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Clinical effects of major aortopulmonary collateral arteries in term neonates diagnosed with transposition of the great arteries

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Abstract

Background: Transposition of the great arteries is a severe CHD that affects term neonates. The presence of major aortopulmonary collateral arteries in neonatal transposition of the great arteries patients is rare. This study investigated the clinical and haemodynamic implications of the presence of major aortopulmonary collateral arteries in neonatal transposition of the great arteries patients who underwent an arterial switch operation. *Materials and Methods:* The study was a retrospective analysis conducted on neonates diagnosed with transposition of the great arteries who underwent arterial switch operation within the period from 1 May 2020 to 1 January 2023 at two high-patient-volume paediatric cardiac surgery centres in Turkey. The patients' demographic characteristics, echocardiographic features, and clinical data were analysed. Additionally, the possible clinical effects of the presence of major aortopulmonary collateral arteries were statistically evaluated. *Results:* Two hundred cases of neonatal transposition of the great arteries were included in this study, with 55% of the cases male. All the patients underwent arterial switch operation. The median age at the time of arterial switch operation was 5 days (interquartile range 3–7), with a median weight of 3,100 g (interquartile range 2,900–3,400). The median pre-operative saturation level was 76% (interquartile range 70–82%). Prior to arterial switch operation, 32 patients underwent balloon atrial septostomy.

In all the patients, the interatrial septum was checked to determine if the atrial septum was intact. A patent foramen ovale ($\leq$ 3 mm) was found in 112 patients, and a non-restrictive atrial septal defect (> 3 mm) was found in 88. Forty-eight patients had ventricular septal defects, and 72 had coronary anomalies. Major aortopulmonary collateral arteries were found in 4 patients pre-operatively and in 12 patients after arterial switch operation (echocardiography, n = 8; angiography, n = 4). Of the patients with post-operative detection of cumulative number of major aortopulmonary collateral arteries were on post-operative day 1 in 2 patients, on post-operative day 3 in 5 patients, on post-operative day 7 in 6 patients, and on post-operative day 14 in 11 patients.

Transcatheter closure was performed in 3 cases due to recurrent extubation failure. Major aortopulmonary collateral artery shrinkage was observed in one case under medical treatment. The length of paediatric cardiac intensive care unit stay (10 days versus 8 days; $p < 0.005$), mechanical ventilator time (4 days versus 2 days; $p = 0.02$), and inotrope use time (5 days versus 3 days; $p = 0.04$) were higher in the major aortopulmonary collateral artery cases than patients without major aortopulmonary collateral artery. *Conclusion:* Major aortopulmonary collateral arteries are frequent in transposition of the great arteries patients and may have clinical effects. The presence of major aortopulmonary collateral arteries should be investigated in patients who do not have a favourable post-operative course after arterial switch operation.

Transposition of the great arteries is one of the most common CHDs in the neonatal period and is an important reason for hospitalisation in the paediatric cardiac intensive care unit during the first 2 weeks of life.[1] Arterial switch operation is the primary surgical treatment option for these patients.[2,3]

Low cardiac output syndrome, residual defects, myocardial dysfunction, pulmonary parenchymal disease, and accompanying comorbid problems in patients undergoing arterial switch operation may delay extubation and prolong the duration of mechanical ventilation and paediatric cardiac intensive care unit stay.[4]

Major aortopulmonary collateral arteries are a rare anatomical pathology in some transposition of the great arteries cases.[5,6] While they are generally clinically insignificant, they

can cause congestive heart failure after arterial switch operation through significant left–right shunting, potentially leading to a prolonged intensive care period.

The possible clinical signs and symptoms of haemodynamic relevant major aortopulmonary collateral arteries are pulmonary volume overload, respiratory failure, left atrial and ventricular dilatation, dysfunction, failure to thrive, tachycardia, and arrhythmias.[7,8]

Few studies have investigated the impact of major aortopulmonary collateral artery presence on surgical outcomes in neonatal transposition of the great arteries cases.[7,8] This study investigated the potential clinical and haemodynamic effects of major aortopulmonary collateral artery presence in the early post-operative period in neonatal transposition of the great arteries patients undergoing arterial switch operation.

Materials and methods

This retrospective study was conducted on neonatal patients with transposition of the great arteries who were admitted to the paediatric cardiac intensive care units of two high-patient-volume centres for paediatric cardiac surgery in Turkey (Istanbul Basaksehir Cam and Sakura City Hospital and Istanbul Mehmet Akif Ersoy Research and Training Hospital) within the period from 1 May 2020 to 1 January 2023. Patients with simple transposition of the great arteries and who underwent arterial switch operation were included in the study. Major aortopulmonary collateral artery presence was evaluated through echocardiography and angiography reports, either before or after arterial switch operation. Premature patients, patients diagnosed with major aortopulmonary collateral arteries at an age older than 1 month, and patients with complex transposition of the great arteries (atrioventricular septal defect, double outlet right ventricle, heterotaxia syndromes, hypoplastic aortic arch, and/or coarctation of the aorta) were excluded from the study. The study was planned in accordance with the Declaration of Helsinki after obtaining the required approval from the local ethics committee.

Clinical data were extracted from the patients' medical records. A study form including *pre-operative data* (demographic characteristics, balloon atrial septostomy, cardiac pathology, and imagining findings), *operative data* (cardiopulmonary bypass and surgery time), and *post-operative data* (time for extubation, length of paediatric cardiac intensive care unit and hospital stay, mortality, vasoactive inotropic score, cerebral and renal near infrared spectroscopy changes, major complications [Low cardiac output syndrome (LCOS), arrhythmia, infection, acute kidney injury], and presence of major aortopulmonary collateral artery [proven by echocardiography, catheterisation, or cardiac computed tomography]) was filled out for each patient.[4]

The patients were divided into two groups according to the presence of major aortopulmonary collateral artery on imagining tools: (i) those with major aortopulmonary collateral arteries and (ii) those without major aortopulmonary collateral arteries.

Echocardiographic evaluations were performed using the Philips EPIQ CVx cardiac ultrasound system (Philips Affiniti 50 Cardiac Ultrasound, Bothell, WA, USA) with a 9 MHz probe. All the patients underwent echocardiographic evaluation as defined by the American Society of Echocardiography guidelines.[3] Patent foramen ovale ($\leq$ 3 mm), atrial septal defect ($>$ 3 mm), patent ductus arteriosus with or without a ventricular septal defect, and ventriculoarterial discordance were defined as simple transposition of the great arteries in the present study.

No routine pre-operative or post-operative angiograms were performed. The indications for post-operative cardiac catheterisation were difficulty of intraoperative coronary transfer during arterial switch operation, signs of ischaemia in ECG (ST changes or exceptionally elevated troponin levels), arrhythmia, or prolonged intensive care with prolonged mechanical ventilator support and prolonged need for inotropic agents (milrinone, norepinephrine, or epinephrine).

The operation was conducted with a cardiopulmonary bypass through a standard aortic and bicaval cannula under mild hypothermia. Cold blood cardioplegia was utilised approximately every 20 minutes during cross-clamping. Cardioplegia was given to the aortic root before the aorta was opened. A retrograde approach via the coronary sinus was used for maintenance. The cardioplegia strategy has recently been replaced with single-dose Custodiol® HTK solution (Köhler Chemie GmbH, Germany) application. Arterial switch operation includes switching of the aorta and the pulmonary roots, coronary button transfer, obligatory ligation and transection of patent ductus arteriosus, and closure of atrial septal defect and ventricular septal defect (as indicated).[9] A Lecompte maneuver (translocation of the pulmonary bifurcation anterior to the neo-aorta) was performed routinely. Considering the limitations of a retrospective data analysis, there were no indicators of increased non-coronary blood return during extracorporeal circulation in the major aortopulmonary collateral artery group in the present study, which could be indicative of major aortopulmonary collateral arteries. Ultrafiltration during bypass and modified ultrafiltration after bypass were used. The chest was left open at the end of the surgery in all the patients, except for 2 patients, due to safer early paediatric cardiac intensive care unit follow-up in terms of haemodynamic stability and pulmonary dynamics.[9,10]

The patients were transferred from the operating room to the paediatric cardiac intensive care unit while intubated and attached to a mechanical ventilator. All the patients were monitored for central venous pressure, electrocardiogram, invasive arterial blood pressure, end-tidal carbon dioxide, and cerebral near infrared spectroscopy.

The typical inotropic support in the first post-operative hours was milrinone (0.5 μg/kg/min) and low-dose norepinephrine (0.05 μg/kg/min). Epinephrine was administered only if clinically necessary. Fentanyl and midazolam were used for analgesia and sedation, and 100 mg/kg/day of cefazolin sodium was initiated for post-surgical antibiotic prophylaxis. Antibiotic treatment was regulated according to the blood culture results and acute-phase reactants. On post-operative day 2, total parenteral nutrition and minimal enteral feeding via a nasogastric tube were started for all the patients.[2]

The prolonged mechanical ventilation is defined as a mechanical ventilation duration more than 72 hours for medium prolonged mechanical ventilation and 7 days for extended prolonged mechanical ventilation. For further analysis of paediatric cardiac intensive care unit length of stay, data were dichotomised as the upper (worst) 25th percentile versus lower (best) 75th percentile. Paediatric cardiac intensive care unit length of stay in the upper 25th percentile was considered prolonged paediatric cardiac intensive care unit length of stay.

The distributions of the variables were analysed in a computer environment. Descriptive values were obtained using the Statistical

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Table 1. General characteristics of the patients

Variable	Total	MAPCA (+)	MAPCA (-)	p
n	200	16	184	–
Operative age (days)	5 (3–7)	6 (4–8)	5 (4–7)	NS
Weight (kg)	3.1 (2.9–3.4)	3.3 (3–3.6)	3.2 (3–3.5)	NS
Male gender	110 (55)	8(50)	102(55)	NS
Genetic syndrome	3 (1.5)	–	3 (1.6)	NS
PGE1 infusion	160 (80)	12 (75)	148 (80)	NS
Preoperative Inotropic agent	30 (15)	3 (18)	27 (14)	NS
Preoperative SpO2	76 (70–82)	75 (70–84)	76 (70–82)	NS
Preoperative mechanical ventilation	18 (9)	2 (12)	16 (8)	NS
Septostomy	32 (16)	4 (25)	28 (15)	**0.04***
SpO2 before septostomy	65 (60–70)	70 (67–75)	65 (60–70)	NS
SpO2 after septostomy	84 (80–88)	82 (78–86)	85 (80–88)	NS
Usual coronary artery Unusual coronary Artery 1LAD2 RCx (1 intramural) 1LCxR 2RLCx (1intramural) 1LRCA 2Cx 1R 2LCx	128 (64) 72 (36) 30 (15) 22 (11) 13 (6.5) 4 (2) 3 (1.5)	9 (56) 7 (44) 2 (12) 2 (12) 1 (6) 1 (6) 1 (6)	119 (65) 65 (35) 28 (15) 20 (10) 12 (6) 3 (1.6) 2 (1)	NS
Aorta-pulmonary artery relationship Anterior and to the right Side-by-side, aorta to right Directly anterior Posterior and to the right Anterior and to the left	 143 (71.6) 30 (15) 13 (6.6) 7 (3.3) 7 (3.3)	 10 (62) 3 (18) 1 (6) 1 (6) 2 (12)	 133 (72) 27 (14) 12 (6) 6 (3) 5 (2)	NS
VSD	48 (24)	6 (37)	42 (22)	NS
ASD	88 (44)	8 (50)	80 (44)	NS
Intakt or PFO (≤3 mm)	112 (56)	8 (50)	104 (59)	NS
PDA	176 (88)	13 (82)	163 (89)	NS

ASD = atrial septal defect; Cx = circumflex; LAD = left anterior descending; PDA = patent ductus arteriosus; PGE1 = prostaglandin E1; RCA = right coronary artery; VSD = ventricular septal defect.
Median (IQR) or n (%).
*$p < 0.05$ (significance).

Package for the Social Sciences for Windows software package and were expressed as median (interquartile range) and percentage–percentile values. Pearson's chi-square test and Mann–Whitney U test were used to compare the variables between the groups. Major aortopulmonary collateral arteries and without major aortopulmonary collateral arteries patients (16 versus 16) were matched 1:1 on post-operative characteristics using propensity score matching. The outcome variables were then compared between the two groups. A p-value of < 0.05 was considered statistically significant.

Results

Seven patients whose records could not be reached, 5 patients who were premature, and 26 patients with a diagnosis of complex transposition of the great arteries were excluded from the study. After the application of the exclusion criteria during the study period, 200 simple transposition of the great arteries cases were included in the study. Of these cases, 55% (n = 110) were male. The median operative age was 5 days (interquartile range: 3–7), the median weight was 3,100 g (interquartile range: 2,900–3,400), and the pre-operative median saturation rate was 76% (interquartile range: 70–82%). Thirty-two patients underwent balloon atrial septostomy before arterial switch operation. Additional ventricular septal defect closure was performed in 48 patients (24%). The baseline characteristics of all the patients are presented in Table 1.

Major aortopulmonary collateral arteries were detected in 16 patients (8%; 8 males, 8 females), in 4 patients before arterial switch operation and in 12 patients after arterial switch operation. Of the patients with post-operative detection of cumulative number of major aortopulmonary collateral arteries were on post-operative day 1 in 2 patients, on post-operative day 3 in 5 patients, on post-operative day 7 in 6 patients, on post-operative day 14 in 11 patients, and the last one was on post-operative 29th day. Angiography was performed in four cases and transcatheter closure in three cases, and one case showed shrinkage under medical treatment (Table 2).

The median age at the time of the procedure was 6 days (interquartile range: 4–10 days), and the median body weight was 3.3 kg (interquartile range: 3–3.9 kg). Echocardiographically, patent foramen ovale (≤ 3 mm) was present in 44% (7/16) of the patients with major aortopulmonary collateral arteries, and atrial septal defect (> 3 mm) was present in 50% (8/16) of the

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Table 2. Anatomical characteristics of TGA patients with MAPCAs

Patients	Sex	Imaging	Atrial septum	PDA	VSD	Coronary pattern	MAPCAs details	Timing of intervention or diagnosis	Type of intervention	At 1-year follow-up
1	Male	Echo	Intakt	Yes	Yes	Unusual	MAPCAs from AoD	1 day before ASO	–	No symptoms/ signs
2	Male	Echo	PFO	Yes	No	Usual	2 MAPCAs aorta to PA	2 days before ASO	–	Exitus
3	Female	Echo	PFO	No	No	Unusual	1 MAPCA arising above PDA to RPA	3 days before ASO	–	No symptoms/ signs
4	Male	Echo	ASD	Yes	Yes	Usual	1 MAPCA connecting AoD with PA	Same day before ASO	–	No symptoms/ signs
5	Female	Echo	PFO	Yes	No	Unusual	Multiple MAPCAs	1 day after ASO	–	No symptoms/ signs
6	Female	Echo/Angio	PFO	Yes	Yes	Usual	MAPCAs rising from AoD	2 days after ASO	Coil	No symptoms/ signs
7	Male	Echo/Angio	ASD	Yes	No	Usual	2 MAPCAs connecting AoD with left lung	3 days after ASO	Vascular plug	No symptoms/ signs
8	Male	Echo/Angio	PFO	Yes	Yes	Unusual	3 MAPCAs arising for AoD to right lung	29 days after ASO	Vascular plug	Mild mitral regurgitation
9	Female	Echo/Angio	ASD	Yes	No	Unusual	MAPCAs arising from arch	2 days after ASO	Medical	Moderate mitral regurgitation/CHF
10	Male	Echo	ASD	Yes	No	Usual	1 MAPCA connecting AoD with PA	9 days after ASO	–	Exitus
11	Female	Echo	ASD	Yes	No	Usual	MAPCAs from AoD	7 days after ASO	–	No symptoms/ signs
12	Female	Echo	PFO	Yes	Yes	Unusual	Multiple MAPCAs; prominent BA	10 days after ASO	–	No symptoms/ signs
13	Male	Echo	ASD	Yes	No	Unusual	2 MAPCAs aorta to PA	8 days after ASO	–	No symptoms/ signs
14	Female	Echo	PFO	No	No	Usual	1 MAPCA connecting AoD with PA	13 days after ASO	–	Moderate pulmonary stenosis
15	Female	Echo	ASD	Yes	Yes	Unusual	1 MAPCA arising above PDA to RPA	14 days after ASO	–	No symptoms/ signs
16	Male	Echo	PFO	No	No	Unusual	2 MAPCAs aorta to PA	1 day after ASO	–	Moderate pulmonary stenosis

ASD = atrial septal defect; AoD = descending aorta; ASO = arterial switch operation; BA = bronchial arteries; CHF = congenital heart failure; MAPCAs = major aortopulmonary arteries; PA = pulmonary artery; PDA = patent ductus arteriosus; PFO = patent foramen ovale; RPA = right pulmonary artery; VSD = ventricular septal defect.

patients. Thirteen patients had patent ductus arteriosus (82%), and six patients had ventricular septal defect (27%). Four patients underwent balloon atrial septostomy (25%), and the median SpO2 values before and after the balloon atrial septostomy procedure were 70% (interquartile range: 67–75%) and 82% (interquartile range: 80–86%), respectively. Epinephrine support was needed in three patients (18%) after arterial switch operation.

The patients with major aortopulmonary collateral arteries had a longer paediatric cardiac intensive care unit stay than those without major aortopulmonary collateral arteries (10.2 days versus 8.1 days; $p < 0.005$) and required longer mechanical ventilation (4.5 days versus 2.0 days; $p = 0.02$) and longer inotropic support (5.3 days versus 3.1 days; $p = 0.04$). Extracorporeal membrane oxygenation was not needed by any of the patients with major aortopulmonary collateral arteries but was needed by 10 patients without major aortopulmonary collateral arteries, and 14 (7%) patients without major aortopulmonary collateral arteries died.

Major aortopulmonary collateral artery was detected by echocardiography in 12/16 patients. Two patients had moderate mitral valve regurgitation (Patient 12 and Patient 15). At the end of first post-operative month, there was evidence of mild valve regurgitation. In addition to echocardiography, cardiac catheterisation and angiography were performed in four cases. Catheter angiography was performed in Patient 6 and Patient 9 due to post-operative low cardiac output syndrome and haemodynamic instability. Patient 6 demonstrated improvement following coil closure while Patient 9 exhibited improvement after adjustment to medical treatment. In Patient 7, cardiac catheterisation was performed due to pulmonary oedema and pulmonary haemorrhage and symptoms resolved following the closure of major aortopulmonary collateral artery using a vascular plug. Patient 8 underwent cardiac catheterisation due to recurrent intubation. In this procedure, closure of major aortopulmonary collateral artery was achieved using a vascular plug. Following the intervention, the

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patient successfully underwent extubation and was subsequently discharged.

Discussion

In this study, we investigated the clinical effects of major aortopulmonary collateral arteries in neonates with transposition of the great arteries in two high-patient-volume paediatric cardiac centres in Turkey. Although major aortopulmonary collateral arteries were identified in 8% of the cases, only 2% (25% of all the major aortopulmonary collateral artery patients) required interventional procedures. However, we recommend that the presence of major aortopulmonary collateral arteries be investigated in cases with unfavourable and/or unexpected post-operative outcomes. Our study is among the few in the literature with this focus.

Although it is normal to detect major aortopulmonary collateral arteries within the first weeks of the gestational term, if they develop with a normal pulmonary arterial system, they regress over time.[11] However, major aortopulmonary collateral arteries usually persist if there is a problem with the growth of the pulmonary arterial system or the pulmonary valve, like pulmonary atresia or Tetralogy of Fallot, where the pulmonary blood flow decreases. In addition, reduced oxygen saturation levels are seen in transposition of the great arteries patients.[6,11]

In patients with transposition of the great arteries and major aortopulmonary collateral arteries, visualisation of the collateralised vessels may be difficult prior to surgical repair, even with selective angiography.[12] This may be due to the large ventricular septal defect or patent ductus arteriosus, both of which steal blood flow from the descending aorta flow. Echocardiograms should raise the suspicion of major aortopulmonary collateral arteries in the presence of diastolic runoff in the descending aorta, such as a large patent ductus arteriosus, unexpected left heart chamber dilatation, and mitral valve regurgitation in the presence of a normal mitral valve anatomy. However, even though echocardiography is a highly specific diagnostic tool, it has low sensitivity in identifying major aortopulmonary collateral arteries. Additionally, major aortopulmonary collateral arteries can be revealed via CT imaging during the clarification of the coronary artery anatomy. The initial medical management pathway is the same in patients with transposition of the great arteries, either with major aortopulmonary collateral arteries or not: optimise intracardiac blood mixing and perform balloon atrial septostomy if indicated and maintain patent ductus arteriosus patency with PGE1 infusion if needed. In addition, surgeons should keep in mind that, during cardiopulmonary bypass, excessive left atrial venous return can be a sign of the presence of major aortopulmonary collateral arteries.[8] Wibf et al.[7] suggested that echocardiography does not sufficiently detect relevant major aortopulmonary collateral arteries in transposition of the great arteries patients (53% sensitivity). However, a positive echo finding (left atrial/left ventricle dilatation, left ventricle dysfunction, flow in colour Doppler suspicious for a collateral vessel in the descending aorta, or a backflow in the descending aorta) correlates well with a positive cardiac catheterisation result (100% specificity).[7] In Doulamis et al.'s[8] case series, catheterisation was performed in only 4 of 13 cases, and the other cases were diagnosed via echocardiography. In our study, 25% of the cases were diagnosed via catheterisation, and 75% via echocardiography. There is limited information available in medical journals regarding the frequency and effects of major aortopulmonary collateral arteries in transposition of the great arteries patients, with most of the available data being in the form of case reports. Wibf et al.[7] observed major aortopulmonary collateral arteries in 15% of 100 transposition of the great arteries cases, making their case series one of the largest ever. In contrast, the incidence of major aortopulmonary collateral arteries was found to be only 1.9% in Doulamis et al.'s[8] case series. In our study, we found a 16% major aortopulmonary collateral artery rate in the transposition of the great arteries cases. These variations in incidence rates may be attributed to differences in the use of imaging techniques, such as echocardiography and angiography, which can affect major aortopulmonary collateral artery detection.

Currently, neonatal patients with transposition of the great arteries have a high survival expectancy (over 95%) with arterial switch operation. Mortality in these patients is mainly associated with low cardiac output and coronary anomalies, which can lead to myocardial ischaemia.

Given the sparsity of reported cases, it is not known whether clinically significant major aortopulmonary collateral arteries alter arterial switch operation outcomes. However, based on our study and previous reports, the presence of clinically significant major aortopulmonary collateral arteries presents clinical challenges in optimising post-operative cardiac or pulmonary functions following a successful corrective surgery and complicates the post-operative course if not diagnosed. In addition, it may cause morbidity and even mortality in some cases due to LCOS and organ failure.[5,7,8,12] Several treatment options have been proposed for the management of major aortopulmonary collateral arteries, including closure with a vascular plug, coil closure, and surgical ligation.[5–8]

We found that haemodynamically significant major aortopulmonary collateral arteries can be identified after arterial switch operation due to the development of airway bleeding, pulmonary congestion, or symptoms of heart failure. Our findings indicate that the patients with major aortopulmonary collateral arteries in our study had a longer inotropic usage duration, mechanical ventilation time, and paediatric cardiac intensive care unit stay, which is consistent with previous studies, such as that by Wibf et al.[7] However, it is important to note that only 25% (n = 4) of the patients with major aortopulmonary collateral arteries in the present study had haemodynamically significant major aortopulmonary collateral arteries. We successfully managed two patients using a vascular plug, one patient with a coil and one patient with anticongestive therapy.

This study had the intrinsic limitations of a retrospective study covering a wide era encompassing changes in routine diagnostic and management strategies in the care of neonates with transposition of the great arteries. Furthermore, the low number of patients who underwent cardiac catheterisation and angiography in our study may have had an impact on the observed incidence of major aortopulmonary collateral arteries. In addition, the small sample size, non-random patient selection, low number of patients with major aortopulmonary collateral arteries, and more all affect this study.

Conclusion

Major aortopulmonary collateral arteries are frequent in transposition of the great arteries patients and may have negative clinical effects. Therefore, identifying major aortopulmonary collateral arteries, especially in cases where the post-operative course is complicated and after implementing appropriate management strategies, may have a favourable effect on morbidity and mortality.

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