A RANDOMIZED STUDY OF THE INFLUENCE OF PERFUSION TECHNIQUE AND pH MANAGEMENT STRATEGY IN 316 PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

I. Mortality and cardiovascular morbidity

The impact of perfusion technique and mode of pH management during cardiopulmonary bypass has not been well characterized with respect to postoperative cardiovascular outcome. *Methods:* This double-blind, randomized study comparing outcomes after alpha-stat or pH-stat management and pulsatile or nonpulsatile perfusion during moderate hypothermic cardiopulmonary bypass was undertaken in 316 patients undergoing coronary artery bypass operations. *Results:* Cardiovascular morbidity and mortality were not affected by pH management, and the incidence of stroke (2.5%) did not differ between groups. Overall in-hospital mortality was 2.8%, eight of the nine deaths occurring in the nonpulsatile group (5.1% versus 0.6%; $p = 0.018$). The incidence of myocardial infarction was 5.7% in the nonpulsatile group and 0.6% in the pulsatile group ($p = 0.010$), and use of intraaortic balloon pulsation was significantly more common in the nonpulsatile group (7.0% versus 1.9%; $p = 0.029$). The overall percentage of patients having major complications was also significantly higher in the nonpulsatile group (15.2% versus 5.7%; $p = 0.006$). Duration of cardiopulmonary bypass, age, and use of nonpulsatile perfusion all correlated significantly with adverse outcome. *Conclusions:* Use of pulsatile perfusion during cardiopulmonary bypass was associated with decreased incidences of myocardial infarction, death, and major complications. (J THORAC CARDIOVASC SURG 1995;110:340-8)

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Optimal perfusion characteristics during cardiopulmonary bypass (CPB) remain controversial.^{1,2} The use of pulsatile perfusion has been variously demonstrated to improve myocardial perfusion,^{3,4} oxygenation,⁴⁻⁶ compliance, and indices of contractility,^{7,8} as well as to lower plasma catechol-

amine levels,^{9,10} renin activity,¹¹ angiotensin, aldosterone,¹² and lactate¹³ levels, and to provide better preservation of pituitary responsiveness.^{14,15}

Many clinical studies have also demonstrated improved myocardial function and lower morbidity and mortality after pulsatile compared with nonpulsatile perfusion during CPB.^{9,16-19} In contradistinction, however, a seemingly equal number of clinical studies have been unable to detect benefit associated with pulsatile perfusion.²⁰⁻²⁶

Ideal pH management during moderate hypothermia for CPB has also been the subject of contention. Several studies have assessed the influence of pH management on brain and heart function, and most have demonstrated relative improvements with alpha-stat in comparison with pH-stat management.²⁷⁻²⁹ Some animal studies have also shown improved myocardial performance and an elevated fibrillation threshold with alpha-stat management,^{27,28,30,31} whereas others have been unable to detect differences in the functional capacity of the myocardium whether the blood perfusate was controlled by means of either alpha-stat or pH-stat management strategies.³²

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Prospective, randomized outcome studies assessing the differential impact of perfusion technique or pH management strategy on mortality and cardiovascular morbidity have been conducted. However, few have used sufficiently large sample sizes to demonstrate possible outcome benefit for such low base rate events as death and myocardial infarction (MI). In most cardiac centers, use of nonpulsatile perfusion during CPB continues to be routine, although use of alpha-stat pH management has been increasing over the past decade. We therefore undertook a prospective, randomized, double-blind study in 316 patients undergoing coronary artery bypass (CAB) operations to assess differences in clinical outcome after use of pulsatile or nonpulsatile CPB and alpha-stat or pH-stat pH management strategies.

Methods

This prospective, double-blind, clinical trial, randomized with respect to pH management and perfusion technique, was conducted as a part of a study assessing neurologic and cognitive outcomes in patients having cardiac operations.³³

Study population. After institutional review board approval and written informed patient consent were obtained, 316 patients undergoing hypothermic CPB for CAB (excluding concomitant open chamber procedures) were enrolled in this study. To account for differences in surgical technique, randomization was stratified by surgeon (four surgeons) and patients were randomly assigned to undergo either pulsatile or nonpulsatile perfusion and alpha-stat or pH-stat pH management.

Outcome measures. Each patient was assessed before and after the operation by a blinded research nurse, while an independent study technician obtained intraoperative hemodynamic data. Mortality and major complications, including MI, cerebrovascular accident (CVA), arrhythmia, use of an intraaortic balloon pump (IABP), and renal impairment, were recorded before the operation for each patient. Arrhythmia was defined as onset of atrial or ventricular arrhythmias necessitating cardioversion or institution of specific antiarrhythmic therapy in the postoperative period. CVA was diagnosed on the basis of clinical presentation and either confirmatory brain imaging or postmortem evidence of cerebral infarction. MI was diagnosed on the basis of development of new Q waves on the electrocardiogram and an elevation of creatinine kinase myocardial band levels greater than 10% of total creatine kinase. MI data do not include patients dying during the operation, in whom such data could not be obtained, although these latter patients were included in mortality statistics. IABP use was defined as successful insertion of the IABP. Renal impairment was defined as elevations of creatinine concentration 50% above the upper limit of laboratory reference normal values.

CPB. Routine monitoring, including radial and pulmonary artery cannulation, and high-dose opioid anesthesia,

supplemented as necessary with volatile anesthetics, were used similarly in all groups. After sternotomy and heparinization, moderate systemic hypothermia (nasopharyngeal temperature 26° to 28° C) with a hollow-fiber membrane oxygenator (Cobe CML, Cobe Stockert Inc., Lakewood, Colo.; Terumo Capiro E, Terumo Corp., Tokyo, Japan) having a 40 μ m arterial line filter and nonocclusive roller pump, was used for CPB in all patients. Flows of 2.0 to 2.5 L·min⁻¹·m⁻² were used. Crystalloid cardioplegia was used by two surgeons, the other two used a 4:1 blood/crystalloid cardioplegic mixture, and all surgeons used topical cooling with saline slush. Ventricular venting was either through the ascending aorta or the pulmonary vein. After completion of all distal coronary anastomoses, the crossclamp was released, rewarming commenced, and proximal graft anastomoses performed by means of side-clamping of the aorta.

In the pulsatile group a pump flow interrupter (Pulsatile Flow Controller II, Cobe Stockert Inc.), initially set at rate of 65 cps with an ejection time of 65% of cycle time, was used from placement of the aortic crossclamp until commencement of ventricular ejection after rewarming. Analog displays of pulse pressure and mean arterial pressure were recorded continuously and analyzed specifically after 10, 30, and 60 minutes of hypothermic CPB, at commencement of rewarming, and after rewarming was completed (i.e., rectal temperature at or above 34° C). Hemodynamic data during hypothermia are reported as the means of all specific time point values during stable hypothermia. Values for normothermia were based on those obtained after completion of rewarming.

Arterial blood gas analysis was performed with a Radiometer ABL2 analyzer (Radiometer Als, Copenhagen, Denmark). For alpha-stat management during CPB, arterial blood gas was measured at 37° C and carbon dioxide was adjusted to produce an arterial carbon dioxide tension of 40 mm Hg and an arterial pH of 7.4. For pH-stat management, arterial blood gas was measured at 37° C and corrected to the patient's nasopharyngeal temperature with exogenous carbon dioxide adjusted to maintain a temperature-corrected arterial carbon dioxide tension of 40 mm Hg and a temperature-corrected arterial pH of 7.4. During CPB, intermittent blood gas analyses, based on samples drawn at intervals corresponding to the specific time points for hemodynamic measurements, were used to maintain either temperature corrected (pH-stat management) or non-temperature corrected (alpha-stat management) arterial pH 7.4 and arterial carbon dioxide tension 40 mm Hg. Simultaneously with arterial blood gas sampling, blood was obtained for glucose and hemoglobin measurements.

Statistical analysis. Log-linear model analysis was first performed to ensure that no interaction existed between pH management, perfusion technique, and outcome events. Outcome events were compared between treatment groups by the χ^2 test. Fisher's two-tailed exact test was used if the expected cell sizes were small. Demographic characteristics were assessed similarly for categorical variables. Two-way factorial analysis of variance was used to examine continuous variables and to confirm that pH management did not interact with perfusion tech-

Table I. CAB group demographics (numbers of patients, or mean $\pm$ standard deviation)

	Alpha-stat		pH-stat		CAB total (n = 316)
	Pulsatile (n = 79)	Nonpulsatile (n = 79)	Pulsatile (n = 79)	Nonpulsatile (n = 79)	
Age (yr)	60.9 $\pm$ 8.7	61.2 $\pm$ 7.8	60.2 $\pm$ 8.5	61.4 $\pm$ 8.4	60.9 $\pm$ 8.3
Gender (M/F)	66/13	65/14	70/9	63/16	264/52
CVA/TIA	8	11	9	4	32 (10%)
DM	20	17	8	13	58 (18%)
MI <1/12	9	9	9	6	33 (10%)
Prev. CAB	4	9	8	7	28 (9%)
LVEF <50%	23	23	29	22	97 (31%)
LVEF <35%	5	6	4	2	17 (5%)

CVA/TIA, History of cerebrovascular accident or transient ischemic attack; DM, diabetes mellitus; MI <1/12, myocardial infarction in previous month; Prev. CAB, previous coronary bypass surgery; LVEF <50%, LVEF <35%, patients with left ventricular ejection fraction less than 50% or 35%.

Table II. Distribution and intraoperative characteristics by CAB group (numbers of patients, or mean $\pm$ standard deviation)

	Alpha-stat		pH-stat		CAB total (n = 316)
	Pulsatile (n = 79)	Nonpulsatile (n = 79)	Pulsatile (n = 79)	Nonpulsatile (n = 79)	
Surgeon 1	22	24	24	24	94
Surgeon 2	26	25	22	26	99
Surgeon 3	5	6	6	4	21
Surgeon 4	26	24	27	25	102
NPT ($^{\circ}$ C)	28.5 $\pm$ 2.1	28.5 $\pm$ 1.2	28.5 $\pm$ 2.0	28.2 $\pm$ 1.2	28.4 $\pm$ 1.7
Hgb (gm/L)	78.4 $\pm$ 18.4	78.9 $\pm$ 11.5	81.5 $\pm$ 14.5	78.4 $\pm$ 12.3	79.3 $\pm$ 14
Glu (mmol/dl)	10.6 $\pm$ 3.5	11.3 $\pm$ 3.0	10.4 $\pm$ 3.1	10.4 $\pm$ 3.0	10.7 $\pm$ 3.1
CAB	2.9 $\pm$ 0.6	2.9 $\pm$ 0.8	3.0 $\pm$ 0.8	3.0 $\pm$ 0.8	3.0 $\pm$ 0.7
CAB >4	10	16	22	17	65 (21%)
AoXC (min)	43.9 $\pm$ 17.4	44.1 $\pm$ 18.1	47.8 $\pm$ 17.2	46.9 $\pm$ 15.5	45.7 $\pm$ 17
CPB (min)	92.1 $\pm$ 29.1	95.1 $\pm$ 29.1	98.5 $\pm$ 36.7	98.6 $\pm$ 32.6	96.1 $\pm$ 32
OR (min)	271 $\pm$ 48	280 $\pm$ 76	279 $\pm$ 59	282 $\pm$ 57	278 $\pm$ 61
Hosp (days)	13.4 $\pm$ 10.8	12.2 $\pm$ 5.1	14.8 $\pm$ 24.8	12.9 $\pm$ 11.1	13.3 $\pm$ 15

Surgeon N, Number of patients in each group operated on by individual surgeon; NPT, mean nasopharyngeal temperature during hypothermic CPB; Hgb, lowest mean hemoglobin concentration during hypothermic CPB; Glu, highest mean glucose values during hypothermic CPB; CAB, mean number of coronary bypass grafts; CAB >4, patients having four or more coronary bypass grafts; AoXC, aortic crossclamp time; CPB, duration of cardiopulmonary bypass; OR, duration of operation; Hosp, operation to discharge time with in-hospital deaths excluded.

nique. No adjustments were made for multiple comparisons. Logistic regression analysis was applied to examine potential risk factors for adverse outcomes.

Results

Characteristics of patients. Demographic and clinical characteristics of the 316 patients in the study are shown in Table I. Table II shows distribution of patients into study group according to surgeon and intraoperative and postoperative values. No significant differences were identified between groups in any parameters including demographics, CPB duration, ischemic time, ventricular function, or numbers of coronary vessels bypassed.

Alpha-stat versus pH-stat groups. For pH management groups, intended treatments during CPB were achieved such that there was a significant difference in arterial pH of 0.11 ± 0.18 pH units and of arterial carbon dioxide tension of 20.6 ± 7.8 mm Hg between alpha-stat and pH-stat groups during hypothermic CPB (Table III).

Pulsatile versus nonpulsatile groups. During hypothermia, mean arterial pressure was similar between the two groups. Pulsatile perfusion was associated with a significantly greater pulse pressure, averaging 14.8 ± 6.7 mm Hg higher during hypothermic CPB and 6.8 ± 14 mm Hg higher during normothermic CPB than in the nonpulsatile group (see Table III). During CPB there were no differ-

Table III. Perfusion characteristics by CAB group (mean $\pm$ standard deviation)

CAB total (n = 316)	Alpha-stat		pH-stat	
	Pulsatile (n = 79)	Nonpulsatile (n = 79)	Pulsatile (n = 79)	Nonpulsatile (n = 79)
PP-C (mm Hg)	16.9 $\pm$ 6.1*	1.8 $\pm$ 2.4	15.5 $\pm$ 6.8*	1.6 $\pm$ 2.4
PP-NT (mm Hg)	11.1 $\pm$ 9.9*	5.5 $\pm$ 12.6	12.0 $\pm$ 9.3*	4.1 $\pm$ 7.3
MABP (mm Hg)	57.9 $\pm$ 12.3	61.0 $\pm$ 11.3	57.2 $\pm$ 10.1	57.6 $\pm$ 11.9
pHa†	7.42 $\pm$ 0.18‡	7.43 $\pm$ 0.12‡	7.54 $\pm$ 0.13	7.54 $\pm$ 0.06
Paco ₂ (mm Hg)†	38.1 $\pm$ 4.1‡	37.5 $\pm$ 4.1‡	57.5 $\pm$ 6.9	59.3 $\pm$ 6.4

PP-C, Mean pulse pressure during hypothermic CPB; PP-NT, pulse pressure during normothermic CPB; MABP, lowest mean arterial blood pressure during hypothermic CPB; pHa, arterial pH; Paco₂, arterial carbon dioxide tension.

* $p < 0.001$ versus nonpulsatile.

†Mean of all values as measured at 37° C during hypothermic CPB.

‡ $p = 0.001$ versus pH-stat.

ences in urine output between pulsatile or nonpulsatile groups (367 $\pm$ 346 ml versus 378 $\pm$ 358 ml, respectively), consistent with what we had observed in a subset of 100 of these patients in whom fractional excretion of sodium and potassium, as well as renal failure index, did not differ between perfusion groups.³⁴

Surgical morbidity and mortality. Data on cardiovascular and other major complications were assessed and patients with major complications are listed individually in Table IV. There was no difference in cardiovascular outcomes related to pH management (e.g., mortality 3/158 versus 6/158; MI 3/158 versus 7/158; alpha-stat versus pH-stat, respectively). A significant difference in cardiovascular outcomes was observed that strongly favored pulsatile perfusion, however. In the nonpulsatile group there were significantly higher rates of mortality (8/158 versus 1/158, $p = 0.018$), MI (9/158 versus 1/158, $p = 0.010$), and IABP use (11/158 versus 3/158, $p = 0.029$) than in the pulsatile group. These factors contributed toward a decreased overall incidence of major complications in the pulsatile group (24/158 versus 9/158, $p = 0.006$). The percentage of patients who died or had major complications, broken down by perfusion technique, is presented in Fig. 1. To assess the effect of patients with complications disproportionately influencing morbidity data, we undertook a repeat analysis of complications involving only surviving patients. A trend ($p = 0.062$) for fewer MIs in the pulsatile group persisted (1/157 versus 6/150, respectively). Of the patients who died, three died during the operation of cardiac failure, three died within 14 days after the operation of MI with irreversible low output state, one of whom also had a CVA, two died within 5 days of a

CVA with irreversible brain injury, and one patient died 4 months after the operation of multisystem failure.

Cardiovascular risk factors. Univariate logistic regression was used to determine the relationship between the presence of adverse outcomes, defined as death, MI, arrhythmia, or IABP insertion, and potential risk factors, identified as insulin-dependent diabetes mellitus, MI within the previous month, gender, left ventricular ejection fraction less than 0.5, left ventricular ejection fraction less than 0.35, number of coronary arteries grafted, perfusion technique, pH management strategy, cardioplegia type (blood or crystalloid), cardioplegia volume, age, duration of crossclamping, and duration of CPB. Significant correlations were found for use of nonpulsatile perfusion ($p = 0.0082$), age ($p = 0.0211$), and CPB duration ($p = 0.0006$). When examined multivariately, these factors remained significant risk factors ($p = 0.0106$, $p = 0.0223$, and $p = 0.0003$, respectively) for adverse outcome. The other factors listed did not correlate with adverse outcome. Although cardioplegia type did not correlate with adverse outcome, surgeons using crystalloid cardioplegia completed more CAB grafts (3.1 $\pm$ 0.8 versus 2.8 $\pm$ 0.6, respectively; $p = 0.001$) with shorter crossclamp times (41.5 $\pm$ 14.1 minutes versus 59.3 $\pm$ 13.3 minutes, respectively; $p < 0.001$) than those using blood cardioplegia.

Discussion

The current study demonstrated significantly lower incidences of mortality and cardiovascular morbidity in patients undergoing pulsatile CPB but no detectable influence of pH management strategy on these outcome variables. The overall incidences

Table IV. Individual mortality and major morbidity for pulsatile versus nonpulsatile CPB

Patient	Death	MI	Arrhythmia	CVA	IABP	Renal
<i>Nonpulsatile CPB (n = 158)</i>						
1		X	X			X
2		X				
3		X				
4		X				
5		X	X		X	
6		X			X	X
7	X	X			X	
8	X	X			X	X
9	X	X	X	X	X	
10	X			X		
11	X				X	
12	X				X	
13	X			X		
14	X				X	
15				X		
16						
17			X			
18			X			
19			X			
20			X			
21			X			
22			X			
23					X	X
24					X	
<i>Pulsatile CPB (n = 158)</i>						
1				X	X	
2				X		
3				X		
4				X	X	
5		X	X			
6			X		X	X
7						
8			X			
9	X		X			
<i>p</i> = 0.006*	<i>p</i> = 0.018	<i>p</i> = 0.010	<i>p</i> = 0.157	<i>p</i> = 1.0	<i>p</i> = 0.029	<i>p</i> = 0.371

The incidence of death, myocardial infarction (MI), postoperative arrhythmia necessitating treatment, cerebrovascular accident (CVA), use of intraaortic balloon pump (IABP), and renal insufficiency for those patients undergoing pulsatile versus nonpulsatile perfusion during cardiopulmonary bypass (CPB). The *p* values comparing incidences of complications between the two groups are along the bottom of the table.

*This value refers to the relative incidences of any complications in the two groups.

of MI (3.2%), IABP use (4.4%), CVA (2.5%), and mortality (2.8%) reported in the current study are consistent with results reported in the literature. In a recent survey of 1513 patients undergoing CAB, MI occurred in 5.5%, 4.7% required IABP, CVA occurred in 2.8%, and overall mortality rate was 3.1%.³⁵

pH management. Two divergent strategies for pH management have generally been used clinically: (1) pH-stat—addition of exogenous carbon dioxide to the oxygenator to achieve a temperature-corrected arterial pH of 7.4 and an arterial carbon dioxide tension of 40 mm Hg; (2) alpha-stat—

during which total carbon dioxide is kept constant and pH and arterial carbon dioxide tension vary with body temperature.²⁹

In the current study, we did not find any influence of mode of pH management on cardiovascular morbidity or mortality. This observation likely reflects both the relatively insensitive clinical end points used (e.g., MI and IABP use) and, more fundamentally, the fact that the heart is not perfused and is effectively excluded from the systemic circulation (and thus largely uninfluenced by mode of pH management) during hypothermia by virtue of the aortic crossclamp. Rewarming, and thus conver-

Fig. 1. The incidence of death, MI, postoperative arrhythmia necessitating treatment, CVA, and use of IABP for those patients undergoing pulsatile versus nonpulsatile perfusion during CPB.

gence of both alpha-stat and pH-stat strategies, generally commences during performance of the last of the distal coronary anastomoses, while the heart is still isolated from systemic perfusion.

Pulsatile perfusion. The current study documented markedly lower mortality in patients undergoing pulsatile CPB. Although nonfatal adverse outcomes (e.g., MI, IABP) and mortality overlapped, analysis of data from surviving patients still demonstrated a trend for a higher incidence of MI in the nonpulsatile group (6/150 versus 1/157). Reasons for these differences in outcome remain speculative. They are unlikely to reflect differences in surgical technique, because stratification by surgeon ensured that the number of patients in both pulsatile and nonpulsatile groups was balanced between surgeons. Assignment into pulsatile or nonpulsatile groups was also undertaken in a blinded fashion, and there was no subsequent crossover during the operations. Disproportionate weighting of patients at higher risk into one group or the other is thus unlikely, although no attempt was made preoperatively to stratify patients into treatment groups according to cardiovascular or other risk factors. Review of patient characteristics (see Tables I and II) confirms the randomization process and does not

reveal any significant differences in preoperative risk factors.

To date only two other large-scale studies assessing cardiovascular outcomes after pulsatile or nonpulsatile CPB have been presented, and they have similarly reported salutary effects of pulsatile perfusion. Significantly decreased mortality rates with pulsatile perfusion were reported by Taylor and associates¹⁸ in a series of 350 patients with cardiac disease randomized to pulsatile or nonpulsatile perfusion; Taylor's group used a roller-pump system similar to the one we employed. In that series significantly lower requirements for postoperative circulatory support modalities were demonstrated, and mortality from low-output cardiogenic shock was significantly decreased from 6.3% to 1.1%. More recently, Minami and coworkers¹⁹ reported that in a retrospective comparison of 175 patients undergoing CPB for greater than 120 minutes, pulsatile perfusion decreased the incidence of cardiovascular morbidity, although overall mortality was not affected.

The mechanism responsible for the decreased incidence of cardiovascular complications remains speculative. However, it is possible that during the early reperfusion phase reductions in neurohumoral

stress responses and improvements in myocardial contractility and subendocardial blood flow are contributory.^{3, 4, 7-10}

In fibrillating hearts, increased myocardial oxygen and lactate extraction, improved subendocardial blood flow,^{3, 4, 36-38} and increased diastolic compliance⁴ have been observed with pulsatile perfusion. Clinical studies also demonstrated increased ejection fractions, lower incidences of MI, and increased coronary graft blood flow.^{16, 17, 39} In the presence of acute coronary stenoses, pulsatile perfusion is associated with higher oxygen tension, lower tissue carbon dioxide tension, and greater subendocardial blood flow.^{5, 38} A recent study of dogs with coronary artery ligation and profound heart failure has confirmed increased coronary blood flow and an improved ratio of diastolic time index/tension time index with pulsatile as compared with nonpulsatile perfusion for left ventricular bypass.⁴⁰ Lower levels of thromboxane and increased concentrations of prostacyclin, changes favoring coronary vasodilatation and augmented myocardial blood flow, have also been demonstrated with pulsatile perfusion.⁴¹

However, other studies have been unable to demonstrate any significant influence of perfusion technique.²¹⁻²⁶ Overall, benefit does appear to be more likely at lower rather than higher perfusion flow rates,² in fibrillating rather than beating hearts,^{3, 4, 6} and in the presence of global ischemia,⁸ ventricular hypertrophy,⁷ and acute⁵ rather than chronic⁴² ischemia.

Whether any of these experimental conditions are directly comparable to the clinical situation encountered during CAB operations, given that the heart is isolated and nonperfused for over half the duration of CPB, is unclear. It is apparent that pulsatile perfusion can significantly increase subendocardial myocardial perfusion during ventricular fibrillation, particularly in the presence of coronary stenoses. It can also enhance subsequent load-dependent performance. In clinical practice the heart is often nonbeating or fibrillating for a variable period after removal of the aortic cross-clamp, during which time the proximal graft anastomoses are being made. During this critical postischemic reperfusion phase, it may be that improved subendocardial perfusion, in conjunction with increased prostacyclin and decreased catecholamine levels, may be factors in the im-

proved clinical cardiovascular outcomes demonstrated with pulsatile flow.

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