New insights on post-myocardial infarction ventricular tachycardia ablation: defining patient-tailored endpoints to improve outcome

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Myocardial calcification is associated with endocardial ablation failure of post-myocardial infarction ventricular tachycardia

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ABSTRACT

Background

In patients with post-myocardial infarction (MI) ventricular tachycardia (VT), the presence of myocardial calcification (MC) may prevent heating of a subepicardial VT substrate contributing to endocardial ablation failure.

Objectives

The aims of this study were to assess the prevalence of MC in patients with post-MI VT and evaluate the impact of MC on outcome after endocardial ablation.

Methods and Results

In 158 patients, presence of MC was retrospectively assessed on fluoroscopy recordings in 7 standard projections obtained during pre-procedural coronary angiograms. MC, defined as a distinct radiopaque area that moved synchronously with the cardiac contraction was detected in 30 patients (19%). After endocardial ablation, only 6 patients (20%) with MC were rendered non-inducible compared to 56 (44%) without MC (P=0.033) and of importance, 8 (27%) remained inducible for the clinical VT (compared to 9 (6%) patients without MC; P=0.003) requiring therapy escalation. After a median follow-up of 31 months, 61 patients (39%) had VT recurrence and 47 (30%) died. Patients with MC had a lower survival free from the composite endpoint of VT recurrence or therapy escalation at 24-month follow-up (26% vs. 59%; P=0.003). Presence of MC (HR 1.69; P=0.046), a lower LV ejection fraction (HR 1.03 per 1% decrease; P=0.017) and non-complete procedural success (HR 2.42; P=0.002) were independently associated with a higher incidence of VT recurrence or therapy escalation.

Conclusion

MC was present in 19% of post-MI patients referred for VT ablation and was associated with a high incidence of endocardial ablation failure.

INTRODUCTION

Catheter ablation is an effective therapy for preventing ventricular tachycardia (VT) recurrence in patients with prior myocardial infarction (MI). However, despite improvement in the understanding of the VT substrate and technical developments, 10% of patients remain inducible for clinically relevant VTs at the end of the procedure and up to 50% of the patients experience VT recurrence at 6-month follow-up.(1) It has been suggested that both acute procedural failure and VT recurrence after endocardial ablation may be due to epicardial VT circuits that cannot be interrupted from the endocardium.(2) However, less than one third of patients with post-MI VT in whom a first-line endo-epicardial approach was performed had an epicardial ablation target site.(3) In addition, in a majority of patients with post-MI VT, at least part of the epicardial substrate located in areas of wall thinning could be abolished by endocardial ablation.(4) Considering the reported 4-7% additional risk of complications and the significant patient discomfort related to epicardial mapping and ablation (5,6), non-invasive identification of post-MI patients who may benefit from a primary epicardial approach is desirable.(7-9)

MI leading to myocyte necrosis is the most frequent cause of dystrophic myocardial calcification (MC).(10) Although its real prevalence is unknown, significant MC defined as thin curvilinear radiopaque areas were seen in thorax radiographies of up to 8% of patients with MI older than 6 years, frequently associated with the presence of apical aneurysms.(11,12) We hypothesized that in patients with prior MI, MC protecting a subepicardial VT substrate from thermal injury may be one potential cause of endocardial ablation failure despite the presence of wall thinning.

The aims of our study were: 1) to assess the prevalence of MC in a consecutive cohort of patients referred for ablation of post-MI VT and 2) to evaluate the impact of the presence of MC on the acute and long-term outcome of post-MI endocardial VT ablation.

METHODS

Consecutive patients with prior MI referred for ablation of scar-related VT to the Leiden University Medical Center between January 2009 and February 2016 were included. The diagnosis of MI was based on the presence of wall motion abnormalities, non-reversible perfusion defects and/or subendocardial or transmural late gadolinium enhancement areas in the perfusion territory of a significant stenotic coronary artery (>75 %). All patients were treated according to the clinical protocol and provided informed consent for the procedure. The research protocol was accepted by the Institutional Review Board.

Assessment of myocardial calcification

Fluoroscopy recordings in 7 standard projections obtained during pre-procedural coronary angiography (n=132) and/or during the ablation procedure (n=26) were retrospectively analysed for the presence of MC by two experienced cardiologists (J.M.M. and M.R.) blinded to the patient clinical characteristics and ablation outcome. MC was defined as the presence of a distinct and curvilinear radiopaque area that moved synchronously with the cardiac contraction. Calcifications corresponding to the valvular annuli or to the trajectory of an epicardial coronary artery were excluded.

In a subgroup of patients (n=18), presence of MC was also visually assessed on ECG-gated cardiac computed tomography (CT).

Assessment of infarct transmurality

As previously described,(8) an infarction was classified as transmural when the late gadolinium enhanced area extended to >75% of the wall thickness on contrast-enhanced magnetic resonance imaging (CE-MRI), a region of wall thinning ≤5mm was detected on cardiac CT and/or an area of thinned (≤6mm), hyperechogenic and aki/dyskinetic myocardium was observed on echocardiogram. See Supplementary Methods for details.

Ablation procedure

Electrophysiological study

Programmed electrical stimulation was conducted (3-4 drive cycle lengths (CL) [600, 500, 400, 350ms], 3-4 extra's [≥200ms] from 2 right ventricular (RV) and ≥1 left ventricular (LV) site). Positive endpoint of stimulation was induction of a sustained monomorphic VT lasting >30s or requiring termination because of hemodynamic compromise. Induced VTs were regarded (presumed-) clinical if the 12-lead ECG matched that of a spontaneous documented VT or the VTCL was ±30ms of the CL of the implantable cardioverter defibrillator (ICD)-recorded VT.

Substrate mapping and ablation

The initial ablation approach was endocardial in all cases with the exception of 3 patients who had failed ≥1 endocardial ablation attempts in another centre and in whom an epicardial VT origin was suspected by the referring electrophysiologist.

A LV endocardial bipolar voltage map was constructed during stable rhythm using a 3.5mm irrigated-tip catheter (NaviStar ThermoCool or Thermocool Smarttouch SF; Biosense Webster, Inc, Diamond Bar, CA) and the CARTO 3 system. Standard voltage cut-off values of 1.5mV and 0.5mv were used to define scar and dense scar. From 2009 to 2013, all patients underwent substrate-based ablation which was based on elimination of late

potentials and fragmented electrograms (EGMs). Pace-mapping was used to identify VT exit sites. Since October 2013, a systematic pacing protocol was used for substrate identification.(12) In brief, EGMs located in the presumed infarct area, as derived from cardiac imaging and coronary anatomy, independently of their voltage or morphology during sinus rhythm, were analysed during RV pacing at a fixed rate of 500ms and during the application of a short-coupled RV extra-stimulus. Sites showing low voltage, near-field potentials which delayed >10ms or blocked in response to RV extra-stimulation were categorized as *evoked delayed potentials* (EDP) and targeted for ablation. In addition, during the whole study period, if the patient was in VT at the beginning of the procedure, if a hemodynamic stable VT remained inducible after substrate modification or it was repeatedly induced during catheter manipulation, activation and entrainment mapping were performed with the aim of identifying the VT critical isthmus and terminating the VT during ablation.

Radiofrequency (RF) energy was delivered (45-50W, temperature limit 43°C, flow rate 15-30 ml/min, 60-120 seconds, CF>9gr) until stimulation with high output pacing (10 mA, 2ms) failed to capture.

Acute outcome definition

After the last RF application, a re-map was systematically performed (including RV extra-stimulation since October 2013) and the entire induction protocol was repeated. Complete acute success was defined as non-inducibility of any VT, partial success as elimination of the clinical VT but persistent inducibility of any non-clinical VT and procedural failure as persistent inducibility of clinical VT after ablation. Fast non-clinical VTs with a CL close to ventricular refractory period (fast VT_{VERP}) were considered of unknown clinical relevance and not targeted. Accordingly, induction of only fast VT_{VERP} was defined as acute clinical success.(13)

Management after endocardial ablation

After endocardial ablation failure, an epicardial ablation attempt was offered to all patients with the exception of those with prior cardiac surgery. In those patients, "escalation" of anti-arrhythmic drugs (AAD) was the next attempt to control VT, including sotalol with a dose of ≥160mg per day, initiation or increase of the dose of amiodarone or combination of amiodarone with a class I AAD. In patients who did not use amiodarone before ablation, amiodarone was started at a dose of 400mg three times per day for one week, followed by a dose of 400mg per day for one week and 200 mg per day thereafter. In patients receiving amiodarone 200mg per day at the time of ablation, the dose was increased to 300-400mg per day (after one week re-loading dose of 400mg three times a day) or mexiletine (600mg per day) was added. *Therapy escalation* after endocardial

ablation was defined as either escalation of anti-arrhythmic drugs or performance of a successful epicardial or surgical ablation. In the remaining patients, pre-procedural AAD were continued until the first follow-up visit. ICD implantation was offered to all patients without a device before ablation.

Follow-up after hospital discharge and study endpoints

Patients were followed 3 months after ablation and every 6 months thereafter. After acute endocardial ablation success, in the absence of VT recurrence at first follow-up visit, discontinuation of AAD was recommended. For patients followed at other institutions or in case of death, the referring cardiologist or the general physician was contacted for VT recurrence and cause of death.

Endpoints of the study were: 1) VT recurrence, defined as occurrence of any VT requiring ICD therapy, recorded within the ICD monitor zone lasting >30s or documented on 12-lead ECG and 2) Composite endpoint including VT recurrence or need of therapy escalation for controlling the clinical VT.

Statistical analysis

Continuous variables are reported as mean±SD or medians with interquartile range and compared with the Student's t or the Mann-Whitney U test when appropriate. Categorical variables are expressed as numbers and percentages (%) and compared with the Chi-squared or the Fisher exact test. Freedom from the composite endpoint of VT recurrence or escalation of therapy was estimated by Kaplan-Meier method and compared with log-rank test between groups. Predictors of acute procedural outcome and VT recurrence were assessed with univariate logistic regression and Cox regression analysis respectively. Independent predictors of acute ablation failure and VT recurrence or therapy escalation were analysed with multivariable models using a backward stepwise selection. Variables with a p value < 0.10 were initially included. At each step the least significant variable was removed from the model, until all variables reached a p value <0.20. All tests were 2-sided and a P value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 23.0 (SPSS Inc, Chicago, IL).

RESULTS

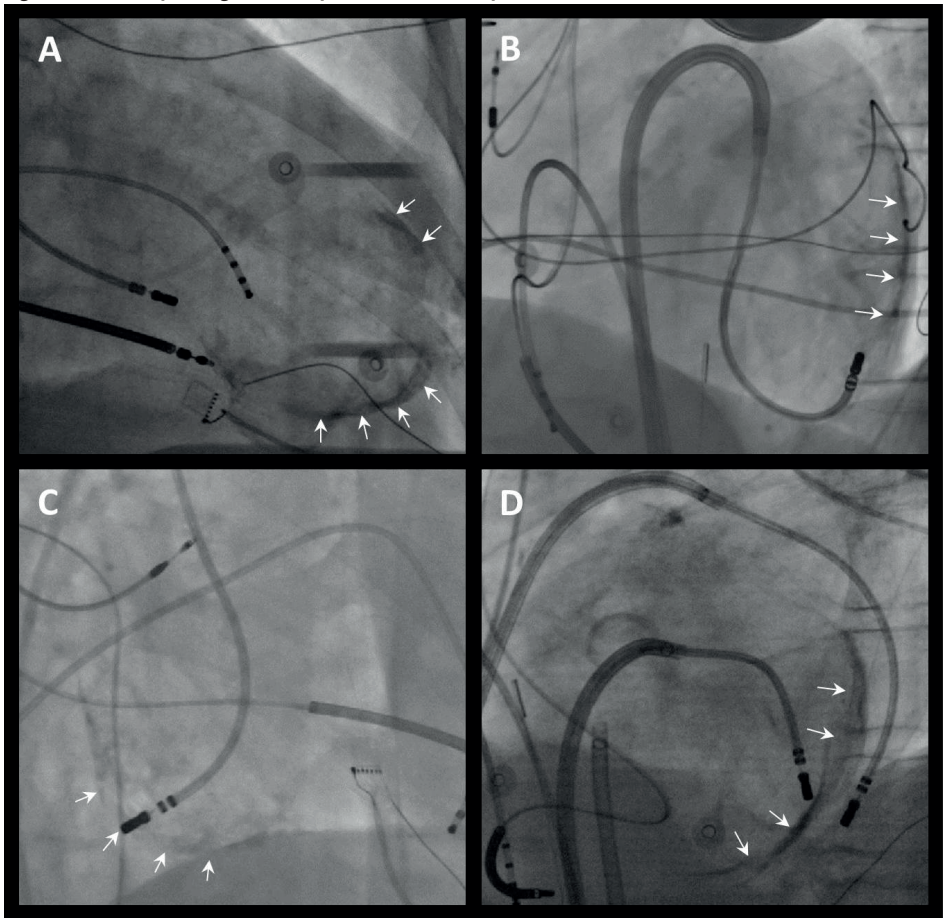
Patients

During the study period, 168 patients underwent ablation for post-MI VT in our centre. Ten patients in whom cine-fluoroscopy recordings were not available or had insufficient

quality for the assessment of MC were excluded. Finally, 158 patients (68±9 years, 87% men, LV ejection fraction 33±12%) constituted the study population.

In 30 patients (19%), an area of MC was detected on cine-fluoroscopy which corresponded in all cases with the infarcted area on echocardiogram. (**Figure 1**) In 5 of them, a cardiac CT was available which confirmed the presence of MC in all. (**Supplementary Figure 1**) Of note, no patient without MC on CT (n=13) had MC on fluoroscopy.

Figure 1. Fluoroscopic images of MC in patients referred for post-MI VT ablation



In panels A, B and C, a large apical calcified aneurysm (right anterior oblique (RAO) view), a lateral MC (left anterior oblique (LAO) view) and an infero-posterior calcified aneurysm (RAO view) are respectively shown. In panel D, a large infero-lateral MC (LAO view) is shown. Note the presence of two ablation catheters at the endocardial and epicardial side of the MC. MC are indicated by white arrows.

The rate of acute reperfusion during the index MI (10 vs. 20%; P=0.294), the baseline LV ejection fraction (31±12 vs. 34±12; P=0.214), the time from the acute MI (median 21 vs. 19 years; P=0.438), the prevalence of renal failure (37 vs. 33%; P=0.832) and the rate of amiodarone use before ablation (47 vs. 41%; P=0.546) were similar in patients with and without MC. Patients with MC were younger (64±11 vs. 69±8 years in patients without MC; P=0.019), had experienced more often an anterior MI (63% vs. 36%; P=0.008) and had undergone more often a prior VT ablation attempt (27% vs. 11%; P=0.038). Baseline characteristics are displayed in **table 1**.

Table 1. Baseline clinical characteristics

	All patients (n=158)	MC (n=30)	No MC (n=128)	*P-value*
Age, years	68±9	64±11	69±8	0.019
Male, n (%)	137 (87)	26 (87)	111 (87)	1.000
Diabetes, n (%)	24 (15)	7 (23)	17 (13)	0.169
Anterior MI, n (%)	66 (42)	19 (63)	46 (36)	0.008
Acute reperfusion, n (%)	29 (18)	3 (10)	26 (20)	0.294
Time since MI	19 (13-26)	21 (15-26)	19 (13-26)	0.438
Atrial fibrillation, n (%)	47 (30)	9 (30)	38 (30)	1.000
Heart failure, n (%)	72 (46)	13 (43)	59 (46)	0.841
Renal failure, n (%)	53 (34)	11 (37)	42 (33)	0.832
CABG, n (%)	60 (38)	9 (30)	51 (40)	0.405
Prior VT ablation, n (%)	22 (14)	8 (27%)	14 (11%)	0.038
LVEF, n (%)	33±12	31±12	34±12	0.214
Clinical VT CL, ms	401±93	420±97	396±91	0.200
Electrical storm, n (%)	27 (17)	5 (17)	22 (17)	1.000
Incessant VT, n (%)	18 (11)	4 (13)	14 (11)	0.750
ICD before ablation, n (%)	110 (70%)	23 (77%)	87 (68%)	0.388
AADs pre-ablation				
Amiodarone, n (%)	66 (42)	14 (47)	52 (41)	0.546
Sotalol, n (%)	38 (24)	7 (23)	31 (24)	1.000

Values are reported as mean ± standard deviation, median and IQR or n (%). MC indicates myocardial calcification; MI, myocardial infarction; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; CL, cycle length; ICD, implantable cardioverter defibrillator and AADs, anti-arrhythmic drugs.

Procedural data and acute outcome after endocardial ablation

Patients with MC had a comparable endocardial electroanatomical scar area (71 vs. 62cm^2; P=0.105) but with a larger dense scar component than those without MC (median 31 vs. 21cm^2; P=0.005). Procedural details are shown in **table 2**. In addition to substrate modification, at least one stable VT was mapped and eventually terminated by RF in 110 patients (70%).

Table 2. Procedural characteristics and acute outcome after endocardial ablation

	All patients (n=158)	MC (n=30)	No MC (n=128)	P value
Number of induced VTs	3 (2-5)	3 (2-5)	3 (2-5)	0.753
Induced VT max CL, ms	420±110	433±114	417±110	0.500
Bipolar scar area, cm^2	64 (42-86)	71 (50-94)	62 (39-86)	0.105
Dense scar area, cm^2	24 (78-43)	31 (22-60)	21 (6-42)	0.005
Border zone area, cm^2	35 (22-49)	31 (27-47)	36 (22-50)	0.849
Procedural time, min	192±68	197±61	191±70	0.697
RF time, min	17±10	18±10	17±11	0.570
Acute outcome (n=156)				
Complete success, n (%)	62 (40)	6 (20)	56 (44)	0.033
Partial success, n (%)	78 (50)	14 (52)	63 (49)	1.000
Failure, n (%)	16 (10)	8 (26)	9 (7)	0.003
ICD after ablation, n (%)	136 (86)	29 (97)	107 (84)	0.079
AADs at discharge				
Amiodarone, n (%)	74 (47)	17 (57)	57 (46)	0.310
Sotalol, n (%)	41 (26)	9 (30)	32 (25)	0.644
Mexiletine, n (%)	1 (1)	1 (3)	0 (0)	0.190

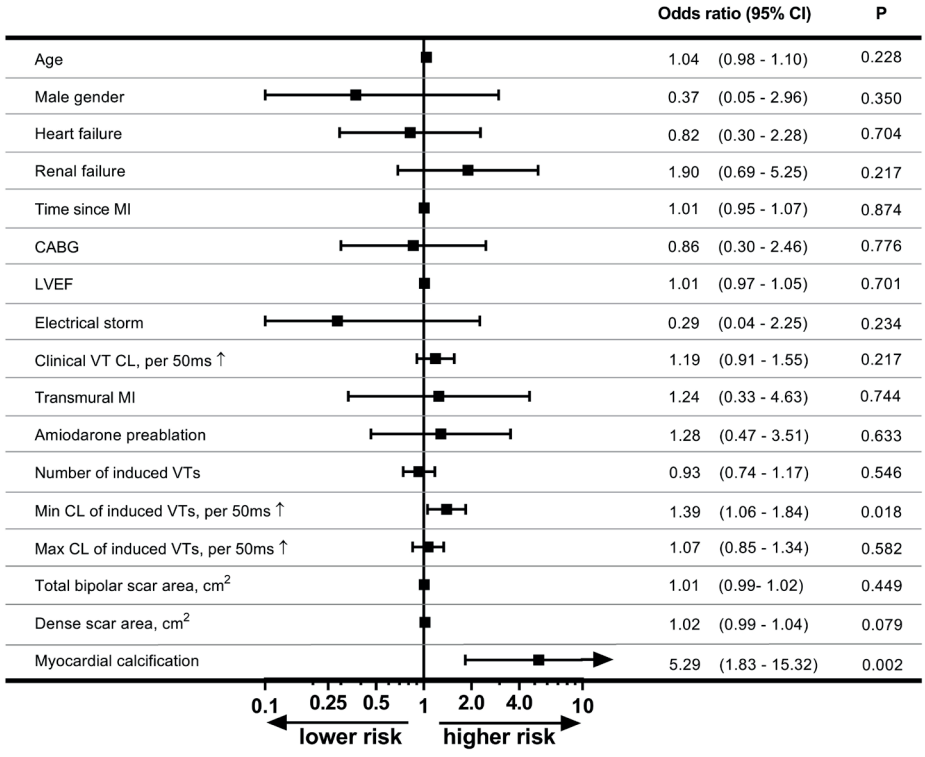
Values are reported as mean ± standard deviation, median and IQR or n (%). RF indicates radiofrequency. Other abbreviations as in table 1.

Acute complete and partial procedural success were achieved in 6 (20%) and 14 (52%) patients with MC (10/14 remained inducible only for fast VT_{VERP}) and in 56 (44%) and 63 (49%) patients without MC (P=0.033 and P=1.000, respectively; 32/63 remained inducible only for fast VT_{VERP}). In 8/30 patients with MC (27%), endocardial ablation failed to eliminate the (presumed-) clinical VT despite extensive activation and entrainment mapping and ablation with high power (50W), long duration applications (120 sec). Critical VT sites were located in areas of calcification in 6 of them (the remaining 2 patients were only inducible for hemodynamically unstable VTs, preventing exact delineation of VT circuits). Of importance, in 5 of these 6 patients, RF applications led to late VT termination but persistent inducibility after extensive ablation, supporting that the critical part of the VT isthmus had been correctly identified but could not be sufficiently abolished. In additional two patients with MC, inducibility at the end of the procedure could not be tested (in one patient ventricular fibrillation was repeatedly induced, in the other patient several cardioversions were necessary to terminate a hemodynamically unstable VT before RF). On the contrary, only 9 patients (7%) without MC remained inducible for the (presumed-) clinical VT after ablation (P=0.003).

Predictors of acute endocardial ablation failure

In univariate logistic regression analysis, presence of MC and induction for slower VTs were associated with acute ablation failure. In multivariate analysis, both (presence of MC: odds ratio 6.898; CI 95% 2.209-21.544; P=0.001 and induction of slower VTs: odds ratio 1.442 per 50ms increase in minimum VTCL; CI 95% 1.084-1.920; P=0.012), remained independently associated with the acute outcome after adjusting for the size of the dense scar area. Of importance, beyond MC, no other pre-procedural factor was found to be associated with acute ablation failure. **Figure 2**

Figure 2. Predictors of acute endocardial ablation failure



CABG indicates coronary artery bypass; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; CL, cycle length; Min, minimum and Max, maximum.

Complications

One patient with prior CABG and recurrent non-tolerated VTs underwent surgical adhesiolysis prior to epicardial ablation after 3 unsuccessful endocardial attempts in another center which was complicated by a bypass occlusion. Despite urgent revascularization, the patient died within 24 hours due to a vasoplegic shock. One patient developed an

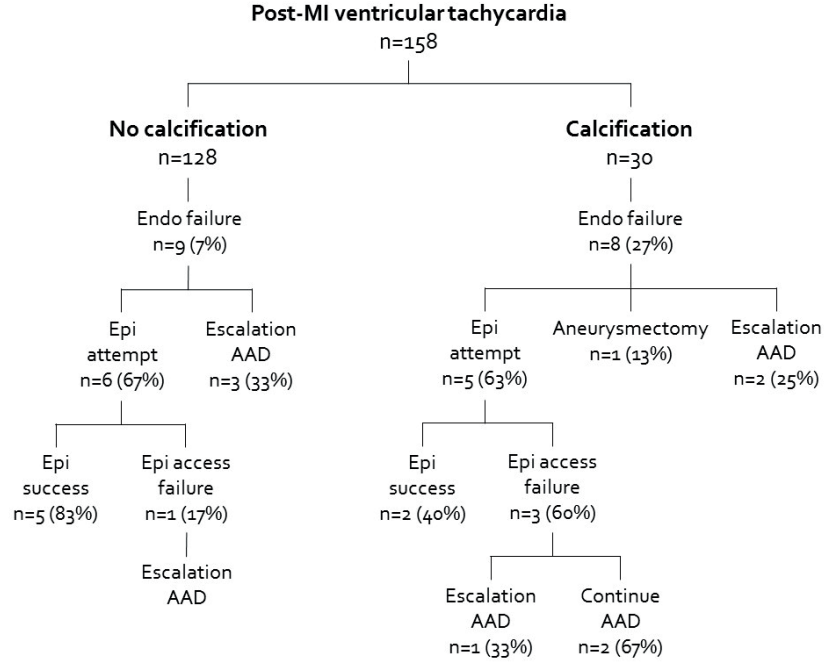
anticipated complete atrioventricular block after ablation of a VT with a basoseptal critical isthmus. Pericardial bleeding with percutaneous drainage occurred in 4 patients.

Management after endocardial ablation

Patients with MC

After endocardial ablation failure, a percutaneous epicardial approach was attempted in 5 of the 8 patients. In 2 of 5 patients, epicardial access and ablation were successful. However, in 3 of the 5, epicardial access was not possible due to the presence of pericardial adhesions. These 3 patients were discharged with AADs (including the combination of amiodarone and mexiletine) (Supplementary Figure 2) One additional patient with an apical aneurysm and a prior valve-sparing replacement of the ascending aorta underwent a surgical aneurysmectomy with concomitant epicardial cryo-ablation. In the remaining 2 patients, AADs were escalated (one refused epicardial ablation, one had prior CABG). After a (partially-) successful endocardial ablation, 22 patients (73%) continued the pre-procedural AADs. (**Figure 3**)

Figure 3. Flow-chart showing the treatment strategy after endocardial ablation failure in patients with and without MC.



Patients without MC

An epicardial ablation attempt was performed in 6 of 9 patients after endocardial ablation failure which was successful in all but one. In this patient, epicardial ablation was prevented by the presence of pericardial adhesions at the area of interest and AADs were escalated. (Figure 2) In the remaining 3 patients (all with prior CABG), AADs were escalated. After a (partially-) successful endocardial ablation, 116 patients (85%) were discharged without modification of the pre-procedural AADs and in 3 patients AAD were initiated for other indications.

At discharge

In total, 136 patients were discharged with an ICD (86%, 97% of patients with MC vs. 84% of patients without; P=0.079) and 115 on AADs (73%, 87% of patients with MC vs. 70% of patients without; P=0.069). Seventy-three patients (43%) were on amiodarone, 41 on sotalol (26%) and one patient on the combination of amiodarone and mexiletine.

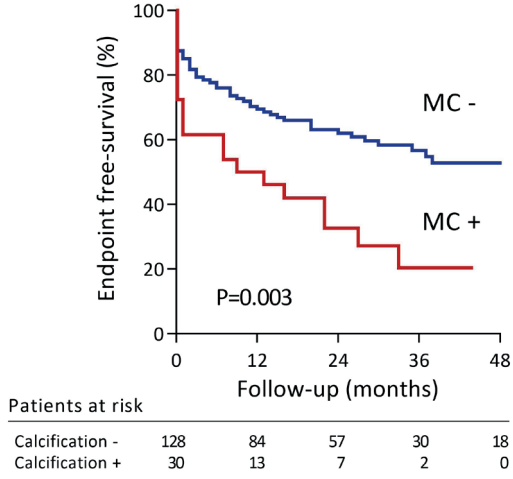
Follow-up after admission for endocardial ablation

In total, 18 patients underwent escalation of therapy after endocardial ablation (6/30 patients (20%) with MC and 12/128 patients (9%) without MC). In 10 patients, AADs were escalated, 7 patients underwent successful epicardial ablation and in one patient, surgical removal of the VT substrate was performed. One patient with MC was lost to follow-up. After a median of 31 months (20-47), 61 patients (39%) had VT recurrence (13 patients with MC [43%] and 48 patients without [38%]; P=0.529, 7/17 patients [41%] with endocardial failure vs. 52/138 [38%] with endocardial success; P=0.779). Forty-seven patients died (30%; 8 patients with MC [27%] and 39 patients without [30%]; P=0.826), 2 patients underwent left ventricular assist device implantation and one patient was transplanted.

After endocardial ablation, patients with MC showed a lower 2-year survival free from the combined endpoint of VT recurrence or need of therapy escalation to control the clinical VT than patients without MC (26% [95% CI 8-44] vs. 59% [95% CI 50-68] in patients without MC; P=0.003). (**Figure 4**)

On multivariate Cox-regression analysis, presence of MC (HR 1.86; CI 95% 1.11-3.10; P=0.018), a lower LV ejection fraction (HR 1.03 per 1% decrease; CI 95% 1.01-1.05; P=0.008) and a higher number of induced VTs (HR 1.12; CI 95% 1.03-1.22; P=0.008) were independently associated with a higher incidence of the composite endpoint of VT recurrence or need of therapy escalation to control the clinical VT. (**Table 3**)

Figure 4. Combined endpoint (VT recurrence or therapy escalation) free survival in patient with vs. without MC.



MC indicates myocardial calcification. Therapy escalation included escalation of AADs, epicardial ablation or surgical ablation.

Table 3. Cox regression analysis for predictors of the combined endpoint of VT recurrence or escalation of therapy.

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Age (per year)	0.99 (0.97-1.01)	0.389		
LVEF (per 1% decrease)	1.04 (1.01-1.05)	0.001	1.03 (1.01-1.05)	0.008
Myocardial calcification	2.04 (1.23-3.38)	0.006	1.86 (1.11-3.10)	0.018
Dense scar area (per $1cm^{2)}$	1.01 (1.00-1.02)	0.003		
Number of induced VTs	1.16 (1.07-1.26)	0.001	1.12 (1.03-1.22)	0.008

Escalation of therapy includes escalation of AADs, epicardial ablation or surgical ablation. Abbreviations as in tables 1 and 2.

Impact of infarct transmurality on acute and long-term outcome after endocardial ablation

A transmural scar was detected in 32 of 36 patients (89%) in whom a CE-MRI was available for analysis and in 89 of 116 patients (77%) in whom scar transmurality was assessed either on CT or on echocardiogram. There were no differences between patients with or without transmural scar nor in the acute neither in the long-term outcome after endocardial ablation (**Table 4**). In 6 patients (4%), no imaging modality of appropriate quality was available for the assessment of scar transmurality.

Table 4. Acute and long-term outcome after endocardial ablation in patients with vs. without transmural scar

	Transmural scar (n=119)	Non-transmural scar (n=31)	*P-value*
Acute outcome (n=150)			
Complete success, n (%)	45 (38)	14 (45)	0.537
Partial success, n (%)	60 (50)	14 (45)	0.688
Failure, n (%)	14 (12)	3 (10)	1.000
24-month endpoint free survival*	52% (95%CI 43-61)	52% (95%CI 33-71)	0.560

*Endpoint includes VT recurrence or escalation of therapy

DISCUSSION

This study systematically evaluated the presence of MC in a cohort of patients with post-MI VT and investigated the impact of MC on acute outcome and long-term results of endocardial ablation. The prevalence of MC assessed on easily available pre-procedural coronary angiograms was 19%. Of note, endocardial ablation failed to eliminate the clinical VT that motivated the procedure in one third of the patients with MC. Subsequently, percutaneous epicardial access was not possible in two third of these patients because of the presence of unexpected pericardial adhesions or due to prior cardiac surgery. At 2-year follow-up, only 26% of patients with MC were free of VT recurrence in the absence of therapy escalation (including percutaneous or epicardial ablation and/or escalation of AADs) compared to 59% of patients without MC. Presence of MC was associated with a lower VT-free survival in the absence of therapy escalation independently of LV ejection fraction, the size of the dense scar area and the number of induced VTs during the procedure.

Post-infarction MC: pathophysiology, prevalence and diagnosis

MI leading to myocyte necrosis is the most common cause of dystrophic MC, this is, calcification occurring in the absence of elevated calcium levels.(10) The process of dystrophic calcification consists ultimately in the formation of calcium phosphate microcrystals that can accumulate both intra and extracellularly.(14) Autopsy studies reporting on the prevalence of MC in patients with prior MI are lacking. However, MC defined as the presence of thin and curvilinear radiopaque areas located at the periphery of the infarcted area was observed in radiographic examinations of up to 8% of patients with MIs older than 6 years.(11) In our study, we detected MC in 19% of patients with post-MI VT. This almost 3-fold higher prevalence of MC than previously reported might be at least partially explained by the different imaging technique that we used for assessment. Fluoroscopic evaluation of the thorax allows for identifying the synchronous motion of the calcium with the beating heart. In addition, the use of sev-

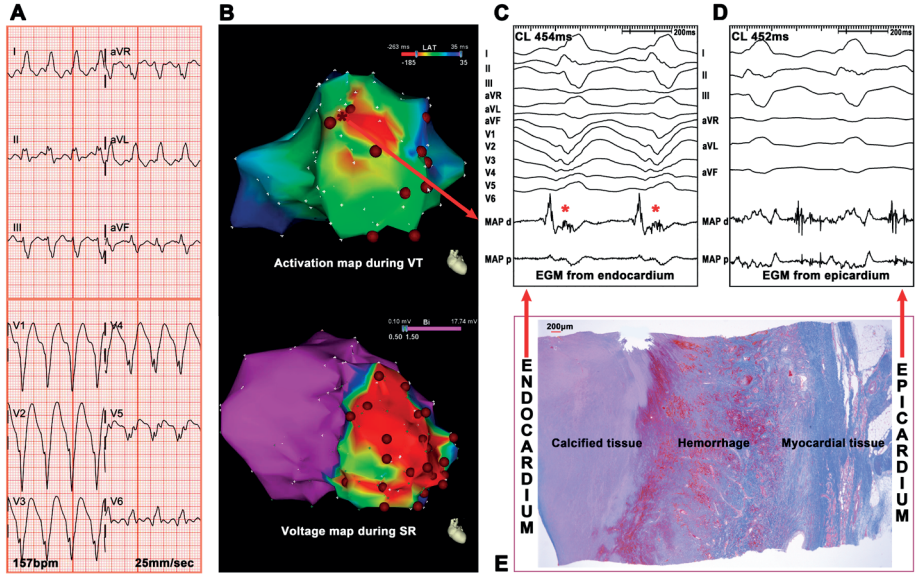
eral complementary fluoroscopic projections, may bring MCs to a heart border-forming location, both improving the sensitivity to detect MC.(12) Whether the selected group of patients with post-MI VT present more often MC than the general post-MI population remains unknown. Recently, a much higher prevalence of 70% of very small MC has been reported from high resolution CT scans. The median volume was only 0.89ml, which may be difficult to detect by standard angiograms and CT scans.(15) ECG-gated cardiac CT is the gold standard for diagnosis, localization and characterization of calcifications in the heart.(16) However, in our study, full agreement on detection/exclusion of MC was found in 18 patients in whom CT *and* cine-fluoroscopy recordings were available for evaluation. In line with prior descriptions, MC was more often observed in patients with anterior MIs. The pathophysiological reason for this location predilection is, however, unknown. Of note, the age of the infarction was not different among patients with and without MC, questioning the assumption that development of MC is a progressive, time-dependent process.

Post-infarction MC: impact on VT catheter ablation

Acute ablation failure, defined as persistent inducibility of the clinically documented arrhythmia at the end of the procedure, has been reported to occur in ≈10% of patients with post-MI VT.(1,17) Of importance, acute ablation failure has been associated not only with high VT recurrence rates of up to 80% at medium-term follow-up but also with occurrence of sudden cardiac death despite the presence of an ICD in patients referred for ablation in the context of an electrical storm.(18) Therefore, current expert consensus on VT ablation recommends elimination of the clinical VT as the minimum endpoint of scar-related VT ablation.(19) One of the potential causes of endocardial ablation failure is the persistence of an epicardial substrate for VT that cannot be eliminated from the endocardium. However, only 14 of 43 (33%) ischemic patients presenting with an electrical storm who underwent systematic epicardial mapping had any epicardial low voltage or abnormal EGM as target for ablation.(3) In addition, considering 1) the association of very low voltage areas and wall thinning, 2) the colocalization of VT related sites and LAVAs with areas of wall thinning (20) and 3) the expected lesion depth with high power (50W) long duration (120s) applications, endocardial ablation failure for post-MI VT substrates remains poorly understood. Even if a subepicardial substrate is critical for VT, it should be possible to abolish the substrate from the endocardium provided that no insulating factors prevent transmurality. Indeed, in up to 84% of patients with post-MI VT undergoing endo-epicardial mapping, at least part of the epicardial LAVAs located in areas of wall thinning as detected by cardiac CT could be abolished by endocardial ablation.(4) In our study, almost one third of the patients with MC compared to less than 10% of patients without MC remained inducible for the clinical VT after endocardial ablation and only 26% of the patients with MC remained free from VT without therapy

escalation on long term follow-up. We speculate that during endocardial ablation, the lower thermal conductivity of calcified myocardium (0.32±0.03 W/m/°C, assuming it to be similar to the bone cortex) compared to the non-calcified myocardium (0.49±0.04 W/m/°C) may protect a surviving layer of epicardium from tissue heating and subsequently, from thermal injury despite the presence of wall thinning.(21) See **Figure 5,** panel E. Of note, percutaneous epicardial access failed in 3 of the 5 patients (60%) with MC in whom it was attempted due to the presence of pericardial adhesions, which is a much higher rate of failure than previously reported in patients with no prior pericarditis or cardiac surgery (2%).(22) Perhaps an inflammatory reaction at the time of the acute infarction may facilitate both formation of MC and pericardial adhesions. Taking into account the potential serious complications associated with epicardial access, mapping and ablation, it is important to identify more specifically post-MI patients who may benefit from a primary endo-epicardial ablation approach. . Although based on our

Figure 5



Representative example of a 53 year-old patient with an anterior calcified MI and prior valve-sparing replacement of the ascending aorta who was admitted with incessant VT. Panel A: the clinical VT is shown (157bpm, left bundle branch block morphology, V6 transition, left superior axis). Panel B, above: LV endocardial activation map during VT in antero-posterior view. No mid-diastolic activity was identified at the endocardium. An entrance site was found at the septal border of the scar (see correspondent electrogram in Panel C). Ablation at this site did not terminate the VT. Panel B, below: LV endocardial bipolar voltage map during sinus rhythm in antero-posterior view. A large part of the scar was unexcitable and despite RF with high power, the VT remained inducible The patient underwent subsequently intraoperative mapping prior to aneurysmectomy. At the epicardial side of the aneurysm, continuous diastolic activity was recorded during VT (see correspondent electrogram in Panel D). Ablation at this site terminated the VT within 5 seconds. In Panel E, a transmural biopsy taken from the site of ablation success is shown. Note the calcification at the endocardial side protecting a layer of viable myocardium at the epicardial side. VT indicates ventricular tachycardia; SR, sinus rhythm and EGM, electrogram.

results, pre-procedural identification of MC helps to non-invasively identify patients with a high chance of endocardial ablation failure, due to the high rate of unsuccessful percutaneous epicardial access, other therapies (including surgery) might be needed in these patients for arrhythmia control.

It has been reported that patients with transmural infarctions defined on routine pre-procedural imaging had higher VT recurrence rates after endocardial ablation and a high prevalence of epicardial substrate for VT, that, when targeted, led to improvement of ablation outcome.(8) Following the same criteria for definition on pre-procedural imaging, patients with transmural infarctions in our cohort had neither higher rates of endocardial ablation failure nor higher VT recurrence rates without escalation of therapy than patients with no transmural infarctions. This difference might be partially explained by the lower prevalence of non-transmural infarctions in our cohort (19% compared to 38%), if the previously according criteria are applied. However, the prevalence of MC in the previous cohort has not been reported and its potential impact on endocardial ablation is unknown. Additionally, animal and human studies have shown that BV <0.5mV are usually recorded at sites with high scar transmurality, which, if localized, may not be detected by all image modalities.(23,24)

CONCLUSIONS

Myocardial calcification was present in 19% of post-MI patients referred for ablation of recurrent sustained VT. The presence of myocardial calcification was associated with high rates of endocardial ablation failure and VT recurrence if no other therapies were applied for arrhythmia control. MC may prevent deep and transmural lesions as a potential explanation for the observed association.

Limitations

This study included a relatively small number of patients and has the intrinsic limitations of an observational retrospective analysis. Our results should therefore be confirmed in a larger prospective cohort. Presence of MC was analyzed on fluoroscopy and not systematically on cardiac CT. Therefore, the prevalence of MC (especially of small calcifications) might have been underestimated. All procedures were performed by an experienced operator in a high volume centre which might limit the generalization of the ablation results. The anti-arrhythmic regimen after ablation was left at the discretion of the referral physician and this might have influenced the outcome of some patients. Currently, discontinuation of AADs is encouraged in patients who are rendered not inducible by ablation or remain inducible for only fast VT_{VERP}.

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SUPPLEMENTARY METHODS

Assessment of infarct transmurality

Contrast enhanced magnetic resonance imaging

With the patient in the supine position, CE-MRI was performed on a 1.5-T Gyroscan ACS-NT/Intera or on a 3.0-T Ingenia MR system (Philips Medical Systems, Best, the Netherlands). Images were obtained during breath-holds of approximately 15 seconds using vector electrocardiographic gating. A standardized protocol was followed including cine sequences in long (2- and 4-chamber views) and short axis covering the entire LV. CE images were acquired 15 min after injection of a gadolinium bolus. The heart was either imaged during one breath-hold with 20 to 24 imaging levels (depending on heart size) in the short axis view, or with 20 to 26 imaging levels in the short axis view in one or two three-dimensional stacks, each stack acquired within one breathhold. All CE images were analysed by an experienced cardiologist. A scar was defined as transmural if the hyperenhanced area extended ≥75% in the radial direction between the endocardial and epicardial borders. A non-transmural scar was defined as the presence of hyperenhancement extending between 25 and 75% of the wall thickness.(23)

Echocardiogram

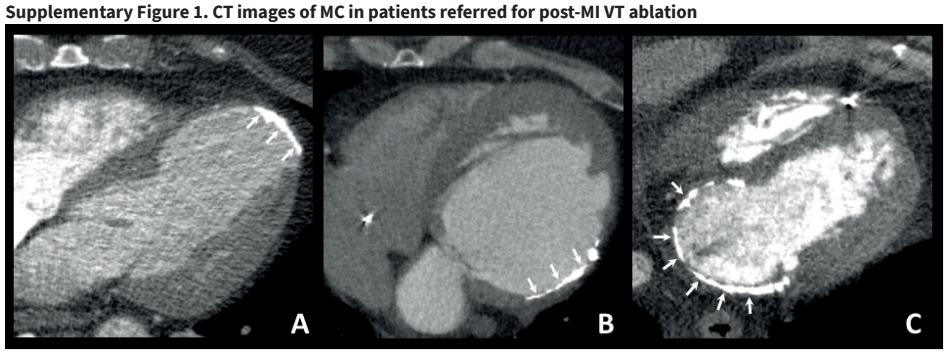
Prior to the procedure, all patients underwent a two-dimensional and color Doppler transthoracic echocardiogram. Images were obtained at rest from the standard parasternal (long- and short-axis), apical (2- and 4-chamber) and subcostal views. Images were analysed offline using EchoPAC (version BT13, GE Medical Systems, Horten, Norway). LV end-diastolic and end-systolic volumes were measured in the apical 2- and 4-chamber views and LVEF was calculated according to the biplane Simpson's method. For the assessment of regional LV function, the LV was divided into 16 segments and according to endocardial motion and systolic wall thickening, each segment was scored as normal (=1), hypokinetic (=2), akinetic (=3) or dyskinetic (=4). As previously reported, it was considered that an abnormal contracting LV segment (score 2-4) had lost the majority of its viable myocardium and therefore, the scar was classified as transmural when 1) the end-diastolic wall thickness was reduced ≤6mm and 2) an abnormal increase in acoustic reflectance was observed.(25,26)

Computed tomography

Contrast ECG-gated cardiac CT was performed on a 64-detector CT scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) or on a 320-detector CT scanner (Aquilion ONE; Toshiba Medical Systems, Otawara, Japan). One hour before the scan, a single dose of metoprolol (25 to 150mg) was administered to patients with a heart rate ≥60 bpm if no contraindications were present. First, a low-dose non-contrast enhanced

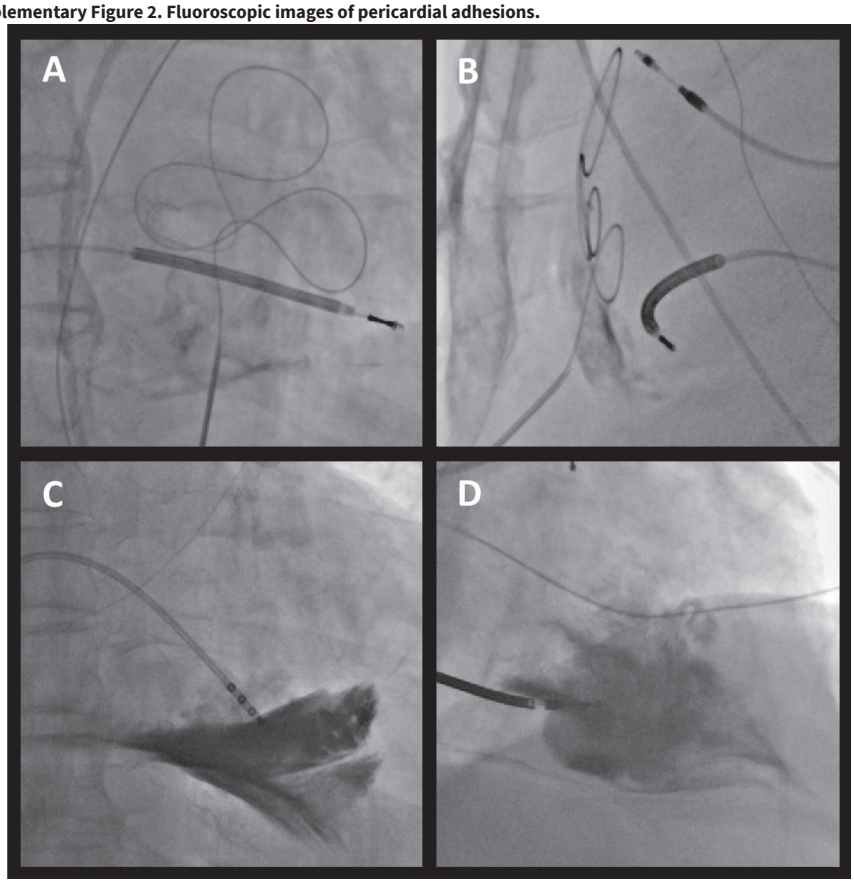
scan of the heart was performed with slice thickness of 3mm. Subsequently, a bolus of a non-ionic contrast (Iomeron 400; Bracco, Milan, Italy; 60-110ml, flow rate 5-6ml/s) was administered. Image acquisition was completed within a single breath hold of 10 seconds with retrospective (64-detector scanner) or prospective (320-detector scanner) ECG gating. The presence of myocardial calcification was visually assessed in both non-contrast and contrast images. In addition, wall thickness was measured between the endocardial and epicardial borders. A scar was classified as transmural when the wall thickness was ≤5mm. (20)

Supplementary Figure 1. CT images of MC in patients referred for post-MI VT ablation



In panels A, B and C, an anterior, a lateral and an infero-posterior area of MC in a long-axis view are respectively shown. MC are indicated by white arrows.

Supplementary Figure 2. Fluoroscopic images of pericardial adhesions.



Panels A and B: antero-posterior and lateral views showing the guide wire used to gain epicardial access that buckles when it cannot be advanced freely in the epicardial space. Panels C and D: RAO images showing contrast retained within the pericardial adhesions.

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