and hemodynamic parameters were also investigated. Renal vasoconstrictor eicosanoid formation, measured in urinary daily excretion, was not different between patients in class I and control subjects. Class II to IV patients showed progressively increasing production of PGF_{2α} (F = 49.8, *p* < 0.001, analysis of variance) and TXA₂ (F = 37.8, *p* < 0.002). PGF_{2α} excretion peaked in class IV (+1266% vs class I, *p* < 0.001). Compared with class I, urinary excretion of thromboxane B₂ was +816% in class III and +1561% in class IV (both *p* < 0.001). PRA was significantly increased only in class IV (+1558%, *p* < 0.001). The current results indicate a progressive increase in renal production of vasoconstrictor eicosanoids directly related to New York Heart Association class and suggest that these prostanoids may have a role in deterioration of renal function. (*Am Heart J* 1997;133:94-100.)

The long-term outcome of patients with congestive heart failure (CHF) depends on progressive deterioration of ventricular performance and on neurohormonal reactions set in motion by the disease.¹ Sympathetic activation and enhanced activity of different vasoconstrictor systems, including the renin-angiotensin system and vasopressin, play a major role in maintaining perfusion pressure and blood volume.² The increased formation of vasoconstrictive mediators is associated with enhanced formation of vasodilating factors, such as atrial natriuretic peptide and renal prostaglandins E₂ and I₂.^{3,4} Their increase pre-

vents the deleterious effect of a nonmodulated vasoconstrictor system and maintains renal filtration.⁴

Whereas the synthesis of vasodilating eicosanoids is known to increase in heart failure,⁴ the renal synthesis of vasoconstrictive prostanoids (i.e., prostaglandin F_{2α} [PGF_{2α}] and thromboxane A₂ [TXA₂]) has not yet been investigated in cardiac failure despite their relevant vasoconstrictor activity. In animal studies, PGF_{2α} has been shown to facilitate the response of sympathetic nerve stimulation and to increase responsiveness to norepinephrine.⁵ Moreover, when systemically injected, it provokes an increase in blood pressure in animals and in human beings.⁶ TXA₂ exhibits very potent constrictive effects in different vascular beds, including the renal bed, and within the kidney it causes a decrease in renal blood flow and glomerular filtration rate.⁷ Thus, although in healthy subjects neither TXA₂ nor PGF_{2α} seems to be involved in the maintenance of renal function,^{6,8} their enhanced renal formation, particularly that of TXA₂, may play a significant role in reducing renal perfusion and glomerular filtration in pathologic circumstances.^{9,10}

The TXA₂ and PGF_{2α} synthesized by the kidney are excreted in the urine as thromboxane B₂ (TXB₂) and PGF_{2α}. Therefore renal production of these prostaglandins can be evaluated by measuring their urinary excretion.^{11,12} The aim of this study was to investigate the role of renal TXA₂ and PGF_{2α} in patients affected by CHF with different degrees of disease severity according to New York Heart Association (NYHA) classification.¹³

METHODS

Study subjects and patient selection. Twenty-five women affected by CHF (aged 28 to 79 years; mean age 46 ± 33 years) and 8 healthy, age-matched female control subjects (aged 26 to 82 years; mean age 51 ± 25 years) were studied. Only female subjects were studied because

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renal prostaglandins were to be measured in urine, which may have an extrarenal origin in males.¹⁴ None of the subjects was taking oral contraceptives. Patients were considered eligible for the study if CHF had been diagnosed by clinical examination or by echocardiographic or other instrumental evaluation (chest radiography or cardiac radioisotopic scanning). Exclusion criteria included diabetes, hypertension, liver disease, or malignant neoplasm as well as any primary or secondary cause of renal disease according to the results of clinical examination or of renal ultrasound examination with serum creatinine levels at ≥ 2.0 mg/dl and positive results on urinalysis. The types of heart disease underlying cardiac failure and their percentages in the different classes are described in Table I. Patients were subdivided into four functional classes.¹³ All subjects refrained from taking nonsteroid antiinflammatory drugs for 15 days before being examined. All subjects gave their informed consent before participating in the study.

Study protocol

Experimental procedure. In all patients, diuretic agents and angiotensin-converting enzyme inhibitors were withdrawn 48 hours before urine collection. Patients of class IV received close clinical surveillance. Among class IV patients, only those whose condition had remained stable after the 12-hour drug withdrawal period were admitted into the study and completed the 48-hour washout period according to the study protocol.

For the total period of hospitalization, the subjects received a diet that contained 108 mmol sodium chloride and 60 to 80 mmol potassium per day. Daily water intake was measured and controlled. At admission, after a 48-hour period of pharmacologic washout, 24-hour urine samples were collected for eicosanoid (urinary $\text{PGF}_{2\alpha}$ and urinary TXB_2), creatinine, and electrolyte (sodium and potassium) determinations. Venous blood samples were collected for serum electrolyte, serum creatinine, and plasma renin activity (PRA) determinations at 8:00 AM after overnight bed rest. Glass tubes devoid of anticoagulants (Vacutainer Systems, Becton Dickinson, Heylan Cedex, France) were used to collect the blood for serum electrolyte and creatinine determinations; blood samples for PRA were collected in cold glass tubes that contained 0.037 mol/L ethylenediamine tetracetic acid. Urinary collection and blood sampling were repeated whenever changes in clinical findings indicated that the patient's functional NYHA class had changed.

Systemic hemodynamic parameters. Arm blood pressure was measured with a sphygmomanometer. The first Korotkoff sound was taken as an index of systolic blood pressure (SBP) and the fifth as an index of diastolic blood pressure (DBP). Mean blood pressure was obtained by adding one third of the pulse pressure to the value of the diastolic pressure. An average of six blood pressure and heart rate recordings (measured at 6:00, 8:00, and 12:00 AM and at 4:00, 8:00, and 12:00 PM) was taken as an index of the 24-hour study period. If tricuspid regurgitation was present, mean pulmonary artery pressure (PAP_m) was determined by Doppler echocardiography according to the method described by Currie et al.,¹⁵ given that values thus obtained correlate well with those from invasive techniques. Only

when tricuspid regurgitation was not present, PAP_m was calculated by estimating pulmonary acceleration time, which has been shown to be directly and strongly correlated with PAP_m .¹⁶ Venous pressure (VP) was determined by a direct method.¹⁷ Pressure values were expressed as centimeters of water and were then converted into millimeters of mercury by dividing by a factor of 1.36. The values obtained by this method exhibit a high degree of correlation with the measurements in the right atrium as obtained by heart catheterization.¹⁷

Sodium balance and volume status. Variations in water and sodium metabolism were assessed during the hospitalization period by daily evaluation of serum and urinary electrolytes (sodium and potassium), patient weight, and water balance. Urinary and serum sodium and potassium were measured with a flame photometer (System 243 Instrumentation Laboratory, Lexington, Mass.).

Plasma renin activity. PRA was determined by radioimmunoassay with a commercially available kit (Angiotensina RIA CT, RADIM, Rome, Italy) according to Haber et al.¹⁸ The intraassay coefficient of variation was 7.5% at 2.3 pg/ml, 5.4% at 8.8 pg/ml, and 9.9% at 13.5 pg/ml. The interassay coefficient of variation was 7.7% at 2.6 pg/ml, 8.1% at 8.6 pg/ml, and 11.5% at 13 pg/ml. The detection limit of the method is 0.15 ng/ml/hr, and the standard curve ranges between 0.15 and 50 ng/ml/hr.

Urinary prostaglandin assay. Immediately after collection, the urine was frozen and stored at -20°C until extraction and purification procedures could be performed. Renal $\text{PGF}_{2\alpha}$ and TXB_2 were measured by radioimmunoassay after extraction from urinary samples by using an organic solvent and chromatographic purification in a silicic acid column. Details of the method have been reported elsewhere.¹⁹ Carlo Patrono (Istituto di Farmacologia, Università di Chieti, Italy) provided the antibodies to $\text{PGF}_{2\alpha}$, obtained from the guinea pig. The antibody to TXB_2 was provided by Luciano Caprino (Istituto di Igiene, Università Cattolica del Sacro Cuore, Rome, Italy). The average calculated recovery was $58\% \pm 15\%$ for $\text{PGF}_{2\alpha}$ and $60\% \pm 10\%$ for TXB_2 . The intraassay and interassay coefficients of variation were 9% and 10%, respectively. The data are expressed as picograms per gram urinary creatinine (UCr) per 24-hour period. Normalization was aimed at correcting any change in renal function in the various study groups.

Statistical analysis. Results are expressed as mean values \pm SD. Student *t* test was used to compare healthy subjects with patients of NYHA class I. Comparison among patient groups was performed by analysis of variance (ANOVA). Simple linear correlation (Pearson) was used to evaluate the relation among variables. If a variable was found to be significantly related to multiple dependent variables on linear correlation analysis, multiple regression analysis was carried out to rule out spurious correlations and to assess the best relation between different predictor variables and a dependent variable. Statistical significance was set at $p < 0.05$.

RESULTS

No significant differences in hemodynamics, urinary volume, or urinary electrolytes were found be-

Table I. Etiology of heart disease and patients characteristics

Etiology	NYHA class			
	I (n = 6)	II (n = 6)	III (n = 7)	IV (n = 6)
Ischemic heart disease	n = 15 (60%)			
Dilated cardiomyopathy	n = 6 (24%)			
Valvular heart disease	n = 4 (16%)			
Patient characteristics				
Blood urea nitrogen (mg/dl)	0.5 ± 0.09	0.3 ± 0.06	0.4 ± 0.04	0.9 ± 0.05
Serum creatinine (mg/dl)	1.20 ± 0.28	0.96 ± 0.19	1.15 ± 0.13	1.46 ± 0.27
Serum sodium (mmol/dl)	140.7 ± 2.4	139.6 ± 2.3	138.8 ± 4.8	137.7 ± 3.2
Medication at time of 48 hr washout				
Digoxin (0.125-0.25 mg uid)	50%	66.7%	85.7%	83.3%
Furosemide (25 mg orally from uid to bid)	16.7%	16.7%	85.7%	100%
Potassium canrenoate (100 mg orally bid)	16.7%	33.3%	57.1%	50%
Captopril (25 mg uid)	0%	16.7%	28.6%	66.7%
Ramipril (2.5-5 mg uid)	16.7%	0%	0%	0%

bid, Two times per day.

uid, Once a day.

*According to clinical status.

Table II. Hemodynamic variables among NYHA classes

	NYHA class				ANOVA for all patient groups	
	I (n = 6)	II (n = 6)	III (n = 7)	IV (n = 6)	F	p Value
SBP (mm Hg)	127.5 ± 3.5	126.9 ± 26.6	126.9 ± 10.3	115 ± 12.9	0.45	NS
DBP (mm Hg)	75 ± 7	72.5 ± 10.7	73.7 ± 10.3	78.7 ± 13.1	0.30	NS
PAP _m (mm Hg)	28.8 ± 8.2	30.5 ± 5.4	41.7 ± 10.4*	58.8 ± 9.9†	14.7	<0.001
		‡				
		§				
VP (mm Hg)	5.2 ± 1.8	7.1 ± 1.6	9.2 ± 2.9*	11.9 ± 5.0†	5.2	<0.03
		‡				

NS, Not significant. * $p < 0.03$, † $p < 0.001$ vs class I by Duncan ANOVA.‡ $p < 0.03$ and § $p < 0.001$ between classes by Duncan ANOVA.

tween healthy subjects and patients of NYHA class I (data not shown). SBP and DBP were similar in all patient groups (Table II). In healthy control subjects, average PGF_{2α} urinary excretion was 374.8 ± 176.7 pg/gm UCr/24 hr and was not significantly different from that observed in class I patients (148.2 ± 52.6 pg/gm UCr/24 hr). Urinary excretion of PGF_{2α} was significantly increased in class II patients compared with healthy control subjects and class I patients (+290%, $p < 0.03$) (Table III and Fig. 1). Urinary excretion of PGF_{2α} was higher in class III and IV patients than in class I patients (+835%, $p < 0.001$ and +1266%, $p < 0.001$, for classes III and IV, respectively) and higher than in class II patients (+139.6%, $p < 0.001$ and +250%, $p < 0.001$, for classes III and IV, respectively). Thus greater disease severity by NYHA functional class was associated with a progressive and significant increase in PGF_{2α} excretion ($F = 49.8$, $p < 0.001$, by ANOVA) (Table III and Fig. 1).

The average TXB₂ urinary excretion in control subjects was 98.1 ± 54.1 pg/gm UCr/24 hr. This value was not significantly different from that either in class I patients (58.2 ± 43.3 pg/gm UCr/24 hr) or in class II patients (214.3 ± 168 pg/gm UCr/24 hr) (Table III and Fig. 1). Urinary excretion of TXB₂ was markedly higher in class III patients (+816%, $p < 0.001$ vs class I patients; +149%, $p < 0.002$ vs class II patients) and even more so in class IV patients (+1561%, $p < 0.001$ vs class I patients; +351%, $p < 0.001$ vs class II patients). Thus, with greater disease severity according to NYHA class, TXB₂ excretion was progressively higher ($F = 37.8$, $p < 0.001$) (Table III).

In NYHA class III and IV patients, urinary TXB₂ was linearly related to PAP_m ($r = 0.62$, $p < 0.02$) and PRA ($r = 0.67$, $p < 0.01$) (Fig. 2).

A progressive increase in PAP_m and VP was also found in relation to functional class. The increase

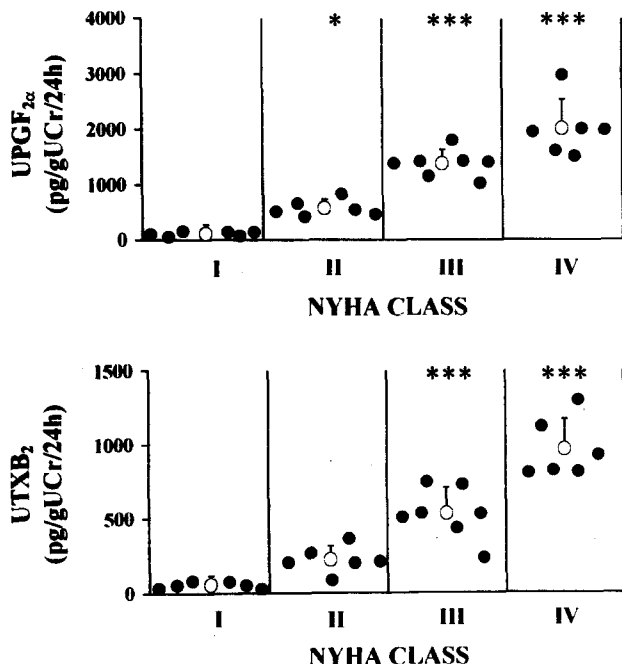


Fig. 1. Urinary vasoconstrictive prostaglandins vs NYHA class. $UPGF_{2\alpha}$, urinary prostaglandin $F_{2\alpha}$; $UTXB_2$, urinary thromboxane B_2 . * $p < 0.03$ and *** $p < 0.001$ vs patients of NYHA class I (ANOVA). Individual values are shown as solid circles; mean values are open circles.

was significant in NYHA class III and even more significant in class IV patients (PAP_m and VP, $p < 0.001$ vs class I patients) (Table II and Fig. 3). Urinary volume decreased in class III and IV patients in comparison with control subjects and class I patients ($p < 0.03$ for classes III and IV vs class I patients) (Table III). Urinary sodium was lower only in class III and IV patients ($p < 0.03$ and $p < 0.002$ respectively vs class I patients).

There was a consistent trend toward higher values of PRA in relation to greater severity by functional class, but the increase was significant only in class IV patients ($p < 0.001$ vs class I patients) (Table III).

Multiple regression analysis indicated that urinary $PGF_{2\alpha}$ was positively related to PAP_m ($\beta = 0.65$, $p < 0.001$), but not to VP (Fig. 4). Renal excretion of TXB_2 correlated with PAP_m ($\beta = 0.61$, $p < 0.001$) and more weakly with VP ($\beta = 0.33$, $p < 0.04$) (Fig. 4). Neither urinary $PGF_{2\alpha}$ nor TXB_2 was related to SBP or DBP.

DISCUSSION

Results of this study indicate for the first time that renal excretion of vasoconstrictor eicosanoids $PGF_{2\alpha}$ and TXB_2 is enhanced in patients with cardiac failure and parallels the severity of heart disease as evaluated by clinical data and PAP_m measurement.

The increase in $PGF_{2\alpha}$ excretion was already evi-

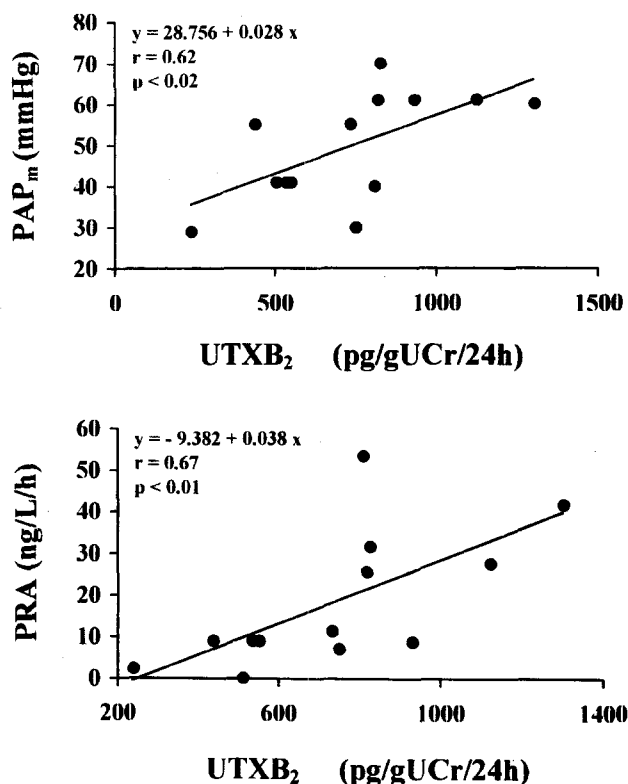


Fig. 2. Regression analysis of relation between PAP_m and urinary thromboxane B_2 ($UTXB_2$) and relation between PRA and $UTXB_2$ in patients of NYHA classes III and IV.

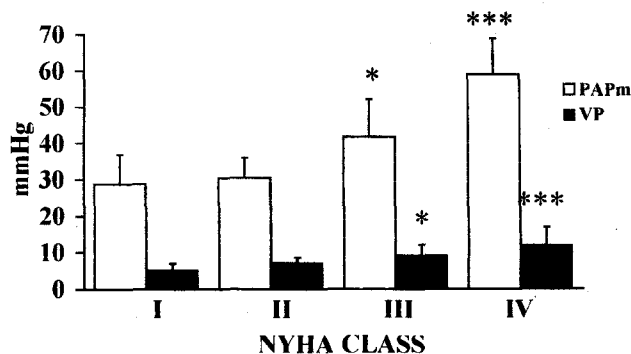


Fig. 3. PAP_m and VP vs NYHA class. * $p < 0.03$ and *** $p < 0.001$ vs patients of NYHA class I (ANOVA).

dent in class II patients, whereas TXB_2 excretion showed noteworthy increases only in class III and IV patients. However, both eicosanoids showed a strong correlation with PAP_m ($\beta = 0.85$, $p < 0.001$ for $PGF_{2\alpha}$; $\beta = 0.80$, $p < 0.001$ for TXB_2), suggesting that the progressive impairment of cardiocirculatory function may be important in causing increases in vasoconstrictor renal eicosanoid formation.

Because urinary excretion of $PGF_{2\alpha}$ and TXB_2 reflect their renal synthesis^{11, 12} and increased formation of the vasodilating prostaglandins, prostaglan-

Table III. Hormonal variables, diuresis, and sodium among NYHA classes

	NYHA class				ANOVA for all patient groups	
	I (n = 6)	II (n = 6)	III (n = 7)	IV (n = 6)	F	p Value
Urinary PGF _{2α} (pg/gm UC/r/24 hr)	148.2 ± 52.6	578.3 ± 103.8*	1385.6 ± 245.5‡	2023.7 ± 522.4‡	49.8	<0.001
		§				
		§				
			§			
Urinary TXB ₂ (pg/gm UC/r/24 hr)	58.2 ± 43.3	214.3 ± 168.0	533.1 ± 174.6‡	966.7 ± 202.3‡	37.8	<0.001
		§				
			§			
PRA (ng/L/hr)	1.9 ± 1.3	2.3 ± 3.4	7.0 ± 4.1	31.5 ± 15.1‡	19.2	<0.001
		¶				
			¶			
Urinary volume (ml/24 hr)	1008.3 ± 156.3	850.0 ± 327.1	614.3 ± 254.5*	608.3 ± 241.7*	3.69	<0.03
Urinary sodium (mmol/24 hr)	100.0 ± 27.9	86.2 ± 34.2	55.3 ± 19.4*	50.3 ± 10.6†	5.93	<0.004
		§				
		§				

**p* < 0.03, †*p* < 0.002, ‡*p* < 0.001 vs class I by Duncan ANOVA.§*p* < 0.03, ||*p* < 0.002, ¶*p* < 0.001 between classes by Duncan ANOVA.

din I₂ and prostaglandin E₂ (PGE₂), have already been reported in severe congestive heart failure,⁴ the current results indicate that renal prostaglandin system is globally involved in heart failure.

Increased renal formation of PGF_{2α} and TXA₂ may be pathophysiologically relevant in cardiac failure. Biologic activity of renal prostaglandins is finely compartmentalized in the kidney and depends on the capacity of cyclooxygenase activity at the site of eicosanoid formation and on the potential of prostaglandin inactivation by prostaglandin dehydrogenases in renal compartments.²⁰ This functional organization may explain the very precise localization of their renal activity.

PGF_{2α} formation is widely and homogeneously distributed among all renal structures, except the renal arteries,²¹ and its inactivation takes place preferentially at the cortical level.²⁰ As a consequence, PGF_{2α} may lead to a redistribution of renal blood flow from the more superficial nephrons toward the juxtamedullary nephrons that exhibit the greatest sodium reabsorption.²² PGF_{2α} acts as a vasoconstrictor; there is little evidence of any diuretic and natriuretic activity.²³ Therefore increased renal formation of PGF_{2α} may result in enhanced sodium retention as a consequence of its vasoconstrictor activity on more superficial cortical nephrons. The increased PGF_{2α} formation in patients of NYHA class II with its consequent slightly antinatriuretic effects probably contributes to the maintenance of effective plasma volume even during the early phases of heart disease and then during the more advanced stages with progressively increasing PGF_{2α} formation.

Under physiologic conditions, renal production of TXA₂ is less than PGF_{2α} formation, and it occurs mainly in the glomeruli.²⁴ Molecular biologic studies have indicated that thromboxane receptors are localized primarily within the mesangial cells²⁵ and in the smooth-muscle cells of the afferent and efferent arterioles²⁶; in this way TXA₂ affects glomerular filtration rate both hemodynamically and through a reduction in the ultrafiltration coefficient. Renal TXA₂ acts preferentially at the preglomerular level by selective constriction of the afferent artery, thus leading to a decrease both in effective renal plasma flow and in glomerular filtration rate.²⁷ Increased TXA₂ renal formation, as found in class III and IV patients, results in a marked antidiuretic and antinatriuretic effect that potentially can help to maintain blood volume by reducing renal blood flow and the glomerular filtration rate.²⁷ However, detrimental effects on renal function can easily ensue because of the marked decrease in glomerular filtration. Thus, from the pathophysiologic point of view, increased renal formation of PGF_{2α} and TXA₂ may result in augmented renal vasoconstriction and sodium retention, which may be transiently useful with regard to effective blood volume but ultimately may be dangerous in relation to renal function.

No conclusions can be drawn regarding the mechanisms responsible for the enhanced renal formation of PGF_{2α} and TXA₂. The increased formation of these prostanoids seems to reflect the progressive activation of the various renal vasoconstrictor systems. The earlier increase in PGF_{2α} formation (present in class II patients) than in TXA₂ suggests that two

	$\beta \pm se$	R^2	p
PAP _m	0.65 ± 0.18	0.44	< 0.001
VP	0.29 ± 0.18	0.41	ns
SBP	0.04 ± 0.18	0.46	ns
DBP	-0.14 ± 0.19	0.47	ns
Dependent variable PGF _{2α}			

	$\beta \pm se$	R^2	p
PAP _m	0.61 ± 0.15	0.44	< 0.001
VP	0.33 ± 0.15	0.41	< 0.04
SBP	-0.04 ± 0.15	0.46	ns
DBP	0.02 ± 0.16	0.47	ns
Dependent variable UTXB ₂			

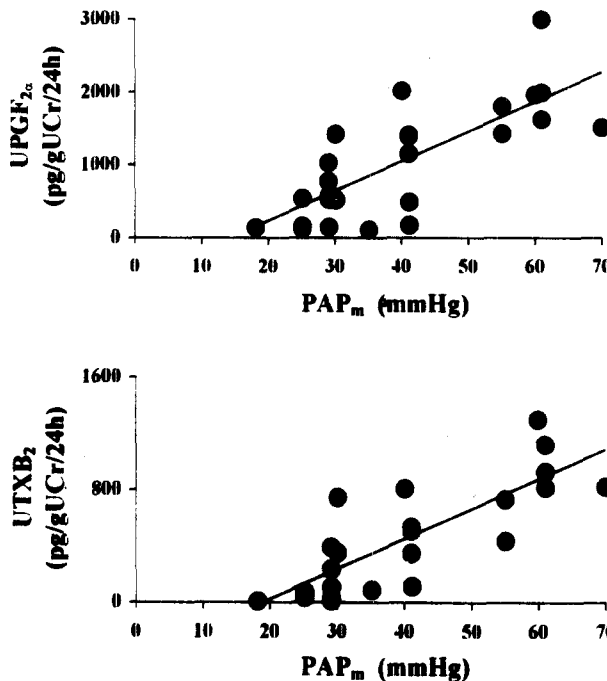


Fig. 4. Stepwise multiple regression analysis of relations between hormonal and hemodynamic factors in all patients. UPGF_{2α}, Urinary prostaglandin F_{2α}; UTXB₂, urinary thromboxane B₂. β , Multiple regression coefficient.

distinct mechanisms may be operating. The progressive lowering of cardiac output is considered to be responsible for the boosting of a broad spectrum of vasoconstrictor mechanisms, including the sympathetic nervous system, renin-angiotensin system, vasopressin, and endothelin systems,^{4,28} each of which is able to activate arachidonic acid metabolism directly.^{29,30} The sympathetic activation in the course of cardiac failure⁴ is probably responsible for the early increase in PGF_{2α} formation. Catecholamines are able to enhance the activity of phospholipase A and as a consequence to activate the arachidonic acid metabolism causing the global increase in renal formation of PGF_{2α}, PGE₂, and prostaglandin I₂ (PGI₂).²⁹ At this early phase of heart failure, the activation of the renal prostaglandin systems still seems to be well balanced between vasodilating PGI₂ and PGE₂ and the vasoconstrictor PGF_{2α} because TXA₂ formation was found to occur in the later stages (class III and especially class IV) (Table III and Fig. 1).

After activation of arachidonic acid, PGF_{2α} can be formed directly from prostaglandin H₂ either by a reductase³¹ or through the transformation of PGE₂ to PGF_{2α} by PGE₂-9-ketoreductase.³² In addition, transformation of prostaglandin D₂ by 11-ketoreductase gives rise to an epimer of PGF_{2α}, 9 α ,11 β -PGF_{2α}, that has been found in human beings.³³ This prostaglandin cross reacts with antisera to PGF_{2α} and may contribute to the increase in PGF_{2α} excretion. The

increased renal TXA₂ formation may have been due only in part to the activation of arachidonic acid metabolism by catecholamines because TXA₂ production in class II patients was not different from class I.

The enhanced formation of angiotensin II and probably endothelin may have been responsible for the increased production of renal TXA₂. Both of these vasoconstrictor hormones have been reported to cause TXA₂ formation by selectively acting on specific receptors linked to phospholipase C.³⁴ Our patients with higher TXB₂ excretion were found to have higher PRA and PAP_m values. Likewise, plasma endothelin concentration in patients with CHF has been shown to be closely related to pulmonary artery pressure values.²⁸

In our study, PRA was significantly increased only in class IV patients. Our observations confirm and extend the findings of others who have shown that angiotensin activity is increased only in the more advanced phases of heart disease.³⁵ The dependence of the increase in renal thromboxane formation on angiotensin activation is underlined by its positive correlation with PRA, as observed in our study.

Even if the values of PGF_{2α} and TXB₂ excretion were homogeneously distributed within the groups and the differences among the classes were highly significant, this study was not designed as prospective one. As a consequence, the urinary excretion of vasoconstrictive eicosanoids cannot be taken as a

predictive index of cardiac decompensation. Nonetheless, because the increase in urinary TXB₂ and urinary PGF_{2α} was constantly associated with progressive severity in the course of heart disease, our results strongly suggest that the increased renal formation of the vasoconstrictor eicosanoids and their renal effects should be included among the mechanisms involved in the aggravation of heart disease. Therefore the inhibition of vasoconstrictive prostanooids and particularly that of the more powerful TXA₂ may be considered in the future treatment of more severe cases of CHF because this inhibition may reduce renal vasoconstriction.³⁶

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