European Journal of Surgical Oncology 45 (2019) 2451–2456

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

# CPET and cardioesophagectomy: A single centre 10-year experience

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ARTICLE INFO

*Article history:*
Received 10 January 2019
Received in revised form
10 May 2019
Accepted 7 June 2019
Available online 8 June 2019

*Keywords:*
CPET
Cardiopulmonary exercise testing
Cardioesophagectomy
Pre-operative assessment
Cardiac ischaemia

ABSTRACT

*Introduction:* CPET is a routine investigation prior to cardioesophagectomy. Over a 10-year period 200 patients had CPET before elective cardioesophagectomy. We examine the relationship between CPET and outcomes in these patients.

*Materials and methods:* Complication data were prospectively collected using the Clavien-Dindo system. Logistic regression analysis was used to determine whether 90-day mortality and morbidity were significantly different between fitter and less fit patients.

*Results:* 90-day mortality was 5.5%. In univariate analysis the following factors were associated with a significantly increased risk of death at 90 days: anaerobic threshold $<11\ ml\ kg^{-1}\ min^{-1}$ OR (95% CI) = 4.38 (1.23,15.6), p = 0.023; VO2 peak $<15\ ml\ kg^{-1}\ min^{-1}$ $O_2$ OR (95% CI) = 5.0 (1.42,15.55), p = 0.012; $VE/VCO_2 > 34$ OR (95% CI) = 4.07 (1.19,14.0), p = 0.026; diabetes mellitus OR (95% CI) = 5.76 (1.55,21.35) p = 0.009. In multivariate logistic regression analysis both diabetes (OR = 5.76 [1.55,21.4] p = 0.009) and presence of ≥ 1 subthreshold CPET value (OR = 6.72 [1.32,29.8] p = 0.021) were significantly associated with increased risk of death at 90 days. Median (95% CI) survival for patients who had a CPET with 'normal' parameters was 1176 (565, 1787) days, compared with 642 (336, 948) days for patients with ≥ one subthreshold parameter. 15.5% of patients had ECG ischaemia; there were no deaths in this group.

*Conclusion:* Presence of at least one sub-threshold CPET value at pre-operative testing is associated with increased risk of 90-day mortality and shorter long term survival. These results allow us to better define risks during shared decision-making with patients.



## Introduction

Cardioesophagectomy is a high-risk operation with 90-day mortality estimates ranging between 4.3 and 8.9% in recent patient cohorts [1,2]. Post-operative morbidity is also common. Risk prediction models are therefore desirable, and a variety of pre-operative patient characteristics including performance status, smoking history and age have been shown to be associated with an increased risk of perioperative death [3,4]. However, such risk prediction models show only modest discriminatory ability [5].

Aerobic fitness is a key determinant of a patient's ability to withstand the stress of major surgery and is incorporated into international guidelines on perioperative risk assessment [6]. Cardiopulmonary exercise testing (CPET) is widely used to predict risk and target post-op care appropriately [7]. Poor CPET performance is associated with increased risk of mortality and morbidity in various surgical populations including hepatobiliary [8,9], vascular [10] and major elective intra-abdominal [11,12]. However, the predictive power of CPET varies widely between studies, and evidence in patients undergoing cardioesophagectomy is limited. A recent systematic review acknowledged the paucity of evidence in this patient population and called for further studies [13].

Patients undergoing elective cardioesophagectomy in our

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https://doi.org/10.1016/j.ejso.2019.06.013
0748-7983/

institution have undergone CPET as part of their routine pre-operative workup since 2007. Their outcome data including mortality, length of stay and complication data is collected in a prospectively maintained database, which feeds into regular multidisciplinary team discussion with the aim of minimizing perioperative risk. We analysed this data to determine whether CPET is associated with 90-day mortality and complications in our patients, and also its relationship to longer term survival. We also qualitatively examined the contribution CPET makes to decision-making in our service, and in particular the role of CPET in identifying myocardial ischaemia.

## Materials and methods

### *Cardiopulmonary exercise testing*

Patients undergoing cardioesophagectomy in our institution performed a maximal, symptom-limited cardiopulmonary exercise test (CPET) as a routine part of pre-operative assessment using a ramped Wasserman protocol [14]. A cycle ergometer and gas exchange analysis system (Ultima™ CardiO$_2^{®}$ MedGraphics (Medical Graphics, St Paul, MN, USA) were linked with a BreezeSuite™ software package (Medical Graphics, St Paul, MN, USA). Patients performed resting spirometry followed by a maximal, symptom-limited CPET. Following baseline measurement of gas exchange, ECG and arterial oxygen saturation, patients commenced a 3-min period of unloaded cycling at a rate of 60 rpm followed by a ramped protocol with work rate increasing at a rate between 10 and 20 Watts/min maintaining this speed. All patients performed a maximal test defined as peak heart rate >80% peak predicted, or reaching a respiratory exchange ratio (RER) of >1.15. Prospectively collected CPET data included anaerobic threshold (AT), $V_{O2}$ peak, ventilatory equivalent for $CO_2$ at anaerobic threshold ($V_E/V_{CO2}$) and % predicted peak $V_{O2}$ for age and gender according to the modified prediction algorithm of Hansen et al. [15]. This data was stored in our CPET Research Database which has received ethical approval.

### *Outcome data collection*

Outcome data were collected using the Clavien-Dindo classification where post-operative complications are graded according to the level of intervention required [16]. Complications were also classified as cardiopulmonary or non-cardiopulmonary, with cardiopulmonary complications defined as by Girish et al. [17] to include: myocardial infarction; unstable angina; arrhythmia requiring treatment; pneumonia; atelectasis requiring medical intervention; congestive cardiac failure and pulmonary embolism. Radiologically confirmed anastomotic leaks were excluded from this definition. Length of stay data was obtained from the hospital Patient Administration System database. 90-day mortality was determined with reference to the NHS Demographic Batch Service. Patient clinic letters, MDT minutes and other electronic records were interrogated for qualitative information around the decision to operate and for any details of relevant pre-operative specialty input.

### *Statistical analysis*

Logistic regression analysis was conducted using both continuous and categorical predictor variables (IBM SPSS Statistics 22). CPET cutoff values identified in other surgical populations were used to determine whether 'subthreshold' patients (defined as any of AT<11 ml kg$^{-1}$ min$^{-1}$, $V_{O2}$ peak <15 ml kg$^{-1}$ min$^{-1}$ or $V_E/V_{CO2}$ >34) had a significantly increased risk of 90-day mortality. Multivariate logistic regression was performed with significant predictors from the latter analysis. To assess longer term survival, Cox proportional hazard analysis was used to calculate the hazard ratios for the risk factors of overall mortality. Length of hospital stay was compared with incidence of complications using a Student's T-test or Mann-Whitney *U* test as appropriate and also Pearson's correlation coefficient to assess the strength of relationship with the CPET variables.

## Results

200 patients underwent CPET followed by completed elective cardioesophagectomy between October 2007 and April 2015. The median age was 65 years, and 78% were male. Median time from CPET to operation was 44 days, and 70% of patients had pre-operative neoadjuvant chemotherapy. Operative approach varied: 57% open (Ivor-Lewis); 33% laparoscopic abdomen/open chest; 10% thoracoscopic with either open or laparoscopic abdominal phase. A further 75 patients had a CPET as part of pre-operative workup but ultimately did not proceed to operation. Compared with patients who proceeded to operation, these patients were older, more likely to be female, and had significantly lower AT and $V_{O2}$ peak but higher $V_E/V_{CO2}$ values. This non-operated group also had a significantly higher prevalence of renal impairment; demographics are presented in Table 1. The most common surgical pathology was adenocarcinoma of the oesophagus (75% of operated cases), and the most common outcome following histological assessment was stage 3 disease according to the TNM classification. These data are presented in Table 2.

### *90-Day mortality*

90-day mortality following cardioesophagectomy in our institution was 5.5% over the 10-year period. In univariate analysis the following factors were associated with a significantly increased risk of death at 90 days: anaerobic threshold <11 ml kg$^{-1}$ min$^{-1}$ OR (95% CI) = 4.38 (1.23,15.6), p = 0.023; $V_{O2}$ peak <15 ml kg$^{-1}$ min$^{-1}$$O_2$ OR (95% CI) = 5.0(1.42,15.55), p = 0.012; $V_E/V_{CO2}$ >34 OR (95% CI) = 4.07 (1.19,14.0), p = 0.026; diabetes mellitus OR (95% CI) = 5.76 (1.55,21.35), p = 0.009; The presence of ≥ 1subthreshold CPET value carried an OR (95% CI) of 6.3 (1.3,29.8) p = 0.021. Univariate logistic regression analysis of continuous variables also showed a significant relationship between $V_{O2}$ peak and $V_E/V_{CO2}$ and 90-day mortality. A 1 ml/kg/min increase in $V_{O2}$ peak was associated with an odds ratio of death at 90 days of 0.73 (CI 0.58,0.92), p = 0.007; a 1 unit increase in $V_E/V_{CO2}$ at AT increased the odds ratio of 90-day mortality by 1.2 (CI 1.1,1.3), p = 0.003.

Both diabetes and the presence of ≥ 1 subthreshold CPET value remained significantly associated with increased risk of death at 90 days in multivariate logistic regression analysis; diabetes OR = 6.08 (CI 1.58,23.49), p = 0.009; presence of ≥ 1 subthreshold CPET value OR = 5.54 (CI 1.1,27.7), p = 0.037. For those patients with at least 1 subthreshold CPET value, 8/75 = 10.7% died within 90 days of operation, while for patients with no subthreshold CPET values the death rate was 3/126 (2.4%). The 90-day mortality rate fell across the 10-year period with 7/92 deaths in the first 5 years (7.6%) and 4/108 in the latter 5 years (3.7%). However, the timepoint at which patients had surgery was not an independent predictor of 90-day mortality in multivariate analysis.

### *Long term survival*

Median follow up time for survivors was 597 days (range 2 days–9.7 years). 101 patients had died at the time of analysis (50.5%). The risk of mortality in the first 5 years was 1.6 times

**Table 1**
Patient characteristics.

| | CPET then operation (n = 200) | CPET but no operation (n = 75) | p value |
|---|---|---|---|
| Age (years)[a] | 64.7 (8.7) | 69 (8) | 0.005 |
| Male/female | 79% male | 71% male | 0.15 |
| $V_{O2}$ peak[a] (ml $kg^{-1}$ $min^{-1}O_2$) | 19.1(4.5) | 16.8 (5.0) | <0.0005 |
| AT[a] (ml $kg^{-1}$ $min^{-1}O_2$) | 12.7 (3.2) | 11.8 (3.5) | 0.02 |
| $V_E/V_{CO2}$[a] | 31.4 (4.8) | 35.6 (7.5) | <0.0005 |
| Ischaemia present[b] | 15.5% | 23% | 0.39 |
| Presence of at least 1sub-threshold CPET value | 44% | 67% | <0.0005 |
| Comorbidities[c] | | | |
| Cerebrovascular disease | 4% | 8% | 0.18 |
| Congestive cardiac failure[d] | 14% | 21% | 0.18 |
| Ischaemic heart disease | 16% | 23% | 0.63 |
| Diabetes mellitus | 16% | 22% | 0.27 |
| Renal Impairment[e] | 1% | 14% | 0.00001 |

[a] Data presented as mean (standard deviation) – all data normally distributed.
[b] Data incomplete – no data in 27 patients in operated group and 14 patients in non-operated group.
[c] Data incomplete – no data in 13 patients in operated group and 12 patients in non-operated group.
[d] Defined as New York Heart Association Classification >1.
[e] Defined as serum creatinine >170 μmol/L as per Lee's Revised Cardiac Risk Index.

**Table 2**
Disease classification for operated patients (n = 200).

| | | | | | |
|---|---|---|---|---|---|
| Histology | Adenocarcinoma | 75% | Disease staging (TNM Classification) | 0 | 9% |
| | Squamous cell carcinoma | 10% | | 1a | 15% |
| | | | | 1b | 9% |
| | Barrett's oesophagus | 2% | | 2a | 15% |
| | | | | 2b | 6% |
| | High grade dysplasia | 5% | | 3a | 17% |
| | | | | 3b | 8% |
| | | | | 3c | 10% |
| | Other[a] | 8% | | 4 | 5% |
| | | | | N/A[b] | 6% |

[a] Incudes complete response; neuroendocrine tumour; tumour not found.
[b] Non-neoplastic disease including Barrett's oesophagus and high grade dysplasia.

compared to the last 5 years. After adjustment for this, both presence of ≥ 1 subthreshold CPET parameter and diabetes mellitus were associated with a significant increase in long term mortality, hazard ratio (95% CI) 1.70 (1.11,2.61) and 2.24 (1.36,3.70) respectively. The median survival for patients who had a CPET with normal parameters was 1176 (CI 565,1787) days, compared with 642 (CI 336,948) days for patients who had at least one subthreshold CPET parameter. The Kaplan-Meier survival curve for patients with an abnormal vs normal CPET is shown in Fig. 1. The log-rank test which compares the difference for the whole of the survival curves for either a subthreshold or normal CPET gave p = 0.03.

*Length of stay and morbidity*

38.5% of operated patients suffered a serious complication or death (Clavien-Dindo III-V). These patients had significantly lower $V_{O2}$ peak (18.2 vs 19.7 ml $kg^{-1}$ $min^{-1}O_2$, p = 0.01) and significantly higher $V_E/V_{CO2}$ (32.9 vs 30.4, p = 0.0001) when compared with patients suffering no or minor complications (Clavien-Dindo 0-II). A 1 ml/kg/min increase in $V_{O2}$ peak was associated with an odds ratio of serious complication or death (Clavien-Dindo III-V) of 0.93 (CI 0.57,0.99), p = 0.03 and a 1 unit increase in $V_E/V_{CO2}$ at AT increased the odds ratio of Clavien-Dindo III-V by 1.12 (CI 1.05,1.20), p = 0.001. There was no statistically significant association between hospital length of stay and any CPET variable.

*Myocardial ischaemia*

Prospectively collected ECG ischaemia data were available in 171/200 operated patients and a further 61/75 patients who did not proceed to operation. There was no significant difference in the incidence of ischaemia between the operated and non-operated groups (18% vs 23%, p = 0.39). 31/200 (15.5%) of patients in the operated group had CPET evidence of ischaemia, of whom 6 were known to have ischaemic heart disease prior to

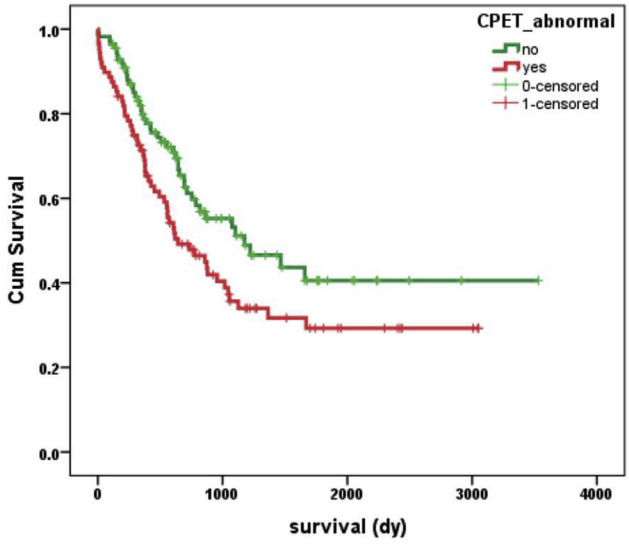


**Fig. 1.** Kaplan-Meier survival curve comparing patients with a normal CPET with those with at least one subthreshold CPET parameter.

testing. Patients judged to have high risk ischaemia on CPET were investigated with either dobutamine stress echocardiography or radionucleotide scanning (Myoview™), with abnormal studies triggering cardiology review. No patient proceeded to coronary angiography or revascularisation pre-operatively. No patient with CPET ischaemia died within 90 days, and one patient had a post-operative non-ST elevation myocardial infarction. This patient had mild ischaemia on CPET, previous coronary artery bypass grafting, and was reviewed by a consultant cardiologist pre-operatively.

A further 13 patients had ECG ischaemia but did not proceed to surgery. Ischaemia was considered significant in 7 cases, but in only one case was surgery cancelled as a result, based on a combination of significant inducible ischaemia on non-invasive testing coupled with poor tumour grade. In most other cases surgery was not appropriate based on tumour staging, and non-operative management was indicated. These findings are summarised in Fig. 2.

*Decision not to operate*

CPET was deemed to have contributed to the decision not to operate in 34/75 of patients who had non-surgical management (46%). In the remainder of non-operated cases the most common reasons were progression of disease (16 patients), clinical impression of frailty (8 patients) and patient declining surgery (4 patients). There was insufficient information to determine the reason for not proceeding to surgery in 12 cases.

## Conclusion

*CPET and mortality*

In our cohort of 200 cardioesophagectomy patients over a 10-year period, inability to perform CPET exceeding pre-specified variables of $V_{O2}$ peak, $V_E/V_{CO2}$ and AT was associated with a significantly increased risk of death both in the first 90 post-operative days and longer term. During this time period, mortality rates in our institution fell corresponding with the national picture which has seen 90-day mortality fall from 5.7% to 3.2% between 2007 and 2015 [18]. Using pre-specified threshold values (AT 11 ml $kg^{-1}$ $min^{-1}$, $V_{O2}$ Peak 15 ml $kg^{-1}$ $min^{-1}$ and $V_E/V_{CO2}$ 34), the presence of at least one subthreshold value at pre-operative CPET was associated with an odds ratio of death by 90 days of 5.5 in multivariate analysis. This association seemed to persist over the longer term, patients with at least one subthreshold CPET variable having a significantly shorter median survival as shown in Fig. 1. Due to the relatively low number of deaths confidence intervals are wide, and these results are best viewed as hypothesis-generating. They are however in keeping with other studies where a composite sub-threshold CPET performance has been found to be an independent predictor of in hospital and longer term mortality after elective surgery [10,19].

To date little association has been found between CPET markers and mortality in upper GI surgical patients. Most published studies have had smaller patient cohorts and a correspondingly small absolute number of deaths, and have therefore focussed mainly on morbidity [20–22]. More recently, in the only published cohort of comparable size, Sinclair et al. found no association between absolute values of AT, $V_{O2}$ Peak and $V_E/V_{CO2}$ and risk of death following oesophagectomy, although the ratio of observed to expected $V_E/V_{CO2}$ was found to be significant [23]. These differences in candidate markers of risk highlight the need for large multicentre data registries to develop valid and clinically useful risk prediction models.

*CPET and morbidity*

Patients with a major complication (defined as Clavien-Dindo III-V in line with previously published work [24]) performed significantly worse on pre-operative CPET testing compared with those suffering only minor complications. However, we were unable to identify a specific threshold which was predictive of major complications when considering individual CPET parameters. This is in keeping with previous studies in cardioesophagectomy patients; Forshaw et al. found in a series of 78 patients that while $V_{O2}$ peak was significantly lower in patients suffering a cardiopulmonary complication, neither this nor AT were usefully predictive over a range of "cutoff" values [20]. Similarly, Moyes found in a series of 108 patients that while AT was significantly lower in patients with post-operative cardiopulmonary morbidity, the discriminatory ability was poor [21]. More recently, Sinclair et al. found a range of CPET variables including $V_E/V_{CO2}$ to be associated with cardiorespiratory morbidity, although no cutoff values were determined

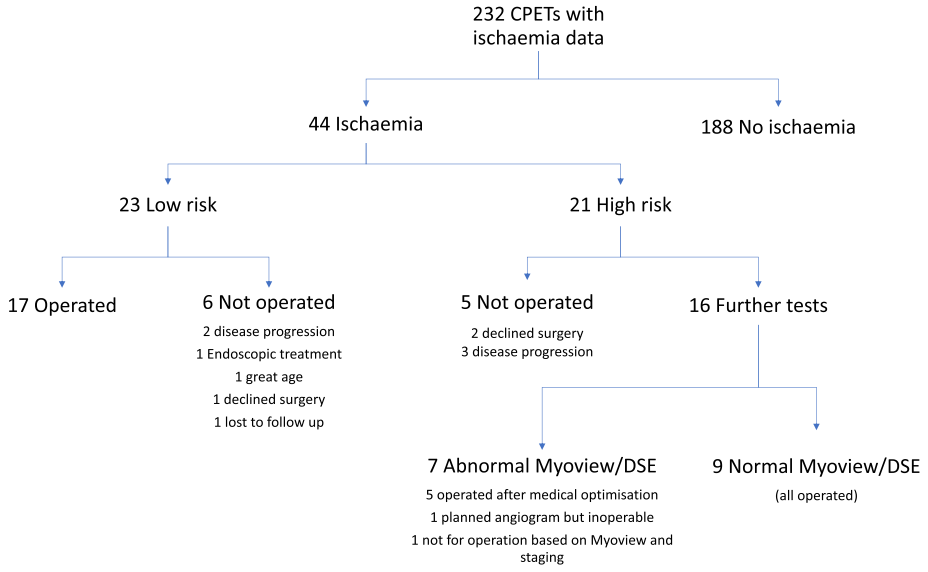


**Fig. 2.** Investigation and outcome of patients with CPET evidence of cardiac ischaemia.

[23].

We also examined whether CPET might predict resilience in the post-operative period. Cardioesophagectomy has a significant morbidity rate, and the ability of the patient to overcome complications is therefore a key determinant of survival. Indeed, 'failure to rescue' has been proposed as a quality indicator for centres performing major elective surgery [25]. It might be expected that patients with good cardiorespiratory fitness would be better able to overcome complications, and that this might be reflected in a shorter length of stay. However, we found no correlation between hospital length of stay and CPET in the subset of 67 patients who suffered a major non-fatal (Clavien Dindo III-IV) complication. This is perhaps unsurprising; length of stay is a notoriously unreliable marker of morbidity as it is dependent on multiple factors including delays to discharge for social reasons. Numerous previous studies have failed to demonstrate an association between length of stay and CPET performance possibly for similar reasons [8,20,26,27].

*Myocardial ischaemia on CPET*

CPET evidence of cardiac ischaemia was present in around 15.5% of our operated patients. When compared with a 'gold standard' such as myocardial scintigraphy, exercise-induced ECG changes found at CPET have only limited accuracy, although this improves when combined with gas exchange analysis [28]. Patients judged to have significant ischaemia on CPET were referred for further investigation with either myocardial perfusion scan (Myoview™) or dobutamine stress echocardiography. All patients with significant ischaemia on stress testing were reviewed by a cardiologist and managed medically. No patient proceeded to coronary angiography; there is little evidence to support a strategy of pre-operative coronary intervention in patients not meeting standard symptom-based criteria, and this is not currently recommended by consensus guidelines [6].

Given the high incidence of CPET ischaemia and the reluctance of cardiologists to proceed to angiography, this presents an opportunity for a pre-operative pharmacological management pathway in this patient group. Statins have a low incidence of clinically significant side effects, and may reduce the risk of mortality and perioperative myocardial infarction even in non-cardiac surgical patients [29]. While acute beta blockade is not recommended due to increased risk of stroke and overall mortality [30,31], the most recent ESC guidelines advocate titrated beta blockade as a reasonable approach in patients with myocardial ischaemia is reasonable (Class IIb recommendation), initiating treatment at least a week prior to surgery [32]. CPET takes place several weeks in advance of surgery in our pre-operative pathway, giving ample time for this to take place if ischaemia is detected.

*Role of CPET in the decision not to operate*

Seventy-five patients performed a CPET but ultimately did not proceed to operation. A third of this cohort was deemed 'fit' based on CPET with no subthreshold values. Determining the contribution of the CPET to the decision not to operate is subjective, and was made with reference to the MDT notes, clinic correspondence and CPET report. Overall poor CPET performance was considered to be a factor in the decision not to operate in 45% of cases, although rarely the sole determinant. This included three patients who were unable to complete a test due to frailty; although no objective information was obtained in these patients, inability to complete a CPET has been linked with poor outcome after major elective surgery [33]. In many cases the CPET supported the surgeon's clinical impression of a patient unfit for operation, providing objective evidence of this frailty.

The decision to operate is a complex one, requiring balancing the perioperative risk of death and morbidity against the chances of long-term survival. The ability to use CPET as an objective marker of perioperative risk in our patient population can usefully inform this decision-making process between the patient, surgeon and multidisciplinary team.

## Funding

We have no source of funding to declare

## Declarations of interest

None

## Acknowledgements

We would like to thank Ms Julie Morris, Honorary Reader in Medical Statistics, The University of Manchester for her assistance with data analysis and statistical advice.

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