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, MD; Sebastiaan R.D. Piers, MD; Marta de Riva Silva, MD; Olaf M. Dekkers, PhD; Daniël A. Pijnappels, PhD; Martin J. Schalij, MD, PhD; Adrianus P. Wijnmaalen, MD, PhD; Katja Zeppenfeld, MD, PhD

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. N-terminal pro-B-type natriuretic peptide (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 men; 49±15 years) with idiopathic PVCs and normal LV function referred for PVC ablation were included. Type of symptoms (palpitations, fatigue, and [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 92 pg/mL (Q1–Q3 50–156), and cESS 143±35 kdyne/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 and P=0.036, respectively). Fatigue was independently associated with a significantly larger reduction in NT-proBNP. In patients with nonsuccessful 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 sustained successful ablation. These findings support a link between fatigue and PVC-induced increased ventricular wall stress, despite preserved LV function. (Circ Arrhythm Electrophysiol. 2015;8:1452-1459. DOI: 10.1161/CIRCEP.115.003091.)

Key Words: arrhythmias ■ cardiac symptom evaluation ■ catheter ablation ■ natriuretic peptide, brain
WHAT IS KNOWN
• High PVC burden, a broad PVC-QRS, longstanding palpitations and absence of symptoms have been associated with PVC-induced cardiomyopathy
• Fatigue is often considered a nonspecific symptom and its association with frequent idiopathic PVCs in patients with preserved LV function is unclear

WHAT THE STUDY ADDS
• 47% of patients with frequent idiopathic PVCs and preserved LV function experience fatigue
• Fatigue is associated with increased PVC-induced ventricular wall stress, determined by elevated NT-proBNP levels and circumferential end-systolic wall stress on echocardiography, and can be successfully treated by catheter ablation
• 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 or a certain PVC burden.

The preceding sinus beat QRS complex to the earliest onset of the PVC-QRS complex in any lead. A right bundle branch block-like morphology was defined as a dominant positive deflection in V1, and a left bundle branch block 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 bundle branch block and QRS duration of the dominant morphology were used for analyses.

Echocardiography
Two-dimensional echocardiography and color Doppler data were obtained in parasternal (short and long axes) 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, cESS was calculated using LV end-systolic dimension and posterior wall thickness at end-systole. cESS was calculated according to the previously described formula:

\[ \text{cESS} = \text{systolic blood pressure} \times a^2 \times (1 + b^2 / c^2) \times 11 / (b^2 - a^2) \]

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.

N-Terminal proBNP
Serum NT-proBNP level was measured before ablation using an automated immunoassay (Elecsys, Roche, Basel, Switzerland). NT-proBNP level ≥125 pg/mL was considered abnormal. The estimated glomerular filtration rate (mL/min per 1.73 m\(^2\)) was calculated to exclude renal dysfunction as a cause for increased NT-proBNP concentrations.

Mapping and Radiofrequency Catheter Ablation
Antiarrhythmic drugs were discontinued for at least 5 half-lives. Heparin was administered to maintain an activated clotting time of 250 to 300. The right ventricle was accessed via the femoral vein and the aortic sinus cusps and the LV via a retrograde approach. Using a 3.5 mm or 4 mm irrigated-tip catheter (Navistar ThermoCool, Biosense Webster or Cool Path, St. Jude Medical) and a 3-D nonfluoroscopic 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 µg/min), and programmed electrical stimulation was performed. The stimulation protocol consisted of 3 drive-cycle lengths (600, 500, and 400 ms) with ≤3 ventricular extra stimuli and incremental burst pacing from 2 right ventricular sites.

Ablation target sites were selected based on local activation time, unipolar QS-pattern, and presence of reversed polarity. Radiofrequency energy was applied at 20 to 45 W depending on the location (maximum temperature 45°C, flow 20–30 mL/min, 60 s). If the PVC was abolished by radiofrequency delivery without recurrence after 30 minutes of monitoring, this site was defined as site of origin and categorized as right ventricular 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 reevaluated at the outpatient clinic at 3 months. Additional follow-up was scheduled if clinically indicated. The reevaluation 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±SD or median (quartiles 1–3 [Q1–Q3]) as appropriate. Differences between patient groups were analyzed using the χ² test, Fisher exact test, Student 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 the Table 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 relationship between the baseline variables, including previously described risk factors for PVC-induced cardiomyopathy, provided in the Table and both NT-proBNP levels and cESS were analyzed by Mann–Whitney U tests or Student t tests and linear regression analysis for dichotomous and continuous baseline variables, respectively. For paired data (eg, pre- versus postprocedure NT-proBNP values), no adjustment for confounding was considered necessary given the paired design of the analysis. Statistical analysis was performed using SPSS, version 20.0 (IBM, Somers, NY). P values were all 2 sided, and a P value of <0.05 was considered statistically significant.

Results

Patient Characteristics
Eighty-three patients (41 men [49%]; 49±15 years) with 24-hour Holter-derived PVC burden of 23±13% were included in the analyses. At first presentation, 61 patients (73%) reported palpitations, 25 (30%) (near-)syncope, and 39 (47%) fatigue. Eight patients (10%) were asymptomatic. In 73 patients, 2±1 antiarrhythmic drugs failed to control presenting symptoms and reduce PVC burden; 10 patients refused to take drugs.

Despite a normal LV function and volume indices, 74 patients (89%) had at least 1 clinical or PVC parameter that has been associated with PVC-induced cardiomyopathy in previous studies; 41 patients (49%) had a PVC burden ≥24%, 53 patients (64%) had a PVC–QRS duration ≥150 ms, and 40 patients (48%) had symptoms lasting ≥30 months. The Table

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<th>Table. Baseline Characteristics (n=83)</th>
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<td>Amiodarone/sotalol, n (%)</td>
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cESS indicates circumferential end-systolic wall stress; EDV, end-diastolic volume; eGFR, estimated glomerular filtration rate; ESV, end-systolic volume; LV, left ventricle; and PVC, premature ventricular contraction.

*P value calculated between patients with vs without fatigue.
summarizes baseline clinical parameters, PVC characteristics, and echocardiographic results.

Median NT-proBNP was 92 pg/mL (Q1–Q3, 50–156 pg/mL) before ablation. In 34 patients (41%), baseline NT-proBNP level was elevated (≥125 pg/mL). Only 1 patient had reduced renal function (glomerular filtration rate, 56 mL/min). The average cESS on echocardiography was 143±35 kdyne/cm².

Markers of Ventricular Wall Stress, Presenting Symptoms, and PVC Characteristics

Patients presenting with symptoms of fatigue had significantly higher NT-proBNP concentrations than patients without fatigue (144 pg/mL [Q1–Q3, 107–359 pg/mL] versus 52 pg/mL [Q1–Q3, 28–87 pg/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 than in patients without fatigue (153±38 versus 134±30 kdyne/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 (P<0.001).

Figure 1. Top, Baseline N-terminal proBNP (NT-proBNP) according to symptoms and premature ventricular contraction (PVC) characteristics. Median and quartiles 1–3 are depicted. Bottom, Baseline circumferential end-systolic wall stress (cESS) according to symptoms and PVC characteristics. Mean with standard deviation are depicted. BBB indicates bundle branch block; LV, left ventricular; and RV, right ventricular.

Figure 2. Correlation between N-terminal proBNP (NT-proBNP) and premature ventricular contraction (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 vs without fatigue. The gray dotted lines illustrate the PVC-burden cutoff value of 24% and NT-proBNP cutoff value of 125 pg/mL. The y-axis is log-scaled.
sex, hypertension, and BMI. A left-sided site of origin, a right bundle branch block–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 bundle branch block, 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, LV ejection fraction, LV end-diastolic volume-index and LV end-systolic volume-index. 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 right ventricle 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 because of an intramural/epicardial site of origin. In 2 patients (2%) radiofrequency delivery was withheld because of the proximity of the His-bundle and the ostium of the right coronary artery. Procedure and fluoroscopy times were 140±48 and 16±11 minutes. There were no procedure-related complications and no early PVC recurrence was observed.

**Follow-Up**

Reevaluation 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 preprocedural complaints of fatigue. This included the 2 patients in whom 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 1 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 LV end-diastolic volume-index from 57±14 to 54±15 mL/m² (\(P=0.039\)) and LV end-systolic volume-index from 23±8 to 21±9 mL/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 antiarrhythmic 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 93 pg/mL (Q1–Q3, 52–169 pg/mL) to 53 pg/mL (Q1–Q3, 37–90 pg/mL; \(P<0.001\)), resulting in a ΔNT-proBNP of 37 pg/mL (Q1–Q3, 6–108 pg/mL). In 51 of 59 patients (86%) NT-proBNP normalized to <125 pg/mL.

Among patients with SSA, those presenting with fatigue showed a significantly larger decrease in NT-proBNP levels than patients without fatigue (ΔNT-proBNP, 73 pg/mL

![Fatigue](https://example.com/fatigue.png)  
**ΔNT-proBNP: 73 (38-209)**  
\(p<0.001\)

![No fatigue](https://example.com/no-fatigue.png)  
**ΔNT-proBNP: 19 (-7-38)**  
\(p=0.021\)

**Figure 3.** N-terminal proBNP (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.
[Q1–Q3, 38–209 pg/mL] versus 19 pg/mL [Q1–Q3, –7 to 38 pg/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 \( \geq 24\% \) before ablation also demonstrated a significantly larger decrease in NT-proBNP levels after SSA than those with a burden of \(< 24\% \) (\( \Delta \)NT-proBNP, 68 pg/mL [Q1–Q3, 29–237 pg/mL] versus 23 pg/mL [Q1–Q3, –1 to 74 pg/mL]; \( P = 0.015 \)). When adjusting for age, sex, hypertension, and BMI in multivariate analysis, \( \Delta \)NT-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).

cESS decreased after SSA from 144±35 kdyne/cm\(^2\) at baseline to 134±35 kdyne/cm\(^2\) during follow-up (\( P = 0.036 \)), resulting in a median \( \Delta \)cESS of 11 kdyne/cm\(^2\) (Q1–Q3, –12 to 34 kdyne/cm\(^2\)) in this group. No difference in \( \Delta \)cESS 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 84 pg/mL [38–132 pg/mL] to 67 pg/mL [Q1–Q3, 41–86 pg/mL]; \( P = 0.272 \) and from 142±45 to 138±45 kdyne/cm\(^2\); \( P = 0.778 \), 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 before 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.\(^4\) 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 than patients with only classical PVC related symptoms. In addition, when compared with previous 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 <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 cutoff value.

**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 nonoutflow tract (predominantly LV) site of origin are potential risk factors for a PVC-induced cardiomyopathy. In addition, asymptomatic patients, in whom the duration of PVC cannot be evaluated, have been considered to be particularly prone to develop a cardiomyopathy. Interestingly, we found that fatigue, which is not systematically reported as a PVC-related symptom in previous 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 >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 because 84% of our patients were successfully treated and PVC-induced cardiomyopathy may develop over several years.

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 when compared with NT-proBNP for detection of PVC-induced increased ventricular wall stress.

**Biomarker as a Sensitive Indicator for PVC-Induced Wall Stress**

Two previous studies have reported elevated BNP levels in ≤64% of patients without LV dysfunction who underwent ablation for both idiopathic VTs and PVC. When compared with the 41% of patients with elevated NT-proBNP levels in our study, this percentage is remarkably high, in particular, because previous published data have demonstrated that NT-proBNP is an even more sensitive marker to detect LV dysfunction. The high BNP levels decreased to normal levels in ≥61% after successful ablation. Both previous 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 caused by aging and hypertension may contribute to the higher prevalence of increased BNP level in these previous 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 toward 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 before ablation and 3 months after ablation. The currently described patient cohort is unlikely to be representative for the general population of patients with PVCs because all patients were referred for ablation because of the PVC burden, symptoms, or patient’s preference. Because we did not follow up 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 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.

Conclusions
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 elevated NT-proBNP levels may benefit from ablation even in the absence of classical PVC-related symptoms or LV dysfunction.

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Disclosures
None.

References


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