BMJ Open  Predictive value of heart rate in patients with acute type A aortic dissection: a retrospective cohort study

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ABSTRACT
Objective  Heart rate (HR) is a risk factor of mortality in many cardiovascular diseases but no clinical studies have focused on the association between HR and prognosis in patients with acute type A aortic dissection (ATAAD). This study aimed to evaluate the association between HR and long-term mortality and establish the criteria of HR in patients with ATAAD who underwent total aortic arch replacement combined with the frozen elephant trunk (TAR+FET).

Design, setting and participants  Retrospective cohort study that studied all consecutive patients with ATAAD who underwent TAR+FET in the Fuwai Hospital between 2009 and 2015.

Main outcomes and measures  30-day postoperative, and estimated long-term mortality.

Results  Overall, 707 patients with ATAAD who underwent TAR+FET were followed up for a median duration of 29 months (range, 5–77 months). In multivariate logistic analysis, HR (p<0.001), age (p<0.001), renal insufficiency (p=0.033), ejection fraction (p=0.005), cardiopulmonary bypass time (p<0.001) and intraoperative blood loss (p=0.002) were significantly associated with 30-day postoperative and estimated long-term mortalities. A hinge point with a sharp increase in estimated long-term mortality was identified at 80 beats/min (bpm), and compared with HR <80 bpm, HR >80 bpm was associated with an almost threefold higher long-term mortality. HRs ≤60, 60–70, 70–80, 80–90, 90–100, 100–110 and >110 bpm were associated with 3.9%, 4.0%, 3.8%, 7.2%, 9.5%, 10.1% and 14.4% yearly risks of death, respectively.

Conclusions  HR is a powerful predictor of long-term mortality in patients with ATAAD undergoing TAR+FET. HR >80 bpm is independently associated with elevated long-term mortality for patients with ATAAD.

INTRODUCTION
Many studies have demonstrated that heart rate (HR) is a risk factor of mortality in many cardiovascular diseases,1–5 including type B aortic dissection.6–8 However, to the best of our knowledge, no clinical studies have focused on the association between HR and long-term prognosis in patients with acute type A aortic dissection (ATAAD) who underwent total aortic arch replacement combined with the frozen elephant trunk (TAR+FET).

Because of the urgency and fatalness of ATAAD, all of the current guidelines6–12 highlight the importance of emergency surgery and blood pressure control. Most guidelines do not recommend a target HR in patients with ATAAD. Although the use of beta-blockers is suggested in all these guidelines, beta-blockers were mainly used for blood pressure control and reduction in dP/dt and not for HR reduction. In the 2011 Japanese Circulation Society guidelines,10 pulse rate control is recommended as one of the most important aspects of treatment in acute aortic dissection, whereas no specific target of HR is suggested. Only the 2010 American College of Cardiology Foundation/American Heart Association guidelines9 recommend titrating to a target HR of 60 bpm or less (class I, level of evidence: C). However, this was referenced only in a review published in 2005,13 and the review did not provide any relevant clinical trials. Similarly, Nienaber and Powell14 suggested a target HR of 60–80 bpm as the initial medical therapy for acute aortic syndromes in a review published in 2011, and they did not provide any relevant clinical
Therefore, this study aimed to evaluate the association between HR and long-term all-cause mortality and explore the hinge point of HR among patients with AED who underwent TAR+FET.

**METHODS**

**Patients and data collection**

After receiving approval from the Ethics Committees of Fuwai Hospital in Beijing, China, and under a waiver of informed consent, the authors conducted this retrospective observational study of all consecutive patients with AED who underwent TAR+FET between December 2009 and December 2015. ATAAD was defined by observing an intimal flap separating two lumina in the ascending aorta that occurred within 14 days of symptom onset. Patients were monitored using electrocardiography, pulse oximetry and the Intellivue MX700 monitor (Philips, Amsterdam, the Netherlands) (left radial and dorsalis pedis arterial pressures) in the operating room. Data related to demographic and hospital clinical variables were retrospectively collected from medical charts and electronic medical records, and patients were followed up by telephone and outpatient review.

HR was recorded every 5 min when a patient arrived in the operating room and the average of the first three values of HRs before anaesthesia induction was used in our study from electronic medical records. Long-term mortality was defined as 5-year postoperative mortality.

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>Total (N=707)</th>
<th>Survivors (n=612)</th>
<th>Non-Survivors (n=95)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46.6±10.4</td>
<td>46.0±10.1</td>
<td>50.2±11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>552 (78.1)</td>
<td>486 (79.4)</td>
<td>66 (69.5)</td>
<td>0.041</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6±4.00</td>
<td>25.6±4.07</td>
<td>25.5±3.50</td>
<td>0.704</td>
</tr>
<tr>
<td>Hypertension</td>
<td>512 (72.4)</td>
<td>441 (72.1)</td>
<td>71 (74.7)</td>
<td>0.674</td>
</tr>
<tr>
<td>Current/past smoker</td>
<td>296 (41.9)</td>
<td>257 (42.0)</td>
<td>39 (41.1)</td>
<td>0.951</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (2.1)</td>
<td>13 (2.1)</td>
<td>2 (2.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>48 (6.8)</td>
<td>41 (6.7)</td>
<td>7 (7.4)</td>
<td>0.811</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>260 (36.8)</td>
<td>216 (35.3)</td>
<td>44 (46.3)</td>
<td>0.050</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>35 (5.0)</td>
<td>24 (3.9)</td>
<td>11 (11.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Stroke</td>
<td>34 (4.8)</td>
<td>29 (4.7)</td>
<td>5 (5.3)</td>
<td>0.788</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>99 (14.0)</td>
<td>85 (13.9)</td>
<td>14 (14.7)</td>
<td>0.744</td>
</tr>
<tr>
<td>Chest pain</td>
<td>623 (88.1)</td>
<td>540 (88.2)</td>
<td>83 (87.4)</td>
<td>0.997</td>
</tr>
<tr>
<td>Back pain</td>
<td>223 (31.5)</td>
<td>196 (32.0)</td>
<td>27 (28.4)</td>
<td>0.757</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>255 (36.1)</td>
<td>215 (35.1)</td>
<td>40 (42.1)</td>
<td>0.113</td>
</tr>
<tr>
<td>Time form onset of symptom to surgery (days)</td>
<td>7.1</td>
<td>7.0</td>
<td>7.4</td>
<td>0.755</td>
</tr>
<tr>
<td>Haemoglobin level, g/L</td>
<td>131.7±19.3</td>
<td>132±19.3</td>
<td>129±19.1</td>
<td>0.197</td>
</tr>
<tr>
<td>White cell count, ×10⁹/L</td>
<td>11.1±4.13</td>
<td>11.1±4.06</td>
<td>11.3±4.60</td>
<td>0.692</td>
</tr>
<tr>
<td>EF &lt;50%, %</td>
<td>32 (4.5)</td>
<td>20 (3.3)</td>
<td>12 (12.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR in ED, bpm</td>
<td>87.8±15.6</td>
<td>87.7±15.5</td>
<td>88.3±16.8</td>
<td>0.564</td>
</tr>
<tr>
<td>Preoperative HR, bpm</td>
<td>83.4±15.2</td>
<td>82.6±14.9</td>
<td>88.2±16.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136±25.7</td>
<td>136±25.5</td>
<td>135.5±27.3</td>
<td>0.997</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>61.2±15.8</td>
<td>61.2±15.4</td>
<td>61.2±18.0</td>
<td>0.803</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>85.7±17.3</td>
<td>85.7±17.0</td>
<td>85.2±19.2</td>
<td>0.548</td>
</tr>
<tr>
<td>History of cardiac surgery</td>
<td>17 (2.4)</td>
<td>13 (2.1)</td>
<td>3 (3.2)</td>
<td>0.466</td>
</tr>
<tr>
<td>Concomitant procedures</td>
<td>301 (42.6)</td>
<td>252 (41.2)</td>
<td>49 (51.6)</td>
<td>0.072</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>199.8±66.2</td>
<td>193±51.3</td>
<td>241±118</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative blood loss, mL</td>
<td>959.0±766.1</td>
<td>959.0±766.1</td>
<td>959.0±766.1</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%), as appropriate. BMI, body mass index; bpm, beats/min; CPB, cardiopulmonary bypass; ED, emergency department; EF, ejection fraction; HR, heart rate.
induction (according to systolic blood pressure (SBP)). The four-variable Modification of Diet in Renal Disease equation was used to calculate the estimated glomerular filtration rate. Renal insufficiency (RI) was defined as the preoperative estimated glomerular filtration rate <90 mL/min or dialysis.

### Statistical analysis

Values are expressed as mean±SD or number of patients (%), as appropriate. Multivariate logistic regression models were used to identify independent predictors of long-term mortality. To minimise selection bias and obtain comparable groups, propensity score matching (PSM) analysis was used to confirm the association between HR and long-term mortality. PSM of 1:1 ratio and 0.20 calliper by the ‘nearest neighbour’ method was performed with the ‘Matching’ package. The area under the receiver operating characteristic curve (AUC) was used to assess the discriminative performance of the logistic regression model. The long-term survival rate was analysed using the Kaplan-Meier analytical method and Cox regression analysis. The predictive models were built using the average of the predicted 5-year risk from the Cox proportional hazard model via the ‘coxph’ function of the ‘survival’ package in the R software package (R Foundation for Statistical Computing, Vienna, Austria). The Kaplan-Meier survival analyses were visualised using ‘survminer’ and ‘ggplot2’ packages in the R software package. The R software package,
V.3.5.1 was used to analyse the data, and GraphPad Prism V.7.00 for Windows (GraphPad Software, San Diego, California, USA) was used for data analysis and visualisation. A two-tailed p value <0.05 was considered statistically significant.

**Patient and public involvement**
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**RESULTS**

**Clinical features and surgical data**

From December 2009 to December 2015, 960 patients with ATAAD had surgeries in the Fuwai Hospital (online supplemental table 1). Of which, 746 patients underwent TAR+FET. After excluding, 39 of them for failure of follow-up, 707 patients were enrolled in this study. The clinical characteristics of the 707 patients are shown in table 1. Concomitant procedures included aortic valve repair in 22 patients, aortic root replacement in 227 patients, mitral valve operations in 9 patients, and coronary artery bypass grafting in 76 patients. Patients’ mean age was 46.6±10.4 years, and male sex was predominant (78%). During a median follow-up of 29 months (range, 5–77 months) 95 patients died.

**Association between HR and estimated long-term mortality**

In the multivariate logistic regression analysis, HR (p<0.001), age (p<0.001), RI (p=0.033), ejection fraction (EF) (p=0.005), cardiopulmonary bypass time (p<0.001) and intraoperative blood loss (p=0.002) were identified as independent predictors of estimated long-term all-cause mortality. After adjusting for the
demographic data, history of cardiac surgery and preoperative tests results, the above-mentioned six variables remained independently associated with long-term all-cause mortality (table 2). When we replaced SBP with diastolic blood pressure or mean blood pressure, the results were similar. There was a significant improvement in the discrimination of the logistic regression model by introducing HR (an increase in AUC of 0.04, p=0.024; figure 1). According to the Kaplan-Meier curves, increased HR was significantly associated with lower cumulative survival rate than lower HR (figure 2). In addition, a 5-bpm increment of HR was associated with an 11.8% increased risk of all-cause mortality in the univariate Cox regression analysis, and additional adjustment for other variables did not change the significance of the association. However, we failed to find a significant relationship between heart rate in emergency department (defined as the heart rate from the first electrocardiograph when a patient arrived in emergency department) and long-term mortality.

**Risk stratification based on HR**

As illustrated in figure 3A, a significant ‘rightward shift’ of HR was observed in the long-term non-survivor group compared with that in the long-term survivor group (p<0.001). The long-term survival, estimated using Kaplan-Meier analysis as a function of preoperative HR, is shown in figure 2. HRs ≤60, 60–70, 70–80, 80–90, 90–100, 100–110 and >110 bpm were associated with a 3.9%, 4.0%, 3.8%, 7.2%, 9.5%, 10.1% and 14.4% yearly risk of death, respectively, which suggest that the risk of death sharply increased when HR >80 bpm.

To confirm an appropriate cut-off value of HR for risk prediction, a hinge point (HR of 80 bpm) was observed, that is, a sharp increase in the estimated probability of long-term death occurred when HR >80 bpm (figure 3B,C).
Two hundred and sixty-six pairs of patients were matched, and all covariates were well balanced (figure 3D). In the matched cohorts, the 30-day postoperative and long-term mortality were significantly higher among patients with preoperative HR >80 bpm than among those with HR ≤80 bpm (all, p<0.01). Results of the PSM analysis are displayed in table 3. Remarkably, preoperative HR >80 bpm was associated with an almost threefold long-term mortality compared with HR ≤80 bpm.

Convenient prediction tool for estimated long-term mortality
To categorise patients undergoing TAR+FET into different risk zones, we created a risk stratification nomogram (figure 4) based on all the preoperative independent risk factors (HR, age, RI and EF). We were able to calculate the probability of long-term mortality in patients undergoing TAR+FET with given values of HR, age, RI and EF. The AUC of the nomogram was 0.72 (95% CI 0.67 to 0.77).

Recalculation of 30-day postoperative mortality
To further consolidate our findings, we recalculated the results above with 30-day postoperative mortality, and found that our results remained stable (online supplemental table 2). In addition, to minimise the bias caused by the 39 patients who failed to undergo follow-up, we inputted their data as either long-term mortality or long-term survival, and the results were similar. Univariable
DISCUSSION

Our study is the first to systematically evaluate the association between HR and long-term mortality, and we found a cut-off HR and established a convenient predictive model of long-term mortality in patients with ATAAD who underwent TAR+FET. We also used comprehensive methods to further consolidate our findings.

In this study, we demonstrated that HR is an influential independent risk factor for long-term mortality in patients who underwent TAR+FET, and higher HR is associated with significantly increased long-term mortality. These findings are in agreement with those of Zhang et al’s18 study that analysed 360 patients with acute aortic dissection and found that patients with slower HR had a higher in-hospital survival rate, although this was not statistically significant (p=0.064). Similarly, Suzuki et al19 analysed 1301 patients with acute aortic dissection by analysing the International Registry of Acute Aortic Dissection global registry database and showed that the use of beta-blockers was associated with improved outcomes in both type A and type B aortic dissection patients. This finding supports our results. Importantly, we detected that a cut-off HR of 80 bpm was associated with a sharp increase in long-term mortality. Long-term mortality was almost threefold greater in patients with HR >80 bpm than in those with HR ≤80 bpm. Therefore, HR >80 bpm may be considered as an independent risk factor in patients with ATAAD undergoing TAR+FET.

Aggressive medical treatment of aortic dissection was first advocated in the 1960s.20 The authors established the reduction of SBP and diminution of the rate of left ventricular ejection (dP/dt) as the two primary goals of pharmacological therapy. According to previous studies,21, when HR decreases, both blood pressure and left ventricular dP/dt decrease. This may be the main reason that slower HR is associated with improved long-term mortality in patients with ATAAD. Besides, HR has been reported in association with the prognoses of various diseases.22 One study23 enrolled 112 680 subjects in 12 cohort studies and reported a continuous, increasing association between having a rest HR above approximately 65 bpm and the risk of both cardiovascular and all-cause mortalities. Similarly, Wang et al24 analysed 92 562 participants in the Kailuan Study and demonstrated that elevated HR was independently associated with an increased risk of myocardial infarction and all-cause death. These large clinical investigations may help explain the benefit of a slower HR in our study from another viewpoint. It is generally believed that a faster HR is beneficial in severe aortic regurgitation (AR), as it potentially shortens the diastolic period during which AR occurs. In our study, 260 patients had moderate to severe AR but we did not find a significant association between preoperative HR and long-term mortality in patients with AR. This result was in line with that of Yang et al’s1 study that investigated 820 patients with moderate to severe AR; they demonstrated a robust association between increased HR and elevated all-cause death, which was independent of demographics, comorbidities, guideline-based surgical triggers, the presence of hypertension and use of medications. Similarly, Sampat et al24 conducted an observational study that included 756 consecutive patients with severe AR and found that beta-blocker therapy was an independent predictor of better survival for patients with higher HR.

In previous studies and guidelines,9,12,25 blood pressure control was one of the main medical treatments and multivariable Cox regression analyses of long-term mortality showed similar results.

**Figure 4** Nomogram for long-term mortality. We can calculate the probability of long-term mortality in patients undergoing TAR+FET with given values of HR, age, RI and EF. bpm, beats/min; EF, left ventricular ejection fraction; HR, heart rate; RI, renal insufficiency; TAR+FET, total arch replacement combined with the frozen elephant trunk.
in patients with aortic dissection. However, this study failed to demonstrate a significant relationship between blood pressure and long-term mortality. Because this study only included patients who underwent TAR+FET, we could not determine the effects of blood pressure on postoperative time. Indeed, many patients in our study received treatment for blood pressure control, and we defined blood pressure as the higher values between radial and dorsalis pedis pressures. In our study, patients had higher blood pressure than previous studies, and patients with an SBP ≤100 mm Hg only accounted for 8.77% (62 cases). These differences might have caused different outcomes.

We did not include intraoperative risk factors in the development of predictive models because we wanted to determine the probability of long-term mortality in patients undergoing TAR+FET before the operation started.

In this study, we failed to find a significant relationship between HR in emergency department and long-term mortality. Therefore, we suggest that a patient can benefit from HR reduction if HR could be controlled to lower than 80 bpm no matter how the HR was when a patient arrived in emergency department.

Limitations
This study has several limitations. First, the retrospective and observational nature of the study might have caused bias. To reduce selection bias, only one type of surgery (TAR+FET) was chosen in this study and a PSM approach was used. Second, by design, we could not include patients who did not undergo surgery or died before arriving in operating room. Finally, this was an observational study, patients did not receive the same preoperative treatment, thereby we did not take preoperative medication into consideration. Prospective randomised trials are needed to reveal the association between preoperative control of HR and patients’ outcomes to reduce long-term mortality in this population.

CONCLUSIONS
HR is a powerful predictor of long-term mortality and HR >80 bpm is associated with significantly increased long-term mortality for patients with ATAAD undergoing TAR+FET. We recommend combining HR, age, RI and EF to predict long-term mortality in patients undergoing TAR+FET.

Contributors YZ, QL and XG had full access to all the data in the study and are responsible for the integrity of the data and the accuracy of the data analysis. Study concept and design: YZ, QL, XG, CY, SY. Acquisition of data: YZ, YJ, HW, LF, FY. Analysis and interpretation of the data: YZ, QL, YW, SY. Drafting of the manuscript: YZ. Revision of the manuscript for important intellectual content: all authors. Su Yuan is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Ethics Committees of Fuwai Hospital in Beijing, China (2017-877).

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Data availability statement No data are available.

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