The Impact of Sevoflurane and Propofol Anesthesia on Cerebral Blood Flow in Pediatric Open Cardiac Surgery, a Comparative Randomized Study

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Abstract

Background: Despite improvements in open cardiac surgical techniques and implementation of effective neuroprotective strategies, the brain, an organ highly sensitive to hypoxia, is still threatened by thromboembolic ischemic stroke, hemorrhage, or inflammation during CPB. Cerebral air embolization and hypoperfusion are considered as fundamental causes for these neurological complications. Transcranial Doppler can determine any air emboli entering brain circulation intra-operatively. Together with cerebral oximetry, they can detect any harmful embolic events during open cardiac surgery. New models of neuroprotective strategies were implanted to ameliorate this problem including different anesthetic medications like propofol and sevoflurane.

Methods: 100 patients who were planned for elective cardiac surgery were recruited in this study. Anesthesia was maintained with Propofol infusion at a rate of 150μg/Kg/min or sevoflurane 1 MAC. Transcranial Doppler sonography was used to monitor cerebral blood flow,   and oxygenation with evaluation of their neurocognitive function using ages & stages questionnaire.

Results: Cerebral blood flow maximum velocity was higher in seveoflurane group when compared to propofol group at insertion and removal of aortic cannula as well as on release of aortic cross clamp. Mean arterial pressure and mean velocity of middle cerebral blood flow were higher in sevoflurane group when compared with propofol group. Also velocity mean were lower in comparison to basal values in propofol group. ages & stages questionnaire score comparison between both groups was of no significant difference.

Conclusion: in comparison to sevoflurane, propofol decrease the maximum cerebral blood flow velocity, mean cerebral blood flow velocity and MAP more than sevoflurane. Meanwhile, it has equivalent effect to sevoflurane regarding neurocognitive outcome.

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Abbreviations: TCD: Transcranial Doppler; CPB: Cardiopulmonary Bypass; CBFV: Cerebral Blood Flow Velocity; MES: Micro-Emboli Signals; SPSS: Statistical Package for Social Scientists; SD: Standard Deviation; IQR: Interquartile Range.

Introduction

Cardiac surgery is associated with postoperative complications such as (cardiac, neurological, pulmonary and acute renal failure) and prolonged care in the hospital. These neurological deficits are mostly subclinical with optimistic long term outcome, however cognitive impairments may continue to affect the neurological development and daily life [1,2]. Cognitive domains including attention, memory, learning, visual, motor skills, and executive function may be affected alone or accompanied by behavioral change. As hippocampus is the main part responsible for memory, this might explain why all of cognitive problems, anterograde memory deficits are mostly reported after cardiac surgery [3].

Mechanisms of brain injury related to perioperative processes are not fully characterized, Three principle factors were demonstrated; cerebral hypoperfusion, cerebral arterial embolization, and systemic inflammatory response following CPB [4]. All these mechanisms were rooted mainly to air embolization and hypoperfusion. Air emboli presence in the cerebral circulation intra-operatively can reduce cerebral perfusion and obstruct blood flow by either direct mechanical effect or by increasing platelets aggregation and thrombus formation. [5-8].

In addition, circulating gaseous bubbles may induce functional endothelial injury with transient, increased permeability to macro and micro molecules. Moreover, a rise in brain water uptake, glucose utilization and protein extravasation are also associated with gaseous emboli [9]. Experimental cerebral air embolism is found to have a two-step effect on the brain. Shortly after air entry, there is multifocal brain lesion with widening of the extracellular space, later shrinkage and necrosis of neurons and neuronal sheath [10].

The origin of tiny emboli may originate frombubble oxygenators, venous reservoirs, air in the CPB venous line, inadequate surgical deairing in open chamber procedures, introduction by perfusionist during drug administration and collection of blood samples, and entrainment of air into the blood in the cardiotomy suction and vacuum assisted drainage [11]. Cooling causes of microbubbles inside somatic blood vessels [12,13].

Currently, advanced monitors represent a fundamental tool for early recognition and implantation of preventive measures against embolic events. Transcranial Doppler ultrasound (TCD) is a sensitive, real-time monitor of cerebral blood flow velocity (vCBF) and emboli during congenital heart surgery. Currently available instruments use pulsed-wave ultrasound at 2 MHz frequency, which is range-gated, emits a power of 100 mW, and has a sample volume length of up to 15 mm. A display of the frequency spectrum of Doppler signals is easily interpreted, and peak systolic and mean flow velocities, in cm/second, and pulsatility index are displayed [14]. Although detecting these tiny bubbles in Cardiopulmonary Bypass (CPB) lines is easy nowadays, no previous studies have investigated the possibility of cerebral air embolization during open cardiac surgery and the implications of anesthetic drug on their incidence [15].

Cerebral oximetry with TCD can detect any harmful injurious agents including real-time detection and quantification of microemboli passing through the cerebral circulation in pediatric patients undergoing open cardiac surgery using CPB [11].

Aiming at improving neurological outcome and specifically emboli reduction, new models of neuroprotective strategies were implanted. These include better design of venous reservoirs, increased uptake of CPB arterial line filters, increased surgeon's' awareness about air embolism impact, cell saver processing of cardiotomy blood, meticulous perfusionist interventions, cooling, retrograde cerebral perfusion and adequate surgical deairing of all cardiac chambers [11]. Also, pharmacological neuroprotective strategies were recruited including, hyperbaric oxygen, barbiturate coma, lidocaine, oxygen and inotropic support and some anesthetic agents as well [16,17].

One of the common anesthetic drug used in neuroprotective method is propofol which causes inhibition of glutamate release, reduction in cerebral metabolic rate oxygen consumption with cerebral vasoconstriction [18,19]. Sevoflurane is widely used in neuroanesthesia and shows an intrinsic dose-dependent cerebral vasodilatory effect. Several studies, have demonstrated how it increases the cerebral blood flow velocity (vCBF) and decreases the cerebrovascular resistance (CVR) in a dose-dependent manner [20,21]. With the affordability of many methods to decrease cerebral gaseous embolization, it is difficult to assess whether the use of specific anesthetic agent can attenuate the embolic events.

In this study, we hypothises that propofol is more effective than sevoflurane in reducing the cerebral blood flow velocity in pediatric patients undergoing open heart surgery for congenital heart diseases with better neurocognitive functions outcomes. The principle aim of this study was to assess the effect of two different anesthetic medications (propofol and sevoflurane) on decreasing the cerebral blood flow velocity the Middle Cerebral circulation during open cardiac surgery using CPB.

Patients and methods

This double–blind, randomized, comparative study was conducted on 100 patients of either sex aged 4-7 years who were subjected to elective correction of simple congenital heart diseases using cardiopulmonary bypass after obtaining an informed written consent from their parents/guardians. Patient with neurological, hepatic or renal diseases were excluded from the study. Preoperative clinical examination and laboratory tests were full field according to our unit protocol. On arrival to operative theatre, patients were randomly assigned (using closed envelope method) into two groups: propofol group and sevoflurane group.

Standard monitoring (ECG, SpO_2 and NIBP) were connected to all patients before induction of anesthesia. Supplemental oxygen was provided via a face mask (using Datex monitor, Helsinki, Finland AS). One peripheral intravenous indwelling cannula were inserted in non-dominant hand after using EMLA cream to numb the insertion place.

Anesthesia was induced using I.V. fentanyl 5μg/Kg, propofol 2- 2.5mg/Kg (in propofol group) or sevoflurane 3-4MAC (in sevoflurane group). With loss of consciousness, patients were mechanically ventilated by positive pressure ventilation via face mask at a rate of 18-25 breathes per minute with 100% O2 and 1 mg/kg rocuronium I.V. was given for ETT insertion. A triple lumen central line was inserted under complete aseptic condition in right internal jugular vein. An arterial line was inserted in right hand to monitor MAP at certain intervals, and facilitate blood sampling. Nasopharyngeal temperature probe, cerebral oximetry, entropy probe as well as transcranial Doppler transducer were attached to the patient head for adequate monitoring. End-tidal CO_2 was monitored by side-stream capnograph. Anesthesia was maintained with Propofol infusion at a rate of 150μg/Kg/min (in propofol group) [22] or sevoflurane 1 MAC (in sevoflurane group) and fentanyl 1 μg/Kg/min, to maintain state and response entropy reading between 40-45 and blood pressure within 75% of its basal value with additional doses of rocuronium (0.5 mg/Kg) to maintain muscle relaxation. A pressure controlled mode was used to ventilate all patients aiming at tidal volume 6-8 ml/kg and end tidal CO_2 between 30-35 mmHg.

The preload was gradually increased by reducing the venous return to CBP, and transoesophogeal echo was used to monitor and confirm the de-airing process. After completion of weaning from CPB, the left ventricle vent was stopped and clamped in situ [23].

Transcranial doppler (TCD) sonography to monitor the velocities of blood flow in middle cerebral artery (CBFV), and incidence of air embolization through trans temporal window, a 2.0/2.5 MHz TCD device (Toshiba Xeario model, 3MHz frequency). Although cerebral blood flow velocity is not a direct measurement of CBF, but changes in CBFV is closely correlate with the cerebral blood flow changes because the middle cerebral artery diameter is usually constant [24].

Mean velocity of flow was measured before induction of general anesthesia (basal), after insertion of aortic cannula, 15 minutes after establishment of CPB, on removal of cross clamp, and removal of aortic cannula. Emboli detection was done at different event markers; after insertion of aortic cannula, 15 minutes after establishment of CPB, after removal of cross clamp, and removal of aortic cannula. Event-related micro-emboli signals (MES) were defined as the micro emboli signals that were spotted within 180 second following an event marker. Another experienced radiographer had re-evaluated all stored Doppler signal events in a different cession [22,23,25].

A research with experience in administration of neuropsychological tests were recruited for neuro-cognitive function assessment in this study using the age

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and sex questionnaire. which was designed for assessing the severity of impairments, and identifying changes in cognitive dysfunctions in a wide age range (3-14 years). Moreover, comprehension of instructions was independent of socioeconomic status and educational level. [28,29]. To familiarize the children with the test, we gave an explanation trial and perform a basal assessment for all participants. Postoperative cognitive function assessments were conducted in the ward or at anaesthesia clinic after one week and three months after surgery.

Sample Size

Sample size of this study was calculated using PS software for Windows version 10 according to differences in number of microemboli detected in previous study. It revealed 54 patients in each arm to obtain power of about 80%. We increased the number of patients up to 60 patients in each arm to compensate 20% possible dropouts [30].

Statistical Analysis

Statistical analysis was done using statistical package for social scientists (SPSS) program version 17, USA, Chicago. The mean and standard deviation (SD) were reported as appropriate for continuous data after checking data for normality using the Shapiro–Wilk test. Independent sample t test or Mann–Whitney U test were used to compare perioperative differences between groups. Chi–square test were used for qualitative data. P <0.05 was considered significant (Tables 1 & 2).

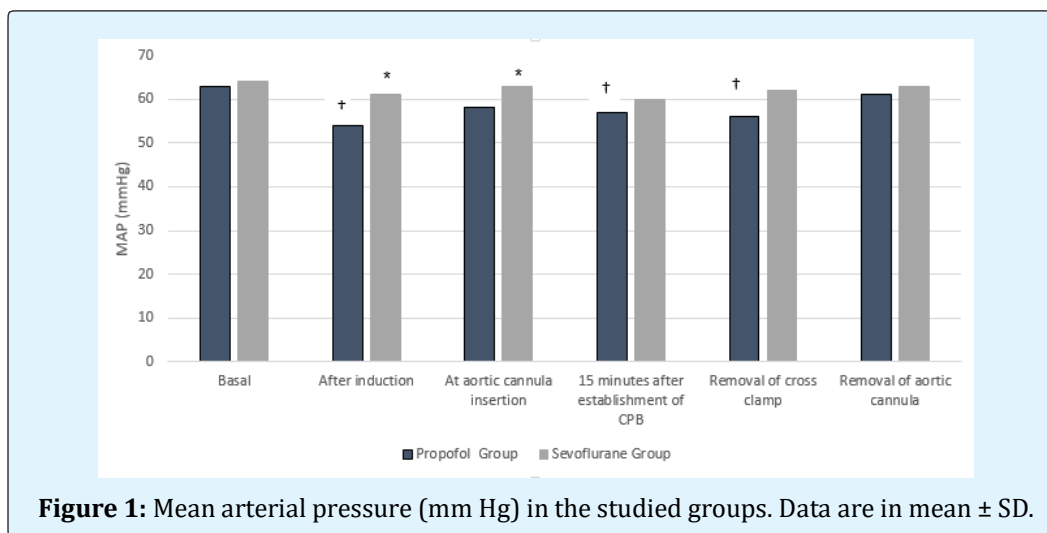|	Propofol Group (n=50)	Sevoflurane Group (n=50)
Age (years)	5.13 ± 0.67	5.38 ± 0.76
Sex Male	70% (15)	60% (31)
Female	30% (13)	40% (19)
Weight (kilogram)	24.50 ± 4.03	25.25 ± 3.47
ASD	50% (25)	45% (22)
VSD	50% (25)	55% (28)

Table 1: Demographic data of the studied groups: Data are presented in number & % or mean ± SD.

All patients have completed the study successfully with no dropouts. No considerable differences were observed between two groups as regard demographic data and type of surgery.

|	PropofolGroup (n=50)	SevofluraneGroup (n=50)
Cross Clamp Time (min)	31.7± 8.57	35.95 ± 20.72
CPB Time (min)	28.9 ± 9.92	29.65 ± 10.62

Table 2: Aortic cross clamp time (min) and CPB time (min) in the studied groups, Data are in mean ± SD.

Both cross clamp time and CPB time were almost the same in both groups (Table 2).

Figure 1: Mean arterial pressure (mm Hg) in the studied groups. Data are in mean ± SD.

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Mean arterial pressure showed statistically higher values in sevoflurane group when compared with propofol group after induction and at aortic cannula insertion. Also mean arterial pressure was statistically lower in propofol group when compared to basal value after induction, 15 minutes after establishment of CPB and after removal of cross clamp.
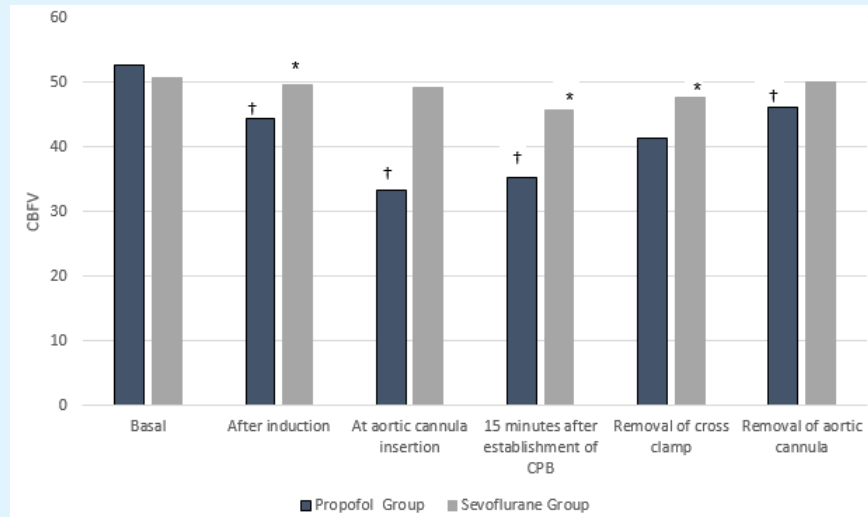
Figure 2: Mean Velocity (cm/s) of middle cerebral blood flow in the studied groups. Data are in mean ± SD.

Velocity mean was significantly higher at aortic cannula insertion, 15 minutes after establishment of CPB and on removal of crossclamp in sevoflurane group when compared with propofol group. Also In propofol group, velocity mean were lower in comparison to basal values after induction, at aortic cannula insertion, 15 minutes after establishment of CPB and on removal of cross clamp.

The average number of embolic events detected within 180 second following every events were higher in seveoflurane group when compared to propofol group at insertion and removal of aortic cannula as well as on release of aortic cross clamp.
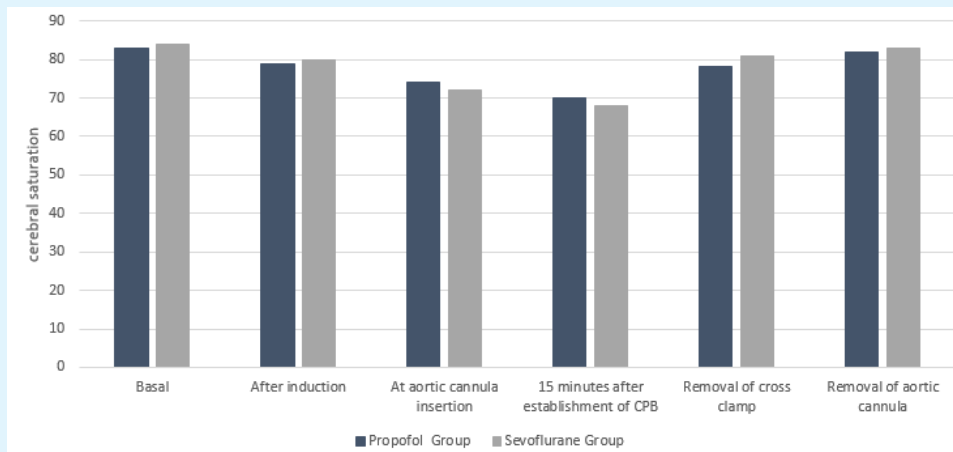
Figure 3: cerebral oxygen saturation of the studied groups (%). Data are in mean ± SD.

Cerebral oxygen saturation showed no differences between both groups throughout the surgery (Figure 3).

	Propofol Group	Sevoflurane Group
Before surgery	36.15±3.63	36.55±6.12
1 week after surgery	30.17±5.13	30.16±4.28
3 months after surgery	35.69±4.10	34.25±4.45

Table 3: Neuro-cognitive function assessment results of the studied groups. Data are in mean ± SD.

The mean average of age and sex questionnaire results statistically insignificant between both groups. However the mean value was slightly lower after one week of surgery and improved by time to be almost near normal three months after surgery in both groups (Table 3).

Discussion

There is a need to identify new strategies to prevent harmful events during cardiothoracic surgery. Neuroprotection may occur as a consequence of reduced O_2 demand, enhanced O_2 delivery, or attenuation of pathologic processes that contribute to cellular injury or death [31]. Neurological brain affection during cardiac surgery can be caused by air bubbles when enter the cerebral circulation intra-operatively [5]. Anesthetic agents are considered as a part of pharmacological preventive measures against air bubbles and brain protective effects.

In this study, all patients in propofol anaesthesia group showed significant reduction in the maximum and mean cerebral blood flow velocity (CBFV) more than patients in sevoflurane anaesthesia group. In addition the mean arterial blood pressure were significantly lower in propofol group than sevoflurane group. There were no differences between the two groups as regard cerebral oxygen saturation and the postoperative neurocognitive function outcome.

According to this study, lower cerebral blood flow velocity and MAP were associated with propofol based anaesthesia when compared to sevoflurane group. The lower maximum cerebral blood flow velocity in propofol group than sevoflurane group can be explained by different mechanisms; the Vasoconstrictor effect of propofol on small arterioles in cerebral circulation. This propofol mediated vasoconstrictor effect increases the resistance force inside small arterioles in arterial side which hinder the smooth passage of foreign materials into cerebral circulation. Propofol causes reduction in CBF which decreases the cerebral regional blood flow with subsequent attenuation of the carrying power and driving force of blood flow to foreign objects including air emboli [32]. The reduction in cerebral blood flow velocity caused by propofol within the cerebral arterial tree can be explained by decreasing the cerebral metabolic rate of oxygen, and suppressing effect on endothelium-dependent relaxation that might reduce the steady-state CBF velocity [33,34]. This leads to decrease the driving force of blood flow associated with lower its carrying ability. This is attributed to decrease in SVR, negative inotropic effect, and resetting of baroreceptors caused by propofol [32,34,35].

On the other hand, a higher load of air emboli was noticed in sevoflurane group. All volatile anesthetic agents cause direct cerebral vasodilatation to different degrees. Desflurane and sevoflurane are more potent cerebral vasodilator than other volatile agents. This vasodilataion with loss of autoregulation decreases the vascular resistance to blood flow with any foreign objects inside. Also sevoflurane Increases cerebral metabolic rate with associated increase or non-significant changes in the global and regional blood flow as well. In addition, sevoflurane maintain MAP with maintenance of the driving force of blood flow to all organs including the brain [36-38]. Sevoflurane is not associated with increases in heart rate, whereas increasing concentrations of sevoflurane slightly decrease blood pressure, myocardial contractility and reduces baroreflex function [39]. In the current study, CBFV was decreased between 13-17% by propofol effect. This study is very similar to the work published by Panel et al., in which the impact of propofol infusion (6 mg/kg/h for 40 min) on CMRO2 was evaluated. He observed a reduction in CBF and $CMRO_2$ with propofol without affecting arteriovenious oxygen delivery, suggesting maintenance of normal cerebral circulation and metabolism [40].

In another study by Newman et al., he tried to evaluate the embolic preventive and brain protective effect of propofol. He did not defined a fixed rate for propofol infusion but took an 80% suppression of EEG as a target point and he reported reduction of cerebral blood flow, embolic exposure, cerebral oxygen delivery and metabolic rate both in normothermia and hypothermia [33].

Regarding sevoflurane, cerebral blood flow was increased by only 1-2%. Kuroda, et al. in his study proved that sevoflurane has cerebral vasodilator effect and can increases CBFV and embolic load which matches the present study [41]. Previous reports indicated that sevoflurane between 0.5–1.0 MAC has minimal vasodilating effect on small brain arterioles and has no systemic hemodynamic effects at the most common used 1 MAC sevoflurane [39,42]. In our study, CBFV was lower in propofol group relative to sevoflurane group. Similarly, previous work by Kaike, et al. has assessed the effect 1 MAC, 1.5, and 2 MAC of sevoflurane and 0 µg/ml, 6 µg/ml, 9 µg/ml, and 12 µg/ml TCI of propofol on regional cerebral blood flow on volunteers. He reported that both anesthetics medications caused a global decrease of rCBF however this reduction was grater in propofol more than sevoflurane [43]. Kaisti, et al. in their study comparing effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans by using positron emission tomography tracers, reported that propofol reduced rCBF more than sevoflurane but reduces rCMRO2 only to an extent similar to sevoflurane [44].

Another study by Engelhard found that propofol caused cerebral vasoconstriction, intact cerebrovascular autoregulation and maintained CO_2 reactivity. On the other hand sevoflurane caused cerebral vasodilatation, decreased CPP, impaired cerebrovascular autoregulation and maintained CO_2 reactivity; and hence supporting our findings [45]. In this study, we hypothise that propofol would associated with better neurological outcome than sevoflurane, however the results showed no significant differences in neurocognitive outcome between propofol and sevoflurane groups. This may be attributed to the facts that propofol decreases cerebral embolic events, conserve cerebrovascular autoregulation regardless metabolism and mitigates intracranial pressure [46-48]. In addition propofol can attenuate glutamate-mediated excitotoxic mechanisms by either decreasing NMDA receptor activation, reducing glutamate release, or or increasing glutamate uptake into neuronal and glial cells. In also potentiates GABAergic neuronal activity [49] and has antioxidant activit [50]. Meanwhile, sevoflurane exhibit its neuroprotective effect by a dose dependant reduction in cerebral metabolic requirements, or related to decreased apoptotic cell death in the post-ischemic period [51,52]. Alteration of body temperature during cooling on CBP that decreased the $CMRO_2$, changes in $PaCO_2$ that may affect CBF and autoregulation mechanisms and small size of microemboli (less than 200 micron) that was not large enough to occlude the small arterioles [53].

Similarly, During this study, it was noticed that the rate of incidence of air emboli is higher in both groups on right middle cerebral artery than left one. We suggested that proximity, size and early origin of brachiocephalic trunk from the aortic arch facilitate trapping and passage of air emboli from left ventricle to cerebral blood vessels on right side.

In conclusion, in comparison to sevoflurane, propofol decrease the Maximum; mean cerebral blood flow velocity, embolic events and MAP to a great extent than sevoflurane. Meanwhile, it has equivalent effect to sevoflurane regarding regional cerebral oxygen saturation and neurocognitive outcome.

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