Journal of Interventional Cardiac Electrophysiology (2018) 53:249–254
https://doi.org/10.1007/s10840-018-0395-2

Evaluation of right ventricular pacing parameters in patients with proliferative scar

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Received: 29 March 2018 / Accepted: 4 June 2018 / Published online: 13 June 2018

Abstract

Background Dermal and myocardial injury results in a healing process, characterized by inflammation and fibrosis. We aimed to investigate association between proliferative scarring at the operation site and right ventricular (RV) pacing and sensing parameters, two clinical outcomes associated with impaired dermal and myocardial healing, respectively.

Methods We performed an observational retrospective study among regularly followed pacemaker (PM)/implantable cardioverter defibrillator (ICD)-implanted patients at our medical center. Patients, who had a first RV active fixation PM/ICD lead implantation procedure and a minimum follow-up of 1 year, were included in the study. Redo procedures, passive fixation RV leads, epicardial leads, generator replacement procedures, and patients using class I and III anti-arrhythmic drugs were excluded. Patients in the control group, matched by age, sex and implanted device and lead type, were randomly selected from the patient pool. Lead impedance, pacing threshold, and R wave measurements obtained at baseline and at 3rd, 6th, and 12th month were analyzed.

Results Baseline characteristics of study and control groups were similar. While baseline and follow-up lead impedance and R wave measurements along with baseline and 3rd-month pacing thresholds showed no significant difference between two groups, 6th- and 12th-month pacing thresholds revealed statistically significant increase in proliferative scar group compared to control group (0.87 vs 0.72 $p = 0.003$ and 0.87 vs 0.71 $p = 0.003$, respectively).

Conclusions PM/ICD-implanted patients with proliferative scar on pocket wound may show increased RV pacing thresholds compared to patients with normal healing of pocket wound.

Keywords Active fixation lead · Implantable cardioverter defibrillator · Proliferative scar · Pacemaker · Pacing threshold

1 Background

Keloids and hypertrophic scars are two types of proliferative scarring at sites of cutaneous injury, and both are characterized by excessive proliferation of fibroblasts and abnormal accumulation of extracellular matrix [1]. Implantable cardiac electronic devices such as pacemakers (PMs) and implantable cardioverter defibrillators (ICDs) are used widely to treat symptomatic bradycardias and patients at high risk for sudden cardiac death, respectively [2, 3]. During implantation of these devices, active or passive fixation right atrial (RA) and right ventricular (RV) leads are implanted in endocardium. Implantation

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of active fixating leads in particular results in endo-myocardial damage and subsequent healing. There are many similarities between dermal and cardiac healing, including cellular and molecular mediators of inflammation and fibrosis [4]. Inflammation and growth factors (such as transforming growth factor-β [TGF-β] and platelet-derived growth factor [PDGF]) have a central role in wound healing; however, excessive inflammation and elevated levels of growth factors are associated with keloids and cardiac healing such as stent restenosis [5–7]. We aimed to investigate relationship between pocket wound healing with proliferative scar and RV pacing and sensing parameters, compared to normal wound healing.

2 Material and methods

2.1 Study design

This observational, retrospective study was designed to compare right ventricular pacing and sensing parameters (pacing threshold, lead impedance, and R wave amplitude) in patients with proliferative scar on their pocket wound versus the control group with normal wound healing.

2.2 Patient population

Among regularly followed PM/ICD-implanted patients in Ankara University PM-ICD follow-up clinic, patients with proliferative scar on their pocket wound, who had a first RV PM/ICD active fixation lead implantation procedure and a minimum follow-up of 1 year, were selected and included in the study group. Patients who received passive fixation or epicardial RV lead, patients who had undergone a redo procedure or a generator replacement procedure, patients with follow-up shorter than 1 year, and patients receiving Vaughan-Williams class I and III anti-arrhythmic drugs were excluded from the study. A group of patients, matched with study group in regard to age, sex, implanted device type (i.e., PM or ICD), and RV active fixation PM/ICD lead, were included in the control group. Baseline and follow-up right ventricular sensing and pacing parameters were compared between two groups.

2.3 Scar evaluation

Pocket wound scars were evaluated using Vancouver Scar Scale (VSS) [8, 9]. Vancouver Scar Scale assesses four variables seen in Table 1: vascularity, height/thickness, pliability, and pigmentation. Especially VSS height score (0–3) performed best for diagnosis of proliferative scar; using a cutoff of ≥ 1, height score was 99.5% sensitive and 85.9% specific for proliferative scar [10]. VSS total score and height score were calculated for all patients. Examples of proliferative scarring and normal pocket wound healing are shown in Fig. 1.

Table 1 The Vancouver Scar Scale (0–13)

Pigmentation (0–2)	Normal	0
	Hypopigmentation	1
	Hyperpigmentation	2
Vascularity (0–3)	Normal	0
	Pink	1
	Red	2
	Purple	3
Pliability (0–5)	Normal	0
	Supple	1
	Yielding	2
	Firm	3
	Banding	4
	Contracture	5
Height (0–3)	Normal (Flat)	0
	0–2 mm	1
	2–5 mm	2
	>5 mm	3
Total score		13

mm millimeter

2.4 Pacemaker/ICD lead features, and measurements

Implanted ICD leads were of different make and models, however, typically, were bipolar/dual coil, 65 cm, active fixation leads with steroid-eluting collar. Typically, PM leads were also bipolar/dual coil, 52 or 58 cm, active fixation leads with steroid-eluting collar. Pacing threshold was defined as the lowest voltage, which can produce five consecutive beats of myocardial capture and was measured at a pulse duration of 0.4 ms. Right ventricular pacing thresholds, lead impedance values, and R wave amplitudes expressed in volts (V), ohms (Ω), and millivolts (mV), respectively, were recorded at the time of implantation and at 3rd-, 6th-, and 12th-month follow-up. All of the operators were experienced in cardiac device implantation.

2.5 Statistical analysis

Statistical Package for Social Sciences (SPSS for Windows, Chicago, IL, USA) version 20 was used for statistical analysis. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as frequencies (%). Categorical differences between groups were compared with the χ^2 test or the Fisher exact test whenever appropriate. Quantitative data of the two groups were compared by means of independent samples *t* test. A p value of < 0.05 was considered as significant.

3 Results

The study group consisted of 86 patients (52 men, 34 women). Mean age of all subjects was 56 ± 14 years. The proliferative scar group was comprised of 43 subjects (25 male, mean age 56.4 ± 14 years). Control group was also comprised of 43 subjects (27 male, mean age 54.7 ± 14 years), which were matched

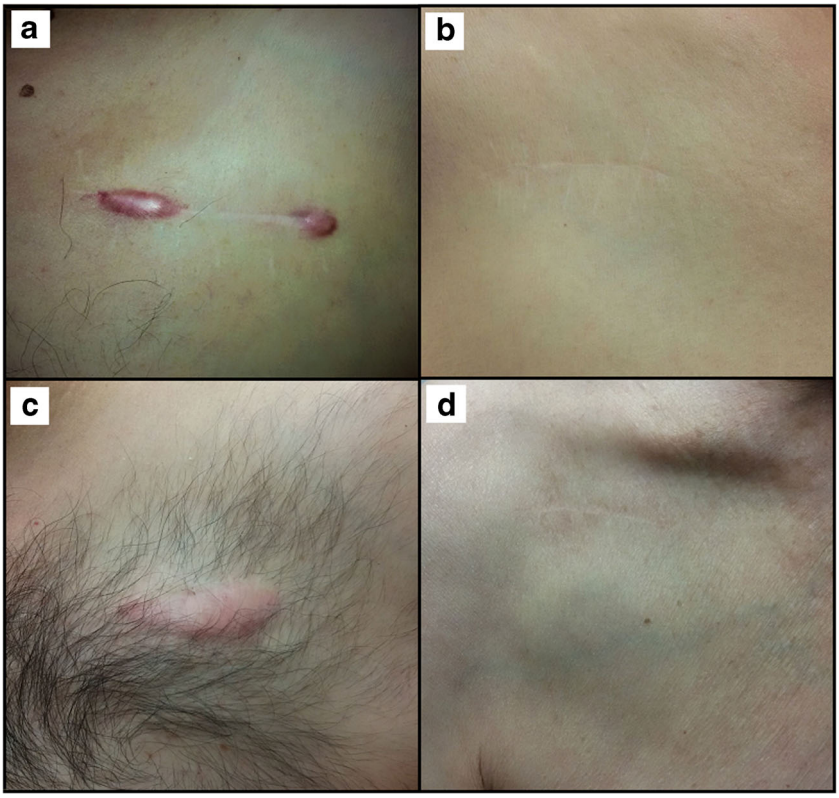

Fig. 1 **a** Proliferative scar (VSS total score, 8; height score, 1). **b** Normal scar (VSS total score, 1; height score, 0). **c** Proliferative scar (VSS total score, 6; height score, 2). **d** Normal scar (VSS total score, 0; height score, 0), VSS, Vancouver Scar Scale

with proliferative scar group according to age, sex, and implanted device type. Active fixation RV pacing or ICD leads were implanted to all patients. There were no differences with regard to age, sex, cardiovascular risk factors, coronary artery disease, ejection fraction (EF), pacemaker/ICD indications and implanted RV lead or device types, and medications between two groups (Table 2). Vancouver Scar Scale score and height score were significantly higher in proliferative scar group.

Baseline, 3rd-, 6th-, and 12th-month follow-up measurements revealed no significant difference in regard to RV lead impedance and R wave measurement between two groups. Analysis of RV pacing threshold at baseline and at 3rd-month follow-up measurement revealed no significant difference; however, statistically significant increase in the pacing threshold was evident at 6th- and 12th-month follow-up measurement ($p = 0.003$) (Fig. 2). RV lead impedance, pacing threshold, and R wave amplitude measurements are presented in Table 3.

4 Discussion

In our study, we have compared temporal trends in right ventricular pacing and sensing parameters at baseline after device implantation, and systematically at 3rd, 6th, and 12th month. We have observed statistically significant increase in pacing threshold in patients with proliferative scar on their pocket wound. This increase in threshold was evident late after implantation at 6th- and 12th-month follow-up measurement. To the best of our knowledge, this is the first study evaluating the effect of proliferative scarring on the RV pacing and sensing parameters in patients undergoing cardiac electronic device implantation.

One of the most important determinants of pacing and sensing parameters of an implanted RV electrode is the myocardial-electrode interface, a histologically dynamic micro-structure [11]. In a process referred to as lead maturation, the initial thrombus formation and acute inflammation, gradually, although not uniformly, transforms into fibrosis and chronic inflammation [12, 13]. The electrically inert connective tissue layer thickness in the myocardial-electrode interface has been previously associated with baseline RV pacing threshold and reduction of it is one of the principal mechanisms of action of steroid-eluting collars [14].

Histological characteristics of proliferative scars are abundance of dermal fibroplasia, excessive and/or disorganized type I and III collagen, and absent myofibroblasts [15]. Differential expression, function, and receptor regulation of various inflammation and healing mediating cytokines including TGF-β, PDGF, insulin-like growth factor-I (IGF-I), and fibroblast-like growth factor-β (FGF-β) along with mediators of extracellular matrix degradation mediators such as matrix metalloproteinases (MMPs) are pathophysiological mechanisms of keloids and hypertrophic scars [15]. One of the most recent hypotheses on pathophysiologic mechanisms of proliferative dermal scars includes endothelial dysfunction, a usual suspect in cardiovascular disease [16].

Table 2 Characteristics of patients with and without a proliferative scar

Characteristic	Controls ($n = 43$)	Proliferative scar ($n = 43$)	p value
Age, years (mean ± SD)	54.7 ± 14	56.4 ± 14	NS
Male, *n* (%)	27 (62)	25 (58)	NS
Smoking, *n* (%)	32 (74)	31 (72)	NS
Systemic hypertension, *n* (%)	22 (51)	21 (49)	NS
Diabetes mellitus, *n* (%)	14 (33)	13 (30)	NS
History of CAD, *n* (%)	18 (42)	17 (40)	NS
Hyperlipidemia, *n* (%)	16 (37)	15 (35)	NS
Medications, *n* (%)			NS
Aspirin	27 (61)	25 (58)	
Beta blocker	30 (70)	31 (72)	
ACE-i/ARB	31 (72)	30 (70)	
Statins	29 (67)	27 (62)	
Calcium channel blocker	4 (9)	3 (7)	
Spironolactone	25 (58)	23 (54)	
EF, % (mean ± SD)			NS
Pacemaker	58.3 ± 3.2	59.1 ± 2.8	
ICD	29.5 ± 3.1	28.9 ± 4.1	
Pacemaker indications, *n* (%)			NS
3rd-degree AV block	5 (12)	5 (12)	
Sick sinus syndrome	8 (19)	8 (19)	
AF with slow ventricular rate	5 (12)	5 (12)	
ICD indications, *n* (%)			NS
Primary prevention	19 (44)	19 (44)	
CRT-D	6 (14)	6 (14)	
Implanted device types, *n* (%)			NS
VVI-PM	5 (12)	5 (12)	
DDD-PM	13 (30)	13 (30)	
VVI-ICD	19 (44)	19 (44)	
CRT-D	6 (14)	6 (14)	
Vancouver Scar Scale (mean ± SD)			
Total score (0–13)	0.58 ± 0.62	5.56 ± 1.03	0.0001
Height score (0–3)	0	1.56 ± 0.5	0.0001

ACE-i angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *AV* atrio-ventricular, *CAD* coronary artery disease, *CRT-D* cardiac resynchronization therapy with defibrillator, *EF* ejection fraction, *ICD* implantable cardioverter defibrillator, *PM* pacemaker, *SD* standard deviation

There are many similarities between dermal and cardiac healing, including cellular and molecular mediators of inflammation and fibrosis [4]. These similarities may represent pathophysiologic basis for altered lead maturation that leads to increased pacing threshold in patients with proliferative scars. Patients with proliferative scars, which have previously been associated with in-stent restenosis [17] and endothelial dysfunction [18], may have exuberant connective tissue formation at the myocardial-electrode interface site, resulting in increased thickness of electrically inert tissue. The excessive fibrosis around the lead may cause pacing exit block, as one of the reasons for increasing pacing threshold. Furthermore, impaired endothelial function, as mentioned previously, may result in tissue hypoxia, which may have accentuated effect on healing and electrical properties of oxygen-dependent myocardium, and myocardial cells, respectively. Hypoxic myocardial cells may have increased pacing threshold [19]. Endocardial damage and impaired healing may also be a factor in impaired lead maturation. Proliferative scars occur late after the initial insult. Keloids occur 3 months to years after the insult while hypertrophic scars may occur earlier [20]. Increase in RV pacing threshold observed in patients with proliferative scarring occurred 6 months after the implantation; this timing is consistent with the era of stent restenosis after implantation [21]. Excluding a single patient with baseline pacing threshold of 1.0 V and 6th- and 12th-month

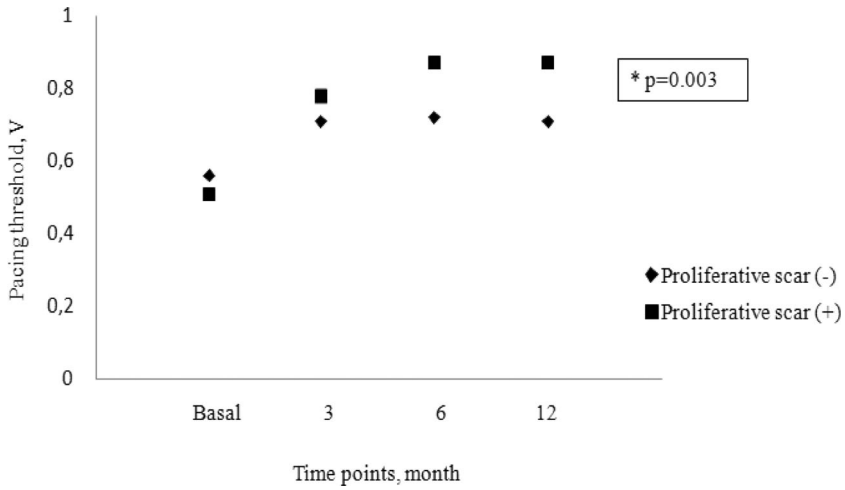

Fig. 2 Comparing RV pacing thresholds between groups at baseline, 3rd-, 6th-, and 12th-month time points (*$p = 0.003$ at 6th- and 12th-month time points)

threshold of 1.5, all RV pacing thresholds in proliferative scar group were in the range of 0.5–1.3 V. The increase in RV pacing threshold, varying between 25 and 100%, was present among all patients in the proliferative scar group and was observed in 6th- and 12th-month follow-up.

One of the most important treatment modalities of proliferative scars are steroids [15]. Intralesional steroids decrease fibroblast proliferation, collagen, glycosaminoglycan, and growth factor synthesis [15]. Patients included in this study have received steroid-eluting collar leads. These leads, by eluting steroids, and decreasing local inflammation and fibrosis, in similar manner to dermal intralesional injection, may have decreased magnitude of effect of altered tissue healing. As steroid-eluting leads are standard in modern practice, the clinical significance of effect on non-steroid-eluting leads may not be relevant. Also, the high percentage of beta blocker treatment in our study population may have decreased the magnitude of effect, as the treatment with beta blockers has been previously reported to decrease proliferative scarring [22].

Although the clinical significance of increase in RV pacing threshold is unknown, the findings of our study may highlight the importance of obtaining good baseline pacing parameters in patients with history of proliferative scarring. In one study, 4.1% of patients undergoing open-heart surgery required a new implant with either a pacemaker or ICD [23]. The rate varied widely across different types of operation, however, ranging from 1.2% for CABG alone to 25% for tricuspid valve replacement [23]. Therefore, the importance of examining previous surgical scars and obtaining good pacing parameters during implantation procedures must be emphasized in patients with history of proliferative scarring.

Limitations to our study include all limitations of observational studies including unaccountable confounding factors that may have altered the analysis. Due to small number of patients in each PM and ICD subgroups, RV pacing and sensing analysis were not performed according to device types. Also, due to low number of implanted atrial (8 active fixation, 11 passive fixation, in total 19) and left ventricular (in total 6) leads, measurements of atrial and ventricular leads were not analyzed. Although, statistically, there was a significant difference between two groups in terms of RV pacing thresholds, this difference is not clinically significant. This small study should be interpreted as hypothesis-generating, and due to short follow-up, larger studies with longer follow-up are necessary to observe clinical significance of our finding. Autopsy/biopsy studies are necessary to confirm pathologic basis of our findings.

In conclusion, the subgroup PM/ICD-implanted patients with proliferative scarring on pocket wound may show increased RV pacing thresholds compared to normal wound healing group. Obtaining good pacing parameters during

Table 3 Comparison of lead impedance, R wave, and pacing threshold values between groups in 1-year follow-up

	Impedance, ohms			R wave, millivolts			Pacing thresholds, volts		
	Controls	Scar (+)	*p*	Controls	Scar (+)	*p*	Controls	Scar (+)	*p*
Baseline	598.3 ± 106.3	606.1 ± 138.5	0.77	13.1 ± 5.4	14.4 ± 6.4	0.3	0.56 ± 0.21	0.51 ± 0.18	0.18
3rd month	612.8 ± 106.8	613.8 ± 104.8	0.9	13.6 ± 5.2	13.8 ± 5.5	0.8	0.71 ± 0.23	0.78 ± 0.24	0.17
6th month	615.1 ± 105.7	612.1 ± 108.5	0.9	13.5 ± 5.4	13.6 ± 5.8	0.9	0.72 ± 0.23	0.87 ± 0.24	0.003
12th month	625.9 ± 109.9	636.4 ± 117.5	0.67	13.5 ± 5.4	13.7 ± 5.8	0.9	0.71 ± 0.23	0.87 ± 0.24	0.003

implantation procedures may be advised in patients with proliferative scar. However, clinical significance of this finding needs to be investigated in larger studies with longer follow-up.

Acknowledgments The authors would like to thank Senay Simsek for her assistance to the follow-up of the patients.

Author contributions V.K.V. and H.G. designed this study. V.K.V., E.B., H.G., N.O., and T.S.T.K. collected and analyzed the data. O.A., A.T.A., and B.C. interpreted results of the study. V.K.V., E.B., and H.G. did statistical analyses, prepared figures, and wrote the paper. All authors edited and revised manuscript and approved final submission of manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethical Committee on Human Research in Ankara University School of Medicine (App No: 05-231-17).

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