Programmed electrical stimulation-guided encircling cryoablation concomitant to surgical ventricular reconstruction for primary prevention of ventricular arrhythmias

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Author Comments:	Friedhelm Beyersdorf, MD Editor-in-Chief, European Journal of Cardio-Thoracic Surgery University Freiburg - Medical Center Department of Cardiovascular Surgery Hugstetter Str. 55 79106 Freiburg, Germany Leiden, 28-8-2017 Dear Dr. Beyersdorf, Herewith we would like to submit our manuscript, entitled 'Programmed electrical stimulation guided encircling cryoablation concomitant to surgical ventricular reconstruction for primary prevention of ventricular arrhythmias' for publication in European Journal of Cardio-Thoracic Surgery. There are only little data on the occurrence of ventricular arrhythmias (VA) and the potential benefit from ICDs in patients who have undergone surgical ventricular restoration (SVR) for ischemic heart failure. The manuscript systematically evaluated the incidence, type and timing of VA after programmed electrical stimulation (PES)-guided endocardial cryoablation concomitant to SVR in patients without previously documented VA during long-term follow-up. The rational of this approach was to target two potential VA mechanisms - scar related reentry and VA due to increased wall stress. We compared the outcome of patients without spontaneous VA, who were referred for SVR and underwent pre-operative PES prior to surgery and who received concomitant endocardial cryoablation of the scar borderzone, if inducible for aneurysm-related VA to a historical cohort of patients without spontaneous VA who did not undergo pre-

	operative PES and anti-arrhythmic surgery. We found that the majority of patients referred for SVR without previously documented VA was inducible for aneurysm related VA and that during follow-up more than one third of the patients experienced appropriate ICD therapy. No difference in VA occurrence, VA cycle length and ICD therapy was observed during long-term follow-up between patients with PES-guided concomitant cryoablation and those without preoperative evaluation and concomitant treatment. Improvement in hemodynamics and concomitant EC in inducible patients appeared not to be sufficient to prevent VAs in this patient population. Considering the favorable long term survival but high incidence of appropriate ICD therapies, other concomitant antiarrhythmic surgical approaches targeting the potential arrhythmogenic substrate need to be considered.. All authors have read and approved submission of the manuscripts and the manuscript has not been published or is not being considered for publication elsewhere. The authors have no conflicts of interest to report. We hope that the manuscript is suitable for publication in European Journal of Cardio-Thoracic Surgery. Looking forward to your response at your best convenience, we remain, Sincerely, K. Zeppenfeld, MD, PhD Department of Cardiology Leiden University Medical Center Email: K.Zeppenfeld@lumc.nl
Abstract:	Background Surgical ventricular reconstruction (SVR) is an effective treatment to improve left ventricular (LV) function in patients with ischemic heart failure and a LV anterior-apical aneurysm. Ventricular arrhythmia (VA) is an important cause for morbidity and mortality in these patients. Encircling cryoablation (EC) targeting the VA-substrate may therefore be required. Programmed electrical stimulation (PES) can identify patients at risk for VA. Objective The objective of this study was to evaluate the incidence and type of VA during long-term follow-up after PES-guided EC concomitant to SVR for primary prevention of VA. Methods Thirty-eight patients without spontaneous VA referred for SVR who underwent pre-operative PES were included (PES-group); 27 patients inducible for aneurysm-related VA received cryoablation (71%). A historical cohort of 39 patients without spontaneous VA, pre-operative PES and anti-arrhythmic surgery served as control group. Patients were discharged with an implantable cardioverter defibrillator (ICD). Results During 74±35 months follow-up no arrhythmic deaths occurred. Five-year survival for the total study population was 78%. Twenty-eight patients (36%) experienced ≥1 VA. There were no differences in number and type of ICD therapies between groups: shocks p=0.699; Anti-tachypacing p=0.403. Five-year VA-free survival was 61% for the PES-group and 65% for the control group (hazard ratio 1.67, p=0.290). Conclusion The majority of patients referred for SVR without previously documented VA was inducible for aneurysm-related VA. During follow-up, more than one third of patients experienced sustained VA and 25% received appropriate ICD therapy. No difference in VA occurrence or ICD therapy was observed between groups.

Programmed electrical stimulation guided encircling cryoablation concomitant to surgical ventricular reconstruction for primary prevention of ventricular arrhythmias

Short title: The occurrence of ventricular arrhythmias after surgical ventricular reconstruction

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ABSTRACT

Background

Surgical ventricular reconstruction (SVR) is an effective treatment to improve left ventricular (LV) function in patients with ischemic heart failure and a LV anterior-apical aneurysm**.** Ventricular arrhythmia (VA) is an important cause for morbidity and mortality in these patients. Encircling cryoablation (EC) targeting the VA-substrate may therefore be required. Programmed electrical stimulation (PES) can identify patients at risk for VA.

Objective

The objective of this study was to evaluate the incidence and type of VA during long-term follow-up after PES-guided EC concomitant to SVR for primary prevention of VA.

Methods

Thirty-eight patients without spontaneous VA referred for SVR who underwent pre-operative PES were included (PES-group); 27 patients inducible for aneurysm-related VA received cryoablation (71%). A historical cohort of 39 patients without spontaneous VA, pre-operative PES and anti-arrhythmic surgery served as control group. Patients were discharged with an implantable cardioverter defibrillator (ICD).

Results

During 74±35 months follow-up no arrhythmic deaths occurred. Five-year survival for the total study population was 78%. Twenty-eight patients (36%) experienced ≥1 VA. There were no differences in number and type of ICD therapies between groups: shocks p=0.699; Anti-tachypacing p=0.403. Five-year VA-free survival was 61% for the PES-group and 65% for the control group (hazard ratio 1.67, p=0.290).

Conclusion

The majority of patients referred for SVR without previously documented VA was inducible for aneurysm-related VA. During follow-up, more than one third of patients experienced sustained VA and 25% received appropriate ICD therapy. No difference in VA occurrence or ICD therapy was observed between groups.

Key words: Ventricular Arrhythmias; Ischemic Heart Failure; Surgical Ventricular Reconstruction; Cryoablation

INTRODUCTION

Late sudden cardiac death due to ventricular arrhythmias (VA) constitutes 30-50% of mortality in patients with ischemic heart failure.[1,2] VA may be due to scar-related reentry typically involving the scar-borderzone or to heart failure related mechano-electric changes resulting in altered ion channel and transporter function.[3-5] Surgical ventricular reconstruction (SVR) is an effective treatment to reduce left ventricle (LV) volumes and improve LV function in ischemic heart failure patients with LV anterior-apical aneurysm.[6,7] However, despite improved function and reduced wall stress patients remain at risk for VA.[3,8,9] These VA can be due to reentry in the scar-borderzone which is left in place and excluded by patch material during surgery.[10] Targeting aneurysm scar-borderzone without additional mapping by an encircling cryoablation (EC) has been proven safe and effective for recurrent slow VA in these patients.[11-13] Programmed electrical stimulation (PES) can identify patients at risk for VA after myocardial infarction as it indicates the presence of an arrhythmogenic substrate.[14,15] Patients who undergo SVR for an LV anterior-apical aneurysm without prior VA who are inducible for aneurysm-related reentrant VA, may benefit from substrate modification by concomitant EC of the scar-borderzone referred to as PES-guided EC, to prevent spontaneous VA.

The objective of this study was to evaluate the incidence, type and timing of VAs after PES-guided EC concomitant to SVR for primary prevention of VA during long-term follow-up.

METHODS

Patient population

In 2007 PES-guided EC of the scar-borderzone was added to the standard clinical protocol for patients without documented VA accepted for SVR. The studied population consisted of 38 consecutive patients with ischemic heart failure and anterior-apical aneurysm, who underwent PES prior to elective SVR and PES-guided EC between 2007 and 2012 (PES-group). Thirty-nine patients who underwent SVR without PES-guided EC for the same indication from 2003 onwards served as a historical control group. This included a comprehensive preoperative evaluation with echocardiography and coronary angiography. The results were evaluated by a team of cardiologists and cardiothoracic surgeons.

The Dutch Central Committee on Human-related Research allows use of anonymous data without prior approval of an institutional review board provided that the data are acquired for patient care. All data used for this study were acquired for clinical purposes and handled anonymously.

Preoperative electrophysiological evaluation

Before PES, anti-arrhythmic drugs were discontinued for ≥5 half-lives. None used amiodarone at time of PES. Two catheters were inserted through the right femoral vein, one placed at the His position and the second at the right ventricular apex and subsequently in the right ventricular outflow tract to perform PES. The PES protocol consisted of 3 drive cycle lengths (CL) (600,500,400ms) with 1-3 ventricular extra stimuli (down to 200ms or refractory period) and incremental burstpacing. An aneurysm-related VA substrate was assumed if PES induced a monomorphic VA, lasting >30s or requiring termination because of hemodynamic compromise, was re-inducible *and* the VA exit site was located at the aneurysm scar-borderzone. The presumed exit site was determined based on the VA 12-lead electrocardiogram morphology.[16] All 12-lead VA electrocardiograms were analyzed by 2 independent observers. In case of discrepancy agreement was reached by consensus. Patients with aneurysm-related VA were candidates for EC concomitant to SVR. Patients without aneurysm-related VA underwent SVR only.

Surgical technique

Patients underwent SVR according to the previously described technique.[7] Operations were performed using cardiopulmonary bypass, aortic cross-clamping and intermittent warm blood cardioplegia. The LV was opened through the infarcted area. At the transitional zone between viable and scarred myocardium, EC was performed using a 4mm diameter malleable cryoprobe (Cardioblate CryoFlex,Medtronic,Minneapolis,USA) using argon gas. Overlapping linear applications, down to -150˚C for 90s, were made to the aneurysm scar-borderzone.[10] After EC, a Fontan-stich was placed at the transitional zone. The residual LV cavity was shaped and sized using a mannequin balloon at 55ml/m^2body surface-area (TRISVR,Chase Medical,Richardson,USA) and the remaining defect was closed through an endoventricular Dacron patch plasty. Excluded fibrous scar-tissue was sutured over the patch to improve hemostasis. Additional concomitant procedures were performed when indicated.

After weaning the patient from extracorporeal circulation, trans-esophageal echocardiography was repeated to assess LV shape and function, patch integrity and valvular competency.

ICD settings

In patients without ICD before surgery one was implanted before discharge based on the preoperative LV ejection fraction (EF) ≤30-35% according to current European Society of Cardiology guidelines. Devices were programmed according to our standard institutional protocol for primary prevention; VA monitor zone (VACL 321-400ms, no therapy), VA zone (VACL 261-320ms, anti-tachycardia pacing (ATP) and if the VA continued ICD shocks), VF zone (VACL ≤260ms, ICD shocks). Settings were adapted when clinically indicated.

Follow-up

Patients were prospectively followed in an outpatient heart failure program and maintained on optimal medical treatment for heart failure. ICDs were interrogated every 6 months. Printouts were reviewed for the occurrence of sustained VA, VACL and therapy mode. VA were classified as sustained when lasting >30s in the ICD monitor zone or when initiated appropriate ICD therapy. Therapy was considered appropriate when occurring in response to any VA. Echocardiography was performed before discharge and afterwards annually.

Statistical analysis

Continuous variables are expressed as mean(standard deviation) or median(interquartile range [IQR]) and categorical variables as percentages(%), where appropriate. Student's T-test, Mann-Whitney U-test, Fishers exact or Chi^2-test were used to compare variables between groups at baseline. For analysis purposes, for each patient the mean CL of all induced and/or spontaneous VAs was calculated. Intrapatient comparison for LVEF, NYHA-class and VACL was performed using the paired samples T-test or Wilcoxon paired-test as appropriate. Incidence rate ratio were estimated for counted data. Univariate and multivariate Cox regression models were constructed to study overall survival and VA-free survival. Selection of potential confounders was based on clinical knowledge and comparing baseline characteristics. Furthermore, overall survival and VA-free survival over time were analysed for the total study population by the method of Kaplan-Meier. All tests were 2-sided and a p-

value of <0.05 was considered significant. Statistical analyses were performed using SPSS software (version 22,SPSS Inc,Chicago,Ill,USA).

RESULTS

Patient characteristics

Thirty-eight patients were included in the PES-group and 39 controls. Baseline patient's characteristics are provided in Table 1. Patients were on optimal medical treatment for heart failure before undergoing SVR.

Preoperative electrophysiological evaluation

28/38 patients were inducible for 34 monomorphic sustained VAs. Based on the 12-lead electrocardiogram, 31/34 induced VAs in 27(71%) patients were classified as aneurysm-related. These had a VACL of 259±54ms, 24 VAs (77%) a superior axis, and 19 VAs (58%) had a left bundle branch block-type morphology; 17 VAs (55%) were hemodynamically not tolerated. In 2 patients 1 aneurysm-related and 1 non-aneurysm-related VA were induced and in 1 patient only a non-aneurysm-related VA was induced.

Surgical characteristics

All patients underwent SVR. EC was applied at the aneurysm scar-borderzone in all patients inducible for aneurysm-related VA. No statistical differences in surgical data were observed between groups (Table 1).

Follow-up

Patients were followed for 74±35 months. 74/77 patients had an ICD during follow-up (96%); 3 patients in the PES-group did not receive an ICD at the preference of the referring cardiologist (LVEF≥35% at discharge, negative PES). There was an improvement in NYHA-class from the majority in 3 at baseline to 2 at 1 year follow-up ($p<0.001$). Mean LVEF improved from 27±8% pre-operatively to 36±9% after 1 year ($p<0.001$). No differences were observed between groups after 1 year (Table 2).

VA occurrence and survival

In 28/74 (38%) patients 99 VA episodes were recorded on ICD (VACL 310±58ms, 3[IQR 1-3] VAs/patient), which prompted appropriate ICD therapy in 26/28 patients (93%); 19 patients (25%) received ATP for 58 VAs and 11 patients (14%) received ≥1 shocks for 18 VAs. In 10 patients 15 VA were registered in the VF-zone. No differences were found between groups regarding type of ICD therapy (Table 2). Two patients in the PES-group had 2 VA registered only in the monitor zone of the ICD and did not receive any ICD therapy. None of the patients without ICD had documented or suspected sustained VA.

Median time to first VA was 11 months (IQR 2-27). 9/ 28 patients (32%) experienced a first VA while on anti-arrhythmic drugs. Anti-arrhythmic drugs were initiated because of postoperative spontaneous VA (n=4) or atrial fibrillation/flutter (n=5).

VA occurrence was similar between groups; 14/38 (37%) patients in the PES-group experienced 45 VAs (CL 314±50ms; 3[IQR 1-3] VAs/patient), and 14/39 (36%) in the control group experienced 54 VAs (CL 305±67ms, 3[IQR 1-3] VAs/patient). VA-free survival was 63% at 5 years for the entire cohort and similar between groups (Figure 1A); 61% for the PES-group and 65% for the control group (hazard ratio 1.13 [p=0.750]; after adjusting for confounders hazard ratio 1.67 [p=0.290], Table 3). At multivariate Cox regression analyses for VA occurrence LVEF at baseline demonstrated to influence VA occurrence: Lower LVEF increased the risk for VA during follow-up. VA characteristics did not differ between groups (Table 2). One patient in the control group underwent successful catheter ablation of 2 presumptive clinical VAs 46 months after discharge and was free from VA afterwards.

Twenty-five patients (32%) died during follow-up; 16 patients (64%) died of heart failure. No arrhythmic deaths were reported. Nine patients died of non-cardiac causes. One patient in the PES-group received a LV assist device as destination therapy 58 months after SVR and 1 patient in the Control group underwent heart transplantation after 28 months; both were censored for further follow-up afterwards. Kaplan-Meier analysis revealed a 5-year overall survival of 78%. No significant difference in 5-year overall survival was observed between groups (PES-group 79% versus Control group 78%, Figure 1B): unadjusted hazard ratio 1.05, p=0.932; adjusted hazard ratio 1.62, p=0.514. When performing multivariate analyses, only older age remained significantly associated with worse overall survival (Table 4).

Encircling cryoablation and VA characteristics

Overall 11/27 patients (41%) with concomitant EC experienced 37 VA episodes (median 2 [IQR 1-3] episodes/patient). VACL did not differ between patients with or without EC: 308±46ms versus 311±66, p=0.919, respectively. Five VA (14%) were terminated by ICD shock and 19 VA (51%) by ATP. The remaining 13 VA (35%) were registered in the ICD monitor zone. There were no differences in type of ICD therapy between patients with or without EC.

DISCUSSION

The present study is the first to systematically evaluate the incidence, type and timing of VA in patients who underwent PES-guided EC concomitant to SVR for primary prevention of VA thereby targeting two potential VA mechanisms; scar-related reentry and wall stress. The main findings are: (1) the majority of patients referred for SVR without previously documented VA was inducible for aneurysm-related VA; (2) during follow-up more than one third of the patients experienced appropriate ICD therapy, despite concomitant EC targeting the scar-borderzone and significant hemodynamic improvement; (3) no difference in VA occurrence, VACL and ICD therapy was observed during long-term follow-up between patients with PES guided concomitant EC and those without preoperative evaluation and concomitant treatment.

Pre-operative VA inducibility

The current investigation comprised of a homogeneous patient group, with a large anterior scar after infarction, the majority in NYHA-class 3 and none treated with amiodarone. 71% of these patients were inducible for an aneurysm-related VA prior to surgery, using a standardized and complete PES protocol. Others have reported lower inducibility rates, ranging from 22-58%. However, included patients were more heterogeneous (with/without apical aneurysm; anterior/non-anterior infarction; NYHA-class 1-3; many on sotalol/amiodarone; LVEF >40%) and in several studies the induction protocol was less extensive which is likely to influence inducibility rates in scar-related VA.[14,17-20] Induction of a monomorphic reentrant VA indicates the presence of an arrhythmogenic substrate and has been associated with VA occurrence and sudden death in patients after myocardial infarction, especially in patients with a LV aneurysm.[14,15,21] Based on VA morphology all but 3 VAs had an exit

site at the aneurysm scar-borderzone in particular involving the inferior apical septal segments. Therefore, targeting the scar-borderzone by cryoablation may abolish at least parts of the substrate for these VA.

VA occurrence after SVR

Previous studies have demonstrated that the substrate for reentrant VA can persist after SVR and may lead to VA occurrence during follow-up.[11,22] This might be partly due to incomplete elimination of VA substrate by SVR as a significant portion of myocardial scar is left behind the inserted patch for stability and hemostasis. Excluded portion of the scar containing the VA reentry circuit can no longer be approached by endocardial catheter ablation, which may further justify preventive substrate elimination.[10] In the historical control group without additional PES guided EC, 36% experienced spontaneous VA during long-term follow-up supporting the importance of preventive methods to identify and target possible VA substrates. Of importance, in the PES-group, 71% of which underwent EC of the scar-borderzone, a similar high VA occurrence rate was registered (37%). Although not randomized, patient groups were comparable in baseline and surgical characteristics suggesting that PES-guided concomitant EC does not prevent late VA. This is confirmed by the multivariate Cox regression analysis demonstrating that PES-guided EC did not influence outcome.

As VA were registered in 41% of patients who underwent EC of the scar-borderzone the technique seems insufficient to eliminate the VA substrate in our population. Catheter mapping studies of post infarct VA have shown that although reentry circuit exit sites are usually located at the scar-borderzone, which may also involve the mid-wall and subepicardial layers, the critical isthmus is often found in the electroanatomical dense scar.[4,5,23,24] A prior animal study could demonstrate that endocardial cryoablation lesions reach a depth of approximately 4.8mm.[25] Endocardial cryolesions, in particular at the septal scar-borderzone may not create transmural or deep lesions and may not be sufficient to eliminate or exclude the VA substrate, allowing for circuits to remain or the reentrant circuit to exit.

VA occurrence rate after EC in this population without prior VA was higher than previously described recurrence rates in patients who underwent EC for the treatment of recurrent VA.[3,9,11-13] This may be in part explained by the large proportion of patients with an ICD (96%) in the current investigation allowing for reliable monitoring of VA recurrence. The high ICD implantation rate is

different from most prior studies with implantation rates of only up to 9.6% after SVR,[3,11-13] except for the investigation of O'Neill[9] in which 48% of patients were discharged with an ICD. Differences in surgical techniques and the frequent use of amiodarone in the prior studies may have also contributed to lower VA recurrence rates.

Of importance, differences in VA substrate may exist between patients with, as in previous studies, and without, as in the current study, spontaneous VA before surgery. While previous studies mainly included patients with hemodynamically tolerated and often slow VA,[10,12,26] the observed VAs in the present study were often fast, and an important number required ICD shocks to be terminated. As the underlying substrate determines VA characteristics, like CL, the occurrence of fast VAs may reflect differences in the VA substrate between the studied population and patients in previous studies.[27] Fast VTs as observed in our cohort, may be due to small anatomical or even functional reentry circuits. The substrate for these fast VAs may not be sufficiently targeted by EC of the scar-borderzone.

The fact that late VA in both groups were similar regarding CL and response to ATP, supports the conclusion that EC had no sufficient impact on the VA substrate. Progressive remodeling and LV re-enlargement may occur after surgery contributing to arrhythmogenity, which is also supported by the high occurrence rate of atrial fibrillation in patients with VA.[10,20]

Survival

We reported a good overall survival of 78% at 5 years follow-up for the total study population. This is comparable with other centers with a large experience in SVR (70-82% 5 years survival).[3,11,28] Furthermore, no arrhythmic deaths occurred. However, the observed fast VAs terminated by ICD shock in 11 patients (14%), may be considered as aborted arrhythmic deaths. Of interest, two prior studies reported similar rates of arrhythmic deaths (17% and 20%).[8,13] In contrast, in 1 study cardiac death constituted 19% of late mortality at follow-up, however sudden cardiac death rate was only 2.5%.[3] Although not all ICD therapy equals aborted sudden death, most of the study period was during the time with relatively short detection times and prior to MADIT-RIT trial results were published, symptomatic and potential fatal VT do occur.[29]

Clinical implications

The majority of patients referred for SVR and without prior VA were inducible for aneurysm-related monomorphic VA prior to SVR. Although all pre-operatively inducible patients underwent concomitant EC targeting the scar-borderzone this was not sufficient to prevent VA in a considerable number of patients. Improvement in hemodynamics and concomitant EC in inducible patients appeared not to be sufficient to prevent VAs in this patient population. Considering the good long-term survival and high incidence of appropriate ICD therapies, other concomitant antiarrhythmic surgical approaches targeting the potential arrhythmogenic substrate like endocardectomy should be (re-)considered; techniques, which have been successfully performed with favorable results in the early days of arrhythmia surgery.[30]

Limitations

Because of the retrospective nature of the study the number of patients included is limited. As a consequence of the inclusion of a historical control group, follow-up duration varied among patients. Furthermore, this study was non-randomized. No comparison between patients with inducible aneurysm-related VA but without concomitant EC was performed. However, because of the reported favorable results of non-mapping guided cryoablation to treat VA, not performing cryoablation in these high-risk patients was considered unethical. Although the treatment strategy was not allocated in a randomized fashion, groups were comparable and treated by the same team. The cohort was too small to evaluate a predictive value of a negative preoperative PES.

Conclusion

The majority of patients referred for SVR without previously documented VA was inducible for aneurysm-related fast monomorphic VA. Despite concomitant EC targeting the scar-borderzone, postoperative hemodynamic improvement and low all-cause mortality, 5 year VA-free survival was only 64%. No difference in VA occurrence or ICD therapy was observed between patients with or without PES-guided concomitant EC. Other strategies for targeting the substrate for VA in this patient population are required.

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Disclosures

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TABLES

Table 1.Baseline characteristics

	All N=77	PES-group N=38	Control group N=39	P-value
Male, n(%)	60(78)	28(74)	32(82)	0.376
Age,years	60±10	63±9	58±11	0.051
Diabetes mellitus,n(%)	16(21)	10(26)	6(15)	0.237
Atrial fibrillation,n(%)	8(10)	6(16)	2(5)	0.125
MI-SVR duration,months(IQR)	36(9-144)	48(10-180)	28(7-132)	0.133
NTproBNP,pg/mL(IQR)	1358 (572-2151)	1346 (616-2253)	1369 (459-1885)	0.518
Primary reperfusion,n(%)	25(32)	8(21)	17(44)	0.035
NYHA,n(%)				<0.001
Class 2	19(25)	17(45)	2((5)	
Class 3	53(68)	21(55)	32(82)	
Class 4	5(6)	0	5(13)	
Euroscore,n(IQR)	6(4-14)	6 (4-14)	7(4-18)	0.537
LVEF,%	27±8	29±8	25±7	0.015
LVESV-index,ml/m^2	80±45	81±52	79±39	0.880
LVEDV-index,ml/m^2	111±53	110±63	112±44	0.894
ACE-I/ARB,n(%)	74(96)	37(98)	37(95)	0.571
Beta-blocker,n(%)	74(96)	37(98)	37(95)	0.571
MRA,n(%)	46(60)	26(68)	20(51)	0.125
CABG,n(%)	41(53)	21(55)	20(51)	0.915
MVR,n(%)	45(58)	21(55)	24(62)	0.576
TVR,n(%)	26(34)	11(29)	15(38)	0.377
AVR,n(%)	4(5)	2(5)	2(5)	0.979
Patch-size,cm^2	14±8	12±5	16±10	0.070

CPB-time,min	204±58	209±52	194±68	0.349
ACC-time,min	141±58	148±41	129±43	0.124

ACC=Aortic cross-clamp; ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CPB=Corporal-pulmonary bypass; AVR=Aortic valve replacement; CABG=Coronary angiography bypass graft; EDV=End-diastolic volume; EF=Ejection fraction; ESV=End-systolic volume; LV=Left ventricle; MI=myocardial infarction; MVR=Mitral valve repair; MRA=Mineralocorticoid receptor antagonists; NYHA=New York Heart Association; SVR=surgical ventricular reconstruction; TVR=Tricuspid valve repair

Table 2.Follow-up

	All N=77	PES-group N=38	Control group N=39	P-value*
Follow-up,months	74±35	61±25	87±39	<0.001
Death(all cause),n(%)	25(32)	12(32)	13(33)	0.869
Cardiac death,n(%)	14(18)	9(24)	7(18)	0.688
ICD,n(%)	74(96)	35(92)	39(100)	0.115
CRT,n(%)	44(57)	23(61)	21(54)	0.299
Anti-arrhythmic drug,n(%)	36(47)	17(42)	19(49)	0.726
Sotalol≥160mg/day	26(34)	13(34)	13(33)	0.953
Amiodarone	21(27)	10(26)	11(28)	0.852
New atrial fibrillation,n(%)	33(43)	15(39)	18(46)	0.544
NYHA 1 year follow-up,n(%)				0.052
Class 1	28(39)	19(54)	9(26)	
Class 2	33(47)	14(39)	19(53)	
Class 3	10(14)	3(8)	7(20)	
LVEF,%	36±9	36±8	35±9	0.845
LVESV-Index,ml/m^2	50±19	50±19	51±19	0.829
LVEDV-Index,ml/m^2	77±22	76±23	79±23	0.600
VA				
Total,n	99	45	54	0.982
Incidence rate, episodes/total follow-up	0.017	0.016	0.019	1.19 (0.78-1.80)†
VA occurrence,patients(%)	28(36)	14(37)	14(36)	0.931
Time to first VA,months(IQR)	11(2-27)	8(2-26)	15(4-29)	0.511
VA episodes/patients(IQR)	3(1-3)	3(1-3)	3(1-3)	0.982
VA cycle length,ms	310±58	314±50	305±67	0.699

Ventricular fibrillation,n	15	8	7	0.841
ICD therapy,patients(%)	26(34)	12(32)	14(36)	0.222
ATP,patients(%)	19(25)	8(24)	11(28)	0.403
Episodes,n	58	19	39	
Shock,patients(%)	11(14)	6(16)	5(13)	0.699
Episodes,n	18	9	9	
Monitor zone,patients(%)	8(10)	6(16)	2(5)	0.092
Episodes,n	22	16	6	
AAD usage during first VA episode	9(12)	5(13)	4(10)	1.0
Sotalol≥160mg/day	6	4	2	
Amiodarone	3	1	2	

Abbreviations as in Table 1. CRT=cardiac resynchronization therapy. VA=ventricular arrhythmia

* p-value calculated between groups

† Incidence rate ratio (95% confidence interval)

Table 3.Cox Regression analyses:VA-free survival

	Univariate		Multivariate	
	HR(CI 95%)	**P-value**	**HR(CI 95%)**	**P-value**
Age	1.02(0.98-1.07)	0.28	1.03(0.99-1.08)	0.13
LVEF baseline	0.97(0.92-1.02)	0.19	0.94(0.89-1.00)	0.03
NYHA-class*	1.15(0.53-2.50)	0.72	1.28(0.51-3.18)	0.60
PES-group	1.13(0.53-2.41)	0.75	1.67(0.65-4.30)	0.29
Primary reperfusion	0.81(0.35-1.84)	0.61	0.83(0.35-1.99)	0.68
Sex	1.81(0.62-5.23)	0.28	2.62(0.87-7.89)	0.09

CI=Confidence interval; HR=Hazard ratio; Abbreviations as Table 1

* NYHA-class as categorical covariate did not alter outcome

Table 4.Cox Regression analyses:Overall survival

	Univariate		Multivariate	
	P-value	**HR(CI 95%)**	**P-value**	**HR(CI 95%)**
Age	0.02	1.10(1.02-1.18)	<0.01	1.12(1.03-1.22)
LVEF baseline	0.59	0.98(0.91-1.05)	0.16	0.94(0.87-1.024)
NYHA-class*	0.24	1.98(0.64-6.10)	0.15	2.54(0.72-8.91)
PES-group	0.93	1.05(0.35-3.12)	0.51	1.62(0.38-6.85)
Primary reperfusion	0.24	0.41(0.09-1.84)	0.33	0.45(0.09-2.25)
Sex	0.35	2.05(0.45-9.25)	0.28	2.45(0.48-12.49)

CI=Confidence interval; HR=Hazard ratio; Abbreviations as in Table 1

* NYHA-class as categorical covariate did not alter the outcome

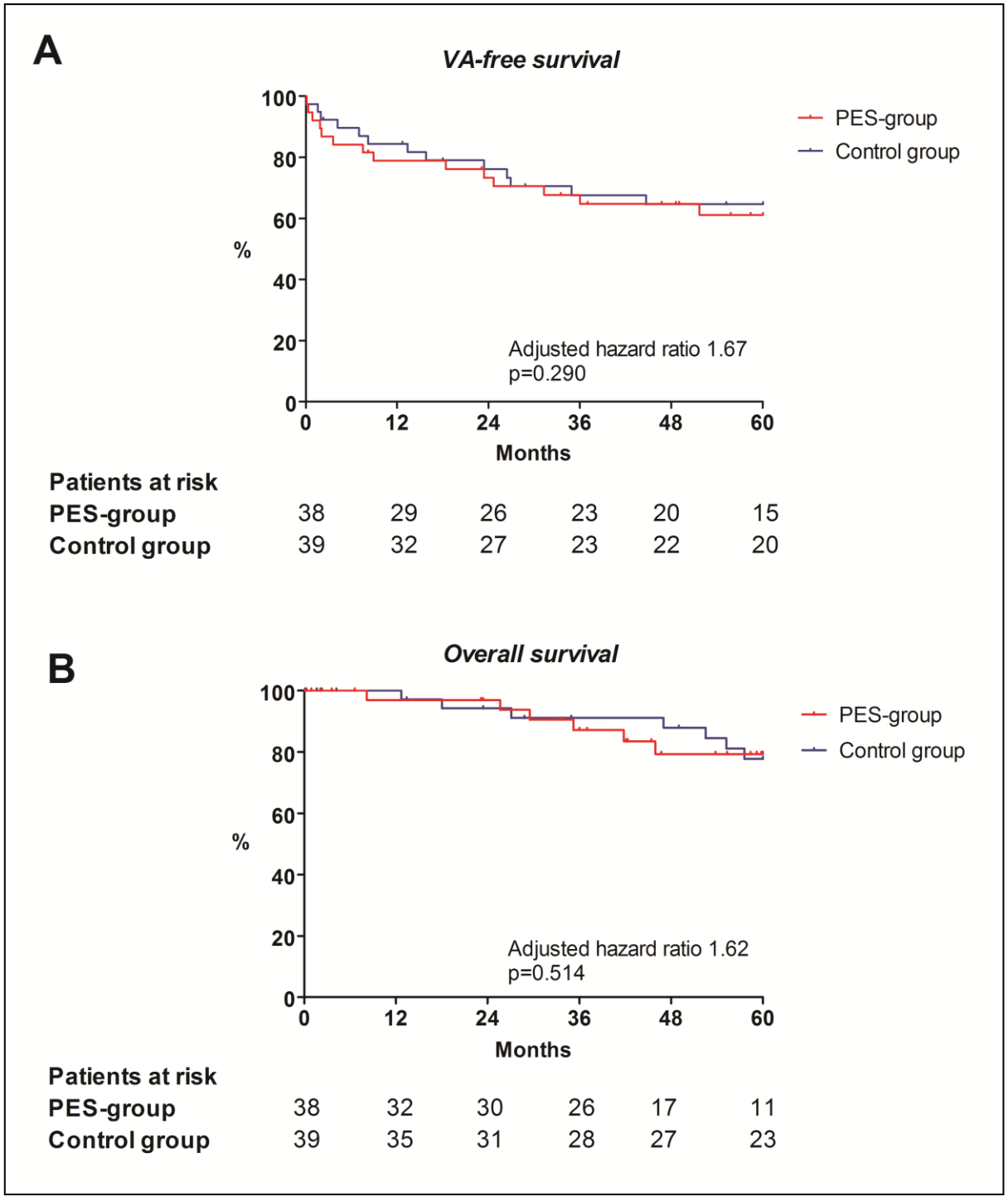
FIGURE LEGENDS

Figure 1.Survival analyses

A: Kaplan Meier curves of 5 year ventricular arrhythmia (VA)-free survival, groups compared using multivariate Cox regression model. B: Kaplan Meier curves of 5 year overall survival, groups compared using multivariate Cox regression model. Curves are according to the different pre-operative strategies of yes/no programmed electrical stimulation (PES).

FIGURES

Figure 1



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