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ORIGINAL ARTICLE

Ventricular Ectopy in the Context of Left Ventricular Systolic Dysfunction: Risk Factors and Outcomes Following Catheter Ablation

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Background Ectopy-mediated cardiomyopathy (EMC) is a potentially reversible form of left ventricular systolic dysfunction. Various risk factors for the development of EMC have been proposed in the literature. We aim to assess medium term outcomes of focal ventricular arrhythmia (VA) ablation in the setting of cardiomyopathy (CMP) and to validate published risk factors for EMC.

Methods Medium term recovery of left ventricular (LV) function and freedom from VA recurrence was assessed and compared between patients undergoing focal VA ablation in the setting of CMP and a control group with normal LV function. Univariate and multivariate analyses for CMP risk factors were performed and compared against prior published risk factors.

Results Of 152 patients who underwent 170 focal VA ablation procedures, 54 (36%) had CMP and the remaining 98 patients had normal LV systolic function. At medium term follow-up, 85% of patients with CMP were free of VA recurrence and median left ventricular ejection fraction (LVEF) had improved from 40 to 52%. Age, male gender, premature ventricular complex (PVC) burden, non- right ventricular outflow tract (RVOT) sites of origin, PVC QRS duration and PVC minimum coupling interval were predictive of CMP on univariate analysis, but only gender persisted on multivariate analysis.

Conclusions Medium term outcome in patients undergoing focal VA in the setting of CMP are satisfactory with improvement in LV function achievable in most patients. Prior risk factors described in the literature are variable and inconsistent, likely reflecting heterogeneous study populations.

Keywords Ventricular arrhythmias • Premature ventricular complexes • Ectopy mediated cardiomyopathy • Catheter ablation

Introduction

Left ventricular (LV) systolic dysfunction due to frequent premature ventricular complexes (PVC), so called ectopy-mediated cardiomyopathy (EMC), is a potentially reversible cause of non-ischaemic cardiomyopathy (CMP). Prior series have demonstrated normalisation of LV systolic function with arrhythmia suppression in a significant proportion of these patients [1,2]. Although suppression can, in theory, be achieved through pharmacologic means, a recent prospective

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study has demonstrated poor efficacy with medications alone [3]. Consequently, catheter ablation is an important management option for these patients.

Currently, the indications for ablation of idiopathic VAs are i) symptoms, and/or ii) LV systolic dysfunction [4]. As not all patients with frequent PVCs or idiopathic VAs develop CMP, ablation is not recommended in asymptomatic patients with normal systolic function. Identification of characteristics that predict evolution to cardiomyopathy would potentially allow for earlier treatment in these patients. Various risk factors predicting this progression to LV systolic dysfunction have been proposed but these are inconsistently reported in the literature.

We aim to describe the demographics and outcomes of all patients who presented to our centre for PVC or idiopathic VA ablation in the setting of CMP. We aim to validate proposed risk factors by comparing this cohort to a group of control patients with structurally normal hearts who are also undergoing ablation of focal VAs.

Methods

Consecutive patients who presented to our centre for ablation of PVCs or idiopathic VAs between 2011 and 2017 were retrospectively reviewed. The patients were divided into two groups: i) CMP group consisting of patients with a left ventricular ejection fraction (LVEF) of <50%; and ii) a control group consistent of patients with an LVEF $\geq$ 50%. Patients with pre-existing scar substrate were included if they underwent a focal ablation procedure. Patients undergoing ablation of macro-reentrant scar VT were excluded.

Demographic, clinical and procedural data was retrospectively obtained through review of medical records, procedural reports and ambulatory care follow-up. Electrophysiologic parameters were measured retrospectively on CardioLab EP recording system (GE Healthcare, Chicago, IL, USA) at 100 mm/s. High/low pass filters were set at 0.05/100 Hz and 30/500 Hz for surface electrocardiogram (ECG) and intracardiac channels respectively. This study was approved by the Human Research and Ethics Committees of The Prince Charles Hospital and the University of Queensland, Brisbane, Australia.

All patients underwent a pre-procedural assessment including demographics, arrhythmia history, comorbidities and current therapies. Left ventricular systolic function and PVC burden was documented via transthoracic echocardiogram (TTE) and 24-hour Holter monitor respectively. Scar substrate was defined as LV dysfunction with a history of prior myocardial infarction or by the presence of late gadolinium enhancement on cardiac magnetic resonance imaging (MRI).

Patients were followed up at 3 months following their procedure. Serial LV function and PVC burden was assessed with repeat TTE and 24-hour Holter. Recurrence was defined as either i) symptomatic PVC burden >1%, ii) PVC burden >10% but asymptomatic, or iii) the need for continued antiarrhythmic therapy (excepting β-blocker therapy in the setting of heart failure). Follow-up time was calculated from the most recent procedure only in patients who had undergone multiple procedures.

Mapping and Ablation

All patients underwent an electrophysiological study to map and ablate the arrhythmic focus of interest after providing informed consent. The majority of procedures (98.8%) were performed under conscious sedation.

Mapping was performed using the CARTO® 3D electroanatomical mapping system (Biosense Webster, Diamond Bar, CA, USA) in conjunction with a 3.5 mm irrigated mapping/ablation catheter (Thermocool™ or Thermocool ST/SF™, Biosense Webster, Diamond Bar, CA, USA) in the majority (98.3%) of cases. In most cases, mapping of the right ventricular (RV) and infundibulum was performed via the inferior vena cava and mapping of the LV (including the aortic cusps) was performed via the retrograde aortic approach depending on the predicted site of origin of the arrhythmia. If the LV summit was a potential site of origin, this area was mapped early via a catheter placed at the anterior interventricular vein/great cardiac vein (AIV/GCV) junction via the coronary sinus (CS). In five cases in which epicardial ablation was performed, access to the pericardial space was performed using the Sosa technique [5].

Activation mapping was the primary technique for localising the arrhythmia site of origin. This involved searching for the earliest near-field electrogram which preceded the surface PVC QRS onset in the region predicted by the ECG morphology of the PVC. Pacemapping was used to complement the findings of activating mapping. Pacemaps were scored out of 24 accounting for the vector (one point) and fine notching (one point) accuracy in each of the surface ECG leads.

Irrigated radiofrequency ablation (RFA) at a power setting of 20–50 W was performed at the arrhythmia site of origin. If this resulted in PVC suppression, RFA was continued for up to 180 seconds. If no recurrence of the clinical PVC occurred despite programmed stimulation and isoprenaline following a 30-minute waiting period, the procedure was deemed an acute success.

Statistics

The distribution of continuous variables was assessed by visual assessment of histograms in conjunction with the Shapiro-Wilk test and are presented as mean ± standard distribution or medians with interquartile ranges as appropriate. Categorical variables are presented as absolute values with percentages. Between group comparisons for continuous variables were performed with independent T-tests or the Mann-Whitney U test as appropriate. Between group comparisons for categorical variables were performed with the Chi-squared or Fisher's exact test as appropriate. Pre- and post-procedural assessments of LVEF and PVC burden were compared using the Wilcoxon signed-rank tests. Medium term freedom from recurrent VAs for both groups are

presented as Kaplan Meier survival curves and compared with the log-rank test.

Baseline variables that differed between groups ($p < 0.10$) and other variables thought to be clinically relevant to the development of cardiomyopathy based on historical literature were selected for multivariate analysis. A step-down binomial logistic regression model was performed, with sequential removal of the least significant variable at each step and confirmation of improvement of the fit of the model as measured by the Nagelkerke R^2 value. If model fit deteriorated, the removed variable was reintroduced and the next least significant variable removed. This process was repeated until the best fit model (highest R^2) was achieved. Receiver operating curves and the Youden index was calculated to determine the optimum PVC burden cut-off that best predicted the presence of CMP.

Statistical significance was defined as a two-tailed p-value <0.05. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

During the study period, 310 ablation procedures were performed for VAs at our centre. Of these, 170 procedures were performed in 152 patients undergoing ablation for focal arrhythmias. Pre-procedurally, 54 (36%) patients had impaired LV systolic function (CMP group) whilst the remaining 98 (64%) had normal systolic function (control group). In the CMP group, PVCs most often arose from the RVOT (22%), multiple sites (20%) and the LV papillary muscles (17%) [Figure 1A]. In those with normal systolic function, the most common sites were the RVOT (49%), the LV summit (15%) and the aortic cusps or sinuses (10%) [Figure 1B]. The median LVEF in the CMP group was 40% compared to 59% in the control group ($p < 0.001$).

Baseline demographics and procedural characteristics are presented in Table 1 and Figure 2. Patients with CMP were older (mean 59 vs 50 years, $p = 0.003$) and more likely to be male, whilst the control group had female predominance (74% vs 40% male gender respectively, $p < 0.001$). The CMP patients had a higher PVC burden (median 27.5% vs 20.6%, $p = 0.001$), were more likely to have a non-RVOT focus than the control group (78% vs 51%, $p = 0.001$). Cardiovascular magnetic resonance imaging (CMR) was performed in 29 of 54 (54%) and 66 of 98 (67%) of patients with CMP and normal LVEF respectively. Those with CMP were more likely to have pre-existing scar substrate (37% vs 7%, $p < 0.001$) as defined by the post-MI state or the presence of late gadolinium enhancement on CMR. A similar proportion of patients (22%) had undergone previous ablation attempts in both groups ($p = 0.60$).

Patients with cardiomyopathy were more likely to be symptomatic of heart failure with ≥ NYHA II symptoms (39% vs 9%, $p < 0.001$). The control group more often suffered the classical arrhythmia symptoms such as palpitations (80% vs 48% $p < 0.001$), chest discomfort (28% vs 11%, $p = 0.02$) and dizziness (65% vs 32%, $p < 0.001$). There was

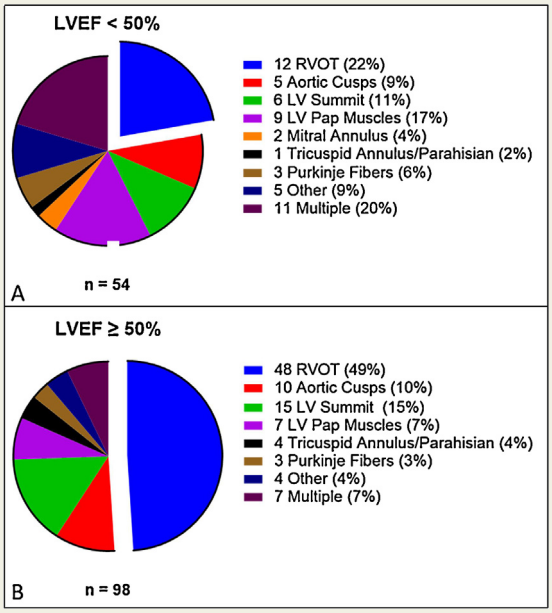

Figure 1 Site of origins of focal ventricular arrhythmias in patients under catheter ablation with CMP (Panel A) and normal LV systolic function (Panel B). Abbreviations: CMP, cardiomyopathy.

no difference in symptom duration between the two groups (median 24 months). There was a higher prevalence of coronary artery disease (28% vs 7%, $p = 0.001$), current smokers (22% vs 6%, $p = 0.003$) and atrial fibrillation (17% vs 5%, $p = 0.04$) in the CMP group.

Heart failure therapies were more frequent in the CMP group with a greater prevalence of ACE-inhibitors or angiotension II receptor blockers (78% vs 27%, $p < 0.001$), heart failure β-blockers (67% vs 5%, $p < 0.001$) and aldosterone antagonists (28% vs 0%, $p < 0.001$). Amiodarone use was more common in cardiomyopathy patients (22% vs 3%, $p < 0.001$). The most common anti-arrhythmic agents in the CMP group were β-blockers (81%) and amiodarone (22%), whilst the control group were most commonly on β-blockers (43%) and sotalol (16%). Thirteen patients (24%) in the cardiomyopathy group had an implantable cardioverter defibrillator (ICD) compared to six (6%) in the control group ($p < 0.001$).

The CMP group had wider median PVC QRS duration (168 vs 156 ms, $p < 0.001$) and longer median minimum PVC coupling intervals (464 ms vs 430 ms, $p = 0.02$). More RF lesions were required during procedures in the CMP group (median 17 vs 9, $p = 0.002$) though there was no difference in procedural/fluoroscopy times or radiation exposure. Acute success rates were comparable in both groups (73% vs 79%, p = ns).

In the CMP group, 24 patients had paired pre-procedural and follow-up Holter monitors. The median PVC burden decreased from 29.2% to 1.3% ($p < 0.001$) [Figure 3A]. The median PVC burden in all CMP patients who had post-procedural Holter monitors was 0.80%. In the 32 patients who had paired pre-procedural and follow-up TTEs, 19 (59%) normalised their LV

Table 1 **Baseline and procedural demographics in patients undergoing catheter ablation of focal VAs by cardiomyopathy status.**

Variable	LVEF < 50%		LVEF ≥ 50%		
Demographics	**n**	**Value**	**n**	**Value**	**p Value**
Age (years)	54	59 ± 15	98	50 ± 16	**0.003**
Gender (male)	54	40 (74%)	98	39 (40%)	**<0.001**
BMI (kgm^{-2})	52	28.3 (25.4–32.8)	97	29.4 (24.0–34.5)	0.91
LVEF (%)	53	40 (32–45)	97	59 (55–64)	**<0.001**
PVC Burden (%)	31	27.5 (19.6–44.3)	63	20.6 (7.6–27.0)	**0.001**
Symptom Duration (months)	45	21 (7–48)	94	24 (10–51)	0.22
Non-RVOT PVC	54	42 (78%)	98	50 (51%)	**0.001**
Epicardial PVC	54	12 (22%)	98	18 (18%)	0.57
Concomitant Scar Substrate	54	20 (37%) [10 post-MI, 10 NICM]	98	7 (7%) [3 post-MI, 4 NICM]	**<0.001**
Prior Ablation Procedure	54	13 (24%)	98	20 (20%)	0.60
Symptoms					
Asymptomatic	53	5 (9%)	98	4 (4%)	0.28
NYHA Class (II/III/IV vs I)	54	21 (39%)	98	9 (9%)	**<0.001**
Palpitations	54	26 (48%)	98	78 (80%)	**<0.001**
Chest Discomfort	54	6 (11%)	98	27 (28%)	**0.02**
Dizziness	54	17 (32%)	98	64 (65%)	**<0.001**
Syncope	54	5 (9%)	98	21 (21%)	0.07
Fatigue	54	11 (20%)	98	26 (27%)	0.40
Comorbidities					
Hypertension	54	22 (41%)	98	27 (28%)	0.10
Diabetes Mellitus	54	5 (9%)	98	8 (8%)	1.00
Coronary Artery Disease	54	15 (28%)	98	7 (7%)	**0.001**
Smoking (Current vs Ex/Never)	54	12 (22%)	98	6 (6%)	**0.003**
Atrial Fibrillation	54	9 (17%)	98	5 (5%)	**0.04**
Therapies					
ACE-i or ARB	54	42 (78%)	98	26 (27%)	**<0.001**
HF β-blocker	54	36 (67%)	98	5 (5%)	**<0.001**
Aldosterone Antagonist	54	15 (28%)	98	0 (0%)	**<0.001**
Non-HF β-blocker	54	8 (15%)	98	37 (38%)	**0.003**
CCB	54	0 (0%)	98	3 (3%)	0.55
Digoxin	54	3 (6%)	98	0 (0%)	**0.04**
Amiodarone	54	12 (22%)	98	3 (3%)	**<0.001**
Sotalol	54	7 (13%)	98	16 (16%)	0.58
Flecainide	54	3 (6%)	98	11 (11%)	0.38
ICD	54	13 (24%)	98	6 (6%)	0.001
Procedural					
Procedure Time (mins)	59	200 (180–250)	109	180 (150–240)	0.16
Fluoroscopy Time (mins)	58	31.6 (18.0–41.0)	108	28.0 (18.1–39.8)	0.60
Dose-Area Product ($Gycm^2$)	58	7.8 (2.4–18.2)	106	4.9 (2.0–14.3)	0.36
RF Lesions	59	17 (9–30)	111	9 (5–18)	**0.002**
ICE	59	23 (39%)	111	19 (26%)	0.08
PVC Width (ms)	59	168 ± 21	110	156 ± 20	**<0.001**
Shortest Coupling Interval (ms)	57	464 (393–508)	100	430 (383–478)	**0.02**
Pre-QRS Time (ms)	57	26 (20–34)	100	26 (22–35)	0.76

Table 1. (continued).

Variable	LVEF < 50%		LVEF ≥ 50%		
Demographics	**n**	**Value**	**n**	**Value**	**p Value**
Pacemap Score	57	22 (19–24)	100	21 (19–24)	0.35
Pleomorphic PVCs	59	24 (41%)	111	46 (41%)	0.92
Acute Success	59	43 (73%)	111	88 (79%)	0.35

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; PVC, premature ventricular complex; RVOT, right ventricular outflow tract; NYHA, New York Heart Association; ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; CCB, calcium channel blocker; ICD, implantable cardioverter defibrillator; RF, radiofrequency; ICE, intracardiac echocardiography.
Bold values indicate significant p-values (i.e. <0.05).

function (LVEF > 50%) and the median LVEF improved from 40% to 52% (p < 0.001) [Figure 3B]. There was complete normalisation of LVEF to >50% in 61% of patients. Following their most recent ablation procedure, at a median follow-up of 7 and 12 months for the CMP and control groups, 85% and 84% of patients respectively were free of recurrent VA with no difference in outcomes between the groups (p = 0.92) [Figure 4].

Predictors of Cardiomyopathy

On univariate analysis, age, male gender, PVC burden, non-RVOT sites of origin, longer PVC QRS durations and longer minimum coupling intervals were found to be predictors of CMP. On multivariate analysis only male gender was found to be predictive of CMP (OR 4.09, p = 0.04). However, there was a trend towards a greater PVC burden predicting CMP (OR 1.47 per 10% increase in burden, p = 0.07). The multivariate model accounted for only a modest degree of variance in LV systolic function (Nagelkerke R^2 = 34%) [Table 2]. This result persisted when only confirmed EMC patients were analysed (by excluding patients with scar substrate, those who had unsuccessful ablation and those who did not entirely recover LV systolic function following ablation) [Supplementary Table 1].

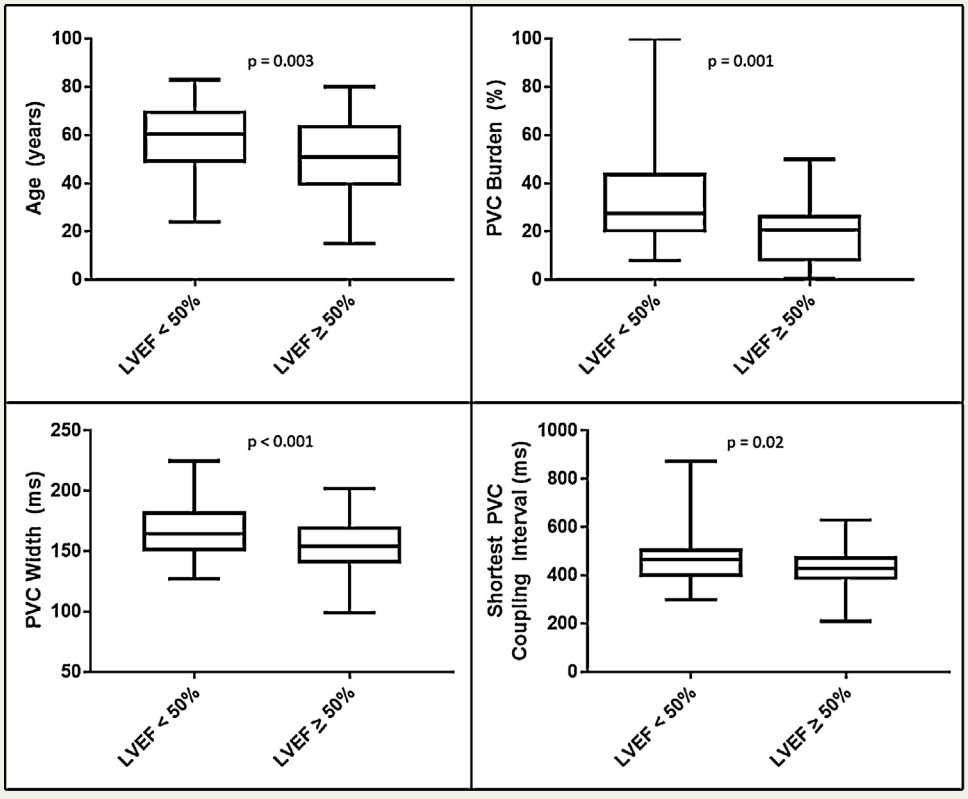

Figure 2 Box-and-whisker plots demonstrating differences in age, PVC burden, PVC width and shortest PVC coupling interval between patients with and without CMP.
Abbreviations: CMP, cardiomyopathy; PVC, premature ventricular complex.

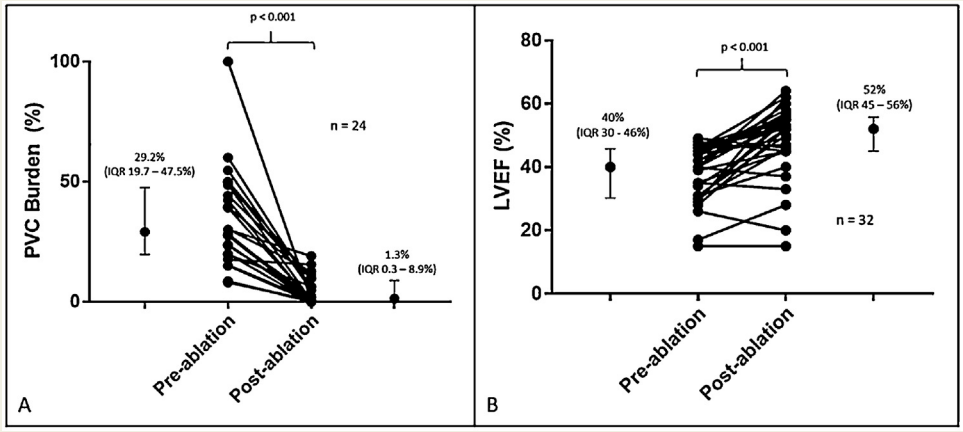

Figure 3 Panel A – PVC burden pre- and post-ablation in patients with paired 24-hour Holter studies in the CMP group. Panel B – Left ventricular ejection fractions pre- and post-ablation in patients with paired TTEs in the CMP group.
Abbreviations: CMP, cardiomyopathy; TTE, transthoracic echocardiogram; PVC, premature ventricular complex.

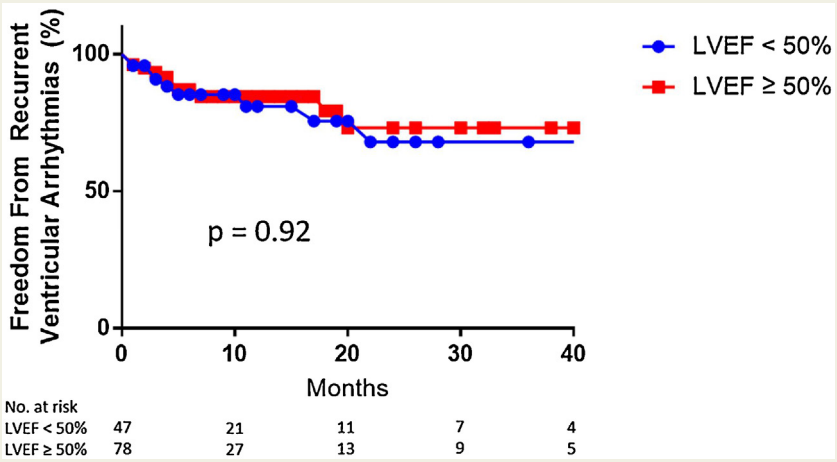

Figure 4 Kaplan Meier curve comparing medium term freedom from recurrent ventricular arrhythmias in patients with CMP and normal LV systolic function.
Abbreviations: CMP, cardiomyopathy; LV, left ventricular.

The ROC curve for PVC burden only had modest ability to differentiate patients with cardiomyopathy from controls (area under the curve 0.715). The best predictive cut-off value was 23% PVCs which results in a sensitivity of 68% and specificity of 67% for cardiomyopathy (Figure 5). All patients with cardiomyopathy had a PVC burden of at least 7.6%. The minimum PVC burden in patients in whom LVEF subsequently recovered was 8.6%.

Complications

In the CMP group, one patient developed a femoral artery false aneurysm requiring thrombin injection and another developed a small femoral arterio-venous fistula that was managed conservatively. In the control group, two patients developed cardiac tamponade, one during endocardial ablation and the other during attempted epicardial access. A third patient's procedure was abandoned following development of transient complete heart block during mapping.

Discussion

In this paper we present the outcomes of a consecutive cohort of patients presenting for focal VA ablation in the setting of CMP. The main findings are:

1. Satisfactory acute and medium-term outcomes can be obtained in these patients with resolution of EMC in the majority.
2. Whilst age, male gender, PVC burden, non-RVOT site of origin, PVC QRS duration and minimum PVC coupling interval were all predictive of LV systolic dysfunction on univariate analysis, only male gender remained predictive following multivariate adjustment.

Table 2 Univariate and multivariate predictors of cardiomyopathy in patients undergoing catheter ablation of focal ventricular arrhythmias.

Variable	Univariate			Multivariate		
	Odds Ratio	95% CI	p-Value	Odds Ratio	95% CI	p Value
Age (per decade)	1.40	1.12–1.76	**0.004**			
Male Gender	4.32	2.08–8.98	**<0.001**	3.01	1.02–8.86	**0.046**
BMI (per additional kgm^{-2})	1.00	0.95–1.06	0.95			
Pre-PVC burden (per additional 10%)	1.82	1.28–2.57	**0.001**	1.47	0.97–2.28	0.07
Symptom Duration (per year)	0.91	0.82–1.05	0.22			
Asymptomatic	2.45	0.63–9.52	0.20	5.00	0.42–58.8	0.20
Non-RVOT	3.36	1.58–7.14	**0.002**	2.36	0.69–8.06	0.17
PVC Width (per 10 ms increase)	1.31	1.10–1.54	**0.002**	1.18	0.91–1.54	0.20
Shortest coupling interval (per 10 ms increase)	1.05	1.01–1.10	**0.01**			

Nagelkerke $R^2 = 0.369$.

Abbreviations: BMI, body mass index; PVC, premature ventricular complex; RVOT, right ventricular outflow tract.

Bold values indicate significant p-values (i.e. <0.05).

Our study confirms the findings of previous retrospective studies [1,6–9] that patients with focal VAs can have significant improvement in LV systolic function following successful ablation. In our series, the LVEF normalised in the majority (61%) of patients. Although pharmacotherapy is often trialled initially, a prospective study has shown this strategy to be ineffective in the setting of RVOT PVCs resulting in an 89% recurrence rate compared to 19% with ablation [3]. Indeed, most of the cardiomyopathy patients in our study were on an anti-arrhythmic agent at the time of presentation for their procedure. Therefore, it seems reasonable to offer catheter ablation to these patients, even if asymptomatic.

Previous studies have demonstrated benefits of outflow tract PVC ablation even in patients with a pre-existing cardiomyopathy [10–12]. Ablation has also been shown to benefit patients with frequent ventricular ectopy in the setting of cardiac resynchronisation therapy (CRT) by enhancing effective biventricular pacing in addition to promoting reverse remodelling of the LV [13]. Whilst a significant proportion (37%) of the CMP group in our study had pre-existing scar substrate, only nine of these patients had paired TTE studies and therefore our study was underpowered to determine a benefit in these patients. Nonetheless, the numerical increase in LVEF was comparable to the overall cohort.

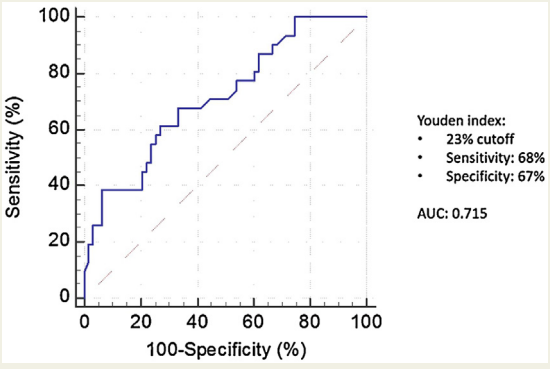

Figure 5 Receive operator characteristics curve for PVC burden against CMP.
Abbreviations: CMP, cardiomyopathy; PVC, premature ventricular complex.

Although numerous factors have been proposed to predict CMP, none have demonstrated a consistent and unanimous relationship across all studies. Of these, PVC burden is generally considered to be the most robust with most studies supporting a relationship between greater PVC burden and CMP risk [14–21]. Even so, two studies demonstrated no relationship between PVC burden and cardiomyopathy [1,22]. In our cohort, PVC burden is a strong univariate predictor, but only demonstrates a trend towards risk of cardiomyopathy in the multivariate model. Although our cohort is of comparable size to other studies, it may still be underpowered to detect such an effect. The best cut-off value in our study of 23% PVC burden is consistent with other values found in the literature [6,14], although the sensitivity and specificity of this cut-off point was only modest.

Older age and male gender have inconsistently been reported as risk factors for CMP. Only one early study suggested older age as a risk factor on an unadjusted analysis [1]. Our study confirms this finding, but this relationship does not persist once adjusted for covariates. Multiple studies have confirmed a link between male gender and cardiomyopathy on unadjusted analysis [6,14,18–21,23]. In a study by Park et al., the gender difference was confirmed on a multivariate model when asymptomatic patients were excluded. Ours is the only cohort in which male gender not only persisted but remained the only significant factor in a multivariate model.

Studies have shown the PVC QRS duration to be predictive of CMP [20–22,24], possibly by reflecting greater dyssynchrony, though two recent studies were unable to demonstrate this relationship [16,18]. In addition, Deyell et al. also found PVC QRS duration to be the only predictor of LV

Table 3 Proposed risk factors for ectopy-mediated cardiomyopathy as reported by previous studies.

Study	n (CMP/ normal)	Variable										
		Age	Male Gender	BMI	PVC Burden	PVC QRS Duration	Pleomorphic PVCs	PVC Interpolation	PVC Coupling Interval	Site or origin	Symptom Duration	Asymptomatic
Yarlagadda (2005) [1]	8/19	Yes (uni)	No	–	No	–	No	–	–	No	–	–
Bogun (2007) [7]	22/38	–	–	–	Yes (uni)	–	–	–	–	–	–	–
Kanei (2008) [15]	21/87	No	No	–	**Yes (multi)**	–	–	–	–	No	–	–
Baman (2010) [14]	57/117	No	Yes (uni)	–	**Yes (multi)**	–	No	–	–	No	–	–
Del Carpio (2011) [24]	17/53	No	No	–	Yes (uni)[a]	**Yes (multi)**	Yes (uni)	–	–	No	No	–
Hasdemir (2011) [6]	17/232	No	Yes (uni)	–	Yes (uni)	–	–	–	–	–	–	Yes (uni)
Olgun (2011) [17]	21/30	No	No	–	**Yes (multi)**	–	–	**Yes (multi)**	–	–	–	–
Yokokawa (2012) [19]	76/165	No	Yes (uni)	–	**Yes (multi)**	–	–	–	–	–	**Yes (multi)**	**Yes (multi)**
Yokokawa (2012) [20]	113/181	No	Yes (uni)	–	**Yes (multi)**	Yes (multi)	–	–	–	**Yes – epicardial (multi)**	**Yes (multi)**	–
Carballeira (2014) [22]	17/28	No	No	–	No	**Yes (multi)**	–	–	No	**Yes – non-outflow tract (multi)**	No	–
Kawamura (2014) [16]	51/163	No	No	**Yes (multi)**	**Yes (multi)**	No	–	–	**Yes** – maximum CI (uni), **CI dispersion (multi)**	No	–	–
Blaye-Felice (2016) [18]	96/72	No	Yes (uni)	–	**Yes (multi)**	No	Yes (uni)	Yes (uni)	Yes (uni)	**Yes – epicardial (multi)**	–	–
Hamon (2016) [21]	36/71	No	Yes (uni)		**Yes (multi)**	**Yes (multi)**	No	Yes (uni)	No	**Yes – epicardial (multi)**	–	–
Park (2017) [23]	28/116	No	**Yes (multi)**	No	**Yes (multi)**	**Yes (multi)**	No	–	No	**Yes – LV (multi)**	No	NA[b]
This study (2017)	54/98	Yes (uni)	**Yes (multi)**	No	Yes (uni)	Yes (uni)	No	–	Yes – minimal (uni)	Yes – non RVOT/ infundibular (uni)	No	No

Abbreviations: uni, by univariate analysis; multi, by multivariate analysis; CI, coupling interval; CMP, cardiomyopathy; BMI, body mass index; PVC, premature ventricular complex; RVOT, right ventricular outflow tract; LV, left ventricular.

[a]PVC burden was significant on multivariate analysis only when another factor (non-sustained VT) was removed.

[b]This study presented the results of a multivariate analysis in symptomatic patients only.

function recovery following PVC ablation [25]. Although patients in our study with cardiomyopathy had longer median PVC QRS durations, this was not found to be predictive on multivariate analysis. Similarly, another potential surrogate for dyssynchrony is the presence of pleomorphic PVCs which may occur in the setting of deeper arrhythmic foci with multiple exits. Whilst these have been shown to predict PVC recurrence [9], only two studies have shown polymorphism to be predictive of CMP on univariate analysis [18,24] and none have demonstrated this after adjustment for covariates. Others, including this study, have demonstrated no relationship at all [1,14,21].

Cardiomyopathy has been shown to be associated with longer PVC coupling intervals on univariate analysis in two studies in addition to our own [16,18]. A potential mechanistic explanation for this is more severe PVC dyssynchrony associated with longer coupling intervals as demonstrated by Potfay et al. in an animal model of PVC cardiomyopathy [26]. Despite this, no studies have shown longer coupling intervals to persist as a risk factor in a multivariate analysis, although one group has shown greater coupling interval dispersion to be predictive of cardiomyopathy [16].

The site of origin of PVCs has been variably and contentiously described as a risk factor for LV systolic dysfunction. Three studies have shown epicardial sites to be a risk factor on multivariate analysis, again possibly due to greater PVC dyssynchrony [18,20,21]. Another study showed non-outflow tract locations to be predictive of cardiomyopathy [22]. We have shown a higher proportion of non-RVOT sites in the cardiomyopathy group, which may reflect greater dyssynchrony from left sided PVCs or referral bias. However, once corrected for covariates, this difference was no longer significant. Epicardial site of origins was not predictive of cardiomyopathy in our study.

Symptom duration and asymptomatic status have been proposed as risk factors for cardiomyopathy presumably via prolonged exposure to the deleterious haemodynamic effects of PVCs. Whilst Yokokawa et al. have demonstrated this in their multivariate model in two studies [19,20], this relationship has not been replicated in other studies including this study [22,24].

Interestingly, Kawamura et al. found BMI to be predictive of CMP in their model. They attribute this to the disease modifying nature of this variable rather than inferring direct causation as obesity is well known to be associated with other cardiomyopathic risk factors [16]. Nonetheless, we were unable to reproduce this finding in our study. Similarly, Olgun et al. uniquely found PVC interpolation to be predictive of CMP [17], despite there not being a clear mechanistic explanation for this finding. Premature ventricular complex interpolation was not tested in our study.

At present, there is no robust predictive model of cardiomyopathy in patients with focal VAs. Our study suggests only male gender, and possibly PVC burden, to be predictive of CMP in these patients in contrast to other comparatively sized reported cohorts in the literature. The various studies examining risk factors for EMC are outlined in Table 3. It is clear that i) many factors initially apparent on univariate analysis no longer remain predictive after adjustment for confounders, and ii) there is a lack of reproducibility and consensus between studies.

This heterogeneity likely represents differences in study populations, local referral bias and significant unmeasured confounders that the various multivariate models are unable to account for. Indeed, the factors that remained in our multivariate model still only accounted for a modest 37% of the variances in LV systolic function between the two groups. Two studies have proposed algorithms based on risk factors which were strongly predictive of EMC in their cohorts [21,23]. These algorithms, however, have not been tested prospectively in external cohorts. Future predictive models of EMC need to be tested prospectively and validated in patient populations external to those from which they were derived.

Limitations

Our study population included all patients who underwent focal VA ablation in the setting of LV systolic dysfunction. It is likely that this represents a heterogeneous population comprising patients that have true EMC in addition to those who simply have focal VAs in the setting of pre-existing cardiomyopathy with scar-based substrate (post-infarction and non-ischaemic aetiologies). Although this may affect acute procedural and medium-term outcomes, this nonetheless has pragmatic relevance to 'real world' patients as i) EMC is a diagnosis that can only be made in retrospect, and ii) patients with apparently fixed substrate can improve LV function following successful ablation. Our study was not powered to separately assess outcomes in those with pre-existing substrate only.

Due to the retrospective nature of this study, not all patients had paired pre- and post-procedural TTEs and Holter studies. The logistic regression analysis required values for all included variables to be present for each patient. As only 94 out of the 152 patients (62%) had pre-procedural Holter studies to assess PVC burden, some patients were included in the univariate but not the multivariate analyses. As such, our multivariate model may have been underpowered to detect significant predictive factors.

The variables in our final multivariate model still only account for a modest degree of variance in LV systolic function, despite our study being of comparable size to others reported in the literature. This probably reflects the limitations of retrospective analyses with likely significant unmeasured confounders and collinearity that cannot be accounted for in our model.

Conclusion

The acute and medium-term outcomes in patients undergoing focal VA ablation in the setting of cardiomyopathy are satisfactory with normalisation of LV systolic function

achievable in most patients. Although factors related to the frequency, timing and origin of ventricular ectopy were associated with reduced ejection fraction, male gender was the only factor that predicted the presence of cardiomyopathy in multivariate analysis. Further research is needed to understand the mechanism of LV systolic dysfunction in this setting and to produce accurate models that predict the development of EMC.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.01.012.

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