Prognostic Significance of Incidental Nonsustained Ventricular Tachycardia Detected on Pacemaker Interrogation

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Symptomatic sustained ventricular tachycardia is a life threatening arrhythmia requiring prompt treatment. However, the risk associated with asymptomatic nonsustained ventricular tachycardia (NSVT) detected on routine permanent pacemaker (PPM) interrogation in patients with known cardiac conduction disease is unknown. Our aim is to determine if asymptomatic NSVT detected on PPM interrogation is associated with increased mortality. As part of a prospective observational cohort study, 582 patients with long-term pacemakers were recruited at a tertiary cardiac centre, and followed for 4 ± 1.96 years (mean ± standard deviation). At each subsequent pacemaker check, any symptoms and ventricular high-rate episodes were recorded. We excluded 17 patients due to incomplete data. In the remaining 565 patients (57% male, age 74.5 ± 19.2 years, left ventricular ejection fraction 50.0 ± 11.3%), NSVT was found in 125 (22.1%) patients with a higher prevalence in males (65% vs 54%; p = 0.033). Those with NSVT were more likely to have had coronary artery disease (p = 0) or previous myocardial infarction (p = 0.015). After correction for baseline variables, NSVT had no impact on survival (n = 52 [42%] vs n = 162 [37%]; log-rank p = 0.331, hazard ratio: 0.927, 95% confidence interval: 0.678 to 1.268, p = 0.697). In conclusion, asymptomatic NSVT identified on PPM interrogation does not appear to be associated with increased mortality, thus whether treatment to suppress this arrhythmia is of benefit remains unproven. **(Am J Cardiol 2019;123:409−413)**

Asymptomatic nonsustained ventricular tachycardia (NSVT) is a short-lived arrhythmia that is often found in both healthy individuals and those with heart disease.[1] The identification of asymptomatic NSVT creates a clinical dilemma because its prognostic significance and therefore the benefit of treatment is unclear.[2] This quandary is especially frequent in patients with confirmed cardiac conduction disorders and implanted permanent pacemakers, which can also function as cardiac monitors capable of identifying atrial and ventricular high rate (VHR) episodes during routine pacemaker interrogation.[3] The approach to managing asymptomatic pacemaker-identified VHR episodes remains limited by lack of evidence on the prognostic significance of NSVT and the effects of suppression.[4,5] We therefore set out to establish the associations and prognostic relevance of NSVT detected during routine pacemaker follow-up.

Methods

Between January 2008 and December 2012, we invited all adult patients (n = 730; Figure 1) listed for pulse generator replacement at a tertiary cardiac referral centre (Leeds General Infirmary) to attend for an assessment and enrolment into a prospective observational cohort study. Patients with resynchronisation and/or defibrillator devices were excluded. At a single study visit we recorded demographic and clinical details, including the presence of predefined covariables, from 582 participants, interrogated the pacemaker and performed an echocardiogram. We defined mild, moderate, and severe left ventricular systolic dysfunction (LVSD) as an LV ejection fraction (LVEF) of ≤55%, ≤45%, and ≤35%, respectively.

Subsequent patient follow-up occurred in line with usual care including documentation of any VHR episodes, and any clinician-mediated management thereof. After the censor point, these episodes were examined by 2 investigators (JG and SM), blinded to the outcome of the patient, and confirmed to be NSVT based upon the most commonly used definition of 3 or more consecutive beats of ventricular origin, with an RR interval of less than 600 ms (>100 beats/min) and lasting less than 30 seconds.[6] Both single (VVI) and dual chamber devices were included. In VVI devices, ventricular tachycardia was defined by speed of onset and rhythm regularity, whereas v-a dissociation was also used in dual chamber device analysis. We also recorded the duration of the longest episode and the total number of episodes.

The primary end point was all-cause mortality, with the censor date set to September 1, 2015.

Data were analyzed within SPSS version 22 for Windows (SPSS, Armonk, New York). Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally

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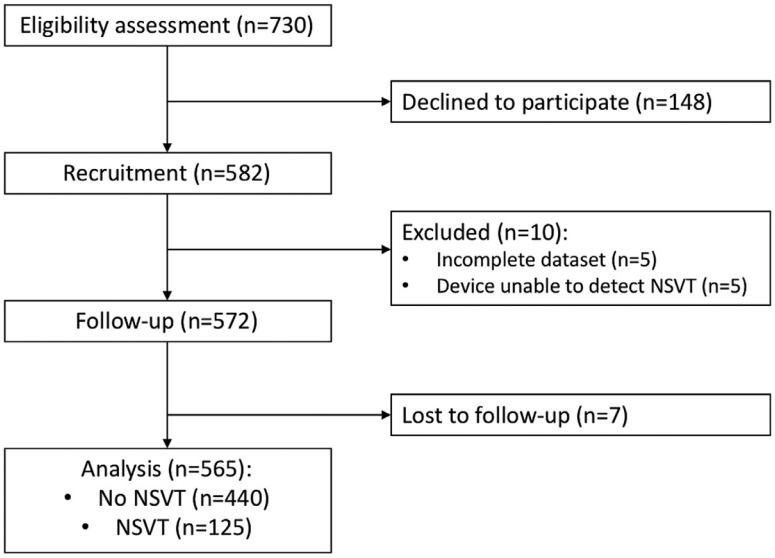

Figure 1. Study recruitment follow chart.

distributed continuous variables are described as mean ± standard deviation whereas non-normally distributed variables are described as median and interquartile range.

Patients were grouped into those with and without NSVT. Normally distributed continuous variables were compared between these groups using 2-sample *t* tests. Where assumptions for the Chi-square test were met, the Chi-square test was used for categorical variables. In exploring NSVT "dose" effect, we categorized patients into clusters of those with no NSVT, those with 1 to 10 episodes, and those with >10 episodes. Continuous variables of relevance were compared across these categories using ANOVA.

Multiple regression analysis was used to predict the importance of covariables in terms of their relation with other covariables and the presence of NSVT. In the subgroup of NSVT patients who received a change to treatment, we used a paired *t* test to assess changes in frequency of NSVT.

Cox proportional hazard analysis was used to determine covariables related to outcomes and their relative importance. Survival (measured in number of days survived from first date of NSVT diagnosis to death or censor date) was depicted using Kaplan Meier survival graphs, and compared using the log-rank test. For all analyses, we accepted a p value <0.05 as significant. The study was approved by the Leeds West Research Ethics Committee (08/H1307/12).

A recent large study exploring the prognostic value of NSVT was able to demonstrate significance using a cohort of 325 participants, of which 90 had evidence of NSVT.[7] Furthermore, several previous pacemaker studies had shown that the prevalence of detected NSVT ranges from 20% to 25%.[3,7–9] Thus our aim was to recruit a minimum of 500 participants, with an estimated minimum NSVT cohort of 100.

Results

The original cohort included 582 patients of whom we excluded 17 patients due to loss to follow-up (n = 7), devices incapable of detecting NSVT (n = 5) and incomplete NSVT data due to having a device upgrade to ICD/CRT during the follow-up period (n=5). We therefore had a complete dataset on 565 patients (Table 1). Those excluded as a group, were not different in terms of age, medication use, and important clinical variables.

Patients in the final cohort (56.5% male, 74.5 ± 19.2 years, left ventricular ejection fraction 50.0 ± 11.3) had their pacemaker for 9.8 ± 5.1 years, with mean RV pacing percentage of 72.3% ± 7.1.

During the follow-up period of 4 ± 1.96 years (mean ± standard deviation), NSVT was confirmed in 125 (22.1%) of the population (Table 1). The prevalence of NSVT was greater in men than women (n = 81, 64.8%; p = 0.033) and in patients with coronary artery disease (CAD; p = 0.000) or previous myocardial infarction (p = 0.015).

There was no significant difference between those with and without NSVT in terms of age or other co-morbidities, including hypertension, atrial fibrillation, diabetes, renal function, or medication use. There was no difference in presence of NSVT in those with mild (LVEF ≤55%; n = 23 [20%]; p = 0.341), moderate (LVEF ≤45%; n = 21 [24%]; p = 0.280) or severe (LVEF ≤35%; n = 7 [20%]; p = 0.624) LVSD. The median NSVT duration was 11 beats (interquartile range: 8 beats), and the median number of episodes was 2 (interquartile range: 5).

We had vital status for 99% of enrolled patients (558 of the 565 in the cohort). Mean total follow-up time (4.0 ± 1.9 years) was the same in the 2 groups. Mortality at the censor point was not different between those with and without NSVT (n = 52 [42%] vs n = 162 [37%]; log-rank p = 0.331, hazard ratio (HR) for mortality: 0.927, 95% confidence interval [CI]: 0.678 to 1.268, p = 0.697, Figure 2). There were also no survival differences between those with and without NSVT in the subgroup with CAD (20/49 [40.9%] vs 34/84 [40.5%]; log-rank p = 0.969, HR for mortality: 1.03, 95% CI: 0.592 to 1.791, p = 0.917), with moderate-severe LVSD (LVEF ≤ 45%; 12/28 [42.8%] vs 48/94 [51.1%]; log-rank p = 0.362, HR for mortality: 1.25, 95% CI: 0.664

Table 1
Baseline patient demographic characteristics (n = 565)

Variable (n)	Overall	NSVT		p value
		No (n = 440)	Yes (n = 125)	
Men	319 [56.5%]	238 [54.1%]	81 [64.8%]	0.033
Age (years)	74.5 ± 19.2	74.8 ± 20.5	73.1 ± 13.0	0.160
Hypertension	127 [22.5%]	96 [21.8%]	31 [24.8%]	0.454
Coronary artery disease	133 [23.5%]	84 [19.1%]	49 [39.2%]	0.000
Prior myocardial infarction	61 [10.8%]	38 [8.6%]	23 [18.4%]	0.015
Prior coronary artery bypass graft	64 [11.3%]	53 [12.0%]	11 [8.8%]	0.075
Prior percutaneous coronary intervention	18 [3.2%]	12 [2.7%]	6 [4.8%]	0.411
Prior stroke	30 [5.3%]	23 [5.2%]	7 [5.6%]	0.747
Atrial fibrillation	194 [34.3%]	148 [33.6%]	46 [36.8%]	0.625
Diabetes mellitus	35 [6.2%]	24 [5.5%]	11 [8.8%]	0.485
Body mass index (kg/m^2)	30.5 ± 4.0	30.3 ± 7.9	34.9 ± 2.4	0.148
LV ejection fraction (%)	50.0 ± 11.3	50.1 ± 11.2	48.5 ± 11.6	0.216
< 55%	236 [41.8%]	185 [42.0%]	51 [40.8%]	0.341
< 45%	123 [21.8%]	94 [21.4%]	28 [22.4%]	0.280
< 35%	35 [6.2%]	28 [6.8%]	7 [5.6%]	0.624
Biochemistry (unit) mean [SD]				
Creatinine (μmol/L)	113.9 ± 36.3	114.4 ± 37.9	111.8 ± 30.1	0.558
Urea (mmol/L)	8.3 ± 4.3	8.4 ± 4.6	8.0 ± 3.4	0.472
Estimated glomerular filtration rate (ml/min/1.73m^2)	56.8 ± 17.0	56.1±17.7	58.2 ± 14.9	0.525
Baseline medication				
Beta blockers	125 [22.1%]	95 [21.6%]	30 [24.0%]	0.651
ACEi/ARB	134 [23.7%]	106 [24.1%]	28 [22.4%]	0.108
Amiodarone	22 [3.9%]	20 [4.5%]	2 [1.6%]	0.229
Calcium antagonist	38 [6.7%]	31 [7.0%]	7 [5.6%]	0.413
Warfarin	80 [14.2%]	64 [14.5%]	16 [12.8%]	0.373
Digoxin	32 [5.7%]	28 [6.4%]	4 [3.2%]	0.560
Diuretics	30 [5.3%]	25 [5.7%]	5 [4.0%]	0.268
Statin	139 [24.6%]	105 [23.8%]	34 [27.2%]	0.793

to 2.362, p = 0.478) or severe LVSD (LVEF ≤ 35%; HR for mortality: 0.817, 95% CI 0.404 to 1.65, p = 0.33) .

We assigned patients with NSVT into 3 quantitative ordinal categories according to the total number of episodes recorded (Table 2). Survival analyses based upon the number of episodes recorded did not reveal any significant differences among these 3 groups (Log-rank p = 0.898).

Discussion

The present project explores an important therapeutic dilemma frequently encountered during routine pacemaker follow-up. Our results are from a representative, prospectively collected and contemporary cohort of pacemaker patients, and are in keeping with recently reported studies by Allen et al and Gabriels et al, showing NSVT to be a benign finding.[7,10] Our data did not show a relation between the presence of NSVT and significant LVSD, however the numbers of patients in the sub-groups were likely too small to reach statistical significance.

NSVT has poor symptom-rhythm correlation, even in patients with heart failure,[11,12] and may be discovered during ambulatory monitoring or on interrogation of implanted cardiac devices. Whilst the prevalence of asymptomatic NSVT found on short-term Holter monitors is thought to be around 4% to 5%,[4,8] the prevalence in our dataset is similar to that found in other studies of pacemaker patients at around 20% to 25%.[3,7,9,13]

The prognostic relevance of asymptomatic NSVT is unclear.[3,5,14] Even in patients with overt cardiovascular disease, including LVSD, there are conflicting reports of whether NSVT is associated with increased mortality.[15–19] This lack of clarity extends to people with pacemakers. The 2 other prospective studies to examine the epidemiology of NSVT in people with pacemakers either did not report on outcomes,[10] or excluded patients with LVSD,[15] making ours the only investigation to date to present the lack of prognostic relevance of NSVT presence/duration within a general pacemaker population.

The mortality rate seen in our cohort was higher than that observed in other similar studies, such as the work of Fleg et al, which looked at 98 healthy subjects aged over 60 years, who were deemed "free of cardiac disease."[14] However, our data represent a larger and older cohort with multiple cardiovascular co-morbidities, thus a higher mortality rate would be expected.

The association with CAD or IHD is likely a consequence of the structural pathophysiological changes that occur within the myocardium in response to cardiac ischaemia, which can lead to fibrosis, scarring, and disruption of cardiac electrical conduction pathways.[5,16] However, we have demonstrated that in our patients NSVT does not appear to predict higher all-cause mortality, even in the context of CAD.[7]

Based upon the finding that asymptomatic NSVT is not a convincing marker of prognosis in patients with pacemakers,

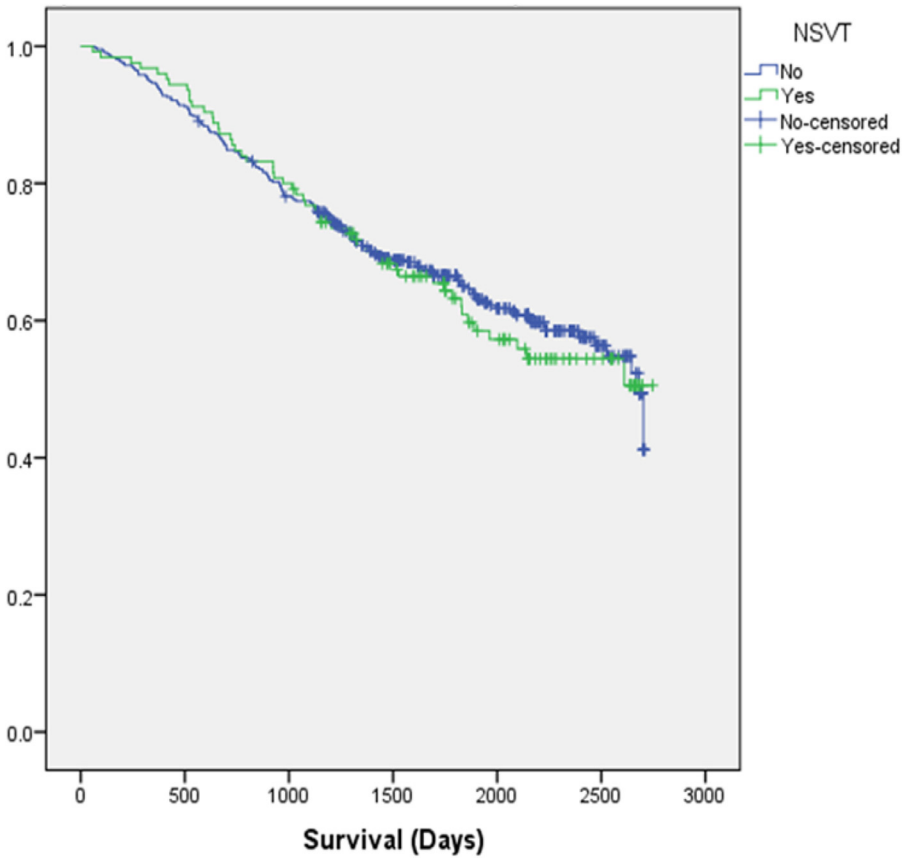

Figure 2. Kaplan Meier survival analysis curve: no significant difference in survival of patients with NSVT compared to those with no NSVT (log-rank analysis p value = 0.697). NSVT = nonsustained ventricular tachycardia.

adding treatments to suppress this rhythm disturbance remains unproven, and may inadvertently lead to iatrogenic sequelae. Previous studies have also indicated that treatment aimed at suppression of NSVT may not be associated with improved outcomes.[20,21]

Furthermore, the most recent European guidelines suggest that NSVT is rarely of any haemodynamic significance and treatment should only be considered in those individuals, who are either symptomatic or have a very high NSVT burden (>24%) that may be contributing to LVSD.[4] In such cases, beta blockers, amiodarone or radiofrequency catheter ablation may be considered.

Although our baseline patient data were collected prospectively, the NSVT data were verified retrospectively at the censor point exposing our analysis to the biases inherent in observational data including unknown confounders of the relation between NSVT and other variables and outcome.

The analysis was also limited to all-cause mortality due to insufficient data to allow differentiation between types or causes of mortality, or other relevant end points, such as hospitalization.

Our results demonstrate that NSVT in an unselected large cohort of pacemaker patients is not a predictor of

Table 2
NSVT episode categories and corresponding characteristics (n = 125)

Variable (n)	NSVT episodes			
	One n = 42 (33.6%)	Two–ten n = 55 (44%)	Eleven or more n = 28 (22.4%)	P value
Men	24 (57.1%)	41 (74.6%)	17 (60.8%)	0.033
Previous coronary artery disease	16 (39%)	18 (32.7%)	12 (42.8%)	0.616
Myocardial infarction	10 (23.8%)	7 (12.7%)	4 (14.2%)	0.292
Mean LV ejection fraction (%)	49.5 ± 11.3	47.8 ± 11.2	46.9 ± 11.0	0.216
LV ejection fraction < 45%	9 (22.0%)	12 (21.9%)	7 (25%)	0.279
Antiarrhythmic use	8 (19.5%)	18 (32.8%)	9 (32.1%)	0.625
Survival log-rank analyses	0.147	0.165	0.616	0.898

adverse outcome, even in the higher risk subgroups and that treatment of asymptomatic episodes may not be beneficial. Our data should serve to reassure physicians managing patients with pacemakers, the patients themselves and their carers of the benign nature of asymptomatic NSVT identified during pacemaker interrogation, irrespective of other co-morbities.

Disclosures

There are no conflicts of interest for any authors.

Authorship

SS and KKW researched the topic and devised the study. SS collected the data and undertook primary statistical analysis. SS and KKW produced the first draft of the manuscript. All other co-authors contributed equally to manuscript preparation.

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