Fatigue as Presenting Symptom and a High Burden of Premature Ventricular Contractions Are Independently Associated with Increased Ventricular Wall Stress in Patients with Normal Left Ventricular Function

Running title: van Huls van Taxis et al.; PVC-induced increased wall stress and fatigue

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Abstract:

**Background** - High idiopathic premature ventricular contractions (PVC) burden has been associated with PVC-induced cardiomyopathy. Patients may be symptomatic before left ventricular (LV) dysfunction develops. NT-proBNP and circumferential end-systolic wall stress (cESS) on echocardiography are markers for increased ventricular wall stress. This study aimed to evaluate the relation between presenting symptoms, PVC-burden and increased ventricular wall stress in patients with frequent PVCs and preserved LV function.

**Methods and Results** - Eighty-three patients (41 male, 49±15yrs) with idiopathic PVCs and normal LV function referred for PVC-ablation, were included. Type of symptoms (palpitations, fatigue, [near-]syncope), PVC-burden on 24-hour Holter, NT-proBNP levels and cESS on echocardiography were assessed before and 3 months after ablation. Sustained successful ablation was defined as ≥80% PVC-burden reduction during follow-up. Patients were symptomatic for 24 months (Q1-Q3 16-60); 73% reported palpitations, 47% fatigue, and 30% (near-)syncope. Baseline PVC burden was 23±13%, median NT-proBNP 92pg/mL(Q1-Q3 50-156) and cESS 143±35kdyne/cm². Fatigue was associated with higher baseline NT proBNP and cESS (p<0.001, p=0.011, respectively). After sustained successful ablation, achieved in 81%, NT-proBNP and cESS decreased significantly (p<0.001, p=0.036, respectively). Fatigue was independently associated with a significantly larger reduction in NT-proBNP. In patients with non-successful ablation NT-proBNP and cESS remained unchanged.

**Conclusions** - In patients with frequent PVCs and preserved LV function, fatigue was associated with higher baseline NT-proBNP and cESS, and with a significantly larger reduction in NT-proBNP after SSA. These findings support a link between fatigue and PVC-induced increased ventricular wall stress, despite preserved LV function.

**Key words**: ventricular arrhythmia; catheter ablation; biomarker; wall stress; symptoms
Introduction

Premature ventricular contractions (PVCs) in the absence of structural heart disease are a common entity in the general population. While sporadic idiopathic PVCs are generally considered benign, a high PVC burden, a broad PVC-QRS, longstanding palpitations, but also the absence of symptoms, have been associated with PVC-induced cardiomyopathy.\(^1-4\) Accepted indications for catheter ablation are frequent PVCs which are presumed to cause ventricular dysfunction\(^5\) and the presence of severe symptoms, when antiarrhythmic drugs are not effective, tolerated or desired.\(^6\) Notably, catheter ablation is considered contraindicated for asymptomatic patients with PVCs that are not suspected of causing and/or contributing to ventricular dysfunction.\(^5\) The relation between presenting symptoms and PVCs may however be indefinite in patients with normal LV function and non-specific complaints such as fatigue and consequently, the potential benefit of PVC ablation in these patients is unclear.

B-type natriuretic peptide (BNP) and, more sensitive, N-terminal proBNP (NT-proBNP) have been used to monitor heart failure, and elevated BNP levels have been found in patients with symptomatic idiopathic PVCs.\(^7,9\) The main stimulus for (NT-pro)BNP secretion is myocardial wall stress.\(^9,10\) Prior studies suggest that BNP may serve as a sensitive marker to detect PVC-induced increased ventricular wall stress, with unclear clinical relevance in the presence of normal LV function.\(^7,8\) Circumferential end-systolic wall stress (cESS) on echocardiography has also been proposed as a marker for ventricular wall stress.\(^11\) Increased ventricular wall stress may be related to fatigue as presenting symptom and perhaps to PVC-induced cardiomyopathy. The objectives of the current study were to evaluate the relation between presenting symptoms, PVC characteristics and markers of increased ventricular wall stress in patients with preserved LV function undergoing PVC ablation.
Methods

Patients

The cohort consisted of consecutive patients with frequent idiopathic PVC and a normal LV function who underwent PVC ablation in the Leiden University Medical Center between July 2007 and June 2012. Reasons for referral were a high PVC burden, symptomatic frequent PVCs causing palpitations, (near-) syncope, or presumed symptomatic PVCs, if fatigue was the dominant presenting symptom. Fatigue was defined as reduced exercise tolerance or disproportionate tiredness interfering with normal daily affairs such as work, family matters, and/or social life. Antiarrhythmic drugs were not effective, tolerated or desired in all patients to control the presenting symptoms.

Before ablation, a detailed medical history was obtained, which included careful evaluation of presenting symptoms, duration of symptoms and anti-arrhythmic drug usage. Presenting symptoms were categorized as palpitations, (near-)syncope and fatigue. Effort was taken to review all prior ECGs and Holter monitoring to determine the time of first PVC documentation. Clinical evaluation was performed in all patients, including physical examination, a 12-lead ECG recording of the PVC, 24-hour Holter monitoring and transthoracic echocardiography. Coronary artery disease and structural heart disease were further excluded by exercise testing, coronary angiography, cardiac multi-detector computed tomography and/or magnetic resonance imaging if indicated. All patients were treated according to the routine clinical protocol and provided informed consent.

ECG and Holter analysis

PVC morphology, PVC-QRS duration, and PVC coupling interval were derived from the 12-lead ECG and during the ablation procedure by using digital calipers at 200mm/s on the
electrophysiology recording system (Prucka Engineering, Houston, TX, USA). The coupling interval was defined as the interval from the earliest onset of the preceding sinus beat QRS complex to the earliest onset of the PVC-QRS complex in any lead. A right bundle branch block (BBB)-like morphology was defined as a dominant positive deflection in V1 and a left BBB as a dominant negative deflection in V1. PVC burden was defined as the percentage PVCs of the total number of QRS complexes during 24 hours. In case of multiple PVC morphologies, the BBB and QRS duration of the dominant morphology was used for analyses.

**Echocardiography**

Two-dimensional echocardiography and color Doppler data were obtained in parasternal (short- and long-axis) and apical views using a commercially available ultrasound system (Vivid 7, General Electric Vingmed, Milwaukee, WI). All images were stored in cine-loop format for offline analyses with EchoPac 108.1.5 (General Electric Medical Systems, Horten, Norway). Echocardiographic measurements were performed on sinus beats, avoiding the first postextrasystolic beat if feasible. LV end-diastolic and end-systolic volumes were obtained from the apical 2- and 4-chamber views and LV ejection fraction was calculated according to the biplane Simpson's method.

In addition, circumferential end-systolic wall stress was calculated using LV end-systolic dimension and posterior wall thickness at end-systole. Circumferential end-systolic wall stress was calculated according to the previously described formula:

\[
\text{cESS} = \text{Systolic BP} \times a^2 \times (1+b^2/c^2) \times 1/(b^2-a^2)
\]

where \(a = (\text{LV end-systolic dimension}/2)\), \(b = (\text{LV end-systolic dimension}/2) + (\text{posterior wall thickness at end-systole})\), \(c = (\text{LV end-systolic dimension}/2) + (\text{posterior wall thickness at end-systole}/2)\). All echocardiographic analyses were performed by an independent experienced
observer, blinded to all clinical and procedural data.

**NT-proBNP**

Serum NT-proBNP level was measured before ablation using an automated immunoassay (Elecsys, Roche, Basel, Switzerland). NT-proBNP level $\geq 125$pg/mL was considered abnormal.$^{13}$ The estimated Glomerular Filtration Rate (ml/min/1.73m²) was calculated to exclude renal dysfunction as a cause for increased NT-proBNP concentrations.$^{14}$

**Mapping and radiofrequency catheter ablation**

Anti-arrhythmic drugs were discontinued for at least 5 half-lives. Heparin was administered to maintain an activated clotting time of 250-300s. The right ventricle (RV) was accessed via the femoral vein and the aortic sinus cusps and the LV via a retrograde approach. Using a 3.5mm or 4mm irrigated-tip catheter (NaviStar ThermoCool, Biosense Webster; or Cool Path, St. Jude Medical) and a 3-D non-fluoroscopic mapping system (CARTO XP, Biosense Webster; or EnSite NavX, St. Jude Medical), limited electroanatomic mapping of the target area was performed to identify the site of origin of the PVC. If PVCs were not present at baseline, isoproterenol was administered (2-10$\mu$g/min) and programmed electrical stimulation was performed. The stimulation protocol consisted of 3 drive-cycle lengths (600, 500 and 400ms) with up to 3 ventricular extra stimuli and incremental burst pacing from 2 RV sites.

Ablation target sites were selected based on local activation time, unipolar QS-pattern and presence of reversed polarity.$^{15}$ Radiofrequency energy was applied at 20-45W depending on the location (maximum temperature 45°C, flow 20-30ml/min, 60s). If the PVC was abolished by radiofrequency delivery without recurrence after 30 minutes monitoring this site was defined as site of origin, and categorized as RV or LV site. The procedure was considered acutely successful when the targeted PVC did not recur spontaneously and could not be evoked by
isoproterenol infusion or programmed electrical stimulation.

**Follow-up**

After the procedure patients were monitored for 24 hours to detect early PVC recurrence. All patients were re-evaluated at the outpatient clinic at 3 months. Additional follow-up was scheduled if clinically indicated. The re-evaluation consisted of careful history regarding the symptoms that were present before ablation, 12-lead ECGs, 24-hour Holter monitoring, transthoracic echocardiography and NT-proBNP measurement. Sustained successful ablation (SSA) was defined as a PVC burden reduction of ≥80% on 24-hour Holter monitoring during follow-up.1-3,16

**Statistical analysis**

Categorical variables are expressed as number (percentage) and continuous variables as mean±standard deviation or median (quartiles 1-3 [Q1-Q3]) as appropriate. Differences between patient groups were analyzed using the chi-squared test, Fisher’s exact test, student’s t-test, or Mann-Whitney U test, as appropriate. For linear regression analysis, NT-proBNP levels were log-transformed because of the skewed distribution. Parameters listed in Table 1 that were associated with NT-proBNP levels or cESS in univariate analysis (inclusion p<0.05) were included in a multivariate model (age, sex, hypertension, body mass index [BMI]). The percent increase in NT-proBNP per percent PVC burden was calculated by reversed transformation.

Differences between baseline and follow-up measurements were analyzed using the paired t-test or Wilcoxon signed rank test. In patients with SSA, the relation between the baseline variables, including previously described risk factors for PVC induced cardiomyopathy, provided in Table 1 and both NT-proBNP levels and cESS were analyzed by Mann-Whitney U tests or student’s t-tests and linear regression analysis for dichotomous and continuous baseline
variables, respectively. For paired data (for example pre- versus post procedure NT-proBNP values) no adjustment for confounding was deemed necessary given the paired design of the analysis. Statistical analysis was performed using SPSS, version 20.0 (IBM, Somers, New York, USA). P-values were all 2-sided and a p-value of <0.05 was considered statistically significant.

**Results**

**Patient characteristics**

Eighty-three patients (41 male [49%], 49±15 years) with 24-hour Holter-derived PVC burden of 23±13% were included in the analyses. At first presentation sixty-one patients (73%) reported palpitations, 25 (30%) (near-)syncope and 39 (47%) fatigue. Eight patients (10%) were asymptomatic. In 73 patients 2±1 anti-arrhythmic drugs failed to control presenting symptoms and/or reduce PVC burden; 10 patients refused to take drugs.

Despite a normal LV function and volume indices, seventy-four patients (89%) had at least one clinical or PVC parameter that has been associated with PVC-induced cardiomyopathy in prior studies; 41 patients (49%) had a PVC burden ≥24%, 53 patients (64%) had a PVC-QRS duration ≥150ms and 40 patients (48%) had symptoms lasting ≥30 months. Table 1 summarizes baseline clinical parameters, PVC characteristics and echocardiographic results.

Median NT-proBNP was 92pg/mL (Q1-Q3 50-156pg/mL) before ablation. In 34 patients (41%) baseline NT-proBNP level was elevated (>125pg/mL).13 Only one patient had reduced renal function (GFR 56ml/min). The average cESS on echocardiography was 143±35kdyne/cm².

**Markers of ventricular wall stress, presenting symptoms and PVC characteristics**

Patients presenting with symptoms of fatigue had significantly higher NT-proBNP concentrations compared to patients without fatigue (144pg/mL [Q1-Q3 107-359pg/mL] versus 52pg/mL [Q1-Q3 28-87pg/mL], p<0.001). This result remained significant after adjustment in a
multivariate model for age, sex, hypertension and BMI (p<0.001). In addition, cESS was significantly higher in patients with fatigue compared to patients without fatigue (153±38kdyne/cm² versus 134±30kdyne/cm², p=0.011). After adjusting for age, sex, hypertension and BMI in a multivariate model this remained significant (p=0.010). No differences were observed in NT-proBNP concentration or in cESS between patients with or without palpitations, with or without (near-)syncope or with shorter or longer duration of symptoms (Figure 1). A multivariate model strengthened these results when correcting for age, sex, hypertension and BMI. A left-sided site of origin, a right BBB-like PVC morphology and in particular a PVC burden ≥24% were associated with higher NT-proBNP concentration. Only a left-sided origin of the PVC was associated with a higher cESS (Figure 1). A significant, although weak, correlation between PVC burden and log-transformed NT-proBNP could be demonstrated; 1% PVC burden increase resulted in 4% increase in NT-proBNP (Figure 2).

The following variables were associated with significantly higher baseline log-transformed NT-proBNP levels in univariate analysis and were therefore included in a multivariate model: age, hypertension, LV site of origin, PVC right BBB, PVC burden and fatigue. Fatigue, LV site of origin and PVC burden remained independently associated with baseline log-transformed NT-proBNP levels (p<0.001, p=0.044 and p=0.015, respectively).

Variables that were associated with high baseline cESS in univariate analysis were: fatigue, LV site of origin, LVEF, LVEDV-I and LVESV-I. These variables were included in a multivariate model and fatigue and LV site of origin remained independently associated with baseline cESS (p=0.003 and p=0.017, respectively).

Mapping and radiofrequency catheter ablation

Acute procedural success was achieved in 68 patients (82%). The site of origin was the RV in 49
patients (59%) and the LV in 34 patients (41%). In 13 patients (16%) catheter ablation was only temporarily successful or not effective likely due to an intramural/epicardial site of origin. In 2 patients (2%) radiofrequency delivery was withheld due to the proximity of the His-bundle and the ostium of the right coronary artery, respectively. Procedure and fluoroscopy times were 140±48 minutes and 16±11 minutes. There were no procedure-related complications and no early PVC recurrence was observed.

Follow-up
Re-evaluation after 3 months was completed in 80 patients (96%); 2 patients did not undergo 24-hour Holter monitoring and 1 did not undergo echocardiography. A sustained PVC burden reduction of ≥80% on 24-hour Holter monitoring was achieved in 67 patients (81%); all were asymptomatic for the presenting symptoms, including the pre-procedural complaints of fatigue. This included the 2 patients in which 24-hour Holter monitoring was not performed during follow-up, however both were highly symptomatic before and free of any symptoms after ablation and were therefore considered as having SSA. In one patient ablation was acutely not successful, but a sustained PVC reduction was achieved by flecainide. Patients with SSA demonstrated a small but significant reduction in LVEDV-I; from 57±14ml/m² to 54±15ml/m² (p=0.039), and LVESV-I; from 23±8ml/m² to 21±9ml/m² (p=0.013). LV ejection fraction did not change during follow-up (60±6% versus 61±8%, p=0.341).

In the 16 patients without SSA, presenting symptoms, LV ejection fraction and volume indices remained unchanged, although the average PVC burden was lower (from 21±14% to 13±12%, p=0.002). Six of these patients were on anti-arrhythmic drugs during follow-up.

Changes in NT-proBNP level and wall stress on echocardiography
In a total of 71 patients the NT-proBNP concentration was measured during follow-up. In the 59
patients with SSA in whom NT-proBNP was measured during follow-up, NT-proBNP decreased significantly from 93pg/mL (Q1-Q3 52-169pg/mL) to 53pg/mL (Q1-Q3 37-90pg/mL) (p<0.001) resulting in a ΔNT-proBNP of 37pg/mL (Q1-Q3 6-108pg/mL). In 51 of 59 patients (86%) NT-proBNP normalized to <125pg/mL.

Among patients with SSA, those presenting with fatigue showed a significantly larger decrease in NT-proBNP levels than patients without fatigue (ΔNT-proBNP 73pg/mL [Q1-Q3 38-209pg/mL] versus 19pg/mL [Q1-Q3 -7-38pg/mL], p<0.001) (Figure 3). When corrected for age, sex, hypertension and BMI in a multivariate model it remained significant (p=0.034). Patients with a baseline PVC burden ≥24% before ablation also demonstrated a significantly larger decrease in NT-proBNP levels after SSA if compared to those with a burden of less than 24% (ΔNT-proBNP 68pg/mL [Q1-Q3 29-237pg/mL] versus 23pg/mL [Q1-Q3 -1-74pg/mL], p=0.015). When adjusting for age, sex, hypertension and BMI in multivariate analysis ΔNT-proBNP remained significantly larger in the patients with a high burden (p=0.004). Other presenting symptoms or PVC characteristics did not correlate with an important decrease in NT-proBNP levels (Figure 4).

Circumferential end-systolic wall stress decreased after SSA from 144±35kdyne/cm² at baseline to 134±35kdyne/cm² during follow-up (p=0.036), resulting in a median ΔcESS of 11kdyne/cm² (Q1-Q3 -12-34kdyne/cm²) in this group. No difference in ΔcESS was observed between patients with or without fatigue (p=0.955). Only a LV site of origin was associated with a larger decrease in cESS after SSA (Figure 4) which remained independently associated in multivariate regression analysis after adjusting for age, sex, hypertension and BMI (p=0.008). In patients without SSA, no significant changes in NT-proBNP or cESS were observed (from 84pg/mL [38-132pg/mL] to 67pg/mL [Q1-Q3 41-86pg/mL], p=0.272; from 142±45kdyne/cm² to
138±45kdyne/cm², p=0.778, respectively).

**Discussion**

The main findings of the present study are that (1) NT-proBNP levels are elevated in 41% of patients with a preserved LV function who undergo catheter ablation for frequent PVCs. (2) Both NT-proBNP levels and cESS on echocardiography decreased after SSA, but not after non-SSA. (3) Symptoms of fatigue and a higher PVC burden are independently associated with higher NT-proBNP levels prior to ablation, and were the only studied parameters associated with a significantly larger decrease of NT-proBNP levels after SSA. (4) Symptoms of fatigue were also associated with increased baseline cESS on echocardiography, but not with a significantly larger decrease after SSA.

**Presenting symptoms, PVC characteristics and wall stress**

Palpitations and (near)syncope are typical PVC-related symptoms whereas fatigue is often not reported or considered to be a nonspecific or atypical symptom. In our cohort fatigue was present at baseline in 47% of the patients despite a normal LV function. Of importance, fatigue was independently associated with higher NT-proBNP levels and cESS at baseline and patients with fatigue showed a significantly larger decrease in NT-proBNP levels after SSA compared to patients with only classical PVC related symptoms. In addition, compared to prior reported cESS values in patients with normal LV geometry, cESS was considerably higher in patients with fatigue, but not in patients without fatigue. These data suggest that fatigue in patients with PVCs may be caused by PVC-induced wall stress in the absence of LV dysfunction, and that fatigue should therefore be considered as clinically relevant and PVC-related symptom.

An important number of patients with fatigue had elevated NT-proBNP levels despite a PVC-burden lower than 25%. The significant decrease in NT-proBNP level and cESS, accompanied
by the relief of symptoms of fatigue after SSA, may therefore justify catheter ablation even if the PVC burden is below the currently suggested cut-off value.¹

Marker of increased ventricular wall stress and risk factors for PVC induced cardiomyopathy

Longstanding palpitations, a high PVC burden, a broad PVC-QRS and a non-outflow tract (predominantly LV) site of origin are potential risk factors for a PVC-induced cardiomyopathy.¹

In addition, asymptomatic patients, in whom the duration of PVC cannot be evaluated, have been considered to be particularly prone to develop a cardiomyopathy.⁴ Interestingly, we found that fatigue, which is not systematically reported as a PVC related symptom in prior studies, the LV site of origin and PVC burden were also all independently associated with increased NT-proBNP levels. In contrast, PVC-QRS and symptom duration were not. Of interest, although 40 patients of our cohort had already symptoms of more than 30 months, none had developed a PVC-induced cardiomyopathy before ablation. This finding does however not exclude that longstanding PVCs may remain a risk factor as 84% of our patients were successfully treated and PVC induced cardiomyopathy may develop over several years.²,¹⁷

Baseline cESS on echocardiography was associated with fatigue and a left-sided origin of PVCs, but not with any of the other parameters that have previously been associated with PVC-induced cardiomyopathy, including PVC burden. These findings suggest that cESS may perhaps be a less sensitive marker than NT-proBNP for detection of PVC induced increased ventricular wall stress.

Biomarker as a sensitive indicator for PVC induced wall stress

Two prior studies have reported elevated BNP levels in up to 64% of patients without LV dysfunction who underwent ablation for both idiopathic VTs and PVC.⁷,⁸ Compared to the 41%
of patients with elevated NT-proBNP levels in our study this percentage is remarkably high, in particular as prior published data have demonstrated that NT-proBNP is an even more sensitive marker to detect LV dysfunction.\textsuperscript{18} The high BNP levels decreased to normal levels in around 61% after successful ablation.\textsuperscript{8} Both prior reports found a correlation between BNP levels before ablation and PVC burden, which is in line with our data.

However, included patients were older and an independent predictor of elevated BNP levels was controlled hypertension. It is likely that LV hypertrophy and diastolic dysfunction due to aging and hypertension may contribute to the higher prevalence of increased BNP level in these prior reports.

In our patient cohort fatigue was associated with a higher PVC burden, NT-proBNP levels and cESS at baseline, and also with a significantly larger decrease in NT-proBNP levels after SSA, supporting the premise that increased wall stress may possibly cause fatigue. In the non-SSA group a trend towards a decrease in NT-proBNP was shown which may be explained by a significant (but less than the predefined 80%) PVC burden reduction in this group. NT-proBNP, which is likely a more sensitive marker for ventricular wall stress and widely applied, may also be preferable over cESS for detection of increased ventricular wall stress in patients with frequent PVCs and fatigue. Whether patients with fatigue and elevated NT-proBNP levels as biomarker for increased wall stress are also more likely to develop a PVC-induced cardiomyopathy requires further investigation.

**Limitations**

NT-proBNP levels and cESS were measured only twice, immediately prior to ablation and 3 months after ablation. The currently described patient cohort is unlikely to be representative for the general population of patients with PVCs as all patients were referred for ablation because of
the PVC burden, symptoms or patient’s preference. As we did not follow patients with frequent PVCs and fatigue without intervention we can only speculate about the potential relation between fatigue, PVC burden, and PVC induced wall stress, and development of LV dysfunction. Furthermore, we recognize that fatigue is a nonspecific symptom and subjective to individual interpretation and therefore difficult to quantify.

**Clinical implications**

According to current recommendations, catheter ablation can be useful in patients with frequent symptomatic PVCs if antiarrhythmic drugs are not effective, tolerated or desired. Ablation is not indicated for asymptomatic PVCs that are not suspected of causing or contributing to ventricular dysfunction.

We could demonstrate for the first time that fatigue, which is often considered a nonspecific symptom and not typically related to PVCs, was associated with elevated NT-proBNP levels and cESS on echocardiography. NT-proBNP and cESS are markers for wall stress and both normalized after successful ablation accompanied by relief of symptoms of fatigue. Although we cannot prove causality, our findings suggest that fatigue may be associated with PVC-induced ventricular wall stress, which can be successfully treated by catheter ablation. In the light of the current findings, clinicians may therefore consider catheter ablation of PVCs in patients presenting only with fatigue, even in the absence of LV dysfunction, classical PVC related symptoms (such as palpitations or (near-)syncope), or a certain PVC burden. Whether elevated NT-proBNP level and fatigue as presenting symptom identify patients at risk to develop PVC-induced cardiomyopathy requires further investigation.

**Conclusion**

In patients without LV dysfunction undergoing PVC ablation, fatigue was independently
associated with higher NT-proBNP concentrations and cESS at baseline, and with a significantly larger reduction of NT-proBNP levels after SSA. These findings suggest that fatigue may be caused by PVC-induced increased ventricular wall stress, even in patients with a preserved LV function. Patients with fatigue and/or elevated NT-proBNP levels may benefit from ablation even in the absence of classical PVC related symptoms or LV dysfunction.

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**Conflict of Interest Disclosures:** None.

**References:**


College of Cardiology (ACC) and the American Heart Association (AHA). *Heart Rhythm*. 2009;6:886-933.


Table 1: Baseline characteristics (n=83)

<table>
<thead>
<tr>
<th></th>
<th>All N=83</th>
<th>No fatigue N=44</th>
<th>Fatigue N=39</th>
<th>P-value*</th>
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<tbody>
<tr>
<td>Male, n(%)</td>
<td>41(49)</td>
<td>24(55)</td>
<td>17(44)</td>
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<tr>
<td>Age, years</td>
<td>49±15</td>
<td>45±14</td>
<td>54±15</td>
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<td>Body mass index, kg/m²</td>
<td>27±5</td>
<td>26±4</td>
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<td>Hypertension, n(%)</td>
<td>24(29)</td>
<td>6(14)</td>
<td>18(46)</td>
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<td>eGFR, ml/min/1.73m²</td>
<td>81±22</td>
<td>83±22</td>
<td>79±22</td>
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<td>Anti-arrhythmic drugs failed, n</td>
<td>2±1</td>
<td>2±1</td>
<td>2±1</td>
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<td>β-blockade, n(%)</td>
<td>51(61)</td>
<td>27(61)</td>
<td>24(62)</td>
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<tr>
<td>Calcium-antagonist, n(%)</td>
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<td>9(20)</td>
<td>8(21)</td>
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<td>Flecainide, n(%)</td>
<td>20(24)</td>
<td>13(30)</td>
<td>7(20)</td>
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<td>Amiodarone/Sotalol, n(%)</td>
<td>40(48)</td>
<td>22(50)</td>
<td>18(46)</td>
<td>0.827</td>
</tr>
<tr>
<td>Symptom duration in months, median (Q1-Q3 )</td>
<td>24(16-60)</td>
<td>24(12-48)</td>
<td>36(19-61)</td>
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<td>Presenting symptoms:</td>
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<td>Palpitations, n(%)</td>
<td>61(73)</td>
<td>35(80)</td>
<td>26(67)</td>
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<td>Fatigue, n(%)</td>
<td>39(47)</td>
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<td>39(100)</td>
<td>-</td>
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<td>(near)Syncope, n(%)</td>
<td>25(31)</td>
<td>14(32)</td>
<td>11(28)</td>
<td>0.812</td>
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<td>PVC burden, %</td>
<td>23±13</td>
<td>19±11</td>
<td>28±13</td>
<td>0.002</td>
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<td>PVC characteristics</td>
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<tr>
<td>PVC-QRS duration, ms</td>
<td>159±21</td>
<td>162±20</td>
<td>155±22</td>
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<td>Coupling interval, ms</td>
<td>467±68</td>
<td>471±72</td>
<td>461±63</td>
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<td>Left bundle branch block, n(%)</td>
<td>65(78)</td>
<td>37(84)</td>
<td>28(72)</td>
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<td>Echocardiography parameters</td>
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<td>LV ejection fraction, %</td>
<td>60±6</td>
<td>61±6</td>
<td>60±6</td>
<td>0.538</td>
</tr>
<tr>
<td>LVEDV-index, ml/m²</td>
<td>58±15</td>
<td>60±15</td>
<td>55±14</td>
<td>0.171</td>
</tr>
<tr>
<td>LVESV-index, ml/m²</td>
<td>23±8</td>
<td>24±8</td>
<td>22±7</td>
<td>0.322</td>
</tr>
<tr>
<td>cESS, kdyne/cm²</td>
<td>143±35</td>
<td>134±30</td>
<td>153±38</td>
<td>0.011</td>
</tr>
</tbody>
</table>

cESS=circumferential end-systolic wall stress; EDV=end diastolic volume; ESV=end systolic volume; eGFR=estimated Glomerular Filtration Rate; LV=left ventricle; PVC=premature ventricular contraction.

*P-value calculated between patients with versus without fatigue.
Figure Legends:

**Figure 1:** Top panels: Baseline NT-proBNP according to symptoms and PVC characteristics. Median and interquartile range are depicted. Bottom panels: Baseline circumferential end-systolic wall stress (cESS) according to symptoms and PVC characteristics. Mean with standard deviation are depicted.

**Figure 2:** Correlation between NT-proBNP and PVC burden according to patients with and without fatigue. Linear regression analyses for NT-proBNP and PVC burden. Red dots and line demonstrate patients with fatigue, blue squares and line patients without fatigue. Regression analysis was calculated for patients with versus without fatigue. The grey dotted lines illustrate the PVC-burden cut off value of 24% and NT-proBNP cut off value of 125pg/mL. The y-axis is log-scaled.

**Figure 3:** NT-proBNP levels before and after sustained successful ablation (SSA), in patients with and without fatigue. The y-axis is log-scaled. The boxplots demonstrate the median, quartiles 1-3 and 95% confidence interval.

**Figure 4:** Sustained Successful Ablation: Top panels: ΔNT-proBNP after sustained successful ablation according to symptoms and PVC characteristics. Median and quartiles 1-3 are depicted. Bottom panels: Δcircumferential end-systolic wall stress (ΔcESS) after sustained successful ablation according to symptoms and PVC characteristics. Median and quartiles 1-3 are depicted.
The graph illustrates the relationship between NT-proBNP (pg/mL) and PVC burden (%) for two groups: Fatigue and No Fatigue. The red line represents the Fatigue group, and the blue line represents the No Fatigue group. The graph shows a positive correlation between NT-proBNP levels and PVC burden, with a higher percentage of PVC burden associated with higher NT-proBNP levels.

Key points:
- The vertical line at 24% PVC burden indicates a significant threshold.
- The horizontal line at 125pg/mL NT-proBNP is a reference point.
- The area above 125pg/mL NT-proBNP for PVC burden above 24% is shaded.
- The statistical significance is indicated by P<0.001 and R²=0.197.

This graph suggests that patients with higher PVC burden are more likely to have higher NT-proBNP levels, which may be indicative of underlying cardiac stress or dysfunction.
Fatigue

$\Delta$NT-proBNP: 73 (38-209)

No fatigue

$\Delta$NT-proBNP: 19 (-7-38)

$p<0.001$

$10^0$

$10^1$

$10^2$

$10^3$

$10^4$

$10^5$

$10^6$

$10^7$

Pre ablation

after SSA

Pre ablation

after SSA

$p<0.001$

$p=0.021$
Fatigue as Presenting Symptom and a High Burden of Premature Ventricular Contractions Are Independently Associated with Increased Ventricular Wall Stress in Patients with Normal Left Ventricular Function
Carine F.B. van Huls van Taxis, Sebastiaan R.D. Piers, Marta de Riva Silva, Olaf M. Dekkers, Daniël A. Pijnappels, Martin J. Schalij, Adrianus P. Wijnmaalen and Katja Zeppenfeld

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