Comparison of Effects of Nitroprusside and Prazosin on Left Ventricular Function and the Peripheral Circulation in Chronic Refractory Congestive Heart Failure

NAJAM A. AWAN, M.D., RICHARD R. MILLER, M.D., AND DEAN T. MASON, M.D.

SUMMARY We compared cardiocirculatory actions of nitroprusside (NP) to prazosin (PZ) in eleven chronic coronary patients with refractory congestive heart failure. Each drug equally lowered systemic arterial pressures mildly while heart rate was unchanged. NP decline (P < .001) in left ventricular filling pressure (28 to 17 mm Hg) and rise (P < .005) in cardiac index (2.20 to 2.96 L/min/m²) were similar to PZ (30 to 17) and (2.08 to 3.00). PZ and NP equally enhanced cardiac efficiency of stroke work and myocardial oxygen consumption index. Total systemic vascular resistance declined (P < .001) the same with NP and PZ. Forearm vascular resistance (FVR) and venous tone (FVT) diminished equally with NP and PZ. Similar FVR/FVT percent changes of 0.88 and 0.64 with NP and PZ indicated relatively balanced systemic arteriovenous relaxation. Since PZ effects persisted six hours with symptomatic improvement, oral PZ is the best vasodilator for long-term use, extending in-hospital NP-like actions to ambulatory heart failure therapy.

NITROPRUSSIDE has proved invaluable for therapy of severe congestive heart failure. Its balanced effects on resistance and capacitance vessels permit impedance reduction with enhancement of cardiac output simultaneously with venous pooling and relief of pulmonary congestion. Nitroprusside has therefore been used to improve cardiac performance in acute and chronic ischemic heart disease and valvular heart disease and is the most useful of the systemic vasodilators. However, attempts to continue the benefits of balanced ventricular unloading with an agent such as nitroprusside have been hampered by the lack of impedance-lowering long-acting oral vasodilator agents. Thus the nitrates primarily produce venous pooling with minimal and inconsistent effects on arterial impedance whereas hydralazine primarily reduces arterial impedance without substantially effecting pulmonary congestion. Since we have recently shown in our laboratories that oral prazosin, a new oral systemic vasodilator agent which is a quinazoline derivative structurally unrelated to other antihypertensive drugs, resulted in sustained dilatation of both the arteriolar and venous beds of the human forearm, it occurred to us that this agent might be efficacious in producing long-acting balanced reductions of ventricular preload and impedance, thereby serving as an effective chronic systemic vasodilator with nitroprusside-like properties in the therapy of chronic congestive heart failure. Therefore, it was the purpose of this study to compare the effects of intravenous nitroprusside and oral prazosin on cardiac function and the peripheral circulation in patients with severe, refractory chronic congestive heart failure due to coronary artery disease.

Methods

The study population was a group of 11 patients, six male and five female, 41–72 years in age (mean 59 years), who had arteriographically documented coronary artery disease with severe congestive heart failure without mitral regurgitation, refractory to digitalis, diuretics, and oral nitrates. The characteristics of the patient population studied are given in table 1. The cardiac effects of intravenous nitroprusside and oral prazosin were evaluated in 10 patients by hemodynamic measurements made during cardiac catheterization. In eight patients, the peripheral circulatory actions of the drugs were assessed by forearm plethysmography. Administration of digoxin, diuretics and nitrates to all patients was discontinued one day prior to the studies; none was receiving antihypertensive agents or other medications. The present study was conducted with approval of our institutional Committee on Human Investigation and after consent was obtained from all patients.

An important feature of the design of this clinical investigation was that the patients served as their own controls, with each individual receiving sequentially i.v. nitroprusside (NP) and then oral prazosin (PZ) for both the cardiac function and peripheral circulatory studies. After obtaining control cardiac hemodynamic data with a Swan-Ganz catheter in the pulmonary artery, i.v. NP was begun and the rate of administration was adjusted gradually to achieve optimal relations between left ventricular filling pressure and cardiac output. This provided considerable afterload reduction while maintaining systemic pressure within safe limits (intravascular systolic pressure between 95 and 120 mm Hg). The mean rate of NP infusion was 67 μg/min (25 to 90 μg/min). When the desired blood pressure had been obtained, a stable circulatory state was achieved by maintaining the NP infusion at a constant rate for 10 minutes. Measurements of cardiac hemodynamics were repeated during the continued NP administration. NP was discontinued and a period of 20 minutes was allowed for pre-NP control hemodynamics to return. Then oral prazosin 40 to 50 μg/kg (average 46 μg/kg) was ingested as a single dose. Hemodynamic measurements were obtained again as described for NP. Hemodynamic measurements were made at the time of maximum reduction in systemic arterial pressure; this occurred between 5 and 10 minutes after NP administration and 60 minutes following oral prazosin; this time also corresponded to the greatest decrease in left ventricular filling pressure. The pulmonary artery diastolic pressure was confirmed to be identical with pulmonary artery wedge pressure and was thereafter used to measure left ventricular filling pressure.
TABLE 1. Characteristics of Patient Population Studied

<table>
<thead>
<tr>
<th>Patient/Age/Sex</th>
<th>Diagnosis</th>
<th>NYHA class</th>
<th>Therapy prior to study</th>
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<tr>
<td>1/68/M</td>
<td>CAD: AIMI</td>
<td>IV</td>
<td>Dig, Furos 320 mg, Iso 80 mg</td>
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</tr>
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<tr>
<td>11/72/M</td>
<td>CAD: APMI</td>
<td>IV</td>
<td>Dig, Furos 240 mg, Iso 80 mg</td>
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</tbody>
</table>

Abbreviations: NYHA = New York Heart Association functional class; CAD = chronic coronary artery disease; A = anterior; I = inferior; P = posterior; MI = remote myocardial infarction; Dig = oral digoxin 0.25 mg daily; Furos = oral furosemide (total daily dose); NTG = oral nitrroglycerin (total daily dose of Nitro-Bid 6.5 mg nitrroglycerin capsules).

(LVFP). Triplicate measurements of cardiac output (CO) were made by the thermodilution technique (Edwards Laboratories) in each of the 10 patients before and during administration of each agent. Calculations used to quantify cardiocirculatory variables included: total systemic vascular resistance (TSVR) = (80 \cdot (P - RA))/C, where 80 is the factor to convert mm Hg to dyne sec cm⁻², P = mean systemic arterial pressure, and RA = mean right atrial pressure; pressure × time per minute (PTM) in mm Hg sec per min = SBP × ET × HR, where SBP = systolic arterial pressure, ET = left ventricular ejection time and HR = heart rate; and stroke work index (SWI) in g-m/m² = ([P - LVFP] × SI × 13.6)/1,000 where SI = stroke index.

In eight patients, seven of whom underwent the aforementioned cardiac function studies, forearm plethysmography was carried out with a mercury-filled rubber strain gauge placed around the mid-forearm as previously described. In the seven patients in whom cardiac dynamics were determined, the plethysmographic studies were performed immediately following the heart catheterization measurements, so that the peripheral circulatory measurements coincided with the central hemodynamic data. In all eight patients, NP and prazosin were administered in succession in the same doses as described for the cardiac function evaluation. Thus the systolic arterial blood pressure after NP was 95–120 mm Hg and the 20 minute waiting period was allowed between the two agents to again obtain control hemodynamics. The plethysmographic studies were performed with the patients in the supine position and with the forearm elevated so that venous pressure approached zero; the hand vessels were isolated from the forearm by inflation of a wrist cuff to a suprasystolic pressure. A standard sphygmomanometer cuff was wrapped around the upper arm and, by using a container of compressed air with a special pressure gauge preset at 30 mm Hg, forearm venous occlusion was rapidly achieved by inflation of the upper arm cuff by regulating a stopcock. Forearm blood flow was calculated from the change in forearm circumference during acute venous occlusion and was expressed as ml/100 g of tissue per min. Simultaneous measurement of intra-arterial pressure was obtained through an indwelling brachial artery catheter placed in the opposite forearm. Forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow expressed in units of mm Hg/ml per 100 g per min. The values for forearm blood flow and forearm vascular resistance during control periods and during drug administration were obtained by averaging at least six individual determinations for each agent.

Forearm venous tone was determined in the eight patients by the acute occlusion technique using an indwelling needle placed in a forearm vein just distal to the mercury-in-rubber strain gauge. By the acute method, the pressure-volume characteristics of the capacitance vessels were calculated by determining the ratio of the increment in forearm venous pressure to the increment in forearm volume which occurred during the initial 10 seconds after inflation of the venous occlusion cuff to 30 mm Hg. This was expressed in units of mm Hg/ml.

Results

Cardiac Function

Infusion of NP at a constant rate for 10 minutes reduced systolic and mean systemic arterial pressures in all patients (fig. 1). The average control systolic pressure of 135.0 ± 7.6 (SEM) fell to 107.3 ± 3.6 (−21%, P < 0.001) during NP infusion, while PZ caused a decline in systolic pressure from 135.8 ± 7.9 mm Hg to 111.6 ± 6.5 (−18%, P < 0.001). NP lowered mean arterial pressure from 92.4 ± 4.7 mm Hg to 74.6 ± 2.6 (−19%, P < 0.001) (fig. 1A) and PZ reduced mean arterial pressure from 94.9 ± 5.0 to 78.0 ± 5.0 (−18%, P < 0.001) (fig. 1B). There were no statistically significant differences in the declines of both systolic and mean blood pressures between NP and PZ. The mean heart rate was not changed by NP or PZ.

LVFP declined in each patient after administration of NP and of PZ (fig. 2). The mean control LVFP fell from 28.4 ± 2.8 to 17.1 ± 1.7 mm Hg (−40%, P < 0.001) during NP infusion (fig. 2A); and from 30.4 ± 3.1 to 16.9 ± 1.7 mm Hg after oral PZ (−44%, P < 0.001) (fig. 2B). There was no significant difference in the fall of LVFP induced by NP compared to PZ.

Cardiac index rose during NP infusion from 2.20 ± 0.16 to 2.96 ± 0.17 L/min/m² (＋35%, P < 0.005) (fig. 3A). Similarly the cardiac index was elevated by oral PZ from 2.08 ± 0.13 to 3.00 ± 0.10 L/min/m² (＋44%, P < 0.001) (fig. 3B). The magnitude of cardiac output increase caused by NP was not significantly different from that produced by PZ.

Stoke index rose during NP infusion from 26.3 ± 2.1 to 34.8 ± 2.1 ml/m² (+32%, P < 0.01); while SI increased from 24.7 ± 2.5 to 36.4 ± 1.8 ml/m² (+44%, P < 0.001) with PZ. The degree of elevations of SI between the two agents was not statistically significant.

Mean control stroke work index of 23.0 ± 3.1 was increased to 27.3 ± 2.7 g-m/m² by NP (＋19%, P < 0.05) (fig. 4A). Likewise, PZ resulted in a rise of SWI from 22.0 ± 3.6 to 30.6 ± 3.9 g-m/m² (+39%, P < 0.001) (fig. 4B). There
Effects of nitroprusside (NP) (A) and prazosin (PZ) (B) on systemic mean arterial pressure. C = control.

FIGURE 1.

There was no significant difference in the increase of SWI caused by NP compared to PZ.

The index of myocardial oxygen consumption of pressure × time per minute was reduced from 3,140 ± 186 to 2,641 ± 99 mm Hg sec/min by NP (−16%, $P < 0.005$) (fig. 5A). PTM was similarly diminished by oral PZ from 3,286 ± 207 to 2,696 ± 205 mm Hg sec/min (−18%, $P < 0.005$) (fig. 5B). These reductions of PTM were not statistically different between NP and PZ.

Peripheral Circulation

Total systemic vascular resistance was decreased in each patient by NP and PZ (fig. 6A and 6B, respectively). The mean control value of 1891 ± 140 declined to 1152 ± 96 dynes sec cm⁻² (−39%, $P < 0.001$) with NP infusion, and from 2,172 ± 171 diminished to 1,237 ± 134 dynes sec cm⁻² (−43%, $P < 0.001$) with PZ. The decreases of TSVR were not statistically different between the two vasodilator agents.

Forearm blood flow of 1.13 ± 0.13 ml/100 g/min was increased to 1.88 ± 0.23 by NP (+66%, $P < 0.01$) (fig. 7A). Similarly, forearm blood flow was raised by PZ from 1.29 ± 0.14 to 1.95 ± 0.29 ml/100 g/min (+51%, $P < 0.02$) (fig. 7A); this increase was not significantly different from NP.

Forearm vascular resistance decreased from 92.9 ± 9.8 to 46.6 ± 5.4 mm Hg/ml/100 g/min during NP infusion (−50%, $P < 0.001$) (fig. 7B). Likewise, forearm vascular resistance fell from 86.1 ± 9.8 to 47.8 ± 5.6 mm Hg/ml/100 g/min with PZ (−45%, $P < 0.001$) (fig. 7B). The extent of declines in forearm vascular resistance was not significantly different between the two agents.

FIGURE 2. Comparative declines in left ventricular (LV) filling pressure with NP (A) and PZ (B).
The response of forearm venous tone to the two vasodilator drugs is depicted in figure 7C. Thus with NP forearm venous tone declined from 71.3 ± 22.6 mm Hg/ml to 24.5 ± 5.0 (−65%, P < 0.01). During PZ forearm venous tone fell from 58.9 ± 13.8 mm Hg/ml to 16.4 ± 3.3 (−72%, P < 0.005). The decrease in FVT was not significantly different between the two drugs.

The relative magnitude of effects of the two vasodilator agents on the resistance and capacitance beds of the forearm is shown in figure 8. We determined the ratio of the percent decline in forearm vascular resistance to the percent decline in forearm venous tone for both of the agents. A ratio of unity (1.0) indicates a relatively equal extent of arteriolar and venous dilatation. In the eight patients who received both drugs sequentially the ratio of percent changes of forearm vascular tone to venous tone (FVR/FVT) was 0.88 ± 0.09 with NP while this ratio of 0.64 ± 0.09 with PZ was not significantly different from NP.

Discussion

Increased awareness of the clinical importance of arterial impedance as a determinant of left ventricular function²⁷ has led to the therapeutic use of systemic vasodilator agents for improvement of cardiac performance in heart failure.¹⁴, ¹⁵, ¹¹, ¹² In this regard nitroprusside has been shown to afford marked improvement in cardiac failure in patients with valvular heart disease⁵, ⁸ and acute and chronic ischemic heart disease.¹⁴, ⁶, ⁷ The important role of nitroprusside as the parenteral unloading agent of choice ideally suited for in-hospital treatment of congestive heart failure is related to its vasodilator effects on both the systemic resistance and capacitance vessels; pulmonary congestion is thereby relieved simultaneously with enhanced ventricular emptying and increased cardiac output.

In the present investigation we demonstrate for the first time that oral prazosin has cardiovascular effects similar to...
those of nitroprusside. Thus prazosin markedly lowered both forearm arterial resistance and venous tone (fig. 7) as well as reduced total peripheral vascular resistance (fig. 6). Like nitroprusside, these primary peripheral circulatory actions of prazosin resulted in dramatic improvement in pump function and relief of pulmonary congestion; cardiac output increased an average of 44% (fig. 3) while left ventricular filling pressure declined by an average of also 44% (fig. 2). As with nitroprusside, concomitant improvement in the severity of dyspnea occurred with prazosin in each patient. Furthermore, prazosin produced similar enhancement of cardiac efficiency as did NP, since both agents resulted in an increase in SWI (fig. 4) while the oxygen consumption index of PTM (fig. 5) declined to equal degrees with either agent.

Of substantial clinical importance was our observation concerning the temporal actions of oral prazosin. Thereby hemodynamic effects were demonstrated within 30 minutes consisting of mild reductions in both arterial resistance and left ventricular filling pressure. These vasodilator influences of prazosin became maximal by 60 minutes and thereafter remained essentially unchanged for the succeeding five hours. Thus these data indicate sustained improvement in cardiac performance and relief of congestive symptoms by a single oral dose of the drug.

It is particularly relevant that oral prazosin has potent vasodilator actions similar to those of intravenous nitroprusside, but which are also sustained for several hours. This new knowledge allows extension of the well recognized benefits of vasodilator management to chronic ambulatory therapy. Thus, use of this single oral agent provides the mechanism for enhanced functional rehabilitation of patients with severe congestive heart failure refractory to traditional therapy. In this regard, each of our patients reported considerable improvement in their severity of dyspnea and orthopnea which were present in all patients prior to administration of the oral agent. Consistent with the time-related systemic vasodilator actions was the improvement in dyspnea in the majority of patients within 30 minutes and in all patients by 60 minutes; nine of the patients with orthopnea could recline in a completely supine
position without shortness of breath. This symptomatic benefit which was maintained for several hours was corroborated by the objective hemodynamic improvement which persisted for six hours.

Prazosin is unique among the peripheral vasodilator agents in that its circulatory actions are mediated by inhibition of the enzyme phosphodiesterase in vascular smooth muscle, as well as by post-synaptic alpha-adrenergic receptor blockade.46 The resultant increased levels of intracellular cyclic AMP and blockade of alpha-receptors located in vascular smooth muscle appear responsible for relaxation of the systemic vessels produced by prazosin. Interestingly, PZ-induced phosphodiesterase inhibition in the heart is reported to result in elevation of myocardial levels of cyclic GMP, thereby reducing the catecholamine responsiveness of the heart.47-54 Thus baroreceptor mediated sympathetic reflexes to the heart would be expected to be attenuated in the presence of prazosin. Consequently, the decline in systemic blood pressure, as noted in the present study, is not accompanied by increase in the rate or force of cardiac contraction. Consistent with this biochemical mode of action was that heart rate was unaltered herein by PZ. This lack of increased frequency of contraction coupled with reduction of left ventricular intramyocardial tension, reflected by the fall in the PTM index of myocardial oxygen demand (fig. 5), likely resulted in consequent improvement in the myocardial oxygen supply-demand relation in our patients with ischemic heart disease. These effects of prazosin on the major determinants of myocardial oxygen requirements suggest that the agent may be useful in the management of angina pectoris in addition to improving left ventricular performance. Nitroprusside has been utilized successfully for improving metabolic and electrocardiographic indices of ischemic myocardial injury in patients with acute myocardial infarction.5, 9-13 Further, there are experimental and clinical data to suggest that nitroprusside improves ischemia by enhancing regional blood flow to the ischemic myocardium.9-12 In view of the similarity of prazosin to NP, it is rational to postulate that these beneficial effects in acute ischemia pertain to prazosin as well.

Concerning the cardiocirculatory mechanisms of action of the oral vasodilator agent, prazosin, with its essentially balanced effects on peripheral resistance and capacitance vessels (fig. 8), systemic venodilation produced by the agent results in pooling of blood in the capacitance bed with diminished venous return to the heart. Consequently left

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**Figure 7.** Effects of NP and PZ on forearm blood flow (A), on forearm vascular resistance (B), and on forearm venous tone (C).

**Figure 8.** Effects of NP and PZ on the relation of percent change in forearm vascular resistance (FVR) to percent change in forearm venous tone (FVT). A FVR/FVT ratio of 1.0 indicates a relatively equal extent of arteriolar and venous relaxation. Thus both NP and PZ produced balanced relaxation of the arteriolar and venous beds in the forearm.
ventricular filling pressures declined (fig. 2) and pulmonary congestion was relieved. Despite this reduction in left ventricular preload, cardiac output improved (fig. 3) subsequent to the concomitant decline in ejection impedance thereby facilitating ventricular emptying. In contrast to nitroglycerin which lowers left ventricular preload relatively more than aortic impedance and thus often results in a decline in stroke volume,14-18 prazosin exerted more balanced actions on ventricular preload and systemic impedance, although a slightly increased tendency for greater reduction in venous tone and hence preload, while not statistically significant compared to nitroprusside, may be important in some patients with ventricular decompen-
sation. In our heart failure patients, prazosin effected significant increases in cardiac output while reducing left ventricu-
lar filling pressures, since LVFP was maintained within optimal levels at the upper limits of normal (fig. 2).

The impetus for developing effective oral vasodilator therapy has led to clinical trials of various systemic vasodilator agents14-20 and in this regard the oral and topical long-acting nitrates have been evaluated.15-17, 19 In common with sublingual nitroglycerin,14, 15, 16 these agents exert their principal effect on central hemodynamics by reducing pulmonary congestion by means of venodilation-induced peripheral pooling of blood volume.15, 16 Thus while dyspnea is improved, ejection impedance is usually unaffected and cardiac output thereby minimally changed by the nitrates.15-18 Recently oral hydralazine therapy has been tried alone26 and in combination with the long-acting nitrates.26, 27 Hydralazine alone produces a useful decline in ejection impedance thus improving cardiac output but pulmonary congestion and dyspnea are usually unchanged.26 The combination of hydralazine and long-acting nitrates has been shown to improve both cardiac performance and pulmonary congestion.26, 27 In conclusion, oral long-acting prazosin alone possesses both systemic arteriolar and venodilator effects similar to short-acting nitroprusside and thereby can be used as a single oral agent, eliminating the need for an additional long-acting nitrate. In the moderate doses employed in this investigation, prazosin was well tolerated with only mild transient nausea experienced in two patients and slight headache in three individuals. Importantly, orthostatic hypotension was not associated with the use of prazosin in our heart failure patients. Hydralazine, in contrast, has been reported to be associated with sodium retention, reflex tachycardia, and the development of autoimmune syndromes.29, 39, 40 Further, the not infrequent incidence of tolerance with chronic hydralazine administration20, 36 limits its prolonged usefulness.

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The Absent Pulmonary Valve Syndrome

Considerations of Management

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SUMMARY The absent pulmonary valve syndrome consists of a severely hypoplastic pulmonary valve with anular stenosis, aneurysmal dilatation of the main pulmonary artery with or both pulmonary branches also dilated, and a ventricular septal defect. From 1955 to 1975, 15 patients were seen at Texas Children's Hospital with this syndrome. Although anatamically similar to tetralogy of Fallot, the most significant symptoms during early infancy were secondary to bronchial compression resulting from the dilated pulmonary arteries and enlarged left atrium. Intracardiac repair performed on two infants at four months of age failed to ameliorate the respiratory symptoms and both died. Seven patients from 2.3 to 16 years of age were operated upon, with one late postoperative death. Five other patients have not yet received surgical intervention. We recommend vigorous continual respiratory therapy for infants and small children and intracardiac repair in older children since repair in infancy does not relieve respiratory symptoms. We do not recommend a prosthetic pulmonary valve unless there is persistently elevated main pulmonary artery pressure.

In 1847, Cheever's reported a syndrome of congenital heart defects which included absent pulmonary valve, ventricular septal defect, anular pulmonary stenosis, and dilatation of the main pulmonary artery and one or both pulmonary branches. Approximately 150 cases have been reported according to Emmanuolidis. We reviewed our experience with this syndrome to respond to the following questions: 1) Is this combination of congenital heart defects related hemodynamically or anatomically to tetralogy of Fallot? 2) What is the clinical course of these patients with respect to cyanosis, respiratory distress and congestive heart failure? 3) Should the treatment of the ill infant with this syndrome be directed toward surgical repair or medical palliation?

Materials and Methods

In 15 patients, the diagnosis of absent pulmonary valve syndrome was confirmed by cardiac catheterization and angiography at Texas Children's Hospital in Houston between 1955 and 1975. Twelve of the 15 patients were referred on the day of birth; the other three were referred by three months of age. There were eight males and seven females. All 15 were catheterized at the time of initial admission. In addition, five patients underwent cardiac catheterization following intracardiac repair. The severity of illness was assessed by the presenting symptoms, physical findings, chest radiographs and clinical course. Cardiac catheterization data and angiography delineated the degree of pulmonary obstruction and anatomical orientation of the right ventricular outflow tract. The subsequent clinical course and the operative results indicated the success of therapy.

Results

Symptoms and Signs

All patients had a cardiac murmur typical of pulmonary stenosis and regurgitation. By history all patients were cyanotic to some degree, even though only seven patients presented with cyanosis as the chief complaint; eight other patients presented with respiratory distress as the main symptom with six of the eight having severe symptoms. The lung fields by radiographic examination correlated
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