Effective Renal Plasma Flow Response and Atrial Natriuretic Peptide in Patients with Uncomplicated Acute Myocardial Infarction

Chung-Yin CHEN, M.D., Shih-Jong HUANG, M.D.,
Tsui-May YANG, Ph.D., and Mau-Song CHANG, M.D.

SUMMARY

Effective renal plasma flow was determined by using I-131 labeled iodo-ortho-hippurate in 17 Chinese patients admitted to the coronary care unit with uncomplicated acute myocardial infarction. The first determination, immediately after admission, was significantly higher than the second determination done a week later, 444.5 ± 153.9 vs. 371.1 ± 124.9 ml/min ($p < 0.02$). The initial rise of effective renal plasma flow (ERPF) after acute myocardial infarction seemed to be correlated to the initial elevation of atrial natriuretic peptide (ANP), which was determined sequentially 6 times in each patient (91.3 ± 39.4 , 25.6 ± 9.7 , 37.4 ± 12.3 , 51.8 ± 18.2 , 65.6 ± 20.8 , 57.4 ± 19.2 pg/ml, respectively). It was concluded that, in the presence of uncomplicated acute myocardial infarction, patients may show renal vasodilatation, and that the elevation of ANP may play some role in this. (Jpn Heart J 34: 1-10, 1993.)

Key Words:

Myocardial infarction   Effective renal plasma flow   Atrial natriuretic peptide

ACUTE myocardial infarction (AMI), even though not complicated by congestive heart failure or shock, may suddenly compromise global left ventricular function and activate sympathetic output or tone. This becomes evident through the appearance of symptoms of systemic vasoconstriction, including diaphoresis, apprehension, cold and clammy limbs, etc. This increase may be secondary to impaired baroreflex control of vascular resistance and heart rate in AMI or coronary occlusion.¹⁾⁻⁵⁾ However, Falicov et al have demonstrated different responses between renal and femoral vascular beds during experimentally induced myocardial infarction in dogs.⁶⁾

The purpose of this study was twofold: (1) To determine if effective

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From the Division of Cardiology, Veterans General Hospital-Kaohsiung, Kaohsiung and Department of Medical Research, Veterans General Hospital-Taipei, Taipei, Taiwan.

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Address for correspondence: Chung-Yin Chen, M.D., Division of Cardiology, Veterans General Hospital-Kaohsiung, No. 386, Ta-Chung 1st Rd., Kaohsiung, Taiwan, Republic of China.

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renal plasma flow is changed in patients with uncomplicated AMI. (2) If so, is the change in effective renal plasma flow related to a change in atrial natriuretic peptide levels?

SUBJECTS AND METHODS

Patients: Seventeen patients, 15 males and 2 females, ranging between 44 and 84 years of age (mean 65.2 ± 8.7 years), were studied. Diagnosis of acute myocardial infarction was documented by typical chest pain, typical electrocardiographic (ECG) S-T segment and Q-wave changes, and by cardiac enzyme/isoenzyme elevation. Ten patients were found to have anterior and 7 inferior myocardial infarction; in the latter patients, this was combined with right ventricular infarction in one, posterior infarction in one and anterolateral infarction in one based upon ECG changes (Table I). Patients who had shock or even minimal evidence of congestive heart failure such as very mild basal moist rales, or who were beyond 6 hours of the onset of acute severe chest pain were all excluded. Medication was prohibited throughout the entire period of hospitalization except for a low dose of oral propranolol (5 or 10 mg twice a day) or diltiazem (30 mg twice a day), and

Table I. General Data of Patients with Acute, Uncomplicated Myocardial Infarction

	Age & Sex	Location	Initial CK	Peak CK
1	84 M	Ext. anterior	180	3414
2	61 M	Inferior	69	3450
3	60 M	Anteroseptal and Lateral	125	3400
4	69 M	Ext. anterior	377	2547
5	60 M	Anteroseptal	75	1405
6	61 M	Ext. anterior	70	6834
7	63 M	Anterolateral	60	605
8	69 F	Inferior	71	890
9	71 M	Anteroseptal	774	3010
10	44 M	Ext. anterior	49	1853
11	67 M	Inferior	68	2140
12	73 M	Ext. anterior	448	3718
13	64 M	Inf. and RV	137	2396
14	63 M	Ext. anterior	229	4499
15	60 M	Inferior	448	7227
16	74 M	Inf. and Post.	54	1365
17	55 F	Inf. and Anterolateral	71	794
mean	65		194	2914

Ext.=extensive; Inf.=inferior; Post.=posterior; RV=right ventricular.

intramuscular injection of meperidine or morphine, if necessary. No diuretic or inotropic agent was allowed.

Determination of effective renal plasma flow (ERPF): Soon after the patient arrived at the emergency room and before intravenous infusion of streptokinase (SK), if it was given, ERPF was determined using I-131 iodo-ortho-hippurate (IOH). One week later a second ERPF determination was performed on each patient. I-131 IOH 0.3 mCi, prepared by the Department of Nuclear Medicine of our hospital, was intravenously injected in one arm and venous blood was collected from the other arm exactly 44 min later for radioactivity count using a fixed formula.^{7),8)} In addition, all patients were monitored for urine output, urine electrolytes, renal function and serum electrolytes regularly throughout their hospitalization.

Another 12 patients who had stable coronary artery disease and were receiving regular anti-anginal treatment served as a control group. Using the same procedures, ERPF determinations were repeated at a 1-week interval to examine the reproducibility of ERPF determinations. Control patients were not allowed additional medication other than that taken the previous week.

Determination of atrial natriuretic peptide (ANP): All patients in this study had 6 serial measurements of plasma ANP, immediately after arriving at the emergency room (on average, 2.4 hours after the onset of chest pain), and at 6, 12, 24, 72 and 120 hours after the first determination. Blood taken from a cubital vein was placed in EDTA-coated tubes containing aprotinine, 500 IU/ml, and kept in an ice bath. The plasma was separated within an hour, then stored at -20°C until analysis. A commercial radioimmunoassay kit from Peninsula Laboratories Inc., Belmont, California (Catalog No. RIK8798) was used, and included the step of plasma extraction before analysis. The method of plasma extraction which applied in this study is modified from that of Hartter et al which was first published in 1986.⁹⁾ One milliliter of plasma was first acidified with an equal volume of 1% trifluoroacetic acid and the acidified plasma was applied to the pretreated Sep-pak C18 cartridge (its long end connected by Luer tip to a 5 ml syringe barrel). The sensitivity of the method is reported to be 15.0 pg/tube, and the specificity for alpha-hANP is 100%.

Statistics: All data are presented as mean value $\pm$ 1 standard deviation. Wilcoxon signed ranks test was used for pair variables. $P < 0.05$ is considered to be statistically significant.

RESULTS

ERPF determination: The reproducibility of ERPF determinations in 12 control individuals was good. The variation in the two sets of data obtained 1 week apart was about 8% at most, with a difference of between 8 and 43 ml/min (Table II).

Table II. ERPF Determination in 12 Patients with Coronary Artery Disease

Patient No.	Age & Sex	1st	2nd	Variation (%)
1	64 M	395.1	362.4	8.3
2	58 F	484.6	497.4	2.6
3	70 M	421.7	393.6	6.7
4	67 F	649.8	636.8	2.0
5	73 M	511.7	529.9	3.6
6	56 M	308.6	335.3	8.6
7	62 F	313.3	322.5	3.0
8	62 M	423.4	440.4	4.0
9	66 M	664.4	626.3	5.7
10	61 M	392.3	405.5	3.3
11	68 M	419.1	439.4	4.8
12	64 M	506.9	549.9	8.5
Mean $\pm$ SD		457.7 $\pm$ 113.2	460.3 $\pm$ 107.2	

P value = not significant.

Fig. 1. Effective renal plasma flow at time of admission and 1 week later.

Table III. Acute and 1 Week Post MI Renal Function Testing in 17 Patients with Acute Myocardial Infarction

No.	BUN		Creatinine		UA		Na ⁺		K ⁺	
	A	1 wk	A	1 wk	A	1 wk	A	1 wk	A	1 wk
1	24	23	1.1	1.1	5.0	6.9	137	142	3.5	3.7
2	24	27	2.5	2.4	9.2	13.0	133	140	4.8	4.0
3	14	12	1.2	1.1	9.4	8.8	140	139	3.6	4.3
4	20	17	0.8	1.0	5.9	6.6	134	139	3.6	3.9
5	15	21	1.0	1.2	6.0	5.4	130	142	3.5	4.1
6	12	13	0.8	0.9	5.4	6.1	138	139	3.6	3.6
7	25	27	1.3	1.0	7.1	8.0	141	142	4.4	4.2
8	19	21	1.0	1.0	3.5	4.6	137	138	4.4	4.0
9	12	16	0.8	0.8	4.8	5.4	135	136	4.1	4.6
10	18	19	1.1	1.2	6.6	7.1	140	138	4.0	4.3
11	17	19	1.3	1.3	7.4	8.0	137	142	3.6	4.8
12	14	13	0.8	0.9	3.9	4.3	142	138	4.0	4.1
13	21	14	1.2	1.3	6.8	7.2	139	137	3.5	4.4
14	25	19	1.8	1.7	9.5	7.9	140	141	3.7	5.0
15	19	23	1.1	1.4	5.5	6.1	138	142	3.8	4.1
16	16	7	1.0	0.8	4.1	4.9	135	141	4.4	4.4
17	13	14	0.8	0.8	4.0	4.9	136	138	3.9	4.2
Mean ±SD	18.1 ±4.4	17.9 ±5.3	1.2 ±0.42	1.2 ±0.39	6.1 ±1.9	6.8 ±2.0	137.2 ±3.0	139.6 ±3.0	3.9 ±0.4	4.2 ±0.4

A=acute; 1 wk=1 week later; p value=not significant.

Fig. 2. Changes in atrial natriuretic peptides in patients who suffered from acute uncomplicated myocardial infarction. The first determination was done at the time of arrival at the ER. The later determinations were done at 6, 12, 24, 72 and 120 hours, respectively, after the first determination (* p<0.005).

Fig. 3. The percentage of the initial increase of plasma ANP [$\% \text{ ANP} = (\text{initial ANP} - \text{ANP at day 5}) / \text{ANP at day 5}$] correlated to the initial increase of ERPF [$\% \text{ ERPF} = (\text{initial ERPF} - \text{ERPF at 1 week later}) / \text{ERPF at 1 week later}$].

In the 17 patients in this study, the initial ERPF was 444.5 ± 153.9 ml/min, significantly higher ($p=0.0113$) than that determined 1 week later (371.1 ± 124.9 ml/min, Fig. 1). The initial rise and later decline of the ERPF was seen in all but 3 patients (18%). Nevertheless, renal function (blood urea nitrogen, creatinine and uric acid), urine output and serum electrolytes (Na^+ , K^+ and Cl^-) were well maintained without significant change, whether or not the ERPF rose (Table III).

ANP determination: Although all patients suffered Killip I acute myocardial infarction (indicating no evidence of congestive heart failure), initial elevation of the ANP (91.3 ± 39.4 , significantly higher than the second and third determinations at 6 and 12 hours after the first ANP determination, 25.6 ± 9.7 and 37.4 ± 12.3 pg/ml, respectively, $p < 0.005$) with a subsequent decline over time was found (Fig. 2). The initial elevation of ANP correlated with the initial increase of ERPF ($r=0.89$, $p < 0.03$, Fig. 3).

DISCUSSION

ERPF determination: According to Tauxe, ERPF can be readily measured by the 44-min, single-sample method that uses I-131 IOH. The procedure has been reported to be fast, accurate, noninvasive and readily adaptable to unusual clinical situations. It requires relatively simple in-

struments, and is relatively inexpensive.⁸⁾

Renal blood flow in AMI: Patients with AMI, even those not complicated by congestive heart failure or cardiogenic shock (the so-called Killip Class I), still have evidence of increased sympathetic output with diaphoresis, apprehension, cold and clammy limbs, etc. This increase may be secondary to the impaired baroreflex control of vascular resistance and heart rate in acute myocardial infarction or coronary occlusion.¹⁾⁻⁵⁾ However, Falicov et al have demonstrated different responses to experimental myocardial infarction between the renal and femoral vascular beds in dogs—vasoconstriction in the femoral vascular bed, in contrast to early and persistent vasodilatation in the renal vasculature as evidenced by a decrease in renal vascular resistance of $28 \pm 4\%$ (SEM).⁶⁾ They also mention that this paradoxical renal vasodilatation in response to myocardial ischemia cannot be abolished by vagotomy, nor is the ability of the renal vessels to constrict in response to noradrenaline impaired after coronary embolization. The mechanism of this renal vasodilatation is still undefined. In addition, in experimentally induced myocardial infarction in rats, Hostetter and his colleagues have demonstrated that Na^+ excretion in response to acute volume loading may be reduced even by a small-to-moderate myocardial infarction and minimal changes in ventricular pumping capacity.¹⁰⁾ Both of these animal studies disclose a unique renal response to myocardial infarction.

Blood flow in regional tissue is a critical determinant of function in health and disease. Determination of renal blood or plasma flow in patients with acute myocardial infarction is rare, and perhaps has not been reported previously. Selwyn et al have only mentioned the usefulness of the application of the ^{11}C -labeled human albumin microsphere and external detection, with positron emission tomography, to measure distribution of cardiac output and regional organ flow, e.g. brain, lungs, heart, liver, spleen and kidneys, in patients with past myocardial infarction.¹¹⁾ But they did not demonstrate whether renal blood flow changes after AMI. Razzak and his colleagues have used radioiodinated human serum albumin, rapidly injected as a bolus into the vein, to determine renal blood flow in the follow-up of patients after cardiac surgery as well as in those suffering from myocardial infarction.¹²⁾ In their study, the renal blood flow was $1,144 \pm 100$ ml/min in 15 normal individuals; it was 2,600 ml/min in 1 patient with myocardial infarction, and the ratio of renal blood flow to cardiac output increased from 18.8 to 31.2%. In 3 other nonselected myocardial infarction patients, with unknown functional class, serial determinations of cardiac output and renal blood flow showed no consistent change over the course of the disease.¹²⁾ In the present report the ERPF using ^{131}I -IOH injected intravenously in 17

patients with uncomplicated AMI was increased (444.5 ± 153.9 ml/min) in all but 3 patients, as compared with data obtained 1 week later (371.1 ± 124.9 ml/min, $p < 0.02$, Fig. 1). Even though the ERPF of individual patients fluctuated greatly during the first week following acute myocardial infarction, the renal function of each patient—including serum urea nitrogen, creatinine and uric acid, as well as serum and urine electrolytes—was maintained in all 17 patients. Neither did any of these 17 patients show diuresis in the first post-AMI week.

ANP in patients with myocardial infarction: ANP is a cardiac hormone with potent diuretic, natriuretic and vasodilatory activities; it plays an important role in the regulation of blood pressure and body fluid volume.^{13),14)} Plasma concentration of ANP increases following plasma volume expansion, and is higher than normal in patients with congestive heart failure.^{15)–17)}

Jougasaki and his colleagues have demonstrated immunoreactivity for ANP in the subendocardial cells of infarcted as well as in noninfarcted segments of the left ventricle in all patients ($n=5$) with myocardial infarction, and they believe that the appearance of ANP in the ventricles may be one of the manifestations of a compensatory mechanism.¹⁸⁾ Their detailed observations note that the most intense immunoactivity for ANP is found in patients with severe congestive heart failure, and the weakest immunoactivity is observed in patients with mild or no heart failure.¹⁸⁾ Phillips et al, in their study of plasma ANP concentration in patients with AMI, reported that patients who receive no intravenous streptokinase (IVSK) have significantly higher ANP concentrations than those receiving IVSK.¹⁹⁾ However, a more careful analysis of their study leads to the comment that 33% (14/43) of the patients in the former group and 18% (4/22) of the patients in the latter were in fact in Killip Class >1 , an indication of at least mild left ventricular dysfunction. As also demonstrated by Tomoda in patients with acute myocardial infarction, left atrial overloading (or elevated pulmonary wedge pressure) appears to contribute more to ANP release than does right atrial overloading.²⁰⁾

However, the early decrease of plasma ANP levels 3 hours after the onset, followed by a significant rise in patients with acute myocardial infarction as observed by Tan and Wencker et al^{21),22)} has highlighted the importance of the blood sampling-time in evaluating ANP levels in these patients. In this study, the plasma concentration of ANP seemed contrary to Tan and Wencker's observation, in that all 17 patients showed an initial elevation of plasma ANP with a later reduction in concentration 6 hours after the first determination (about 9 hours after acute myocardial infarction). The

plasma ANP then remained low thereafter. Possible factors responsible for the difference between the two observations are: (1) different time of blood sampling; (2) different criteria of patient selection; and (3) different method of ANP determination.

ANP and ERPF: In an electrophysiologic study of 5 patients, Tsai and his colleagues demonstrated that increased atrial pressure during induced supraventricular tachycardia (SVT) may stimulate ANP release and consequently increase glomerular filtration rate, decrease aldosterone secretion and inhibit water reabsorption. All these mechanisms are responsible for the natriuresis and diuresis associated with SVT.²³⁾ However, as we reviewed the literature, no report has demonstrated that the increase in ANP may result in an increase of ERPF, although theoretically it should. In the present study, although no patients had evidence of diuresis, we still have reason to believe that the initial elevation of ANP may be at least partly responsible for the initial elevation of ERPF (see Fig. 3).

CONCLUSION

The conclusion here is that after acute, uncomplicated myocardial infarction, ERPF may significantly increase without necessarily causing an alteration of renal function or diuresis. The initial elevation of ERPF after AMI in an individual patient seems to be related to plasma ANP. Further investigation is necessary to elucidate the mechanism(s), other than the initial elevation of ANP, responsible for the renal response in patients with AMI.

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