Isoflurane Sedation on the ICU in Cardiac Arrest Patients Treated With Targeted Temperature Management: An Observational Propensity-Matched Study

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Objective: Targeted temperature management after cardiac arrest requires deep sedation to prevent shivering and discomfort. Compared to IV sedation, volatile sedation has a shorter half-life and thus may allow more rapid extubation and neurologic assessment.

Design: Observational analysis of clinical data.

Setting: University hospital, medical ICU.

Patients: Four hundred thirty-two cardiac arrest survivors underwent targeted temperature management; of those, 110 were treated with volatile sedation using an anesthetic conserving device and isoflurane, and 322 received standard IV sedation.

Intervention: No intervention.

Measurement and Main Results: A matched pairs analysis revealed that time on ventilator (difference of median, 98.5 hr; $p = 0.003$) and length of ICU stay (difference of median, 4.5 d; $p = 0.006$) were significantly shorter in patients sedated with isoflurane when compared with IV sedation although no differences in neurologic outcome (45% of patients with cerebral performance category 1–2 in both groups) were observed. Significant hypercapnia occurred more frequently during anesthetic conserving device use (6.4% vs 0%; $p = 0.021$).

Conclusions: Volatile sedation is feasible in cardiac arrest survivors. Prospective controlled studies are necessary to confirm the beneficial effects on duration of ventilation and length of ICU stay observed in our study. Our data argue against a major effect on neurologic outcome. Close monitoring of $Paco_2$ is necessary during sedation via anesthetic conserving device. (*Crit Care Med* 2016; XX:00–00)

Key Words: cardiac arrest; targeted temperature management; volatile sedation

Following current guidelines, cardiac arrest (CA) survivors are treated with targeted temperature management (TTM) if they remain comatose after return of spontaneous circulation (1). During the procedure, deep sedation and muscle paralysis are frequently required, mainly to avoid shivering which is a typical side effect of hypothermia. Sedation might confound reliable neurologic outcome prediction as accumulation of sedatives may occur due to reduced metabolism during TTM (2). National and international guidelines for sedation recommend volatile anesthetics as an equivalent option for long-term sedation (3). This recommendation is based on eight randomized controlled trials including a total of 200 patients, and other studies include more than 300 patients, mainly with isoflurane, indicating feasibility and safety in different patient groups (4–7). A retrospective study of 369 critically ill surgical patients suggested positive effects of long-term sedation with isoflurane on mortality as compared to sedation with midazolam and propofol (8).

In CA survivors, volatile sedation may be advantageous during post resuscitation care, the reasons including a short half-life with low risk of accumulation and rapid reawakening.

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Furthermore, in an animal model, a reduction of the shivering threshold was demonstrated, and in humans, long-term volatile sedation decreased wake-up time and shortened time of ventilation (9, 10). A study on 12 patients indicated feasibility of volatile sedation in the ICU after CA (11).

The aim of this observational study was to evaluate the frequency of major adverse events, whether volatile sedation in post-CA patients undergoing a TTM may reduce time on respirator, length of ICU stay, and frequency of tracheostomy and if volatile sedation may improve neurologic outcome of CA.

MATERIAL AND METHODS

We retrospectively studied consecutive nontraumatic CA patients admitted comatose to our ICU between November 2010 and November 2015. The local ethics committee of the Charité-Universitätsmedizin Berlin approved the study and waived the need for informed consent. All patients underwent TTM irrespective of initial rhythm according to local standard procedures and current guidelines. Patients' temperatures were maintained at 33°C for 24 hours followed by slow rewarming at 0.25°C/hr using an automated feedback cooling device (C.R.BARD GmbH, Karlsruhe, Germany). If necessary, sedation prior to ICU admission was achieved using midazolam (5–10 mg IV) and fentanyl (0.1–0.2 mg IV). After admission to the ICU, patients received either volatile gas sedation with isoflurane or a totally IV sedation with a combination of a benzodiazepine (midazolam, 0.03–0.2 mg/kg/hr) and an opioid (fentanyl, 0.3–2 µg/kg/hr). The anesthetic conserving device (ACD) used is a vaporizer approved for several types of volatile sedation (AnaConDa; model 26000; Sedana Medical, Uppsala, Sweden). The ACD was used in combination with an EVITA ventilator (Dräger, Lübeck, Germany), and exhaled air was filtered from residual gas with a passive gas absorber (FlurAbsorb; Sedana Medical, Uppsala, Sweden; **Fig. 1**). Our local employment protection service evaluated and approved the system for use in the ICU. After the implementation in our ICU in December 2012, which included dedicated training of the ICU staff, isoflurane was used as first-line sedation in CA survivors. According to our local protocol, isoflurane sedation was combined with an IV short-acting opioid (remifentanil, 0.006–0.5 µg/kg/min). Gas- and end-tidal Co_2 concentration were monitored continuously (Vamos; Dräger), and isoflurane was adjusted as needed for deep sedation to attain a mean end-tidal concentration of isoflurane (end-tidal gas fraction) of 0.5–1.5%. All patients were ventilated in controlled biphasic positive airway pressure mode (target tidal volume 6–8 mL/kg bodyweight). Respirator variables were adjusted to arterial blood gas analysis. A Richmond Agitation-Sedation Scale (RASS) score of –5 was targeted during TTM until the patient had been fully rewarmed to 37°C independent of the type of sedation. Shivering was assessed using the Bedside Shivering Assessment Scale (12). To prevent shivering, most patients received early counter warming of hands and feet. Paralytic agents were rarely used in isoflurane-sedated patients, only if shivering occurred and could not be controlled by additional IV magnesium and deepening of sedation (13, 14). The Pittsburgh Cerebral Performance Category (CPC) was used for outcome classification at discharge from ICU (15).

Neurologic outcome prognostication followed our local standard protocol, including determination of neuron-specific enolase (NSE) serum concentration after 72 hours, (repetitive) somatosensory-evoked potentials (SEP), clinical examination, and electroencephalography (16). If patients remained comatose after the end of sedation, a CT was performed (17).

Results are given depending on their scale in proportions (%), median including 25–75% quartiles (interquartile range [IQR]) or arithmetic mean, and 95% CI (mean, 95% CI). As appropriate, tests for statistical significance were performed using two-tailed Student *t* test, Wilcoxon-Mann-Whitney test, or Fisher exact test. A *p* value of less than 0.05 was considered statistically significant. In a first step, we compared all given data between isoflurane and control group. In a second step, we removed the effect of the additional variables by pairwise next neighbor matching for age, time to return of spontaneous circulation, gender, Acute Physiology and Chronic Health Evaluation II-score, and first rhythm. Matching was done using the propensity score method (18). All analyses were performed with R 3.1.2 (The R Foundation, Vienna, Austria).

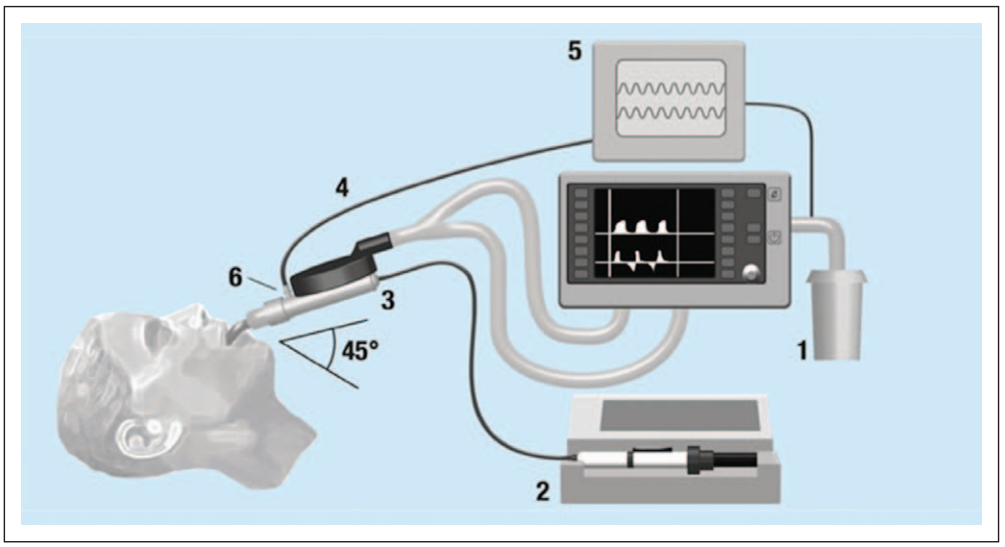

Figure 1. Illustration of the AnaConDa setup at the patients' bed side (with approval of Sedana Medical). 1 indicates Gas scavenging filter; 2 indicates syringe pump; 3 indicates agent supply line; 4 indicates gas monitor line; 5 indicates gas monitor; and 6 indicates gas monitor port.

RESULTS

Analysis was performed in two steps. First, all 432 patients treated in our ICU between November 2010 and November 2015 (110/432

with isoflurane) were analyzed. Second, a matched pairs analysis with the 110 isoflurane-treated patients was performed to reduce the risk of confounding.

Overall Analysis

Four hundred thirty-two consecutive patients treated with TTM after nontraumatic CA were included. Of those, 110 received volatile sedation with isoflurane via ACD plus remifentanil IV after implementation of this regime in our ICU in December 2012.

Time on ventilator was shorter in the isoflurane group (median, 170 hr; IQR, 87–323) compared with the IV sedation group (median, 210; IQR, 91–450) without reaching the level of significance ($p = 0.068$). Duration of ICU stay was also shorter (median, 8 d; IQR, 4–16 vs median, 11 d; IQR, 4–23; $p = 0.116$). Analysis after exclusion of patients who died still revealed a shorter time on ventilator (isoflurane: $n = 59$; median, 226 hr; IQR, 153–426 vs $n = 163$; median, 304 hr; IQR, 166–578; $p = 0.067$) as well as a shorter ICU stay (isoflurane: median, 12 d; IQR, 9–26 vs median, 18 d; IQR, 10–32; $p = 0.070$) without reaching the level of significance.

Matched Pairs Analysis

Baseline characteristics including matching variables and outcome variables of the 220 matched pair patients are given in **Table 1**. **Table 2** indicates the frequency of major adverse events.

Time on Ventilator and Frequency of Tracheotomy

Time on ventilator was significantly shorter in the isoflurane group with a median of 170 hours (IQR, 87–323)

TABLE 1. Baseline Parameters Used for Matched Pair Analysis and Outcome Results

Variables	Baseline (Matched Parameters)		
	IV	Volatile	*p*
n	110	110	
Age, mean (95% CI)	61.9 (58.9–64.8)	62.3 (59.6–65.0)	0.827
Time to return of spontaneous circulation, median (IQR)	12.0 (8.0–20.0)	12.0 (8.0–23.5)	0.931
Gender, female, *n* (%)	29 (26.4)	26 (23.6)	0.755
Shockable, *n* (%)	54 (49.1)	46 (41.8)	0.343
Acute Physiology and Chronic Health Evaluation II, median (IQR)	31 (24–36)	29 (23–35)	0.554
Variables	**Results**		
Cerebral Performance Category, *n* (%)			0.599
1	34 (30.9)	40 (36.4)	
2	15 (13.6)	9 (8.2)	
3	2 (1.8)	3 (2.7)	
4	10 (9.1)	7 (6.4)	
5	49 (44.5)	51 (46.4)	
Ventilation duration, median (IQR)	269.0 (122.2–530.2)	170.5 (87.5–323.5)	0.003
ICU stay, median (IQR)	13.0 (6.0–26.7)	8.5 (4.2–16.0)	0.006
Shivering, *n* (%)	32 (29.1)	28 (25.5)	0.650
Paralysis, *n* (%)	44 (40.0)	15 (13.6)	< 0.001
Bedside Shivering Assessment Scale, *n* (%)			0.962
None	78 (70.9)	81 (73.6)	
Mild	10 (9.1)	9 (8.2)	
Moderate	12 (10.9)	10 (9.1)	
Severe	10 (9.1)	10 (9.1)	
Tracheotomy, *n* (%)	32 (29.1)	21 (19.1)	0.115
Norepinephrine, mg/48 hr, median (IQR)	26.5 (13.0–64.0)	39.50 (15.7–77.0)	0.127
Cardiac cause of arrest (%)	60 (54.5)	57 (51.8)	0.787

IQR = interquartile range.

TABLE 2. Major Adverse Events During the First 48 Hours of ICU Treatment

Variables	Adverse Events		p
	IV	Volatile	
n	110	110	
Hypercapnia[a]	0 (0.0)	7 (6.4)	0.021
Rearrest	19 (17.3)	14 (12.7)	0.450
Repercutaneous coronary intervention	0 (0.0)	2 (1.8)	0.473
Ventricular tachycardia	10 (9.1)	16 (14.5)	0.296
Acute respiratory distress syndrome[b]	4 (3.6)	6 (5.5)	0.746
Bleeding[c]	3 (2.7)	5 (4.5)	0.722

[a]Severe increased Co_2 during isoflurane treatment requiring switch of sedation.

[b]Acute respiratory distress syndrome (ARDS) was defined as oxygenation index less than 200; the patient had a cardiac arrest because of respiratory failure due to a severe pneumonia and developed an ARDS rapidly.

[c]Bleeding was defined as requiring any blood transfusions.

versus 269 hours (122–530) in the IV sedation group ($p = 0.003$) (**Fig. 2**). Analysis after exclusion of patients who died also revealed a significantly shorter time on ventilator (isoflurane: $n = 59$; median, 226 hr; IQR, 153–426 vs $n = 61$; median, 413 hr; IQR, 165–649; $p = 0.032$). Dilative tracheotomy was performed less frequently in the isoflurane group without statistical significance (19% vs 29%; $p = 0.115$). There was no significant difference of the interval between CA and dilative tracheotomy between both groups (isoflurane: $n = 21$; median, 11 d; IQR, 7–13 vs $n = 32$; median, 9 d; IQR, 8–13; $p = 0.454$).

Length of ICU Stay

The median length of ICU stay was significantly shorter in the isoflurane group –8 days (4–16) versus 13 days (6–27) ($p = 0.006$) (Fig. 2). Analysis without patients who died still showed a significant difference (isoflurane: $n = 59$; median, 12 d; IQR, 9–26 vs $n = 61$; median, 23 d; IQR, 11–34; $p = 0.034$).

Neurologic Outcome and NSE Serum Concentration

The frequency of good neurologic outcome (CPC 1–2) was equal in both groups (49/110 [45%]) in the isoflurane and 49/110 [45%] in the IV sedation group). Only a few patients in both groups regained consciousness with severe neurologic deficits (CPC 3). There was no significant difference in the number of patients who died or remained in an unresponsive wakefulness syndrome or coma (Table 1). NSE serum concentration 3 days after CA did not differ between the two groups: median NSE serum concentration was 18.9 ng/mL (14.2–30.9) in the IV sedation group and 18.4 ng/mL (15.3–35.7) in the volatile sedation group ($p = 0.685$; **Supplementary Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C245; legend: NSE serum concentrations 3 d after CA in post-CA patients with volatile vs IV sedation. There was no significant difference in NSE serum concentrations, neither for patients with CPC 1–3 at ICU discharge nor for patients with CPC 4–5 at ICU discharge). In both groups, all patients with bilaterally absent SEP had poor outcomes (CPC 4 or CPC 5).

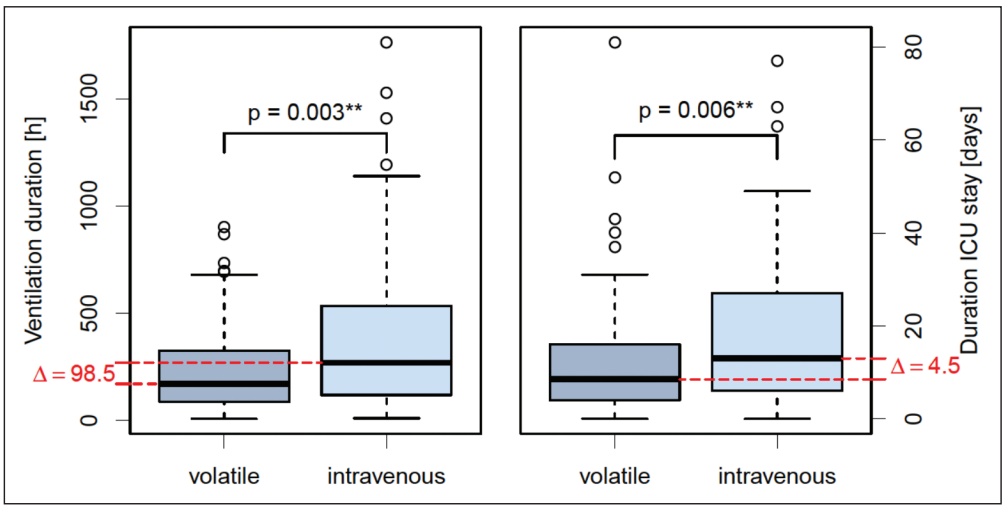

Figure 2. Boxplots of ventilation time and duration of ICU stay for volatile compared with IV sedation group. The significant difference is indicated in red in hours (ventilation) and days (ICU stay).

Severe Adverse Events

Table 2 indicates the frequency of severe adverse events. Hypercapnia was observed more frequently in the isoflurane group (7/110 vs 0/110 patients; $p = 0.021$). In these seven patients, sedation was switched from volatile to IV and $Paco_2$ rapidly improved. We did not observe statistically significant differences in the frequencies of rearrest, repercutaneous coronary intervention, ventricular tachycardia,

acute respiratory distress syndrome (ARDS), or severe bleeding (Table 2).

DISCUSSION

Our main findings are as follows: 1) volatile sedation with isoflurane was feasible in CA survivors in the ICU; 2) volatile sedation was associated with a significantly shorter time on ventilator and reduced duration of ICU stay; 3) neurologic outcome and serum NSE concentrations did not differ between isoflurane/remifentanil and total IV sedation; and 4) isoflurane sedation had to be stopped in a minority of patients (6.4%) because of hypercapnia. There were no other significant differences in major adverse events between isoflurane and totally IV sedation.

The need for deep sedation during TTM in post-CA patients is in conflict with an early and reliable neurologic prognostication and might prolong ICU stay (2). Even short-acting drugs such as propofol can have a prolonged clearance under hypothermia (19). Short-acting volatile sedation is an alternative with the potential benefits of low risk of accumulation and the option for direct monitoring of end-tidal gas concentration (20). Inhalative sedation by volatile sedatives has been investigated preclinically and in different patient populations, for example, critically ill surgical patients, traumatic brain injury patients, patients with status asthmaticus, or status epilepticus (8). Although large prospective randomized controlled trials are lacking, different potential benefits and negative effects have been identified. Potential benefits of isoflurane include neuroprotection in focal cerebral ischemia models, myocardial protection and coronary vasodilation, reduction of the cerebral metabolic rate of oxygen, and increases in cerebral blood flow and bronchodilatation (21–25). Importantly, the effects are dose dependent and thus, duration of isoflurane application and dosages have to be taken into account when interpreting these results. A recent large retrospective study suggested reduced mortality in critically ill patients in the ICU (8).

However, negative effects have also been reported, especially decline of mean arterial blood pressure (19), increases of intracranial pressure (ICP) (18, 19), and accumulation of Co_2 related to an increase of the dead space when using an ACD (26, 27).

Our results are in line with previous studies reporting shorter wake-up times, shorter duration of ventilation, or shorter ICU stay (6, 10). However, other studies did not observe shorter ICU stay or shorter ventilation duration, even when reduced mortality was found (8).

In contrast, we did not observe an effect on neurologic outcome or NSE serum concentrations 3 days after CA, and we found no difference in NSE serum concentration between patient groups, pointing to equal severity of hypoxic encephalopathy. Different patient cohorts and sedative regimes used are the most likely explanation for the differences between our neutral finding regarding outcome and the finding of a reduced mortality in the study by Bellgardt et al (8).

We had to switch from sedation with isoflurane via ACD to IV sedation in seven out of 110 patients due to increases of $Paco_2$. Increased dead space is a well-recognized problem of the ACD, which has been investigated in detail by Sturesson et al (27, 28). Our observation highlights that close attention should be paid to the ACD setup, ventilation variables, and $Paco_2$ as the ACD dead space is around 140 mL. Thus, the total dead space may be more than 50% of the tidal volume. To reduce total dead space, shortening the breathing hose and removing any intermediate pieces for tube connection in the ventilator setup should be considered. Even with an optimized setup, the additional dead space imposes restrictions on the use of ACD, for example, in patients with low tidal volume or with severe lung diseases, for example, ARDS or severe chronic obstructive lung disease (27).

Bösel et al (29, 30) found an insignificant ICP increase in critically ill patients with focal brain lesions (intracranial hemorrhage and ischemic stroke) using volatile sedation with isoflurane but a significant increase in a relevant subgroup of such patients treated with sevoflurane. Thus, potential ICP increases under volatile sedation need to be considered. ICP may increase in patients with hypoxic encephalopathy after CA due to diffuse cerebral edema. Only few small studies report ICP measurements in CA patients (31–33). The limited evidence suggests that ICP remains normal in patients without severe hypoxic encephalopathy and good neurologic outcome. In line with these observations, Inamasu et al (34) reported a poor outcome in all of 20 patients with a "sulcal effacement sign" (indicating brain edema) on brain CT. Thus, the risk of adversely affecting outcome by increasing brain edema and ICP during isoflurane anesthesia after CA may be low. On the other hand, no study has evaluated ICP or brain imaging correlates of cerebral edema over time during the first days after CA in a large cohort of patients. Thus, further studies are warranted to clarify this issue.

Patients with isoflurane sedation tended to require a higher amount of vasopressors during deep sedation. The difference was not statistically significant. A potential explanation is the well-known vasodilatory effect of isoflurane. Our finding indicates that mean arterial pressure and vasopressor use need to be carefully monitored in patients undergoing volatile sedation.

Isoflurane and other volatile anesthetics can cause malignant hyperthermia in rare cases (35). The key symptom might be masked by the cooling procedure itself, but high cooling energy, increasing temperature during cooling, progressive combined acidosis, or rhabdomyolysis should be taken as an early warning sign. Patients undergoing volatile sedation should be monitored closely, and an emergency plan including dantrolene administration should be available. In our cohort, we did not observe a case of malignant hyperthermia. In light of the neutral results of the "TTM study," CA patients in some centers are managed at a body temperature of 36.0°C for 24 hours—as opposed to 33°C in our study (36). Interestingly, as 36.0°C is close to the shivering threshold, use of sedatives did not differ between patients cooled to 33°C and those

treated at 36.0°C in the TTM trial. This may indicate that the effect observed in our cohort could extend to cohorts treated at 36,0°C, but further studies are necessary to investigate this question.

LIMITATIONS

Most importantly, our analysis was retrospective, not randomized and not blinded. Confounders may have contributed to the equal neurologic outcomes, shorter time on ventilator or shorter length of ICU stay. CPC scores were obtained at ICU discharge and treating physicians were not blinded to the type of sedation. Thus, the type of treatment may in principle have influenced assignment of CPC scores. However, in most cases, CPC scores were assigned in consensus with an experienced neurologist unaware of (although not actively blinded to) the sedative regime. The CPC Score is not suitable for detecting more subtle differences in neuropsychologic outcome. Therefore, in future trials, more sophisticated outcome scales and long-term follow-up are desirable.

Over the years, intensive care of patients after CA has been modified repeatedly at our institution. These modifications may have impacted the distribution of CPC scores at ICU discharge. As we included isoflurane patients since 2012 and IV sedation patients only after November 2010, a major influence of changes in ICU procedures on our findings is unlikely.

We compared volatile sedation using isoflurane with standard sedation, mostly by midazolam and fentanyl. In principle, variations in dosage, speed of reduction of sedation at the end of hypothermia, or other modifications may affect the variables investigated in this study for the IV sedation group.

Some patients undergoing volatile sedation needed additional IV sedation to reach a satisfying sedation level from the clinical point of view (RASS –5 during TTM). Despite this potential confounder, time on respirator and length of ICU stay were significantly shorter in the isoflurane group.

CONCLUSION

Volatile sedation using isoflurane in post-CA patients was feasible. In patients sedated with isoflurane, time on ventilator and length of ICU stay were shorter. There was no significant effect on short-term neurologic outcome. A relevant minority of patients under volatile sedation using an ACD developed hypercapnia. We suggest optimizing the respirator setup and closely monitoring ventilation variables and $Paco_2$ in patients undergoing volatile sedation in the ICU. In the heterogeneous group of post-CA patients, a tailored sedation with volatile substances should be evaluated prospectively in randomized studies.

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