学位論文

論文題目

Clinical implication of changes in respiratory instability following transcatheter aortic valve replacement

（経カテーテル的大動脈弁置換術後における呼吸不安定性の変化の臨床的意義）

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ABSTRACT

Background:

Respiratory instability, which can be quantified by a respiratory stability time (RST), is associated with the severity and prognosis in patients with chronic heart failure. However, its clinical implication in patients with severe aortic stenosis receiving transcatheter aortic valve replacement (TAVR) remains unknown.

Methods:

Patients who received TAVR and had paired measurements of RST at baseline and one week following TAVR were prospectively included. Change in RST following TAVR and its impact on post-TAVR heart failure readmissions were investigated.

Results:

Seventy-one patients (median 86 years old, 35% men) were included. Baseline RST was correlated with the severity of heart failure including plasma B-type natriuretic peptide ($p < 0.05$ for all). RST improved significantly following TAVR from 34 (26, 37) to 36 (33, 38) ($p < 0.001$). Post-TAVR lower RST (<33, N = 18) was associated with higher 2-year cumulative incidence of heart failure readmission (21% versus 8%, $p = 0.039$) with a hazard ratio 5.47 (95% confidence interval 0.90-33.2).

Conclusion:

Respiratory instability improved following TAVR overall. However, persistent respiratory instability following TAVR was associated with heart failure recurrence.

Keywords: heart failure; hemodynamics; sympathetic nerve activity.

BACKGROUND

Aortic stenosis (AS) is a dominant cause of valvular heart diseases. Transcatheter aortic valve replacement (TAVR) is an established treatment of the severe AS in a high surgical risk cohort,[1] or even in a low surgical risk cohort given the recent clinical trials.[2,3] The current concern is focusing on optimal patient selection to further improve clinical outcomes following TAVR and investigating for predictors that determine the prognosis of patients undergoing TAVR.

Augmented sympathetic discharge is associated with the progression of worsening heart failure.[4] Respiratory stability is largely affected by the augmented sympathetic discharge via the association among respiratory system, autonomic centers, and hemodynamics.[5-7] Thus, respiratory instability is an established surrogate of heart failure severity. However, there has been no established methodology to accurately quantify the degree of respiratory instability thus far.

Asanoi and colleagues introduced a novel methodology to quantify the severity of respiratory instability by measuring respiratory stability time (RST), which reflects the magnitude of the non-periodic irregular respiratory fluctuations as well as Cheyne-Stokes respiration.[8] The all-night RST is a quantitative measure of respiration and reflects the clinical status of congestive signs and the recovery process from heart failure decompensation.[9]

Patients with AS might also have respiratory instability,[10] given their reduced cardiac output, increased sympathetic nerve activity,[11] and concomitant sleep-disordered breathing. Respiratory instability might improve following TAVR due to hemodynamic amelioration.[10] Detailed analyses of peri-TAVR changes in respiratory instability, which would be quantified by RST measurements, might clarify the association between

respiratory instability and AS and further help us risk-stratify TAVR candidates. In this study, I investigated peri-TAVR changes in RST and its prognostic impact.[12]

METHODS

Patient selection:

Patients who received RST measurements two days before TAVR at the clinically stable condition and one week after TAVR between April 2017 and May 2020 were prospectively included. All patients had severe AS, which was defined as mean gradient >_40 mmHg, peak velocity >_4.0 m/s, aortic valve area <_1 cm^2 (or <_0.6 cm^2/m^2). This study was approved by the local institutional review board on 13 August 2018(IRB 30-415). Written informed consents were obtained from all participants before the enrollment.

TAVR procedure:

The indication and detailed strategies for TAVR were determined by the heart-valve team, consisting of board-certificated cardiologists, cardiovascular surgeons, and anesthesiologists. All patients received balloon-expandable valves (Sapien XT or Sapien 3; Edwards Lifesciences Inc., Irvine, California) or self-expandable valves (Corevalve or Evolut R; Medtronic plc., Minneapolis, Minnesota) under general or local anesthesia.

RST measurement:

Methodology to measure RST is detailed in the appendix (Figure 1A). In brief, RST value is higher when patient's breathing patterns are stable and homogeneous during

all-night. In stable periodic breathing, the frequency spectrum is narrowly distributed and the RST is high (Figure 1B). On the other hand, in unstable breathing, the spectral components are widely distributed and include very low frequency components, resulting in a low RST value (Figure 1C).

Clinical variables evaluated:

Demographics, laboratory, hemodynamics, and echocardiographic data within one week before TAVR as well as TAVR procedure data were obtained as baseline characteristics. Heart failure readmissions that required intravenous diuretics during the one-year observational period following the index discharge was counted.

Statistical Analyses:

Statistical analyses were performed using SPSS Statistics 22 (SPSS Inc, Armonk, IL, USA). Two-sided p-values <0.05 were considered statistically significant. Continuous variables were expressed as median and interquartile. Categorical variables were expressed as number and percentage. RST levels tertile by the several clinical variables were compared by using Kruskal-Wallis test. RST levels at baseline and post-TAVR were compared by using Wilcoxon signed-rank test. A cutoff of post-TAVR RST to predict heart failure readmission was calculated by using time-depending receiver operating characteristics analysis. The impact of the calculated cutoff of post-TAVR RST on stratifying 2-year incidence of heart failure readmissions was investigated by using log-rank test and Cox proportional hazard ratio regression analysis. Multivariate analysis was not attempted given small event number. Change in RST following TAVR was a

primary endpoint. The impact of post-TAVR RST on heart failure readmissions was a secondary endpoint.

RESULTS

Baseline characteristics:

A total of 71 patients who received RST measurements before and after TAVR were included (Table 1). Median age was 86 (83, 88) years and 25 (35%) were men. Maximum velocity at aortic valve was 4.41 (3.99, 4.77) m/s and mean pressure gradient at aortic valve was 46 (36, 55) mmHg. The Society of Thoracic Surgeons (STS) score was 4.6 (4.0, 6.7) and EURO II score was 4.6 (3.6, 5.5). Baseline RST on median was 34 (26, 37). The distribution of baseline RST is displayed in Figure 2.

Baseline RST and other clinical parameters:

All-night trends of RST examples before and after TAVR in patients with high RST (Figure 3A) and with abnormally low RST (Figure 3B) are displayed. Baseline RST had clear correlations with several clinical variables associating with the severity of heart failure. Higher plasma B-type natriuretic peptide level was associated with lower RST level ($p < 0.001$; Figure 4A). Lower left ventricular ejection fraction ($p = 0.011$) and cardiac index ($p = 0.012$) were associated with a decrease in RST (Figure 4BC).

Change in clinical parameters including RST following TAVR:

Following TAVR, aortic valve area, peak velocity at aortic valve, and mean pressure gradient through aortic valve improved significantly ($p < 0.01$ for all). Changes in other clinical variables following TAVR are summarized in Table 2. RST increased

significantly following TAVR (from 34 [26, 37] to 36 [33, 38], p <0.001; Figure 5). Among 37/71 patients with baseline RST ≥33, RST remained high in most of them (36/37). Among 34/71 patients with baseline RST <33, RST increased above 33 in 17/34 patients but remained persistently low in 17/34 patients.

Clinical outcomes:

Following the index discharge, there were 5 heart failure readmissions during the 2-year observational period. Receiver operating characteristics analysis demonstrated a cutoff of 33 for post-TAVR RST to predict the events with sensitivity of 0.77 and specificity of 0.60 (Supplementary figure 1). The cutoff of 33 for RST significantly stratified the 2-year cumulative incidence of heart failure readmissions (21% in the low RST group versus 8% in the high RST group, p = 0.039; Figure 6A). Hazard ratio of RST <33 was 5.47 (95% confidence interval 0.90-33.2) for the events (p = 0.065).

Plasma B-type natriuretic peptide level remained unchanged during the 1-year observational period irrespective of the RST level (p >0.05; Figure 6B). However, plasma B-type natriuretic peptide level remained significantly higher in the RST<33 group than the RST ≥33 group both at index discharge and 1-year follow-up (p <0.05 for both).

DISCUSSION

In this study, I investigated the change in RST following TAVR and the prognostic impact of post-TAVR RST. Major findings are as follows: (1) Baseline respiratory instability, which was indicated by the lower RST, was associated with more progressed heart failure in patients with severe AS; (2) RST increased significantly

following TAVR in the whole cohort; (3) Post-TAVR RST <33 was associated with the heart failure incidence.

Respiratory instability and AS:

No studies are investigating the mechanism of respiratory instability in patients with AS, whereas respiratory instability has a deep association with heart failure.[5-7] Given the various similarity between AS and heart failure, a similar mechanism might be hypothesized.

Sleep-disordered breathing stimulates sympathetic nerve activity and increases afterload on left ventricle in patients with heart failure, reducing their survival. On the contrary, low cardiac output impairs peripheral circulation and increases bicarbonate chemo-sensitivity, leading to unstable respiration.[13-15] Pulmonary congestion stimulates vagal sensors in the lung, also deteriorating respiratory stability.[15] These might be enhanced particularly in patients with advanced AS with impaired systemic circulation and elevated intra-cardiac pressure.

Impact of TAVR on respiratory instability:

Detailed mechanism why RST improved following TAVR in the overall cohort remains unknown. One of the explanations might come from the improvement in inappropriately stimulated sympathetic nerve activity following TAVR, which was demonstrated in the previous studies using muscle sympathetic nerve activity[11] and cardiac metaiodobenzylguannidine scintigraphy.[17] Reduction in volume overload following TAVR would reduce inappropriate vagal nerve stimulation, resulting in respiratory stabilization.

Wide distribution in the degree of RST improvement in each patient remains a future concern. RST might not improve sufficiently in patients with impaired cardiac reserve or other comorbidities that have negative prognostic impacts.

Respiratory instability following TAVR and heart failure recurrence:

Given the above-discussed deep association between respiratory instability and heart failure, it would be plausible that persistently low RST was associated with future heart failure occurrence following TAVR. Consistently, the PROST study demonstrated that RST was correlated with the degree of pulmonary congestion as well as long-term prognosis in patients with heart failure.[9] Aggressive intervention to those with persistent respiratory instability following TAVR and its prognostic impact remain the future concern.

Limitations:

First, this study is a proof of concept and included only a limited sample size. There is a scarcity of studies that validated the association between respiratory instability and RST in patients with AS. Further validation studies are warranted to expand the concept of RST in the AS cohort. Given the small event number, I could not perform multivariate analyses to adjust for potential confounders. I focused on heart failure recurrence as a clinical outcome, but the impact of RST on other outcomes remains unknown. RST remained low even after TAVR, and further optimal strategy to improve RST following TAVR remains the future concern.

Conclusion:

Respiratory instability improved following TAVR overall. Persistent respiratory instability following TAVR was associated with heart failure occurrence.

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FIGURE LEGENDS

Figure 1. Methodology to calculate RST (A), the representative of high RST (B) and low RST (C).

(A) All spectral power was normalized by the power spectral density, the ratio of the maximum power of the components. All respiration frequency points with power spectral density >10% were equally adopted in the assessment of respiratory instability. Very low frequency points of the periodic breathing curve were also adopted only if power spectral density of the very low frequency component was > 50% of the maximum power of the respiratory component. Respiratory frequency points were evaluated by standard deviation, and RST was defined as the inverse of the standard deviation.

(B) In stable periodic breathing, the frequency spectrum is narrowly distributed and the RST is high.

(C) In unstable breathing, the spectral components are widely distributed and include very low frequency components, resulting in a low RST value.

Figure 2. Distribution of baseline RST

Figure 3. All-night trend of RST in a high RST case (A) and in a low RST case (B)

Figure 4. Baseline RST tertiled by baseline plasma B-type natriuretic peptide (A), left ventricular ejection fraction (B), and cardiac index (C).

*$p < 0.05$ by Kruskal-Wallis test.

Figure 5. Change in RST following TAVR

*p <0.05 by Wilcoxon signed-rank test.

Figure 6. Cumulative incidence of heart failure readmissions stratified by the post-TAVR RST (A) and trend in plasma B-type natriuretic peptide following index discharge (B)

*p <0.05 compared with baseline RST ≥33 group

Supplementary Figure 1. Receiver operating characteristics analysis for the post-TAVR RST to predict the heart failure recurrence.

APPENDIX

All-night respiratory measurements were performed using a respiratory monitoring device (Morpheus R, Teijin, Tokyo, Japan). Air flow was measured using a nasal cannula with a pressure sensor, and arterial oxyhemoglobin saturation (SpO_2) was also continuously measured with a pulse oximeter (Morpheus R, Teijin, Tokyo, Japan).

As summarized in Figure 1A, All-night respiratory signals of nasal pressure were digitized and sampled at 32 Hz. The data to be included in the analysis were restricted to those for the fixed hours from 23:00 through 05:00 hours. These respiratory signals were resampled at 4Hz and integrated to obtain instantaneous ventilatory volume. To serially calculate all-night RST, the respiratory signals were divided into serial 5-min segments every 50 sec. More than 420 segments of 5-min data were analyzed. I focused on 2 frequency ranges to estimate RST. One range consisted of respiratory frequency components obtained from the instantaneous ventilation signal, with high or low-frequency noise removed via a 5th order bandpass Butterworth filter with cutoff frequencies of 0.11Hz and 0.5Hz. Other components constituted a very low-frequency range of respiration as an indicator of periodic respiration magnitude. It was obtained by adjusting the baseline to zero, tracing the peak of the instantaneous ventilation signal, and applying a bandpass filter with cutoff frequencies of 0.008 and 0.04 Hz. For each 5-minute epoch, the maximum entropy method was applied to these respiratory and periodic breathing curves to extract the specific components of respiratory variations from each wave.

I applied MEM to these respiratory and periodic respiratory curves and extracted the spectral components of respiratory variability from each wave measured (Figure 1A). All spectral power was normalized by the power spectral density (PSD), the ratio of the

maximum power of the components. This describes how power of a signal or time series is distributed over frequency. All respiration frequency points with PSD >10% were equally adopted in the assessment of respiratory instability. Very low frequency points of the periodic breathing curve were also adopted only if PSD of the very low frequency component was > 50% of the maximum power of the respiratory component.

Respiratory frequency points were evaluated by standard deviation, and RST was defined as the inverse of the standard deviation. The RST throughout the night was averaged as a measure of respiratory stability throughout the night. Since RST is the inverse of frequency (Hz), it has the unit of time (sec). In other words, it corresponds to the time during which the same and stable breathing pattern is repeated, and indicates the stability of breathing.

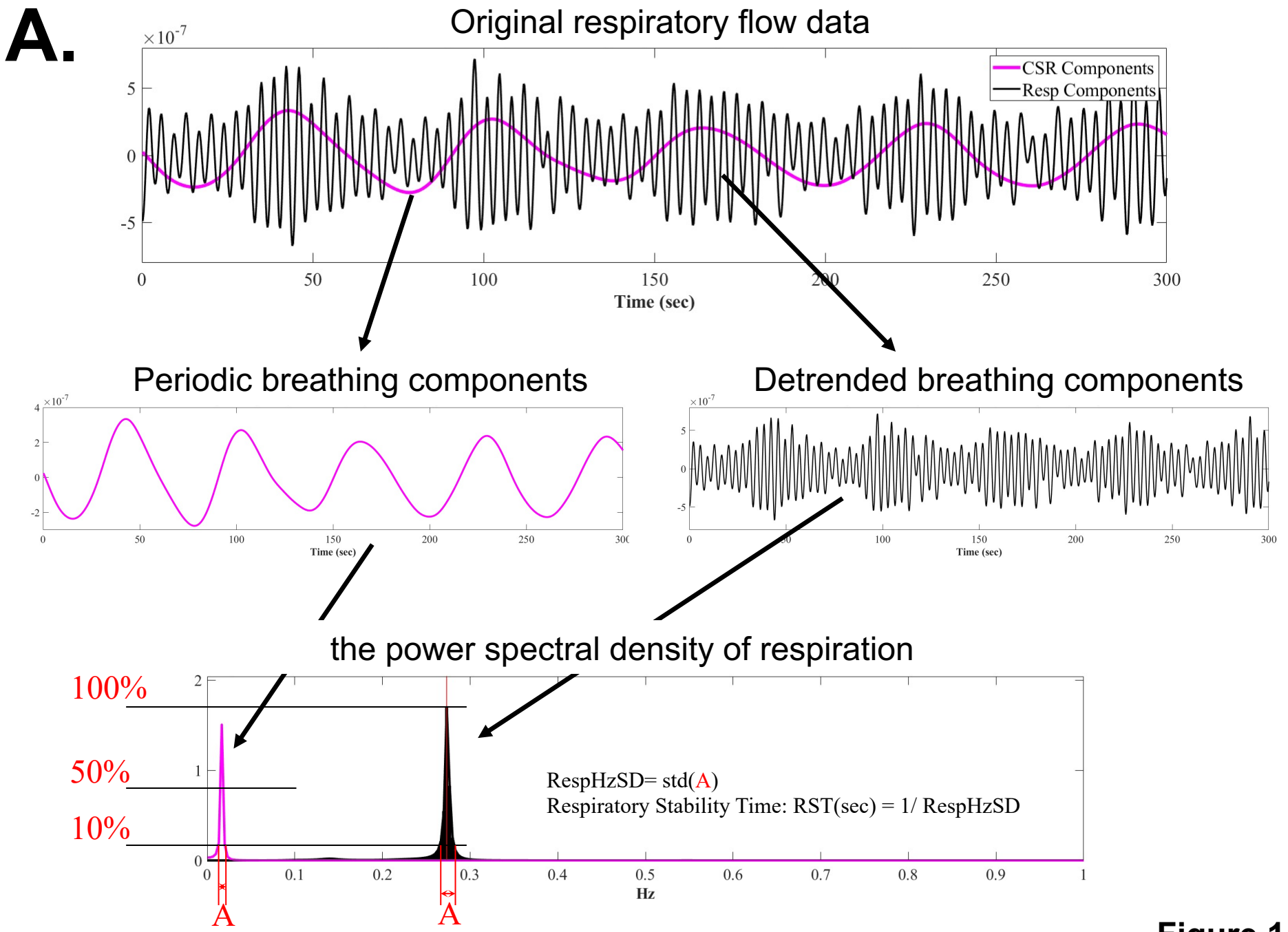

A.
Original respiratory flow data
×10^-7
5
0
-5
CSR Components
Resp Components
0
50
100
150
200
250
300
Time (sec)
Periodic breathing components
Detrended breathing components
Time (sec)
Time (sec)
the power spectral density of respiration
100%
50%
10%
2
1
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Hz
A
A
RespHzSD= std(A)
Respiratory Stability Time: RST(sec) = 1/ RespHzSD

Figure 1

B.

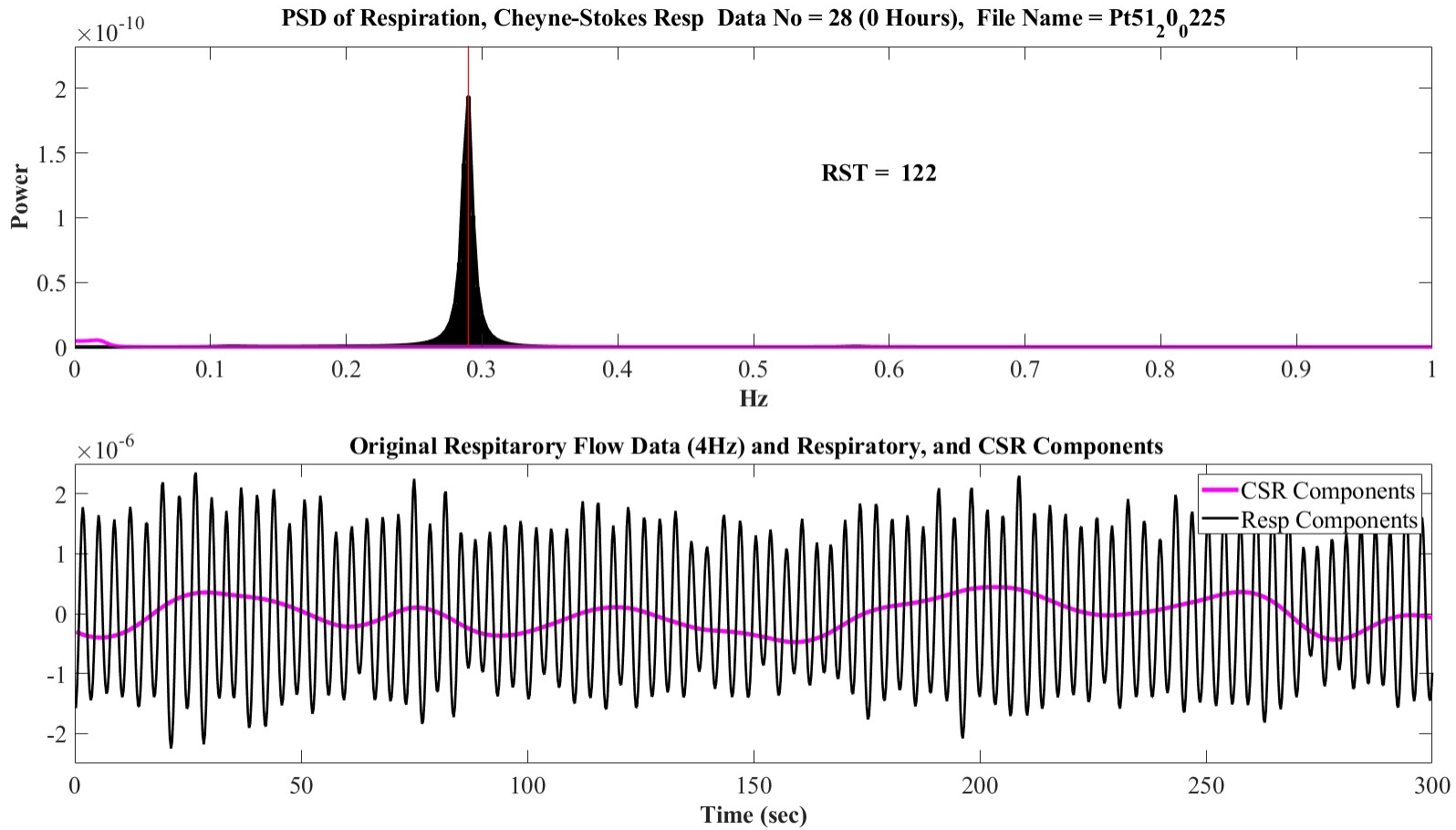

PSD of Respiration, Cheyne-Stokes Resp Data No = 28 (0 Hours), File Name = Pt51200225
×10^-10
Power
RST = 122
Hz
Original Respitarory Flow Data (4Hz) and Respiratory, and CSR Components
×10^-6
CSR Components
Resp Components
Time (sec)

Figure 1

C.

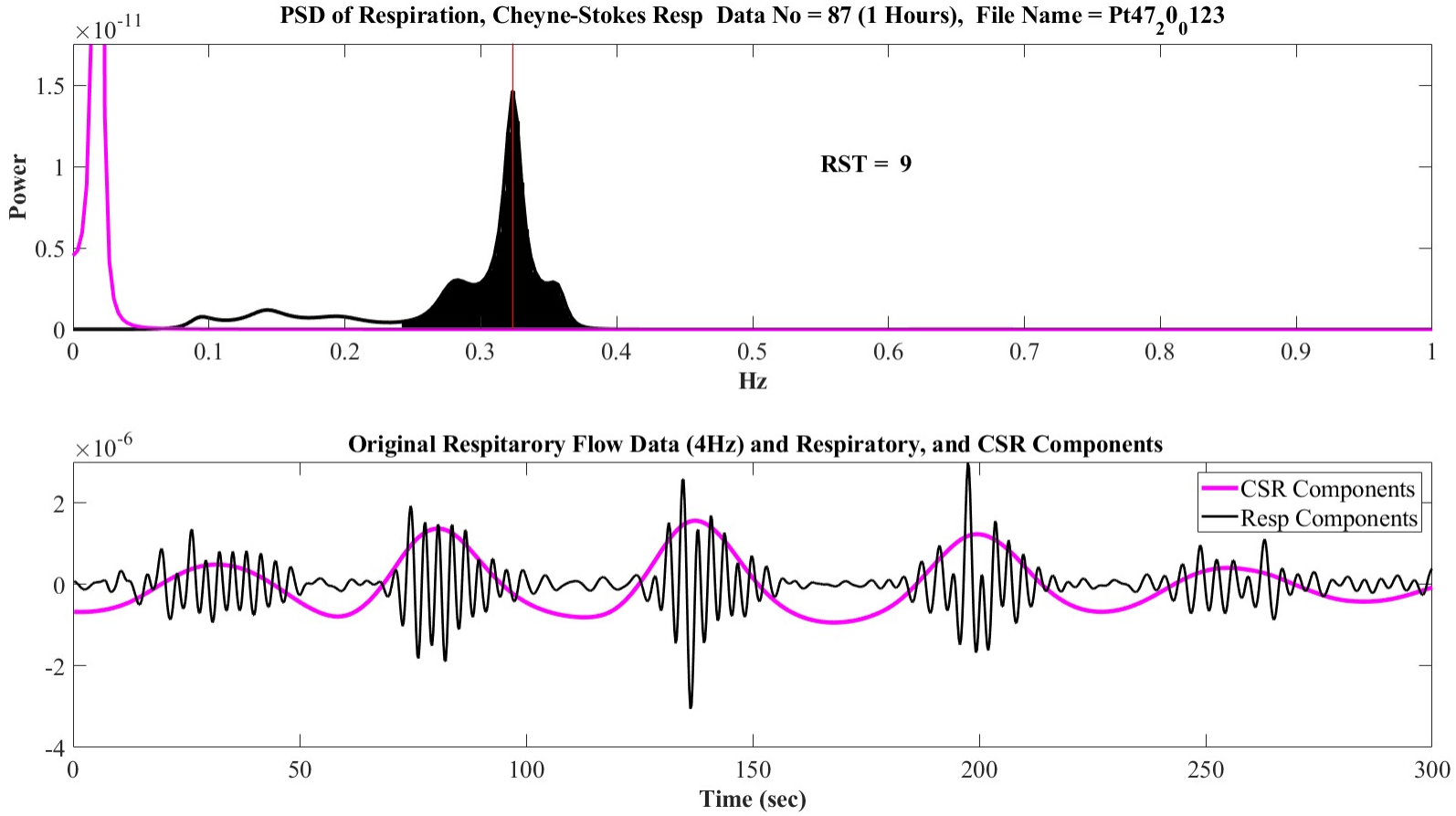

PSD of Respiration, Cheyne-Stokes Resp Data No = 87 (1 Hours), File Name = Pt47200123
×10^-11
Power
RST = 9
Hz
Original Respitarory Flow Data (4Hz) and Respiratory, and CSR Components
×10^-6
CSR Components
Resp Components
Time (sec)

Figure 1

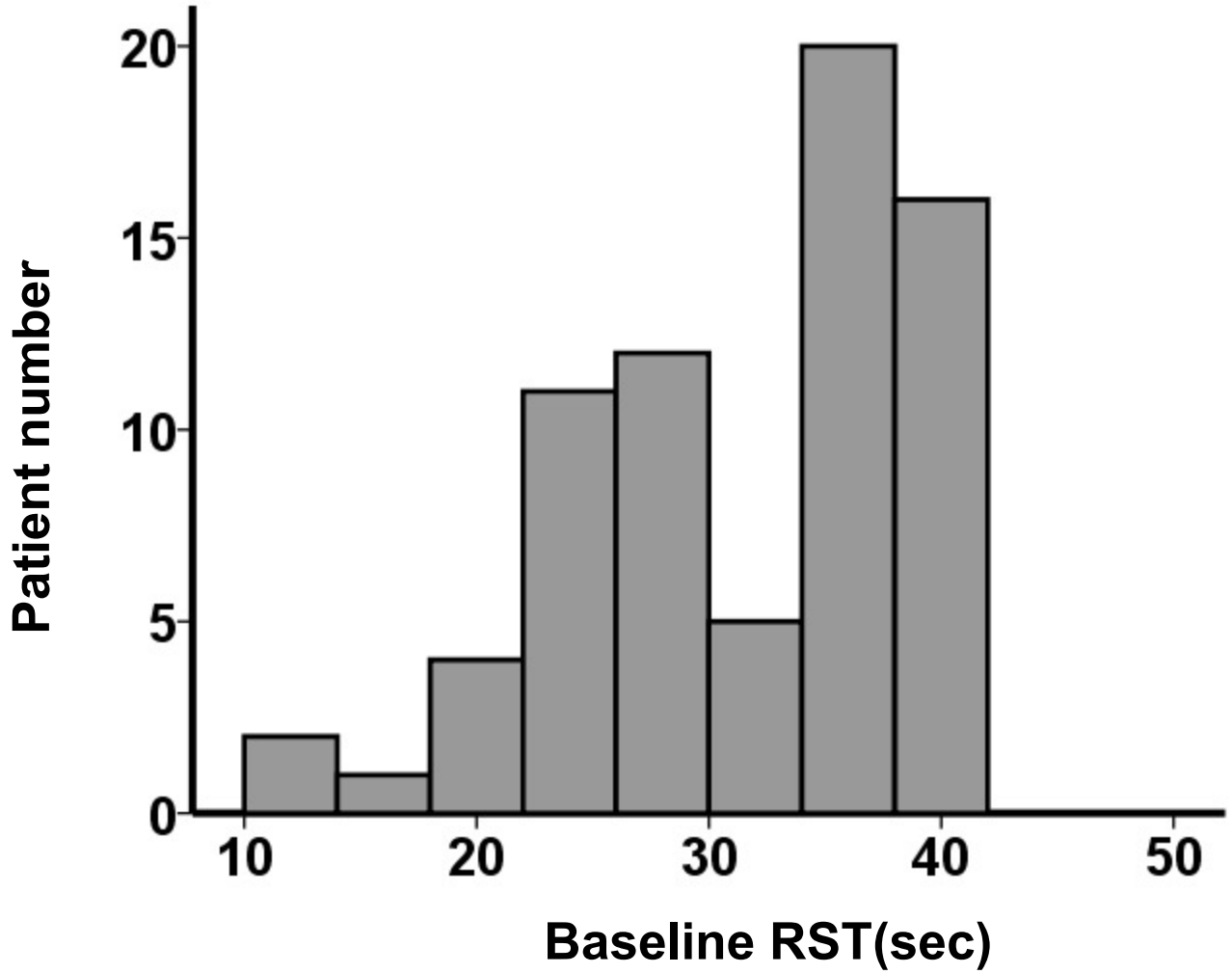


Figure 2

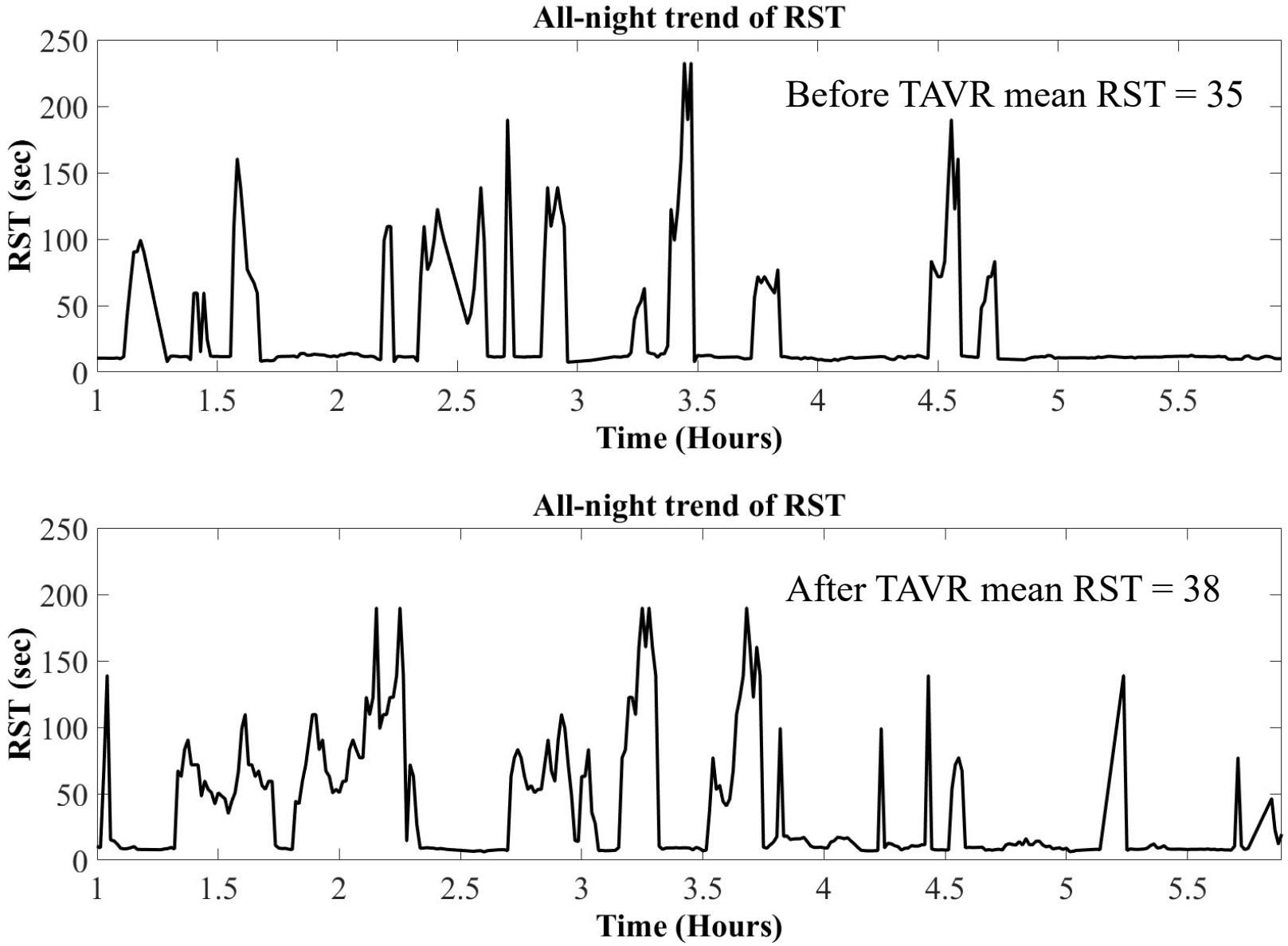

All-night trend of RST
Before TAVR mean RST = 35
RST (sec)
Time (Hours)
All-night trend of RST
After TAVR mean RST = 38
RST (sec)
Time (Hours)

Figure 3

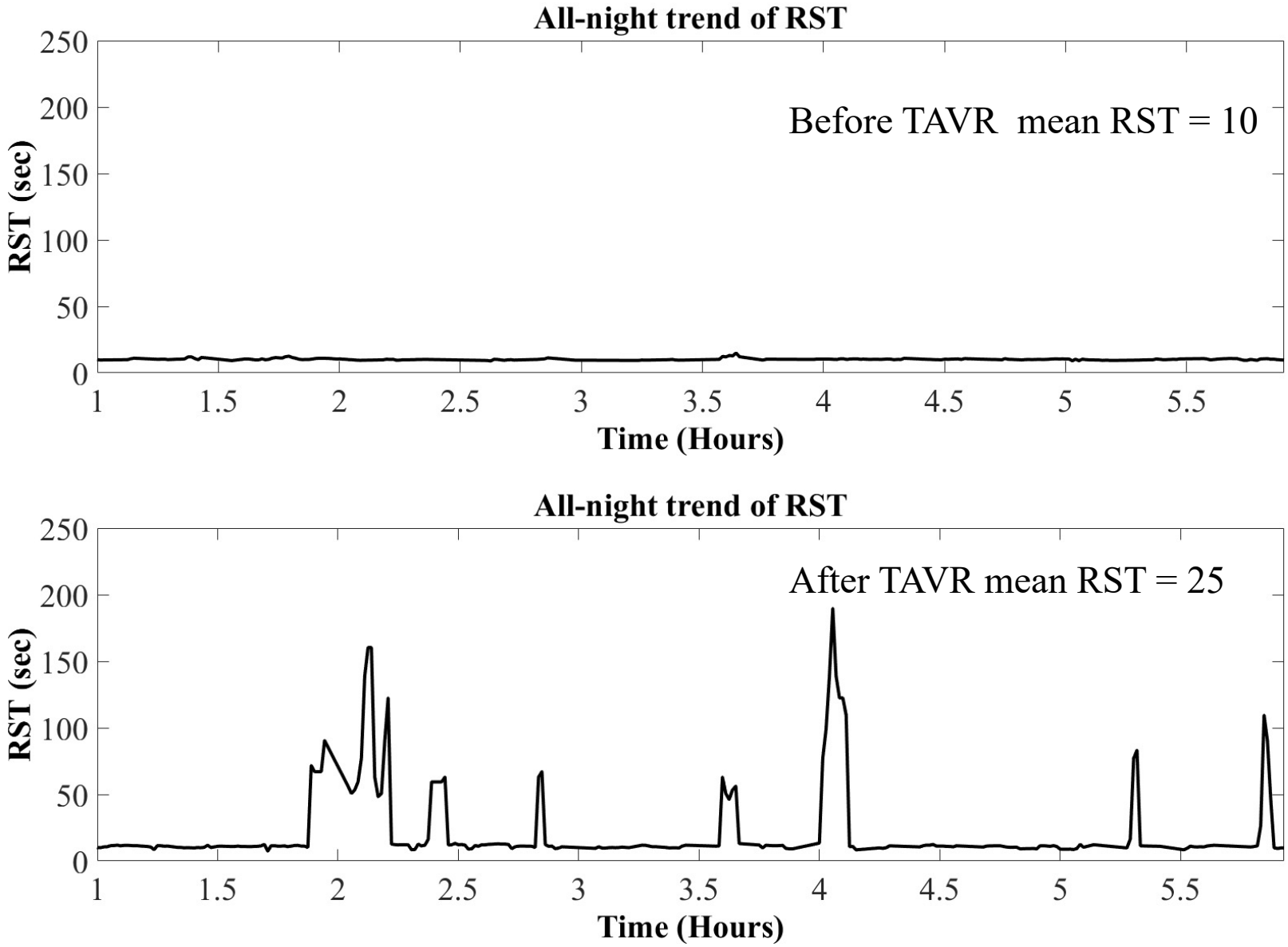

All-night trend of RST
Before TAVR mean RST = 10
RST (sec)
Time (Hours)
All-night trend of RST
After TAVR mean RST = 25
RST (sec)
Time (Hours)

Figure 3

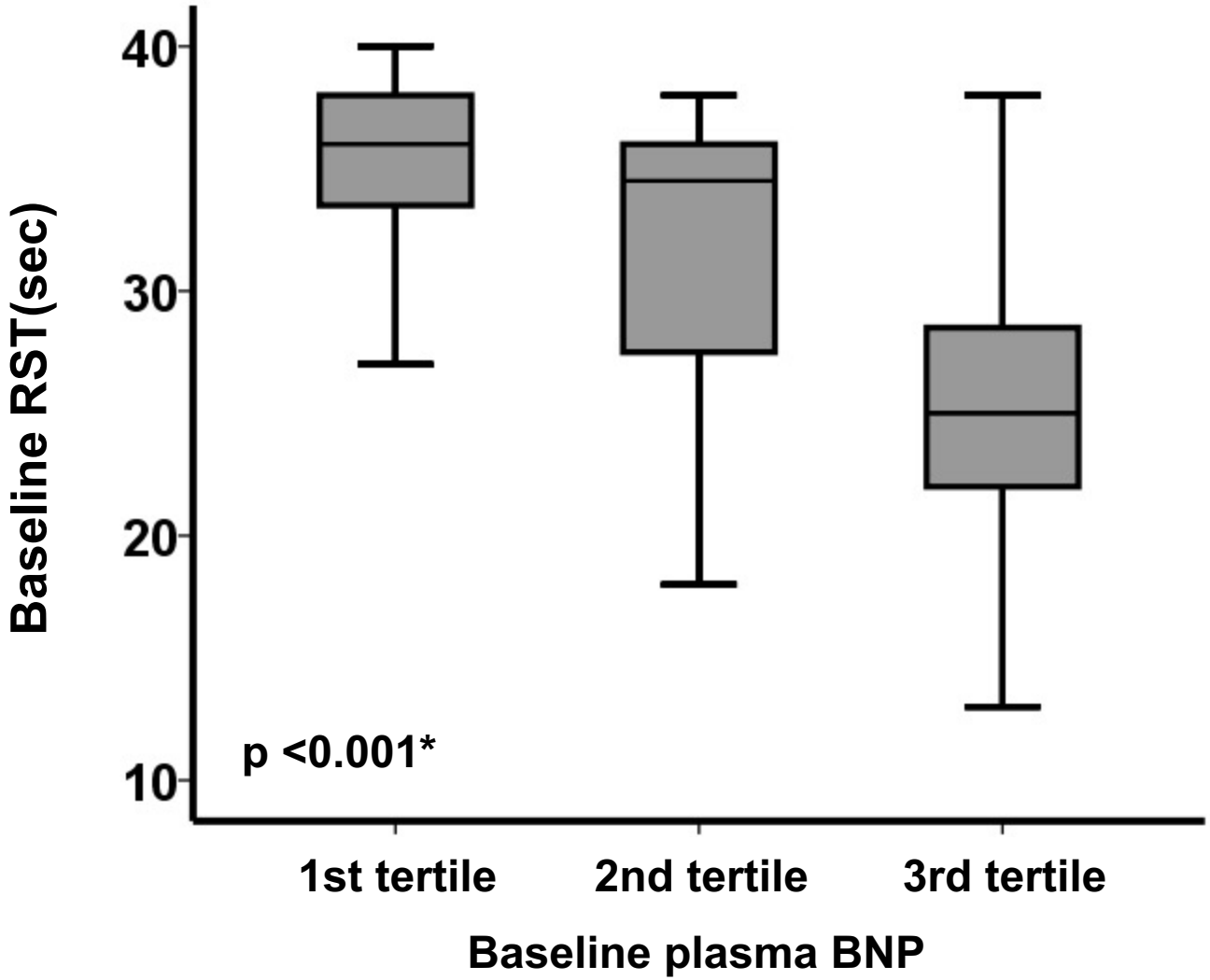

40
30
20
10
Baseline RST(sec)
p <0.001*
1st tertile
2nd tertile
3rd tertile
Baseline plasma BNP

Figure 4

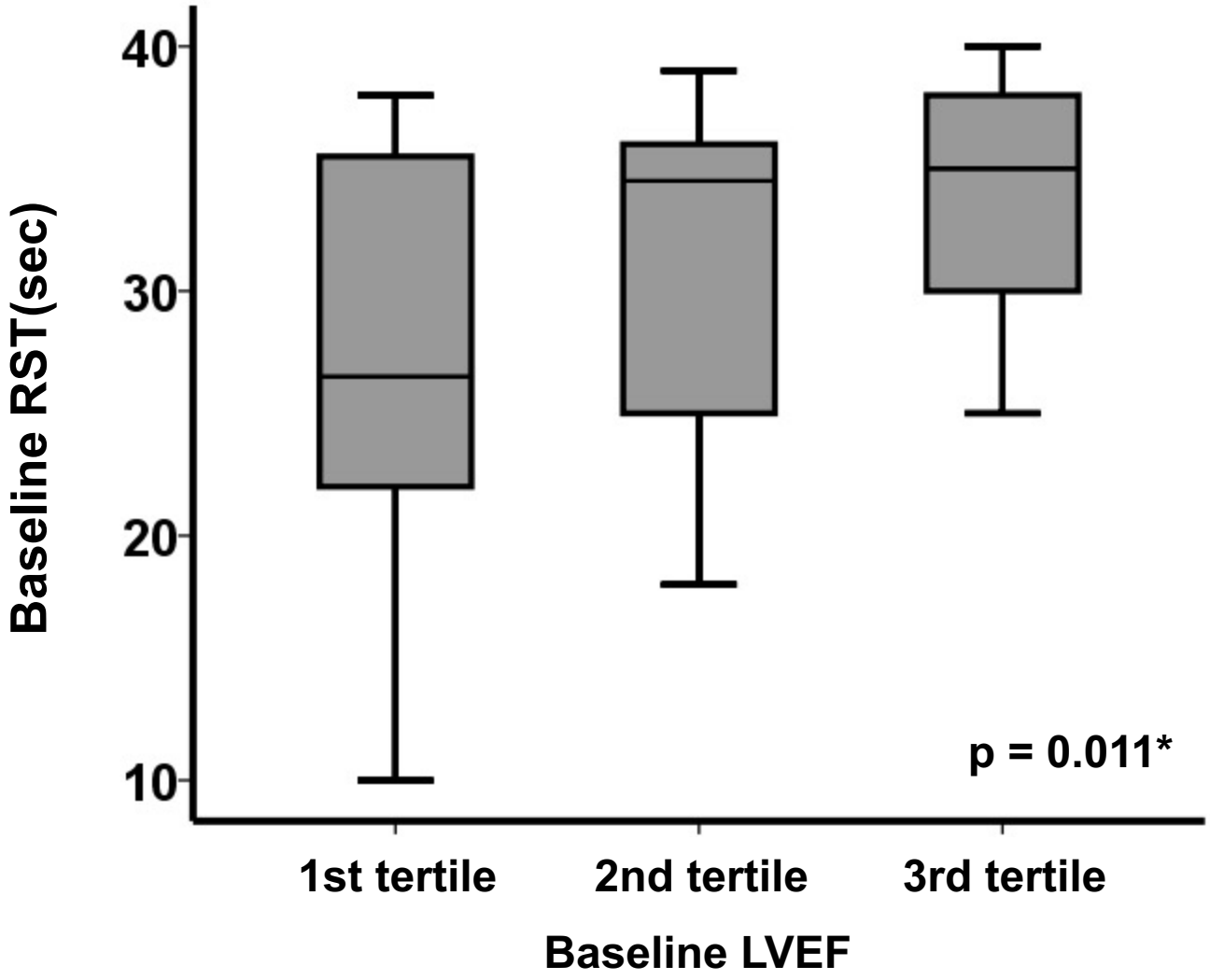

40
30
20
10
Baseline RST(sec)
p = 0.011*
1st tertile
2nd tertile
3rd tertile
Baseline LVEF

Figure 4

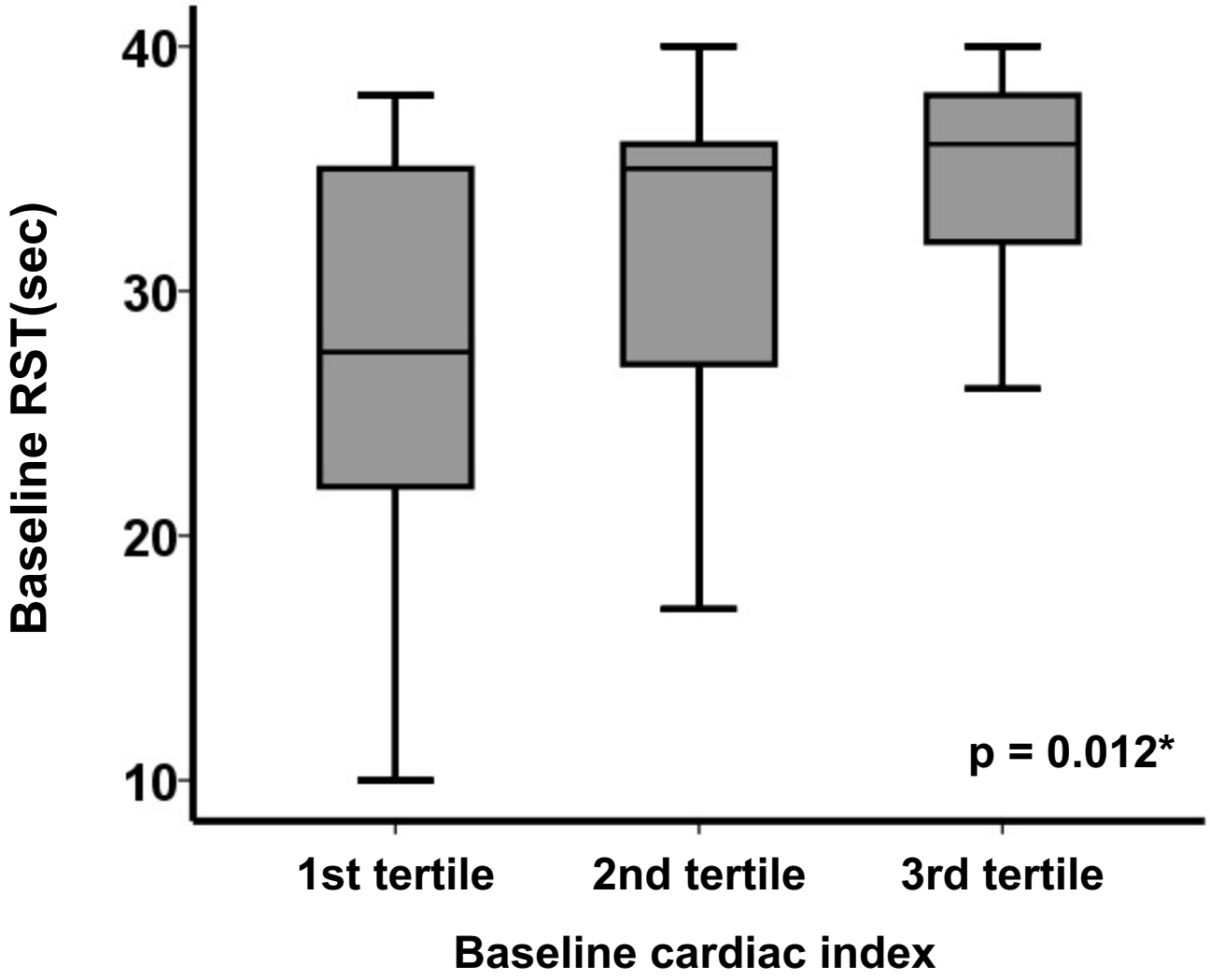

Baseline RST(sec)
40
30
20
10
p = 0.012*
1st tertile
2nd tertile
3rd tertile
Baseline cardiac index

Figure 4

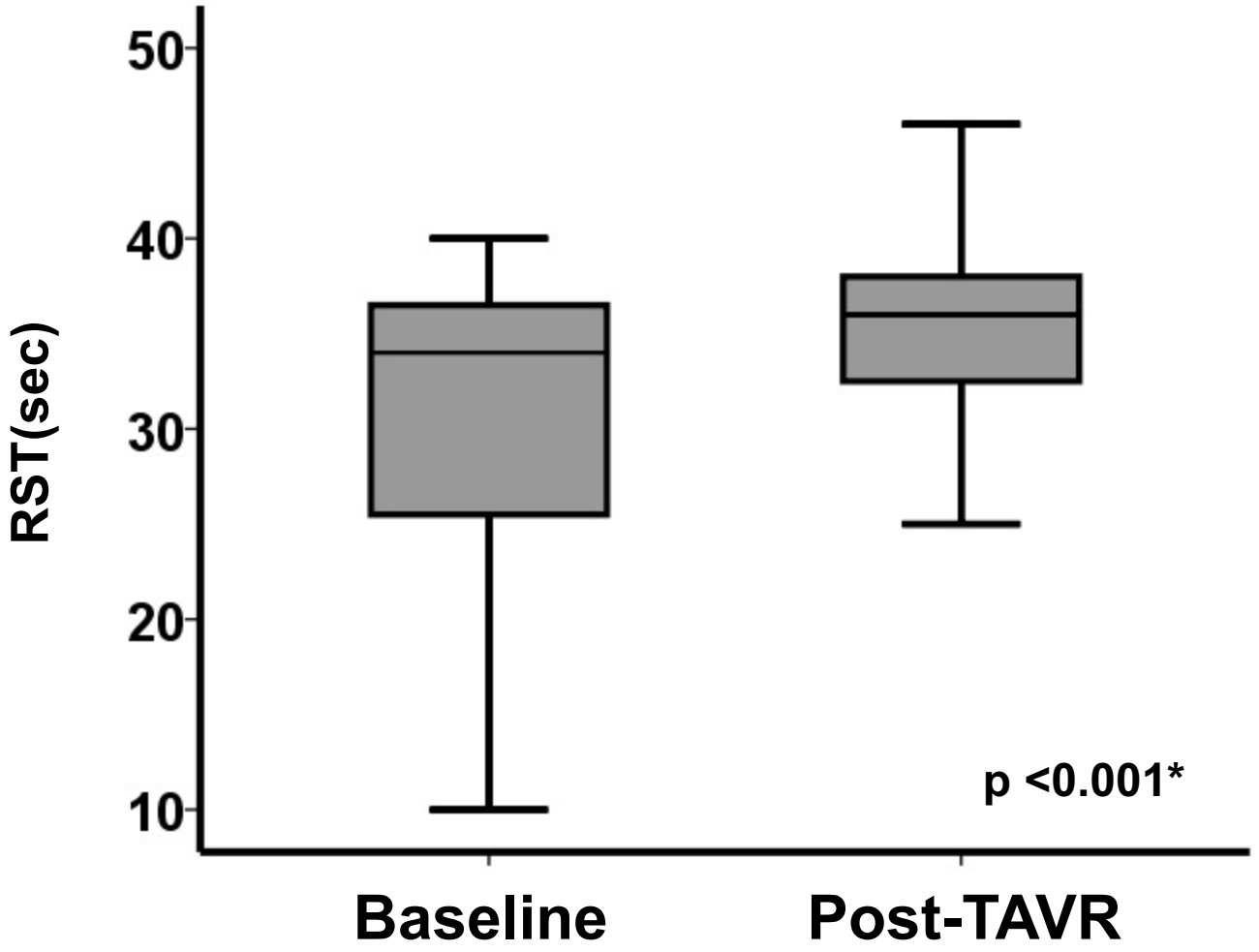


Figure 5

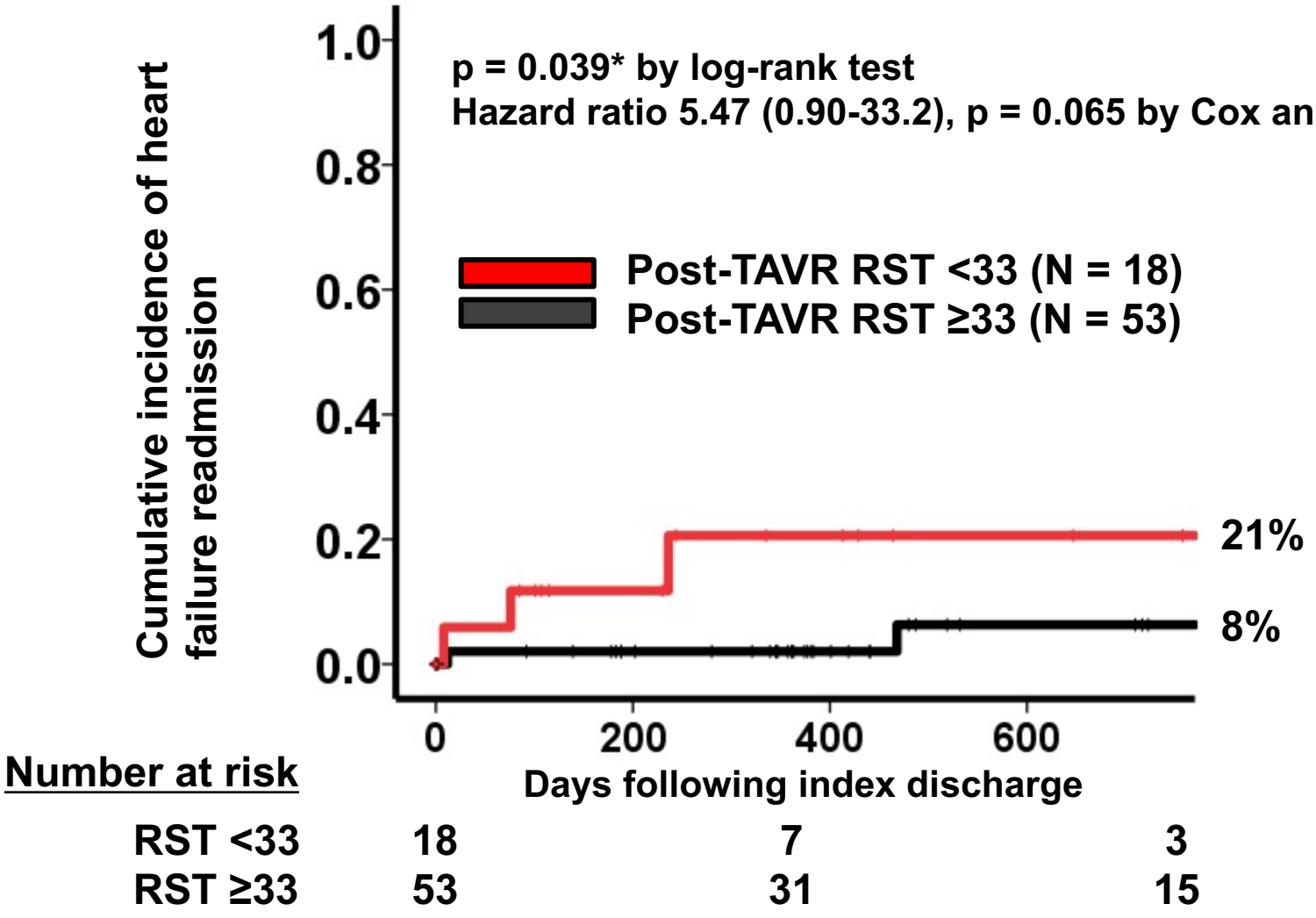

p = 0.039* by log-rank test
Hazard ratio 5.47 (0.90-33.2), p = 0.065 by Cox analysis
Post-TAVR RST <33 (N = 18)
Post-TAVR RST ≥33 (N = 53)
Cumulative incidence of heart failure readmission
1.0
0.8
0.6
0.4
0.2
0.0
21%
8%
0
200
400
600
Days following index discharge
Number at risk
RST <33 18 7 3
RST ≥33 53 31 15

Figure 6

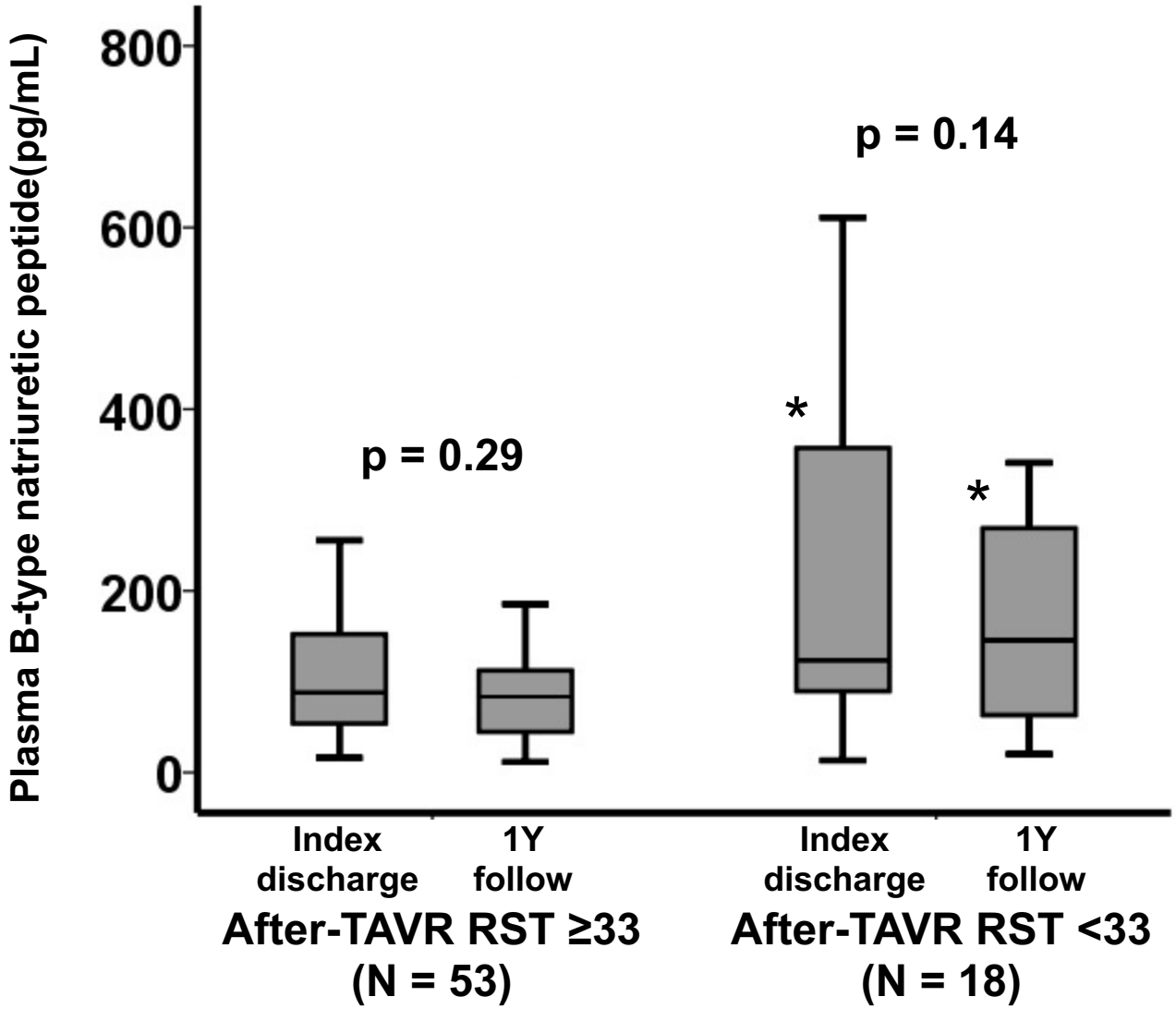
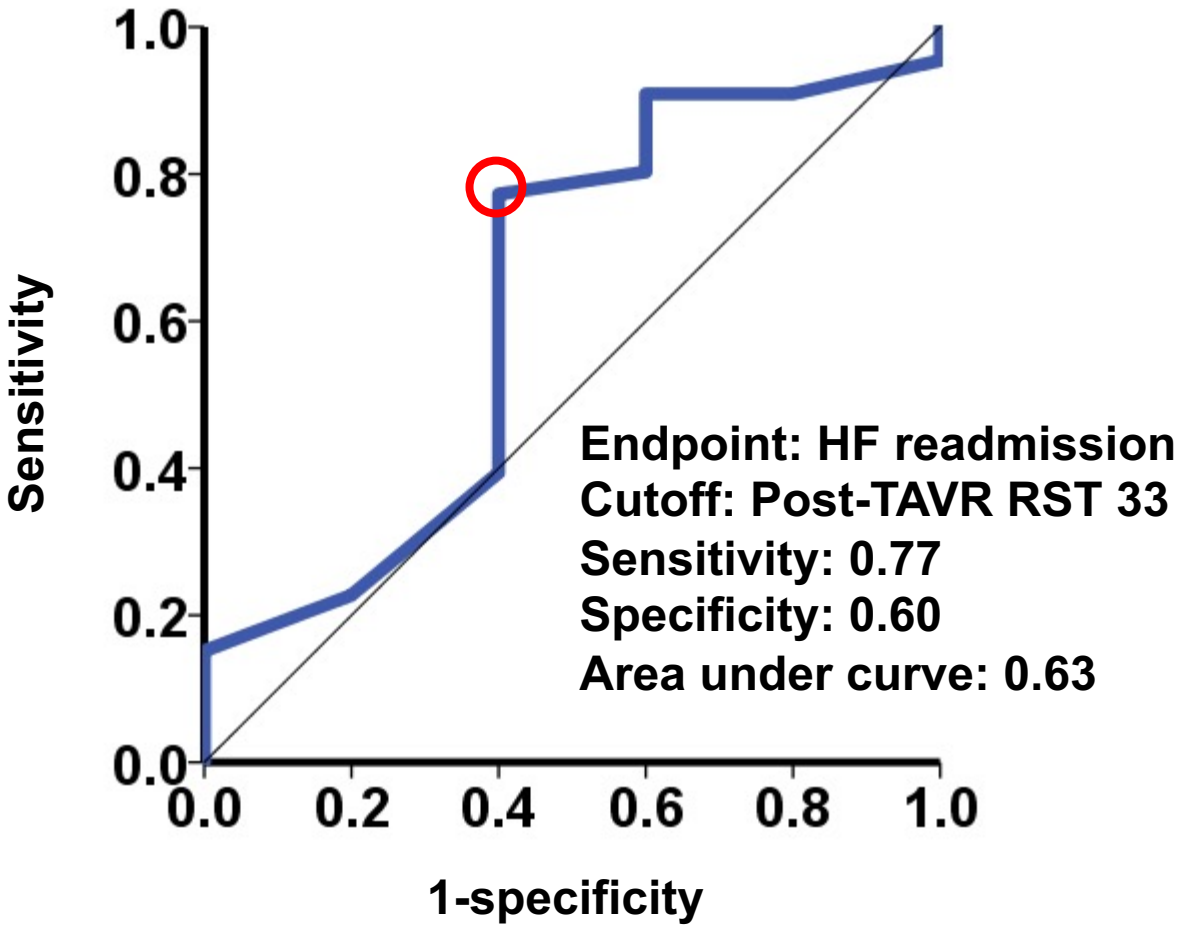

Plasma B-type natriuretic peptide(pg/mL)
800
600
400
200
0
p = 0.29
p = 0.14
*
*
Index discharge
1Y follow
Index discharge
1Y follow
After-TAVR RST ≥33 (N = 53)
After-TAVR RST <33 (N = 18)

Figure 6



Supplementary Figure 1