High-Sensitivity Troponin I and Rhythm Outcome after Electrical Cardioversion for Persistent Atrial Fibrillation

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Key Words
Atrial fibrillation · Cardioversion · High-sensitivity troponin I · Angiotensin II type I receptor blocker

Abstract
Objectives: We hypothesised that high-sensitivity troponin I (hs-TnI) might predict long-term rhythm outcome after cardioversion for persistent atrial fibrillation (AF), and that maintenance of sinus rhythm and/or treatment with the angiotensin II type 1 receptor blocker candesartan would reduce hs-TnI levels. Methods: In a double-blind, placebo-controlled study, 171 patients referred for electrical cardioversion for AF were randomised to receive candesartan or placebo for 3–6 weeks before cardioversion and for 6 months after electrical cardioversion. Blood samples for analysis of hs-TnI (Abbott Diagnostics) were available in 129 patients at baseline and in 60 successfully cardioverted patients at study end. Results: Hs-TnI was detectable in all subjects, with a median value of 5.3 ng/l (25th percentile 3.7, 75th percentile 7.2). Hs-TnI at baseline was not predictive of rhythm outcome 6 months after electrical cardioversion for persistent AF. Treatment with candesartan did not influence the levels of hs-TnI. Hs-TnI was unchanged from baseline to study end in patients who maintained sinus rhythm (4.9 (3.7, 7.0) and 5.0 (4.0, 6.4) ng/l, respectively; p = 0.699). Conclusions: hs-TnI did not predict AF recurrence after cardioversion. Hs-TnI levels were unchanged in patients maintaining sinus rhythm for 6 months after electrical cardioversion. Hs-TnI levels were not influenced by treatment with candesartan.

Introduction
Cardiac troponins are associated with incident atrial fibrillation (AF) [1–3], and with mortality and morbidity in AF patients [4–6]. High-sensitivity troponin T (hs-TnT) might have a modest but statistically significant prognostic power of recurrence of AF [7]. However, the ability of high-sensitivity troponin I (hs-TnI) to predict long-term cardioversion outcome in patients with persistent AF is not clear.

Identifying appropriate predictors of long-term successful cardioversion in AF patients may lead to better management strategies and improve the clinical outcome for selected patients as well as contribute to the understanding of AF pathophysiology [8]. Inflammatory markers have been associated with recurrence of AF [9, 10], although their prognostic abilities appear to be of limited value [11]. Plasminogen activator inhibitor type 1, an inhibitor of fibrinolysis, has also been shown to
forecast AF relapse after cardioversion [12]. Controversy still exists as to whether natriuretic peptides are predictive of rhythm stability, yet there are several reports of decreased levels after the restoration of sinus rhythm [7, 13–15].

While the prognostic role of cardiac troponins in AF has been well established, there is little information concerning whether the cardiac troponin levels remain constant or change over time. Maintaining sinus rhythm for 1 year has been associated with unchanged levels of hs-TnT [7]. Notably, Ulimoen et al. [16] found improved rate control to reduce hs-TnT in their patients with permanent AF. Angiotensin II type 1 receptor blocker (ARB) therapy may prevent atrial structural remodelling [17, 18], and attenuate troponin release in AF [19].

The aim of this study was to investigate whether hs-TnI was predictive of long-term cardioversion outcome, and whether restoration and maintenance of sinus rhythm for 6 months after cardioversion affected the levels of hs-TnI. In addition, the potential influence of candesartan on hs-TnI was analysed.

Methods

Study Design

This was a substudy of the double-blind, placebo-controlled Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study [20]. Briefly, 171 patients with AF were randomised to receive 8 mg of candesartan once daily (n = 86) or placebo (n = 85) for 3–6 weeks before electrical cardioversion and 16 mg of candesartan once daily or placebo for 6 months after electrical cardioversion. Patients with congestive heart failure or renal impairment were not included in the study. Cardioversion was deemed successful if sinus rhythm was established and maintained for at least 2 h. Relapse of AF was defined as the first electrocardiogram-recorded episode of AF. The CAPRAF study was approved by the Regional Ethics Committee (registered at www.clinicaltrials.gov; NCT00130975). All patients provided written, informed consent in accordance with the revised Declaration of Helsinki.

Troponin I Levels

Blood samples were collected at baseline and at the 6-month follow-up. Patients in whom AF recurred before this follow-up had their blood samples taken at the time of the recurrence. Venous blood samples were drawn between 8 and 9 a.m. after an overnight fast. Serum was prepared within 1 h by centrifugation at 2,000 g for 15 min at room temperature. All samples were kept frozen at –70°C and were later analysed in one batch. hs-TnI levels were determined using the ARCHITECTSTAT high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, Ill., USA), with a lower limit of detection of 1.2 ng/l. The 99th percentile upper reference limit for healthy individuals is reported to be 36 ng/l in men and 15 ng/l in women [21]. The coefficient of variation for this assay in our laboratory was 4.0–5.4%, depending on the hs-TnI concentrations.

| Table 1. Baseline characteristics |
|-----------------------------------|
| **Variable**                      | **n = 129** |
| **Medical history**               |            |
| Age, years                        | 64 ± 11 |
| Sex (women/men)                   | 26/103 |
| Body mass index                   | 26 ± 4 |
| Hypertension                      | 41 (32) |
| Coronary heart disease            | 10 (8) |
| Diabetes                          | 9 (7) |
| Chronic obstructive pulmonary disease | 7 (5) |
| Cardiopulmonary disease (hypertension, coronary heart disease and/or chronic obstructive pulmonary disease) | 52 (40) |
| Current cigarette smoking         | 18 (14) |
| **Medication**                    |            |
| Digitoxin                         | 17 (13) |
| Beta-blockers                     | 45 (35) |
| Verapamil                         | 43 (33) |
| Other calcium-channel blockers    | 15 (12) |
| Diuretics                         | 12 (9) |
| Statins                           | 16 (12) |
| **Blood pressure and heart rate** |          |
| Systolic blood pressure, mm Hg    | 135 ± 18 |
| Diastolic blood pressure, mm Hg   | 83 ± 9 |
| Ventricular heart rate, beats/min | 85 ± 16 |
| **Echocardiogram**                |            |
| Left atrial diameter (long-axis view), mm | 47 ± 6 |
| Left atrial area (apical four-chamber view), cm² | 28 ± 5 |
| Fractional shortening of the left ventricle, % | 29 ± 7 |

Values are presented as mean ± standard deviation or n (%).

Statistical Analysis

Data are presented as mean ± standard deviation for normally distributed variables, while continuous variables not normally distributed are expressed as a median (25th percentile, 75th percentile). Categorical variables are shown as frequencies (%). Continuous variables were analysed by the Student t test or the Mann-Whitney U test, depending on distribution. Categorical data were compared by the χ² test or the Fisher exact test where appropriate. The impact of continuous clinical variables on hs-TnI was analysed using bivariate non-parametric correlations (Spearman: correlation coefficient denoted as r). Kaplan-Meier curves for the probability of first recurrence of AF were plotted for quartiles of baseline concentrations of hs-TnI and compared by log-rank test. The relations between levels of hs-TnI at baseline and recurrence of AF were investigated by univariate Cox proportional hazard regression analyses. Concentrations of hs-TnI in patients who were in sinus rhythm compared with those in AF at study end were assessed by the Mann-Whitney U test. The Wilcoxon matched-pairs test was used to compare baseline and end-of-study levels of hs-TnI. The effects of study drug and rhythm outcome on hs-TnI lev-
Blood samples for the analysis of hs-TnI were available in 129 AF patients at baseline. Eighty percent of the study population were men. The mean age was 64 ± 11 years. The median duration of AF before randomisation was 11 weeks, but was unknown in 74 (57%) of the patients. Baseline characteristics are presented in table 1. hs-TnI was detectable in all subjects [5.3 ng/l (3.7, 7.2)]. Baseline concentrations of hs-TnI correlated with age (rs = 0.264; p = 0.003) and systolic blood pressure (rs = 0.348; p < 0.001). Men had higher levels than women [5.5 ng/l (3.8, 7.9) vs. 3.9 ng/l (3.0, 5.8); p = 0.007]. Subjects with cardiopulmonary disease (hypertension, coronary heart disease or chronic obstructive pulmonary disease) had higher values of hs-TnI than subjects without [5.9 ng/l (4.2, 8.2) vs. 4.3 ng/l (3.3, 6.5); p = 0.005].

The prognostic abilities of baseline levels of hs-TnI were assessed in 101 successfully cardioverted patients (fig. 1). Sixty-seven (67%) of these patients experienced a recurrence of AF in the 6 months of follow-up. The median time to recurrence was 8 days. hs-TnI levels at baseline were similar in the 34 patients who maintained sinus rhythm and the 67 who had a recurrence of AF, i.e. 5.2 (3.7, 7.0) and 5.3 (3.6, 7.5) ng/l, respectively (p = 0.980). Kaplan-Meier analysis of hs-TnI quartiles showed similar curves for survival free of AF for each quartile (log rank test; p = 0.916; fig. 2a). Kaplan-Meier analysis of the lowest and the highest hs-TnI quartiles showed similar curves (log rank test; p = 0.771; fig. 2b). There were no significant differences between the lowest and the highest hs-TnI quartile when analysing data with an end point of recurrence of within 30 days after electrical cardioversion (HR 0.75; 95% CI 0.36–1.56; p = 0.445).

Blood samples taken for the assessment of changes in hs-TnI from baseline to study end were available in 60 patients (fig. 1). In the 28 patients with sustained sinus rhythm, the hs-TnI levels at baseline were similar to those measured at 6 months after electrical cardioversion [4.9 (3.7, 7.0) and 5.0 (4.0, 6.4) ng/l, respectively; p = 0.699; fig. 3]. ANCOVA analysis showed neither any effect of sinus rhythm restoration (p = 0.139) nor any impact of candesartan (p = 0.786) on hs-TnI.

**Discussion**

In this randomised, placebo-controlled, double-blind study on AF patients, hs-TnI was detectable in all subjects with available blood samples. hs-TnI did not predict relapse of AF after electrical cardioversion. We could not demonstrate any effect of treatment with the ARB candesartan on hs-TnI release in this population. hs-TnI levels were unchanged in patients who maintained sinus rhythm for 6 months after electrical cardioversion.

Male gender, greater age and concomitant cardiopulmonary disease were associated with higher concentrations of hs-TnI, in agreement with other reports [4, 5]. hs-TnI was not predictive of rhythm outcome in our study, in contrast to Latini et al. [7], who found hs-TnT to independently predict a higher risk of recurrence of AF. These contradictory results may reflect the different study designs; baseline hs-TnI was obtained before electrical cardioversion in our study, whereas Latini et al. [7] included AF patients who were currently in sinus rhythm, regardless of the means of sinus rhythm restoration. Concomitant cardiovascular diseases were also less prevalent in our data.
hs-TnI and hs-TnT concentrations appear to be only moderately correlated [22, 23], which may also have contributed to the discrepancies between the 2 studies.

Our conclusion is in contrast to an emerging body of evidence highlighting the predictive role of cardiac troponins in AF. Conducting assessments with novel, high-sensitivity assays, Hijazi et al. [4, 5] have elegantly displayed the prognostic abilities of cardiac troponins regarding mortality and morbidity in AF. Furthermore, cardiac troponins have been associated with new-onset AF in patients admitted to hospital with acute ischaemic stroke [24] and also with incident AF in community-based cohorts [1–3]. On the other hand, the evidence of any predictive abilities of cardiac troponins in rhythm outcome after electrical cardioversion is scarce, and the results regarding ablation outcome are conflicting [25, 26]. Considering that no survival advantage has been shown from a rhythm control strategy in AF [27], one should perhaps not expect predictors of recurrence and mortality in AF to overlap.

Maintenance of sinus rhythm for 6 months after cardioversion did not affect the levels of hs-TnI in this study. The notable stability of troponin release in patients who remained in sinus rhythm is in contrast to reports of a subsequent decrease in natriuretic peptides when sinus rhythm has been restored [13–15], which is possibly explained by relief of atrial stretch. Despite an initial decline, natriuretic peptides were observed to remain significantly elevated after 180 days of sinus rhythm in AF patients without cardiac comorbidity when compared to a control group of healthy individuals [15]. Regarding inflammatory markers, controversy still exists as to whether AF begets inflammation or whether inflammation acts...
as a background substrate for AF [9–11]. One might speculate that persisting biomarker release in successfully cardioverted patients mirrors the underlying pathophysiological process, resulting in high recurrence rates after cardioversion, sustained hypercoagulability despite sinus rhythm restoration and no survival benefit from strategies of rhythm control versus rate control, but these assumptions need further investigation.

No effect of treatment with candesartan on the hs-TnI levels was found in this study, despite a correlation between hs-TnI and systolic blood pressure at baseline. Mean systolic blood pressure was significantly lowered by treatment with candesartan compared to the placebo group, as previously published [20]. However, one may hypothesize that a longer follow-up period would have shown an effect of candesartan on hs-TnI levels, as ARBs may take years to influence the arrhythmogenic substrate [28].

There is no generally accepted explanation for sustained cardiac troponin release in AF patients, and controversy concerning troponin release in the absence of cardiac cell death still exists [29]. It has been suggested that smaller immunoreactive troponin fragments reach the bloodstream as part of the cellular unleash of proteolytic degradation products [29, 30]. Alternative mechanisms for troponin leakage include apoptosis and cardiomyocyte renewal, although the clinical relevance of physiological cell turnover has been debated [31, 32]. Troponins might be released via cell membrane blistering in cultured myocytes, but in vivo studies are lacking [33]. On the other hand, a transient increase in the permeability of the cell wall due to myocardial stretch could allow troponins from the cytosol to reach the bloodstream [34]. While the mechanism of low-level troponin release remains obscure, Hijazi et al. [35] highlighted the importance of persistent troponin elevation in AF patients by reporting a significant increase in the risk for cardiovascular events and mortality when compared to patients with transient or no troponin elevation.

Study Limitations

This study was a substudy of the CAPRAF study, and was not primarily designed to test the predictive abilities of hs-TnI in electrical cardioversion for AF. We acknowledge the limitations of a post hoc analysis, and emphasize that our results should be interpreted with caution. The number of patients from whom blood samples were available at both baseline and study end was small. To this end, this study may have been underpowered to detect minor effects of sinus rhythm restoration or treatment with candesartan. The exposure time to candesartan was short and the dose was relatively low; we therefore cannot exclude the possibility that a longer exposure time and/or higher dosage may have yielded different results. Patients with heart failure or renal impairment were not included in the study. Hence, an effect caused by sinus rhythm restoration or treatment with ARBs on the hs-TnI levels in such patients cannot be excluded.

Conclusions

hs-TnI measured before electrical cardioversion for persistent AF did not predict long-term maintenance of sinus rhythm after the procedure. hs-TnI levels were unchanged in patients maintaining sinus rhythm for 6 months after electrical cardioversion. Treatment with candesartan was not found to have any impact on hs-TnI levels.

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Conflict of Interest

The authors have disclosed that there were no conflicts of interest.

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