# Low risk patients with acute atrial fibrillation and elevated high-sensitivity troponin do not have increased incidence of pathological stress tests

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## Abstract

**Objectives**—Many patients with atrial fibrillation (AF) or atrial flutter (AFL) and rapid ventricular response (RVR) have elevated high-sensitivity troponin T (hsTnT) values. Elevated hsTnT is an independent risk marker for cardiovascular events and mortality. The aim was to examine if AF/AFL patients with RVR and elevated hsTnT have an increased incidence of pathological cardiac stress tests, indicating need of further evaluation for coronary artery disease (CAD).

**Design**—We prospectively included 90 AF/AFL patients without known heart failure and CAD presenting with AF/AFL and RVR. Half of the patients had elevated hsTnT (cases) and half had levels below the 99th percentile (controls). All patients were discharged in sinus rhythm. After approximately one week in sinus rhythm a new hsTnT was analysed and the patients performed a bicycle exercise stress test within the 30 day follow-up. The primary endpoint was a pathological stress test confirmed by a pathological SPECT myocardial perfusion imaging or a coronary angiography.

**Results**—None of the controls reached the primary endpoint. Two patients (4%) out of the 45 cases reached the primary endpoint ($p = .49$ vs controls), but only one was found to have significant CAD at subsequent coronary angiography.

**Conclusion**—Patients with paroxysmal AF/ AFL, without a history of CAD and heart failure, who present with a RVR and minor hsTnT elevations were not found to have an increased incidence of pathological stress tests compared to patients with hsTnT values below the 99th percentile.

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**Keywords**

Atrial fibrillation; troponin; myocardial injury; coronary artery disease; stress test

## Introduction

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common arrhythmias in the emergency department [1]. Many of these patients present with a rapid heart rate and have symptoms like palpitations, chest pain, dyspnea, dizziness or fatigue [2]. As a consequence cardiac troponins are often analysed in AF/AFL patients with rapid ventricular response (RVR) [3].

High-sensitivity troponin assays have improved the early diagnosis of acute coronary syndrome [4,5] and has also proven to be a strong independent risk factor for cardiovascular events and mortality [6]. The more sensitive assays have also increased the number of AF/AFL patients with minor troponin elevations above the 99th percentile. The causes and significance of these elevations and how to best handle these patients in clinical practise are largely unknown [7].

Some studies suggest that patients with AF have an increased prevalence of subclinical coronary artery disease (CAD) [8,9] and an increased risk of myocardial infarction [10]. However, it is not yet known if elevated troponin in AF/AFL patients with RVR might be due to a significant CAD causing supply-demand mismatch and relative myocardial ischemia in the setting of a rapid heart rate.

The primary aim of this study was to examine if AF/AFL patients without known heart failure and CAD who present with RVR and elevated high-sensitivity troponin T (hsTnT) have an increased incidence of pathological cardiac stress test compared to patients with hsTnT values below the 99th percentile. If the hypothesis proves correct, troponin elevations in this context may indicate need of further evaluation for CAD.

Our secondary aims were to analyse which background factors and clinical parameters differ between patients with elevated hsTnT and patients with hsTnT values below the 99th percentile and to register the occurrence of any adverse events during follow-up.

## Methods

### Study design and setting

We included patients ≥ 40 years old presenting in the emergency department with a primary diagnosis of AF or AFL and a heart rate ≥ 110 beats/min and who had at least one hsTnT sample analysed. The patients had to be discharged in sinus rhythm and be able to perform a bicycle exercise stress test within 30 days.

We excluded patients with other possible explanations for hsTnT elevation than tachycardia related to AF/AFL. Patients with history of CAD, heart failure, moderate to severe valvular heart disease, hypertrophic or dilated cardiomyopathy, significant anaemia, hypotension,

hypoxia, renal failure, acute infection, rhabdomyolysis, thyrotoxicosis, acute ischemic stroke, intracranial haemorrhage or acute pulmonary embolism, were excluded.

Patients with left bundle branch block on ECG were also excluded because of the difficulty to interpret ST-T changes during stress testing in these patients.

In line with the power calculation (see below), we included 45 patients with elevated hsTnT (cases) and 45 patients with hsTnT values below the 99th percentile (controls).

To differ between acute and chronic hsTnT elevations we analysed a second hsTnT sample after about a week in sinus rhythm. Patients were scheduled for an outpatient bicycle exercise stress test within 30 days after inclusion. If a SPECT myocardial perfusion imaging already was scheduled or performed before the planed bicycle exercise test, the bicycle exercise test was considered unnecessary and cancelled. Patients with an inconclusive bicycle exercise test were referred to a subsequent standard SPECT myocardial perfusion imaging study [11].

The follow-up period for incidence of a first major adverse cardiac event or death was 30 days from inclusion and data on these events were retrieved from medical records.

All patients gave their informed consent. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Regional Ethics Committee in Lund, Lund University (registry number 2014/453).

(For details on study site, inclusion, data collection and definitions see https://doi.org/ 10.1080/14017431.2021.1927171 Supplementary data.)

### Primary endpoint

The primary endpoint was a pathological stress test confirmed by a pathological SPECT myocardial perfusion imaging or a coronary angiography depending on clinical indication.

### Blood sampling, troponin T analysis and bicycle exercise stress test

Routine venous blood samples were drawn in the emergency department and directly analysed. The hsTnT method used was Roche (Roche Diagnostics, Basel, Switzerland) high-sensitivity troponin T assay, with a detection limit of 5 ng/L and a 99th percentile cut-off point of 14 ng/L.

The bicycle exercise test was performed on a Monark 939E ergometer bicycle following the protocol used in standard care with gradually increasing work load and subsequent rest [12–16]. (For details on the bicycle exercise stress test protocol and interpretation see https:// doi.org/10.1080/14017431.2021.1927171 Supplementary data.)

### Statistical analysis

A power calculation with an alpha risk of 0.05 and a power of 0.80 was performed. In studies including individuals without suspicion of CAD the prevalence of unknown significant CAD has been reported to be 7% [17] and the incidence of pathological stress test has been reported to be 8% [18]. Based on this we estimated the incidence

of pathological stress test to approximately 7% in the control group and we assumed a clinically highly relevant incidence of 30% in the case group. This resulted in a required sample size of at least 45 patients in each group.

Continuous variables are presented as medians with the interquartile range and compared with the Mann- Whitney test. Categorical variables are presented as numbers and percentages and compared using the chi-square test or Fischer's exact test if the expected count was low <5.

Multivariable logistic regression analyses with elevated hsTnT at inclusion as dependent variable and clinically relevant background factors as covariates were performed. The results are presented as odds ratios with 95% confidence intervals.

All tests were two tailed. Data management and statistical analysis were performed using IBM SPSS Statistics, version 22.

## Results

Of 124 patients eligible for inclusion 18 declined (10 cases and 8 controls) to participate and 16 dropped out during the study period (7 cases and 9 controls), which resulted in a total of 90 patients (45 controls and 45 cases) who completed the study protocol. The baseline characteristics and clinical variables at presentation are shown in Table 1. In summary patients with elevated hsTnT were older and had more comorbidities, resulting in a higher CHA2DS2-VASc score. Echocardiography data were available in 86% of the patients and no one had reduced ejection fraction.

Higher age, hyperlipidemia and diabetes were associated with higher likelihood of hsTnT elevation at presentation (Table 1). We were not able to include diabetes in a multivariable logistic regression analysis because there were no patients with diabetes in the control group. Instead we used glucose levels at presentation, age and hyperlipidemia in the multivariable analysis, which showed that age and glucose levels were independently associated with hsTnT elevation at presentation (Table 2).

The flow charts in Figures 1, 2 and Table 3 demonstrates stress testing outcomes and the results of further evaluation. None of the controls reached the primary endpoint. Two of the cases reached the primary endpoint, of which one underwent elective percutaneous coronary intervention nearly three months after inclusion and the other had normal coronary arteries at subsequent coronary angiography. Two patients had inconclusive stress test results, but declined to be further evaluated.

Among the cases, hsTnT declined from a median of 25 ng/L (IQR 18–35 ng/L) at inclusion in the emergency department to a median of 12 ng/L (IQR 8–15 ng/L) at follow-up and 82% had either hsTnT below the 99th percentile or a significant (>20%) hsTnT decrease at follow-up (Table 3). During a follow-up period of 30 days, none of the patients, neither among the cases nor among the controls suffered a major adverse cardiac event (Table 3).

## Discussion

As a result of the introduction of high-sensitivity cardiac troponins a lot of studies and reviews have been published focusing on the causes and consequences of minor hsTnT elevations in various clinical contexts, emphasizing the need for further research [7,19–22].

In this prospective study we aimed to address the quite common clinical problem of AF/AFL patients with RVR and dynamic hsTnT elevations.

The key finding of this study is that patients with paroxysmal AF/AFL presenting with a RVR and minor hsTnT elevations do not have an increased incidence of pathological stress tests compared to patients with hsTnT values below the 99th percentile. Of the two patients who reached the primary endpoint only one proved to have significant CAD. Since 82% of the patients either normalised or significantly decreased their troponin values within approximately one week, we conclude that most of the hsTnT elevations in this study is due to the acute tachyarrhythmia.

Costabel et al. prospectively studied hsTnT elevations, in 100 patients with supraventricular tachycardia (84% patients with AF or AFL), and its correlation to the presence of significant CAD. Approximately 50% of the patients had elevated troponin (but only 15% of the patients with AF had significant hsTnT dynamics during serial testing) and four of these patients (all with AF) had a pathological stress test or were revascularized during 30 days of follow-up [23]. The reasons why they had slightly more patients with pathological stress tests or revascularisation in their study may be because they included more patients with chronically elevated hsTnT values and also that they included patients with known CAD.

Other previous studies addressing the significance of troponin elevations in AF patients are to our knowledge all retrospective, use the older 4th generation troponin assays and come to different conclusions [2,3,24–27]. Some report an increased risk of myocardial infarction and cardiac death during follow-up [2,3,25], while others fail to show that elevated troponin predicts significant CAD on angiography or adverse cardiac events during follow-up [24,26,27]. Some of the reasons for this diversity may be different study populations and the use of different troponin assays with different cut offs (i.e. different absolute values define elevated troponin). Furthermore, there is probably a difference between acute and chronic hsTnT elevations and it is likely that this important difference cannot be distinguished in the different study populations.

## Limitations

Firstly, two patients in the cases group had inconclusive stress tests and the results from possible further evaluation could have affected our outcomes.

Secondly, to be able to address our clinical problem and hypothesis as strictly as possible we used several inclusion and exclusion criteria. Consequently, our results should not be generalized to the entire population presenting with AF/AFL and RVR. However, we argue that AF/AFL patients without CAD, heart failure, renal failure and no other likely

explanation for acute troponin elevation than AF/AFL with RVR are a real and clinically important problem that we address in this study.

Thirdly, we used a pathological bicycle exercise stress test as a surrogate marker of significant CAD. The reported sensitivity of exercise stress tests in relation to presence of significant CAD varies, but is less than 70% and one might argue that this is not good enough. However, in this population with a low-intermediate pre-test probability of CAD, no prior revascularization, predominantly normal resting ECGs and requirement to reach 85% of age-predicted maximum heart rate, the exercise stress test was recommended in then valid guidelines [28,29] and a normal stress test is associated with an excellent prognosis [29]. Further, some patients primarily and all patients with inconclusive bicycle exercise tests (together approximately 30% of the study population) underwent evaluation with SPECT myocardial perfusion imaging, which make our results more reliable.

Fourthly, our study is not powered to show minor significant differences in our primary analysis. This is important to keep in mind when interpreting the results.

## Conclusion

Patients without known heart failure and without known CAD, presenting with acute paroxysmal AF/AFL with RVR and minor hsTnT elevations were not found to have an increased incidence of pathological stress tests compared to patients with hsTnT values below the 99th percentile.

## Acknowledgements

## Data availability statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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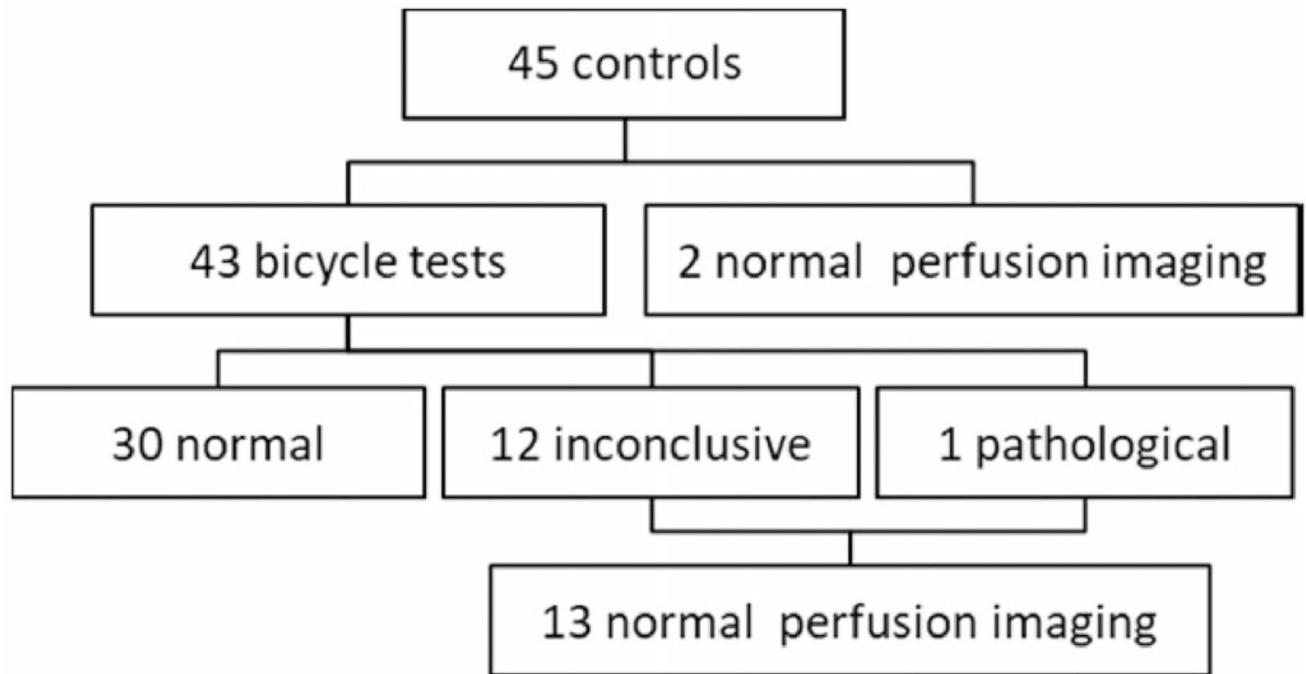
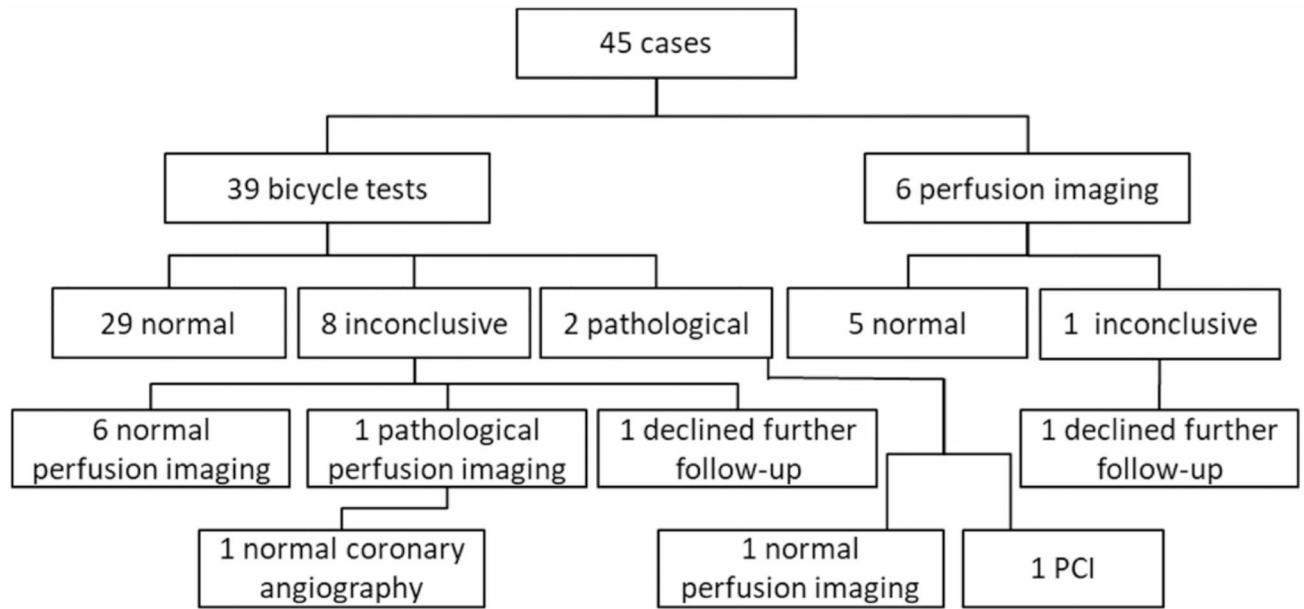**Figure 1. Outcomes and further evaluation in patients with hsTnT below the 99th percentile (controls).**

**Figure 2.**
Outcomes and further evaluation in patients with elevated hsTnT (cases). PCI: Percutaneous Coronary Intervention.

**Table 1**

**Baseline characteristics and clinical variables at presentation.**

|  | Controls (*n* = 45) | Elevated hsTnT (*n* = 45) | *p*-value |
|---|---|---|---|
| Age (years) | 62 (56–70) | 70 (66–76) | <.001 |
| Male sex | 24 (53%) | 23 (51%) | .83 |
| Current smoking | 4 (9%) | 4 (9%) | 1.0 |
| Hypertension | 21 (47%) | 26 (58%) | .29 |
| Hyperlipidemia | 6 (13%) | 16 (36%) | .014 |
| Diabetes | 0 (0%) | 10 (22%) | .001 |
| Prior stroke/TIA | 1 (2%) | 7 (16%) | .06 |
| Prior AF/AFL | 32 (71%) | 30 (67%) | .65 |
| CHA2DS2VASc (median, range) | 1 (0 – 4) | 3 (0 – 7) | <.001 |
| Atrial fibrillation | 40 (89%) | 36 (80%) | .25 |
| Heart rate (beats/min) | 133 (126–147) | 135 (127–147) | .59 |
| Systolic BP (mmHg) | 137 (120–150) | 143 (128–160) | .18 |
| Hemoglobin (g/L) | 152 (141–160) | 151 (140–157) | .57 |
| Creatinine (lg/L) | 83 (69–94) | 77 (68–88) | .32 |
| CRP (mg/L) | 2.6 (0.7–5.9) | 3.0 (1.3–7.7) | .30 |
| Glucose (mmol/L) | 6.4 (5.9–7.7) | 7.0 (6.1–9.2) | .04 |
| Chest pain | 8 (18%) | 11 (24%) | .44 |
| ST depression | 12 (27%) | 10 (22%) | .62 |
| Cardioversion | 35 (78%) | 32 (71%) | .47 |
| Echo data available | 39 (87%) | 38 (84%) | .76 |

Data are presented as *n* (%) of patients or median and 25th–75th interquartile range for continuous variables. hsTnT: high-sensitivity troponin T; TIA: transient ischemic attack; Echo: echocardiography; CRP: c-reactive protein; AF: atrial fibrillation; AFL: atrial flutter; BP: blood pressure.

**Table 2**

**Significance of clinically relevant background factors in predicting elevated high-sensitivity troponin T at presentation.**

|  | Multivariate analysis | |
|---|---|---|
| *n* = 90 | OR (95% CI) | *p*-value |
| Age (years) | 1.11 (1.04–1.18) | .002 |
| Glucose (mmol/L) | 1.32 (1.03–1.69) | .03 |
| Hyperlipidemia | 2.7 (0.83–8.7) | .10 |

OR: odds ratio; CI: confidence interval.

**Table 3**

**Troponin analyses, follow-up and outcomes.**

|  | Controls (*n* = 45) | Elevated hsTnT (*n* = 45) | *p*-value |
|---|---|---|---|
| Baseline hsTnT (ng/L) | 6 (4–8) | 12 (8–15) | <.001 |
| Peak hsTnT (ng/L) | 7 (5–10) | 25 (18–35) | <.001 |
| Significant (>20%) hsTnT at follow-up or follow-up hsTnT 14ng/L |  | 37 (82%) |  |
| Myocardial perfusion imaging | 15 (33%) | 14 (31%) | .82 |
| Primary endpoint | 0 | 2 (4%) | .49 |
| Recurrence of arrhythmia | 9 (20%) | 5 (11%) | .25 |
| MACE during follow-up | 0 | 0 |  |

Data are presented as *n* (%) of patients or median and 25th–75th interquartile range for continuous variables. hsTnT: high-sensitivity troponin T; MACE: major adverse cardiovascular events.