Original Research

Brain Natriuretic Peptide Mediates the Effect of Creatinine Clearance on Development of Left Ventricular Systolic Dysfunction in Patients with Acute Coronary Syndrome

Christina Chrysohoou[1], Christos Pitsavos[1], Panagiotis Aggelopoulos[1], George Metallinos[1], Eleftherios Tsiamis[1], Demosthenes Panagiotakos[2], Christodoulos Stefanadis[1]

[1]First Cardiology Department, University of Athens Medical School, Hippokration Hospital, [2]Nutrition and Dietetics Department, Harokopio University, Athens, Greece

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Introduction: There are only limited data about the role of renal function in the development of left ventricular systolic dysfunction in patients with an acute coronary syndrome (ACS). We sought to investigate whether renal insufficiency is an independent predictor for systolic dysfunction among patients who had an ACS.

Methods: During 2006-2007, 814 consecutive patients who presented with an ACS event were enrolled prospectively; of these, 284 men (65 ± 14 years) and 71 women (71 ± 12 years) developed left ventricular systolic dysfunction (ejection fraction <40%), 306 men (64 ± 12 years) and 78 women (67 ± 10 years) had preserved left ventricular systolic function (ejection fraction >50%), while the rest of the patients (n=75), with ejection fraction between 40-50%, were excluded from this analysis. Creatinine clearance rates were estimated by the Cockcroft-Gault formula.

Results: Eight percent of patients presented with severe and 30% with moderate renal dysfunction. Multiple logistic regression analysis revealed that a 10-unit increase of creatinine clearance levels decreases the odds of developing left ventricular systolic dysfunction by 8% (95%CI per 1 unit: 0.986-0.998), after controlling for potential confounders. Moreover, brain natriuretic peptide levels were inversely correlated with creatinine clearance (r=-0.378, p<0.001). When brain natriuretic peptide was entered into the model, creatinine clearance was not associated with left ventricular systolic dysfunction (OR=0.997, 95%CI 0.989-1.005).

Conclusions: The role of renal insufficiency in the development of left ventricular systolic dysfunction seems to be partially explained by plasma brain natriuretic peptide levels, suggesting a potential pathophysiological mechanism. Thus, patients with impaired creatinine levels and elevated brain natriuretic peptide levels should receive more aggressive medical care, as they are prone to developing left ventricular systolic dysfunction.

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Address: Christina Chrysohoou

46 Paleon Polemiston St., 166 74 Glyfada, Greece
e-mail: chrysohoou@usa.net

Acute coronary syndromes represent the most urgent clinical presentation of atherosclerosis, which is linked with varying morbidity and mortality among populations.[1,2] Among other predictors of death or myocardial infarction in patients hospitalised with an acute coronary event, the presentation of congestive heart failure has a significant impact.[2,3] Thus, the risk stratification of patients after an acute coronary event should include the evaluation of left ventricular function, as the occurrence of systolic heart failure after an acute coronary event has adverse implications for the clinical outcome of those patients.[1,2] Among other factors, renal insufficiency has been recognised as an independent risk factor for

cardiovascular morbidity and for all-cause mortality, as well as for cardiovascular death in the general population.[4] Recent studies have shown that any stage of renal dysfunction (i.e. mild to severe) is an independent risk factor for short- and long-term mortality among patients with myocardial infarction, even after fibrinolytic administration.[5-10]

Brain natriuretic peptide (BNP) levels in the blood are used for the diagnosis of acute congestive heart failure and may constitute a useful marker to establish the prognosis of these patients.[11] BNP is a 32-amino-acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes). Additionally, BNP has been related to the common homeostatic purpose of volume, osmosis and pressure regulation of the circulatory system. BNP regulates salt and water handling, promotes vasodilation and is related to ventricular function, while its levels can provide prognostic information in patients who survive after an acute coronary event.[11-13] The relation of BNP levels with renal function, however, may compromise its prognostic value in patients with renal impairment.[14]

Data evaluating the synergistic role of renal function and serum BNP levels on the risk of heart failure are lacking in the literature. Thus, the aim of this work was to evaluate the effect of renal function at hospital presentation (as expressed using creatinine clearance levels) on the occurrence of left ventricular systolic dysfunction in patients who had had an acute coronary syndrome (ACS), on the spectrum of BNP levels, and on other clinical and biochemical factors that are also related to a poor clinical outcome.

Methods

The study was approved by the Medical Research Ethics Committee of our Institution and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Study population

From May 2006 to June 2007, we enrolled all consecutive patients (n=814) who were hospitalised in our institution after an ACS (first and recurrent). The purpose of the study was to evaluate several demographic, nutritional, lifestyle and medical risk factors in relation to the risk of developing left ventricular dysfunction after a non-fatal acute coronary event, and the prospective evaluation of this population for cardiovascular and other events. Evidence of left ventricular systolic dysfunction after an ACS (i.e. ejection fraction <40%) was found in 355 patients (43.6%), of whom 284 were men (age 65 ± 14 years) and 71 women (71 ± 12 years). The control group included 384 of the ACS patients – 306 men (64 ± 12 years) and 78 women (67 ± 10 years) – who had an ejection fraction above 50%. The rest of the patients (n=75), who had a left ventricular ejection fraction of 40-50%, were excluded from this analysis.

Power analysis showed that the number of enrolled participants was adequate to evaluate a 2% change in the odds of developing systolic dysfunction per 10% change in creatinine clearance rates, achieving statistical power greater than 70% at the 5% probability level (p-value).

Diagnosis of ACS and heart failure

On entry to the study a 12-lead electrocardiogram was recorded and clinical symptoms were evaluated by a cardiologist in all patients. Based on the ECG findings, patients were classified as having ST-segment elevations or non-ST segment elevations (meaning ST-segment depression or other electrocardiographic abnormalities, such as T wave inversion). Blood tests were performed to detect evidence of myocardial cell death. We measured troponin I levels and the MB fraction of total creatinine phosphokinase (CPK). We finally included only cases with discharge diagnoses of ACS (acute myocardial infarction or unstable angina). Acute myocardial infarction was defined according to the latest guidelines,[15] while unstable angina was defined by the occurrence of one or more angina episodes at rest within the preceding 48-hours, corresponding to class III of the Braunwald classification.[16]

Using a Hewlett Packard device (Sonos 5500 Ultrasound system) with a multi-frequency transducer (2.5-4 MHz) we evaluated the end-diastolic and end-systolic left ventricular volumes and evaluated left ventricular systolic function. Systolic heart failure was defined as a left ventricular ejection fraction below 40%, according to the recent European Society of Cardiology guidelines for the diagnosis and treatment of acute heart failure.[17]

Other clinical and biochemical characteristics

In all patients a detailed medical history was recorded, including previous hospitalisation for cardiovascular disease, presence and management of hypertension, hypercholesterolaemia, renal failure and dia-

betes mellitus, as well as patients' family medical history. A family history of premature (<55 years old for males and <65 years old for females) onset of hypertension, hypercholesterolaemia, hypertriglyceridaemia and diabetes, defined as the use of special medication or a known, but untreated, condition, classified the participants in the positive family history group for these co-morbidities.

In addition to troponin I and the MB fraction of CPK, we also measured white blood cell counts, urea, and uric acid. Blood samples for the measurement of troponin I and the MB fraction of creatinine phosphate were collected every 4 hours for the first 2 days. All biochemical evaluations were carried out in the same laboratory, which followed the criteria of the World Health Organisation Reference Laboratories. Total- and high-density lipoprotein (HDL) cholesterols, blood glucose and triglycerides were also measured in all participants, using the colorimetric enzymic method in a Technicon automatic analyser RA-1000 (Dade-Behring Marburg GmbH, Marburg, Germany). Low-density lipoprotein cholesterol was calculated using the Friedewald formula: total cholesterol – HDL cholesterol – 1/5 × (triglycerides). An internal quality control was in place for assessing the validity of the cholesterol and triglyceride methods. The intra and inter-assay coefficients of variation of cholesterol and triglyceride levels did not exceed 4%.

BNP levels at entry were determined by an enzyme-linked immunosorbent assay (Biomedica, Vienna, Austria), inter- and intra-assay coefficients of variation being <5%, with normal range 0-100 pg/ml.

Renal insufficiency was initially quantified by the baseline estimated creatinine clearance rate (CrCl). Based on baseline serum creatinine at entry (Cr), the CrCl was calculated using the Cockcroft-Gault formula:[18] CrCl = (140 - age) × weight / (72 × serum creatinine) for men, while for women the result of the previous equation was multiplied by 0.85. Patients were divided into three groups according to their CrCl: those with normal renal function or mild renal insufficiency (CrCl >60 ml/min), those with moderate renal insufficiency (CrCl 30-60 ml/min), and those with severe renal insufficiency (CrCl <30 ml/min). This stratification was based on the National Kidney Foundation recommendations.[19]

Demographic, anthropometric and lifestyle characteristics

Socio-demographic characteristics included: age, sex, marital status and number of children, years of school, type of occupation and occupational skills. The latter were evaluated using a ten-point scale, from unskilled-manual workers (lower values) to executive-skilled workers (higher values), which was developed for the purposes of the study. Height and weight were measured to the nearest 0.5 cm and 100 g, respectively. Body mass index was then calculated as weight (in kilograms) divided by height (in meters) squared. Physical activity was defined as any type of exercise (occupational or leisure) at least once per week during the past year. Other participants were defined as physically inactive. Current smokers were defined as those who smoked at least one cigarette per day or had stopped cigarette smoking during the past 12 months. Former smokers were defined as those who had stopped smoking more than one year previously. The rest were defined as never smokers or rare smokers.

Statistical analysis

Continuous variables are presented as mean values ± standard deviation if they were normally distributed, or median if they had skewed distribution (e.g. BNP levels). Categorical variables are presented as frequencies. Associations between normally distributed continuous variables and groups of patients were evaluated through Student's t-test or the analysis of variance (ANOVA), after controlling for equality of variances. The normality of continuous variables was tested using the Kolmogorov-Smirnov criterion. Because of the multiple comparisons we applied the Bonferroni correction to correct for the inflation of Type I error. Associations between categorical variables were tested using the chi-squared test. Correlations between continuous variables were tested by Pearson's or Spearman's correlation coefficients for normally distributed or skewed variables. The non-parametric Mann-Whitney test was used to evaluate differences in BNP levels between the study groups, in view of their skewed distribution.

Multiple logistic regression analyses evaluated the association between creatinine clearence and the likelihood of developing left ventricular systolic dysfunction (dependent outcome), after various adjustments were made. The effect size was measured through the estimated odds ratios (OR) and the corresponding 95% confidence intervals. The potential confounding effect of BNP on the previous relationship was evaluated by comparing the effect sizes (i.e. ORs) of crea-

tinine clearance between the model with and without BNP as a covariate. All statistical calculations were performed using the SPSS version 14.0 software (SPSS Inc, Chicago, IL, USA).

Results

Table 1 shows the clinical characteristics of all the patients according to the presence or not of systolic dysfunction. Patients who developed systolic dysfunction had higher entry levels of troponin I, uric acid, creatinine clearance, as well as a higher prevalence of diabetes mellitus and myocardial infarction as a discharge diagnosis. Additionally, 8% of patients presented with severe renal dysfunction, 30% with moderate and the remaining 62% with normal. BNP levels were higher among patients with systolic dysfunction as compared to the rest of the patients (513.23 ± 757.8, median 248, vs. 199.95 ± 449.23 ng/ml, median 64; p<0.001). There was no significant difference between the groups of patients (i.e. those who did and did not develop systolic dysfunction) regarding a previous history of coronary artery disease.

Table 2 gives the baseline characteristics of patients hospitalised with all clinical presentations of ACS across tertiles of BNP levels. In brief, patients having BNP values in the highest tertile were older, more likely to be women, less likely to smoke, more likely to have single-vessel disease and a low ejection fraction, and more likely to have a history of hypertension, previous coronary artery disease, diabetes mellitus, higher troponine I and white blood cell levels, compared to those in the lowest tertile of BNP. Moreover, BNP levels were inversely correlated with creatinine clearance levels (r=-0.378, p<0.001), while subgroup analysis showed that creatinine clearance was inversely correlated with BNP, both in patients with (rho=-0.24, p=0.09) and in those without a history of coronary artery disease (rho=-0.27, p=0.007).

We have previously reported that creatinine clearance levels predict systolic dysfunction in patients who have had an ACS (Table 1). The multi-adjusted analysis, presented in Table 3, revealed that creatinine clearence was inversely associated with the occurrence of systolic dysfunction, with an odds ratio per 1 ml/min equal to 0.99 (p=0.008), after controlling for various covariates (Table 3, model 1). Thus, impaired renal function seems to confer an increased risk for the development of left ventricular systolic dysfunction after a coronary event. This finding was consistent when the sample was divided into patients with a first or a recurrent cardiac event. However, we have also reported that BNP levels are strongly associated with the investigated outcome (Table 1). Thus, BNP levels could play

Table 1. Clinical characteristics of patients according to systolic heart function.

	Left ventricular systolic dysfunction	Preserved left ventricular systolic function	p
N	355	384	
Age (yrs)	65 ± 13	63 ± 11	0.11
Male sex, %	79	78	0.75
Body mass index (kg/m^2)	27.5 ± 4.3	28 ± 4.8	0.14
Diagnosis of MI, %	84	71	0.0001
Left ventricular ejection fraction, %	32 ± 6	51 ± 5	0.0001
One (single) vessel disease, %	26	44	0.0001
Previous CAD, %	33	33	0.99
Troponin I at entry (ng/ml)	39 ± 43	15 ± 32	0.0001
Uric acid (mg/dl)	6.7 ± 2.1	6.1 ± 2.0	0.0001
WBC (count)	11573 ± 3659	10614 ± 6398	0.32
Creatinine clearance (ml/min)	71 ± 33	78 ± 31	0.009
Brain natriuretic peptide (pg/ml)	200 ± 445	510 ± 759	<0.001
Haematocrit, %	43 ± 26	44 ± 33	0.57
LDL-cholesterol (mg/dl)	122 ± 42	124 ± 42	0.48
Current smoking, %	43	43	0.96
Physical activity, %	58	59	0.87
Hypertension, %	59	62	0.47
Diabetes mellitus, %	39	33	0.05
Hypercholesterolaemia, %	57	54	0.49

CAD – coronary artery disease; LDL – low-density lipoprotein; MI – myocardial infarction; WBC – white blood cells.

Table 2. Results from analysis of variance (ANOVA) showing the distribution of clinical and biochemical characteristics according to tertiles of brain natriuretic peptide (BNP) levels.

	BNP < 63.9	63.9 ≤ BNP ≤ 273	BNP > 273	p
Age (yrs)	57 ± 11	63 ± 13*	69 ± 12*	0.001
Male gender, %	92*	85*	75*	0.001
Smoking, %	82*	94*	66*	0.002
Physical activity, %	54	52	59	0.736
Body mass index (kg/m^2)	29.2 ± 4.6	27.9 ± 4.3	27.7 ± 4.1	0.155
One (single) vessel disease, %	20	36	45	0.001
Ejection fraction (%)	47*	41*	35*	0.001
Discharge diagnosis of MI (%)	93	92	96	0.507
Troponin I at entry (ng/ml)	6.4 ± 16	9.6 ± 29.8	18.6 ± 38*	0.003
History of CAD, %	34	12*	26*	0.011
History of hypertension, %	53	57	67*	0.081
History of diabetes, %	22	24	40*	0.003
History of hypercholesterolaemia %	58	49	66	0.18
Creatinine clearence (ml/min)	91 ± 29	82 ± 34*	62 ± 32*	0.001
Haematocrit, %	47 ± 34	42 ± 5*	41 ± 11*	0.228
WBC at entry (count)	10713 ± 3040	11876 ± 13984	13341 ± 13329	0.036
Uric acid (mg/dl)	6.4 ± 1.9	5.9 ± 1.7*	6.6 ± 2.4	0.030

*p<0.01 for the comparisons between moderate or severe vs. normal group, after correcting the p-value using the Bonferronni rule. Abbreviations as in Table 1.

the role of confounder. Therefore, when we entered the admission levels of plasma BNP into the model (Table 3, model 2), creatinine levels lost their significance in the prediction of left ventricular systolic dysfunction in patients with an acute coronary event (OR for creatinine clearance 0.997, p=0.473), while BNP levels still had a highly predictive ability for the development of left ventricular systolic dysfunction (OR per 1 unit increase 1.002, p<0.001).

Discussion

In the present study, we observed that the impact of renal dysfunction on the occurrence of left ventricular systolic dysfunction after an acute coronary event is modified by plasma BNP levels (Figure 1). In particular, an increase of 10 ml/min in creatinine clearance offers 8% protection for the development of systolic dysfunction among patients who have had an acute coronary event, but when BNP levels are entered in the model, creatinine clearance loses its significance. The latter finding underlines the mediating role of BNP levels in the relationship between renal function and systolic dysfunction, and suggests that BNP may be a stronger indicator compared to creatinine clearance for the development of left ventricular systolic dysfunction.

Regarding the baseline characteristics of patients who developed left ventricular systolic dysfunction af-

Table 3. Results from multiple logistic regression analyses.

	Odds ratio	95% confidence interval
Model 1		
Creatinine clearance (per 1 mg/dl)	0.99	0.986-0.998
Diabetes mellitus (y/n)	1.09	0.743-1.611
Hypertension (y/n)	0.91	0.628-1.320
Hypercholesterolaemia (y/n)	1.14	0.860-1.514
Smoking (y/n)	1.43	0.980-2.086
Model 2		
Creatinine clearance (per 1 mg/dl)	0.99	0.989-1.005
Diabetes mellitus (y/n)	0.75	0.416-1.372
Hypertension (y/n)	0.76	0.450-1.303
Hypercholesterolaemia (y/n)	1.23	0.825-1.826
Smoking (y/n)	1.52	0.887-2.608
Brain natriuretic petpide (per 1 pg/ml)	1.002	1.001-1.003

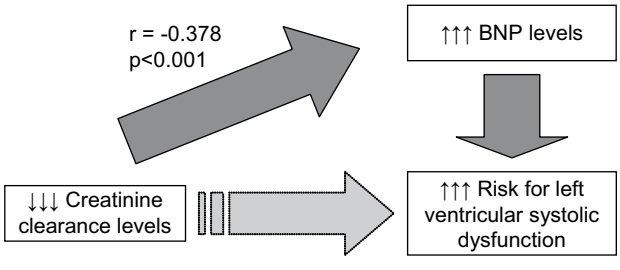

Figure 1. Brain natriuretic peptide (BNP) levels mediate the effect of renal impairment on the risk of developing left ventricular systolic dysfunction among patients who have had an acute coronary syndrome.

ter an ACS, our results are in concordance with those of previous studies.[10,11] We observed that patients who developed systolic dysfunction had higher entry levels of troponin I, uric acid, BNP and lower creatinin clearance, while they had a higher prevalence of diabetes mellitus and myocardial infarction as a discharge diagnosis. Between the two groups of patients (those who did and did not develop systolic dysfunction) there was no significant difference as regards a previous history of coronary artery disease. Furthermore, left ventricular systolic dysfunction seems to be related with impaired renal function, suggesting a possible mechanism for the adverse events often seen in this group of patients. Additionally, impaired renal function seems to be related with higher levels of plasma BNP, which indicates more elevated left ventricular end diastolic pressures, and more elevated C-reactive protein levels, which reflect increased inflammatory activation. Renal insufficiency has been recognised as an independent predictor for in-hospital mortality in patients presenting with a range spectrum of acute coronary syndromes. Masoudi et al, in a study of 2706 patients discharged from 24 Veterans' Health Administration medical centres with a diagnosis of myocardial infarction or unstable angina, demonstrated that moderate and severe renal insufficiency was an independent predictor for 7-month mortality and that this association was similar in both myocardial infarction and unstable angina subsets.[20,21]

BNP was firstly purified from brain, and is made up of 32 amino acids. It is produced predominantly by cardiac ventricular myocardium and much less by atrial myocardium. Both synthesis and secretion of the peptide are stimulated by increased cardiac wall stress during volume and/or pressure overload. As with all natriuretic peptides, its secretion results in diuresis, natriuresis and vasodilatation, while it causes inhibition of the renin-angiotensin-aldosterone system. This mechanism consequently leads to blood pressure lowering.[22] In our study, patients who had BNP values in the higher tertile were older and were more likely to be female, to have a history of hypertension, previous coronary artery disease or diabetes mellitus, compared to those with lower values of BNP. Other investigators have also shown that plasma levels of BNP tend to be higher in women and older patients with or without cardiac dysfunction.[23,24] The increase of BNP values in the elderly could be explained by the loss of clearance receptors with aging.[25] Although obesity is a well-known risk factor for coronary artery disease and heart failure, there is an inverse relationship between BNP and body mass index. One proposed mechanism is abundant clearance receptors expressed on adipocytes, which participate in the removal of BNP from the circulation, inducing salt and water retention.[26] Thus, in our study the body mass index was lower in patients whose BNP levels were in the highest tertile.

Recent studies have shown that BNP and N-terminal pro-BNP (NT-proBNP) correlate with renal function, and that a decreased glomerular filtration rate can markedly influence the cut-off points for heart failure diagnosis. For this reason, a cut-off point of 200 pg/ml for estimated glomerular filtration rate <60 ml/min has been recommended.[27] In our study, BNP values were inversely correlated with creatinine clearance and haematocrit levels.

Troponin levels, and serum uric acid levels at admission were found to be higher in patients with BNP levels in the higher tertile compared to the others, probably reflecting widespread myocardial damage that causes more prominent elevation of left ventricular filling pressure. It is known that plasma concentrations of BNP are sensitive markers of ventricular hypertrophy and left ventricular dysfunction, while BNP is related to stress-induced myocardial ischaemia and/or volume overload—both common in patients with renal dysfunction and heart failure.[22] Thus, in the risk stratification of patients who have had an ACS, BNP levels are related to left ventricular function and have been recognised as prognostic markers for adverse future events.

In the ADHERE study, BNP above 840 pg/ml and increased troponin levels indicated patients at particularly high risk for mortality.[12] As the increased levels of both BNP and NT-proBNP correlate well with impaired left ventricular ejection fraction, they have also been used for the detection of asymptomatic left ventricular systolic dysfunction.[28] In our study, those patients who exhibited left ventricular systolic dysfunction showed threefold higher plasma BNP levels at admission. Furthermore, BNP levels modified the effect of impaired creatinine clearance on the development of left ventricular systolic dysfunction after an acute coronary event. Similarly, the investigators from the GRACE study also concluded that BNP is a powerful predictor of heart failure in patients with an acute coronary syndrome and that it can provide prognostic information above and beyond conventional biomarkers and risk scores.[13] This can be explained by the direct connection of BNP levels with left ventricular filling pressures, which are related

with the extension of coronary atherosclerosis and the severity of the acute coronary event.[22] Thus, BNP levels are strongly related with left ventricular ejection function. On the other hand, renal insufficiency has been recognised as a prognostic marker for adverse cardiac events in patients with known coronary artery disease, and creatinine clearance levels have been related with the severity of coronary artery disease, but renal function is not directly related to left ventricular filling pressures and ejection fraction. It seems that BNP levels have a stronger role compared to creatinine clearance levels as an indicator for left ventricular systolic dysfunction in patients within the first days after an acute coronary event.

Limitations

In retrospective studies, two main sources of systematic errors may exist, the selection and the recall bias. Creatinine clearance was estimated by serum creatinine and was not measured directly. For the estimation of creatinine clearance Cockroft's formula was used, which is not perfect. Concerning the medical information, we tried to avoid recall bias by obtaining accurate and detailed data from subjects' medical records. However, over/under estimation may still exist, especially in the measurement of nutritional and smoking habits, and the onset of the cardiovascular risk factors investigated. Moreover, the coronary patients who died at entry or the day after were not included in the study. Finally, regarding the potential effect of uncontrolled or unknown confounders, we tried to reduce it by using a matching design, the same study base both for patients and controls, but their influence on the outcome may still exist.

Conclusions

As heart failure is a frequent complication in ACS and is associated with higher in-hospital mortality, the role of secondary prevention gains substantial importance. Identifying risk factors for the development of left ventricular systolic dysfunction on admission can certainly influence the immediate therapeutic choices and permit an individualised approach to each patient, which is now considered necessary in clinical practice.[30] This study reveals that low creatinine clearance rates are associated with a higher risk for developing systolic dysfunction, while BNP levels seem to explain, at least in part, the previous relationship.

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