Anesth Pain Med. 2018 October; 8(5):e80158. doi: 10.5812/aapm.80158.

Published online 2018 September 24. **Research Article**

Feasibility of On-table Extubation After Cardiac Surgery with Cardiopulmonary Bypass: A Randomized Clinical Trial

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Received 2018 June 03; **Revised** 2018 September 08; **Accepted** 2018 September 13.

Abstract

Background: The use of short-acting anesthetics, muscle relaxation, and anesthesia depth monitoring allows maintaining sufficient anesthesia depth, fast recovery, and extubation of the patients in the operating room (OR). We evaluated the feasibility of extubation in the OR in cardiac surgery.

Methods: This clinical trial was performed on 100 adult patients who underwent elective noncomplex cardiac surgery using cardiopulmonary bypass. Additional to the routine monitoring, the patients' depth of anesthesia and neuromuscular blocked were assessed by bispectral index and nerve stimulator, respectively. In the on-table extubation (OTE) group (n = 50), a limited dose of sufentanil (0.15 μg/kg/h) and inhalational anesthetics were used for early waking. In the control group (n = 50), the same anesthesia-inducing drugs were used but the dose of sufentanil during the operation was 0.7 - 0.8 μg/kg/h. After the operation, cardiorespiratory parameters and ICU stay were documented.

Results: Demographic and clinical variables were comparable in both study groups. In the OTE group, we failed to extubate two patients in the OR (success rate of 96%). There were no significant differences between the two groups in terms of systolic and diastolic blood pressure at the time of entering the ICU (P > 0.05). Heart rate was lower in the OTE than in the control group at ICU admission (89.4 $\pm$ 13.1 vs. 97.6 $\pm$ 12.0 bpm; P = 0.008). The ICU stay time was lower in the OTE group (34 (21.5 - 44) vs. 48 (44 - 60) h; P = 0.001).

Conclusions: Combined inhalational-intravenous anesthesia along with using multiple anesthesia monitoring systems allows reducing the dose of total anesthetics and maintaining adequate anesthesia depth during noncomplex cardiac surgery with cardiopulmonary bypass. Thus, extubation of the trachea in the OR is feasible in these patients.

Keywords: Anesthesia, Cardiopulmonary Bypass, Cardiac Surgery, Monitoring, Early Extubation

1. Background

Early extubation of the patients from mechanical ventilation within a few hours after a cardiac surgery was proposed as a standard protocol because of major advances in anesthesia and surgical techniques. Nowadays, delayed extubation is reserved mostly for high-risk patients that are at risk of significant cardio-respiratory complications. Of note, prolonged mechanical ventilation (delayed extubation), which has been defined variable ranging from a cut point of greater than 24 hours to seven days, occurs in 3 - 9.9% following cardiovascular surgeries (1-3).

There is a considerable discrepancy respecting the definition of fast and ultrafast track extubation. A wide range of time spans (under 1 h to 24 h) has been recognized. Early attempts for extubation may reduce the length of ICU and total hospital stays. Moreover, the goal of this approach is to decrease the costs of intensive care in the setting of cardiovascular operations along with the maintenance of safety and avoidance of undesirable outcomes (4-6).

In the past decades, the use of high-dose opioids in patients undergoing cardiac surgery imposed the need for postoperative overnight mechanical ventilation and a relatively high incidence of respiratory complications. Prolonged mechanical ventilation delays neuro-cognitive recovery and requires nutritional support to prevent catabolic state after a cardiac surgery (7). Meade et al. evaluated 10 randomized clinical trials to compare early versus late extubation after cardiac surgery and found that

early-extubation protocols in selected patients are related to a shorter period of mechanical ventilation and shorter times of ICU and hospital stays and resources usage (7).

Shortening the duration of endotracheal intubation and simultaneously rapid postoperative recovery may help to back to work earlier in some cases. In fact, a short period of intensive hemodynamic monitoring early after the end of a surgical procedure is essential to protect against major cardiorespiratory compromise. Although respiratory failure usually prevents early extubation or leads to re-intubation, morbidity does not increase after coronary artery bypass grafting (CABG). However, optimal gas exchange and appropriate pain management are the cornerstones of stable spontaneous breathing after extubation (8, 9).

The purpose of this trial was to implement a multimodality protocol for successful on-table (in operation room) extubation of the patients undergoing non-complex cardiac surgery based on close hemodynamic-neuromuscular blocking monitoring, proper hemostasis, and the use of short-acting combined inhalational-intravenous anesthetics.

2. Methods

This study was performed with respect to our local ethics committee and the Helsinki guidelines. We designed a randomized, single-blinded, single-center clinical trial. Patients were enrolled if they agreed with the structure of investigation based upon written informed consent. Potential hazards, probable side effects, duration and protocols of recovery, inconveniences, and benefits were also discussed orally with each participant. This clinical trial registration number in the Iranian RCT registry system is IRCT2016220031487N7 (on 14 March 2018).

We defined the eligibility criteria for patients planned to undergo elective isolated CABG, valve surgery or ASD (atrial septal defect) closure. Subjects who were 18 - 65-years-old, with normal BMI (18 - 25 kg/m^2), and LVEF > 35% entered the trial, whereas patients with COPD, emphysema, cardiogenic shock, and a history of recent myocardial infarction (last seven days) were excluded.

100 consecutive patients were randomly assigned to one of the two study arms. 50 patients were allocated to the conventional recovery and extubation plan in the ICU (control group). The on-table extubation (OTE) group (n = 50) underwent fast-track recovery protocol and tracheal extubation in OR. The patients were randomized in the two groups by using online randomization software (http://www.graphpad.com/quickcalcs/randomize2/). The patients' allocation list was referred to a third person and was concealed from the researchers.

The anesthesia technique used for the OTE group was composed of five steps: (1) premedication with oral lorazepam 1 - 2 mg the night before surgery; (2) midazolam (0.07 - 0.1 mg/kg), sufentanil (0.4 μg/kg), and Cis-atracurium (0.2 mg/kg) administration for the induction of anesthesia and muscle relaxation; (3) the maintenance of anesthesia provided by using intravenous infusion of midazolam (0.05 mg/kg/h) and sufentanil (0.15 μg/kg/h) plus isoflurane 0.5 - 1%, as needed. The bispectral index (BIS) as an indicator of anesthesia level (depth) was kept between 40 and 60. Additional propofol infusion (25 - 50 μg/kg/min) was administered during cardiopulmonary bypass (CPB) to maintain BIS between 40 and 60; (4) supplementary bolus doses (0.3 mg/kg) of atracurium given to maintain one to two twitches of the train-of-four (TOF) in nerve stimulator monitoring; and (5) atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg) used to reverse the neuromuscular block at the end of surgery. Then, we conducted a recruitment maneuver in order to prevent atelectasis. The target core temperature was 36°C or higher. Postoperative analgesia was initiated by a single IV dose of morphine (0.3 mg/kg/24 h) near the end of surgery. Finally, after adequate surgical hemostasis and closing the sternum, the surgeon and anesthesiologist decided whether to extubate the patient in the OR or not. The patients were extubated when they were adequately awake, cooperative, and hemodynamically stable (systolic blood pressure > 90 mmHg, heart rate < 110 bpm, and core body temperature > 36°C). Further necessary parameters consisted of normal respiratory status with the O_2 saturation of > 90% or PaO_2 > 70 with FiO_2 < 50% and arterial pCO_2 of less than 50 mmHg on arterial blood gas analysis, and normal sinus electrocardiographic rhythm. It was also imminent to verify that the patients were not received high levels of inotropic agents. Patient-controlled analgesia (PCA)-morphine was applied to perpetuate postoperative pain management. Then, the patients were transferred to the intensive care unit ultimately. Arterial blood gas analysis was done in both study groups to compare respiratory function immediately after the operation.

The control group of the study also had a similar premedication. Induction of anesthesia was conducted via Midazolam (0.07 - 0.1 mg/kg), sufentanil (0.7 - 0.9 μg/kg), and Cis-atracurium (0.2 mg/kg). We handled the maintenance phase using intravenous infusion of midazolam (0.1 - 0.15 mg/kg/h) to maintain BIS 40 - 60, sufentanil (0.5 μg/kg/h), and Atracurium (0.3 μg/kg/h). These patients were transferred to the ICU while intubated and without early paralysis reversal. A conventional standard extubation was carried out for hemodynamically stable, conscious, alert individuals, who obeyed the orders and had mediastinal drainage < 75 - 100 mL/h (over the last 30 min), RR < 24

rpm, core body temperature > 35°C, $PaCO_2$ < 45, PaO_2 > 70 mmHg, and SPO_2 > 95% ($FiO_2 \leq 0.6$). Postoperative PCA analgesia was provided as in the OTE group with morphine. Respiratory physiotherapy was started as soon as possible and continued according to individuals' cooperation in both study arms.

There were some principal differences regarding the use of each method. Anesthesia in the OTE group was implemented strictly according to the protocol and with lower IV drug doses as compared with the control group, while BIS was maintained between 40 and 60 by additional isoflurane (or propofol during CPB) in the OTE group. In addition, TOF nerve stimulator monitoring of muscle relaxation during operation and early reversal of neuromuscular block at the end of surgery was only planned for the OTE group. We determined primary endpoints as time variables including the success rate of extubation in the OR and the length of stay (LoS) in the intensive care unit. Secondary endpoints consisted of arterial blood gas values and hemodynamic variables during admission to ICU and residual mediastinal drainage at 24 - 48 hours.

Statistical analyses were performed using SPSS V22.0 statistical software for Windows (SPSS Inc. IBM Corp., Chicago, Illinois, USA). We compared variables between the two study groups using the non-parametric Mann-Whitney U test for continuous data without normal distribution. Thus, the median and interquartile range (Q1 - Q3) were calculated. The Chi-square test and independent samples *t*-test were used for comparing the categorical and continuous parameters in the two groups. All P values were two-tailed and a threshold of ≤ 0.05 was considered for statistical significance.

3. Results

100 patients (after initial exclusion) with male predominance (70%) were enrolled in the study. In the OTE group, we successfully extubated 48 (96%) patients. Considering a failure in the extubation of two patients in the OTE group (one patient due to delayed waking and another because of the high risk of postoperative bleeding and surgeon preference), we did the "intention to treat" statistical analyses and compared 48 extubated patients with 50 controls. Table 1 demonstrates a comprehensive list of preoperative and intraoperative characteristics of the participants. General variables of the OTE group did not differ significantly from those of the control group. Furthermore, there were no significant differences between the two groups regarding total surgery time, CPB time, and type of the procedures. However, the aortic cross-clamp time was greater during the surgery of the control group (39.62 vs. 46.58 min, P = 0.014).

We had no case of re-intubation. Likewise, major complications (including neurologic events, acute kidney injury, infections, etc.) did not occur in either of the groups. We did not observe any other major cardiac dysrhythmia. Small or mild pleural and/or pericardial effusions did not vary markedly between the study groups. The overall median (Q1 - Q3) lengths of ICU stay were 34 hours (21.5 - 44) and 48 (44 - 60) hours in the OTE and control groups, respectively.

Table 2 displays arterial blood gas and hemodynamic variables before the induction of anesthesia and after surgery during the admission to ICU. The postoperative status of OTE patients represented somehow lower peripheral O_2 saturation and greater $PaCO_2$ and base excess compared to the control group although all of them were within the normal physiologic values. Blood pressure was comparable in both groups but the control group had a slightly higher heart rate at admission to the ICU (89.4 $\pm$ 13.1 vs. 97.6 $\pm$ 12.0 bpm; P = 0.008, Table 2).

The frequency and total dose of inotropic agents were unremarkable and similar in both groups. We found that the need for blood supplements did not differ between the OTE and control groups. We had four patients in the OTE group and two in the control group who required intraoperative packed RBC transfusion. Nevertheless, no significant difference was detected in terms of total amounts of FFP and platelet concentrates. Table 3 represents the results of primary endpoints and some secondary outcomes for both study groups. Mediastinal drainage was substantially greater in the control group in the first postoperative day. However, this difference diminished in the second postoperative day.

4. Discussion

Multiple avenues of research and an increasing number of papers have affirmed the evidence-based utility of fast track extubation (10, 11). However, the cornerstone of this concept is based upon the appropriate case selection. Although essential advances have occurred in cardiac surgery anesthesia and surgical techniques, the feasibility of early extubation has remained limited to elective patients yet. In addition, we have still multiple controversial problems to deal with. Heterogeneity of pre- and intraoperative risk factors for complicated early extubation or predictors of prolonged mechanical ventilation are in this list (12).

The present study designed a new integrated structural method to extubate patients in the operating room (OR). Utilizing a low-dose anesthesia and following early cessation method joined with rapid reversal of muscle paralysis and focused monitoring were mainstays of the

Table 1. Baseline and Clinical Characteristics of the Study Participants

Variables	On-table Extubation Group (N = 48)	Delayed Extubation Group (N = 50)	P Value
Age (y)	49.26 ± 13.26	53.27 ± 11.05	0.112
Sex (male, %)	35 (72.9%)	35 (70%)	0.961
Height (cm)	164.87 ± 25.48	169.68 ± 8.48	0.215
Weight (kg)	73.56 ± 12.28	76.60 ± 13.11	0.234
Preoperative LVEF	43.28 ± 17.06	45.20 ± 8.53	0.504
Cigarette smoking	7 (14.6%)	7 (14.0%)	0.968
Diabetes mellitus	12 (25.0%)	11 (22.0%)	0.933
Hypertension	26 (52%)	23 (46%)	0.689
Preoperative medications			
Nitrates	23 (47.9%)	20 (40%)	0.686
Beta blockers	33 (68.8%)	31 (62%)	0.835
ACE inhibitors	19 (3935%)	27 (54%)	0.160
Steroids	5 (104%)	2 (4%)	0.056
Aspirin	33 (68.8%)	39 (78%)	0.210
Statins	20 (41.7%)	31 (62%)	0.054
Clopidogrel	5 (10.4%)	5 (10.0%)	0.971
Type of surgery			0.976
CABG	40	39	
AVR	5	6	
MVR	1	3	
ASD closure	2	2	
Average time of surgery (h)	4.24 ± 0.77	4.20 ± 0.76	0.820
Cardiopulmonary bypass time (min)	57.04 ± 23.05	54.97 ± 32.20	0.736
Aortic cross clamp time (min)	39.62 ± 13.79	46.58 ± 12.48	0.014

Abbreviations: ACE, angiotensin-converting enzyme; ASD, arterial septal defect; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MVR, mitral valve replacement.

intervention. Short-acting opioid concept and the criteria for extubation were similar (although not entirely) between the two groups (13, 14). The remifentanil is a short-acting opioid that is suitable for fast-track anesthesia. However, regarding the researchers' personal experience to use sufentanil in fast-track cardiac anesthesia for many years, we preferred to continue the use of sufentanil for on-table extubation protocol. Several reports (e.g. by Hantschel et al.) have shown the cost-effectiveness of this approach (15, 16). Zhu et al. demonstrated that low-dose opioid anesthesia and early extubation approach reduce the ventilation time by 7.40 hours (17).

Our results in primary endpoints were in line with the findings of some investigations (18-20). Wong et al. conducted a Cochrane review of these outcomes. They demonstrated the declined mean length of intensive care unit stay. The mean duration of hospital stay was 0.44 days lower in the intervention groups than in the control groups (5.1 - 13 days, analysis of eight RCTs). Their review declared that most of the studies (except two) showed a similar length of hospital stay between the groups. Their pooled analysis revealed no significant difference in the comparison of low and high-dose opioid groups (20).

Few recent studies declared that early extubation (< 6 h) appears to have mixed results including decreased ventilation time (7.4 to 5.73 h, $P < 0.001$) without reducing ICU or hospital stays. They did not use any post-anesthetic care units and applied different exclusion criteria preoperatively (21, 22).

The aortic cross-clamp time was seven minutes longer in the control group than in the OTE group (39.6 vs. 46.6 min). However, the CPB times were identical. Prolonged CPB and aortic clamp times contributed to adverse outcomes such as stroke, early extubation failure, and ex-

Table 2. Hemodynamic and Blood Gas Parameters Before Anesthesia and at Admission to ICU

Variables	On-table Extubation Group (N = 48)[a]	Delayed Extubation Group (N = 50)[a]	P Value
PaO_2, (mmHg)[b]	101.53 ± 65.38	84.75 ± 29.25	0.087
PaO_2 (mmHg)[c]	89.94 ± 55.60	105.08 ± 46.06	0.151
Peripheral O_2 saturation (%)[b]	92.97 ± 4.33	93.68 ± 5.08	0.788
Peripheral O_2 saturation (%)[c]	94.02 ± 5.53	96.88 ±2.20	0.017
$PaCO_2$ (mmHg)[b]	32.55 ± 6.77	30.95 ± 4.10	0.174
$PaCO_2$ (mmHg)[c]	42.88 ± 6.82	33.18 ± 5.93	0.001
HCO_3^- (mmol)[b]	20.68 ± 3.07	20.66 ± 2.34	0.983
HCO_3^- (mmol)[c]	22.33 ± 6.07	21.14 ± 3.59	0.251
Base excess (mmol)[b]	-1.58 ± 2.20	-1.42 ± 2.46	0.749
Base excess (mmol)[c]	-4.38 ± 2.85	-2.45 ± 3.16	0.003
Lactate (mg/dL)[b]	1.00 ± 0.40	00.78 ± 00.67	0.468
Lactate (mg/dL)[c]	1.26 ± 1.24	0.40 ± 0.56	0.354
Mean SBP at ICU admission (mmHg)	105.25 ± 25.21	109.4 ± 20.13	0.456
Mean DBP at ICU admission (mmHg)	60.17 ± 15.75	62.20 ± 17.70	0.618
Mean HR at ICU admission (bpm)	89.36 ± 13.13	97.62 ± 12.04	0.008

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Values are presented as mean ± SD.
[b]Refers to the pre-anesthesia state.
[c]Refers to at ICU admission.

Table 3. Comparison of Anesthetics Doses and Some ICU Variables Between the Two Groups

Variables	On-table Extubation Group (N = 48)	Delayed Extubation Group (N = 50)	P Value
Total dose of anaesthetics			
Midazolam (mg)	10.10 ± 3.23	29.38 ± 5.92	0.001
Propofol (mg)[a]	118.4 ± 23.6	-	-
Sufentanil (μg)	43.46 ± 31.16	107.34 ± 53.60	0.001
Atracurium (mg)	67.6 ± 43.9	120.9 ± 51.9	0.001
IABP	0	1 (2%)	0.642
First Post-op. day drainage (mL)	243.5 ± 137.9	551.8 ± 326.1	0.001
Second post-op. day drainage (mL)	161.6 ± 152.8	188.7 ± 171.2	0.524
ICU stay time (h)[b]	34 (21.5 - 44)	48 (44 - 60)	0.001

Abbreviation: IABP, intra-aortic Balloon Pump.
[a]Administered only in the on-table extubation group for maintaining BIS between 40 and 60 during CPB.
[b]Expressed as median (interquartile range).

tended LOS in the ICU (23-25). Kianfar et al. demonstrated that ultra-fast track extubation (inside the operating room) was correlated with lower ventilation time and reduced length of ICU stay (4.2 vs. 1.72 days, P = 0.02 for the latter) among heart transplant surgery patients. Cardiopulmonary bypass time was 136.8 ± 25.7 minutes in the FTE and 145.3 ± 29.8 in the delayed extubation groups (P > 0.05), which was similar to our results (26). In another study, CPB and cross-clamp times did not increase the risk of delayed extubation (27). The frequency of intra-aortic balloon pump, inotropic support (secondary to low cardiac output), excessive bleeding, and arrhythmia was similar in both groups, each of which could delay extubation. It reflected the homogeneous case selection and equivalent secondary outcomes (post-operative complications) (28, 29).

Mutsuga et al. divided the patients undergoing a modified Fontan procedure into three categories. Group A was

extubated in the OR. Group B and C were referred to extubation in ICU within 24 hours and delayed extubation, respectively. Patients in the FTE group A had a greater base excess (BE: 0.4 vs. -1.3 vs. -3.4, P < 0.001) and a lower inotrope score (4.6 vs. 6.7 vs. 10.8, P < 0.001). The median length of ICU admission and hospital stay was shorter in the FTE group (2 vs. 3 vs. 6 nights, P = 0.01 and 9 vs. 11 vs. 21 days, P = 0.001, respectively). Similar results obtained by their research and the present study pertain to higher BE and LoS (30).

Salah found that a conventional extubation resulted in the lower pH and higher PCO_2 compared with the FTE group while PO_2 and HCO_3 levels were identical. Contrary to our results, CPB, aortic cross-clamp, and surgery times were significantly longer in the conventional protocol (31). Most studies declared no discernible variation between FTE and conventional approaches with respect to the mean arterial pressure (MAP), heart rate (HR), pH, PCO_2, and oxygenation status (24, 32). We found mild respiratory acidosis and lower O_2 saturation among OTE patients post-operatively although these parameters tended toward normalization after using supplemental oxygen. Although some authors have mentioned pH as a risk indicator for intra-operative mortality, morbidity (33), and extubation failure, much research claimed that mild to moderate acidosis is not a contraindication for FTE (34). Multiple studies demonstrated benefits of FTE regarding lower inotropic demands (20, 29, 35). Inotrope supply reflects the severity of low cardiac output state especially in a subset of patients with diminished preoperative ejection fraction (EF). Potential mechanisms through which early extubation concept works to improve hemodynamic state have been addressed elsewhere (7, 36). Hence, low-dose and short-acting anesthesia permits FTE, which subsequently results in rapid recovery and lower consumption of analgesics (19).

A wide range of FTE failure in previous publications (5 - 49%) underlines variations in the definition of this approach in addition to protocols and patient selection (29, 37-39). Two patients (4%) in the FTE group did not fulfill the criteria for extubation in the OR; however, both of them were extubated below eight hours. The improvements of FTE practice highlight the role of multidisciplinary approach (11), the better physician-to-patient ratio (20), low-dose anesthesia (40), specialized intensive care units (4), rewarming, rapid paralysis reversal, and adequate but limited postoperative analgesia (7, 11, 14). Zarbock et al. stated that using NIV (41). Another reason that favors the FTE method is the great adherence to a predefined protocol. The close involvement of intensivist, anesthesiologist, and trained nurses in this approach leads to shortened extubation time (14, 42, 43).

Badhwar et al. extubated 165 out of 652 cardiac surgery patients of various types in the operating room and concluded that on-table extubation after adult cardiac surgery is safe and results in better outcomes and less cost (44).

4.1. Limitations

The present study faced some limitations. First, we had a male predominance in the sample (70 %), which reflects the demographic properties of cardiovascular disease epidemiology. Although some papers have considered female gender as an independent risk factor for prolonged intubation, we are able to apply the results to female patients (45). Another limitation is excluding overweight and obese individuals in whom early extubation has a greater risk of failure. We cannot also extrapolate the results to patients with severe LV dysfunction (EF < 35%), underlying respiratory diseases (esp. COPD), urgent surgeries, early post-MI state (< 7 days), and the elderly (> 65 y). Moreover, the study was not powered enough to reveal potential adverse events and mortality but these outcomes have been determined previously (17, 21).

4.2. Conclusions

On-table extubation in the OR after cardiac surgery as discussed earlier is a new standardized recovery concept. Novel anesthesia protocols include a relatively lower dose of induction and maintenance, short-acting drugs (especially opioids, sufentanil in this study), early reversal techniques (removing muscle relaxation and fast awakening), and maintenance of adequate anesthesia depth (using BIS monitoring). We executed a precise control to gain optimal postoperative analgesia accompanied by respiratory rehabilitation. Therefore, successful on-table extubation in the OR in our study was attributable to these factors along with accurate hemodynamic monitoring and appropriate patient selection (noncomplex cardiac surgery). An outstanding feature of the trial was the recruitment of a multidisciplinary expert team to conduct the procedures and watchful monitoring. Hence, we found that early extubation from mechanical ventilation reduces the time of ICU stay.

Footnote

Authors' Contribution: Ziae Totonchi: Research conduction anesthetic management manuscript writing; Rasoul Azarfarin: Research conduction anesthetic management manuscript writing; Louise Jafari: Data collection anesthetic management; Alireza Alizadeh Ghavidel: Perform

surgery; Bahador Baharestani: Perform surgery; Azin Alizadehasl: Research design, manuscript writing and submission; Farideh Mohammadi Alasti: Data collection anesthetic management; Mohammad Hassan Ghaffarinejad: Perform surgery.

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