Acute Epicardial Pulmonary Vein Reconnection: Nondurable Transmural Lesion or Late Manifestation of Non-preferential Conduction

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October 5, 2023

Abstract

Background Acute pulmonary vein reconnection via epicardial fibers can be found during observation period after PV isolation, the characteristics and related factors have not been fully studied. *Objective* To investigate the prevalence, locations, electrogram characteristics and ablation parameters related to acute epicardial pulmonary vein reconnection (AEPVR). *Methods* Acute PVR was monitored during observation period after PV isolation, from which AEPVRs were mapped and distinguished from endocardial conduction gaps. The clinical, electrophysiological characteristics and lesion set parameters were compared between patients with and without PVR. So were they compared among AEPVR, gap-related reconnection, and epicardial PVR in repeat procedures. *Results* 56.1% acute PVR were AEPVR, which required a longer waiting period ($P<0.001$) than endocardial gap. The majority of AEPVR were connections from the posterior PV antrum to the left atrial posterior wall, followed by late manifestation of intercaval bundle conduction from the right anterior carina to right atrium. AEPVR was similar to epicardial PVR in redo procedures in distribution and electrogram characteristics. Smaller atrium ($P<0.001$), lower impedance drop ($P=0.039$) and ablation index ($P=0.028$) on the posterior wall were independently associated with presence of AEPVR, while lower inter-lesion distance ($P=0.043$) was the only predictor for AEPVR in acute PVR. An integrated model containing multiple lesion set parameters had the highest predictive ability for AEPVR in ROC analysis. *Conclusions* Epicardial reconduction accounted for the majority of acute PVR. AEPVR was associated with anatomic characteristics and multiple ablation-related parameters, which could be explained by nondurable transmural lesion or late manifestation of non-preferential conduction.

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Data availability statement: The data supporting the findings of this study are available upon the request from the corresponding author.

Funding statement: This work is supported by the Shanghai Municipal Health Commission (Grant No.202340005) and the Interdisciplinary Program of Shanghai Jiao Tong University (Grant No. YG2022QN101) in the collection, analysis and interpretation of data.

Conflicts of interest statement: The authors have no conflicts of interest to disclose.

Ethics approval statement: The study protocol was approved by the institutional review board of Huashan Hospital Fudan University (KY2023-485). Informed consent was provided by all patients.

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Key words acute pulmonary vein reconnection, acute epicardial pulmonary vein reconnection, conduction gap, pulmonary vein isolation, atrial fibrillation

Introduction

Durable pulmonary vein isolation is the determinant of the outcome in patients with atrial fibrillation (AF) after catheter ablation[1-3]. Pulmonary vein reconnection (PVR) has been considered as a major reason for AF recurrence after index ablation[4-5]. Therefore, an observation period in the index procedure was usually given for identification of acute PVR and minimizing the possibility of repeat ablation. However, the detailed conduction property at reconnection sites has not been sufficiently investigated.

Presence of epicardial musculature connecting distal PVs and the atrium is common as the wall of the atrium can be uneven in thickness with bilayer architecture found in a large area[6,7]. Epicardial connection has been recently described as a cause of failed first-pass isolation[8-11]. It can also be observed in the reconnected PVs during the waiting period, which requires treatment but lacks description and exploration including its related ablation parameters.

In this study, we aimed to understand the role of acute epicardial PVR (AEPVR) and its influencing factors by investigating its prevalence, locations, electrogram (EGM) characteristics and related lesion set parameters, which were compared to endocardial gap as well as the epicardial PVR found in repeat procedures.

Methods

Study population

382 consecutive AF patients undergoing index radiofrequency ablation procedure from January 2019 to July 2022 were retrospectively enrolled. Exclusion criteria included: (1) Unsuccessful PV isolation; (2) Unable to maintain sinus rhythm during mapping of insertion sites; (3) Both AEPVR and endocardial gap present in a single case. All patients provided written informed consent. The study protocol was approved by the institutional review board of Huashan Hospital Fudan University (KY2023-485).

PV isolation

The procedures were performed by 3 independent operators under conscious sedation with midazolam and with fentanyl or morphine for analgesia. Intracardiac EGMs were recorded (filtered 30–500Hz for bipolar signals) using LabSystem Pro electrophysiology system (Boston Scientific) or Lead electrophysiology system (Jinjiang Electronic). Mapping and ablation was performed in all patients by using 3-dimensional (3D) mapping system (CARTO3, Biosense Webster). A steerable 6-French decapolar catheter (SinusFlex, APT Medical) was introduced into the coronary sinus. Two 8.5-French long sheaths (SL1, St. Jude Medical or NaviEase L1, Synaptic Medical) were advanced into the left atrium after double transseptal puncture guided by fluoroscopy, or by intracardiac echocardiography (CARTOSOUND catheter, Biosense Webster). 3D map of the left atrium was constructed using a duodecapolar mapping catheter (PentaRay with 2–6–2mm electrode spacing, Biosense Webster).

The circumferential ablation line was designed for antral PV isolation approximately 5–15mm away from the PV ostium based on the 3D shell. Radiofrequency ablation was performed with an 8-French 3.5mm irrigated-tip catheter (SmartTouch SF, Biosense Webster) using the approach based on the initial impedance change and ablation index (AI): Radiofrequency energy was delivered with power of 25-40 watts and contact force ranged from 5-20 grams, for a target impedance drop of at least 5 to 10 ohms within the first 10 seconds[12]. Each application was continued until an operator-tailored target AI was reached, or an impedance drop more than 20 ohms, or an abrupt impedance rise was present. AI was usually decreased at posterior wall when energy was delivered near esophagus localized by intracardiac echocardiography or computed tomography.

Mapping and Ablation of AEPVR and Endocardial Gap-related PVR

All PVs should be isolated before the observation of PVR. Additional ablation was given if first-pass isolation was not achieved after circumferential ablation. Thereafter, PV potentials was continuously monitored. Acute PVR was defined as recovery of conduction between any PV and extra-PV structures after 5 minutes counted from the time of isolation. For the first isolated ipsilateral PVs, PentaRay catheter was remained in the veins until $\frac{1}{2}$ of the second ablation circle was completed. It was then placed into the contralateral PVs to guide ablation. A minimum of 40-minute waiting period, counted from the isolation time were thereafter arranged for each PV to monitor acute PVR with PentaRay and ablation catheter.

Once acute PVR was observed, activation mapping was performed to distinguish AEPVR from endocardial gap conduction using the standard described previously[10]. AEPVR was defined as acute PVR with the earliest activation site within ablation circle >5mm distant from the lesion, plus the absence of near-field EGMs along the circle. In contrast, endocardial conduction gap was characterized by the earliest activation

site at the ablation line (Figure 1). Pace mapping from within the circle was helpful to differentiate AEPVR and far-field potentials[13], and to localize the proximal insertion sites. For patients with suspected AEPVR but in AF rhythm after PV isolation, direct current cardioversion was attempted after additional ablation performed at the discretion of operators, followed by mapping of AEPVRs. Ablation could be performed by targeting the distal insertions of AEPVRs during sinus rhythm or their proximal insertions during PV pacing.

The time from PV isolation to the observation of each AEPVR was recorded. EGMs were measured by two electrophysiologists with average value as the results. The clinical variables, electrophysiologic characteristics and lesion set parameters were analyzed and compared between patients with and without PVR (Control group), so were they compared between patients showing the 2 types of PVR i.e., AEPVR (AEPVR group) and endocardial conduction gap (Gap group). Furthermore, AEPVRs were compared with a group of epicardial PVR confirmed in repeat AF ablation procedures during the same period, which were not present in the index procedure.

Follow-up

Patients were arranged for outpatient clinical visits at the 3^{rd}, 6^{th} and 12^{th}month after discharge, followed by yearly telephone communication. Extra visits were required in symptomatic patients. Holter recording was performed in all patients on the 3^{rd}, 6^{th} and 12^{th} month. Recurrence was defined as any documented atrial arrhythmias longer than 30 seconds after a 3-month blanking period.

Statistics

Clinical variables were expressed as a mean with standard deviation for continuous variables, median with interquartile rate for discontinuous variables, and percentage (%) for categorical variables. Characteristics between groups were tested using the unpaired Student t-test for continuous variables and chi-square test or Fisher's exact for categorical variables. Logistic regression analysis was performed for multivariate analysis, after which Receiver Operating Characteristics (ROC) analysis was used to compare the performances between different prediction models. A two-tailed p-value of <0.05 indicated statistical significance. Statistical analysis was performed using STATA 17.0 software.

Results

Clinical Characteristics

After exclusion, 57 (15.1%) subjects from 370 patients undergoing successful PV isolation (218 paroxysmal and 152 persistent AF) showed acute PVR during waiting period. Each patient showed a single reconnection site. AEPVR was responsible for 32 (56.1%) of the patients, which were observed after a mean time of 40.3±11.9 minutes (left PVs: 45.7±9.2min, right PVs: 39.7±12.0min) counted from isolation of the ipsilateral PVs. Endocardial gap-related PVR was found in the rest 25 (43.9%) patients with a shorter observation time of 29.3±9.4 minutes compared to AEPVR group (P <0.001)(Figure 2). The characteristics of patients in AEPVR, Gap and Control group were demonstrated in Table 1. Additionally, a group of 14 patients showing delayed epicardial reconnection only during repeat ablation was reviewed.

Compared to patients without acute PVR, AEPVR group had a shorter diagnosis-to-ablation time (DAT)(3[2,14.5]months vs. 7[2,31]months, P =0.030), a lower left atrium diameter (37.7±6.9mm vs. 41.6±4.2mm,P <0.001) and volume (109.9±27.0ml vs. 132.4±33.4ml, P <0.001). Differences in age, sex, type of AF, hypertension, diabetes mellitus and other anatomic variations were not shown between AEPVR and the other 2 groups (P >0.05), respectively. AEPVR group had a shorter left atrium diameter (37.7±6.9mm vs. 42.6±6.9mm, P=0.011), a smaller left atrium volume (109.9±27.0ml vs. 133.6±28.9ml, P=0.002), and a slightly lower prevalence of hypertension (34.4% vs. 60.0%, P=0.054) compared to Gap group.

Distribution and EGM Characteristics of AEPVR

Distal Insertion sites of AEPVR were found 12.8±3.6mm distant from the linear lesion (Right PVs: 12.6±3.5mm, Left PVs: 13.3±4.2mm). They were most frequently located at the posterior PV antrum between the ipsilateral PVs (17/32), including 9 from left and 8 from the right PVs, followed by the anterior (12/32) carina of right PVs. In addition, 2 patients showed epicardial connection at anterior and posterior roof in right PV, respectively. The other one demonstrated acute reconnection to the left PVs through the vein of Marshall (Figure 3). Localized distal activation patten was seen in 25/32 (78.1%) patients, followed by widely spread pattern in the others. In 19/32 (59.4%) cases, activation due to AEPVR propagated into both upper and lower PVs during sinus rhythm. In the rest patients, residual potentials could only be observed in a single PV.

Pace mapping discovered 2 major reconnection patterns. AEPVRs found at the posterior PV antrum were connected to the posterior wall of the left atrium. The connections traversed the ablation line generally in an oblique direction. The connections to right anterior carina showed proximal ends at posterior right atrium presumably through the intercaval bundle (ICB). Different from posterior AEPVR, those connections did not pass the prior ablation line (Supplementary Figure 1). Proximal insertion sites could also demonstrate localized or diffuse patterns (Figure 4).

The EGMs at distal insertion sites of AEPVR showed an amplitude of 0.48±0.38 mV and duration of 26.3±10.0ms without fractionation. The mean slope of major deflection was 0.10±0.09mV/ms. AEPVRs at the anterior carina and posterior PV antrum were similar in amplitude (0.55±0.48mV vs. 0.43±0.28mV, P =0.346) and slope (0.12±0.11mV/ms vs. 0.10±0.09mV/ms, P =0.524). Those distribution and EGM characteristics of AEPVRs did not show difference from the delayed epicardial connection in the repeated ablation procedures (Table 2, Figure 3). In contrast, reconnection owing to endocardial gap conduction was distributed in a wide area along the circular lesion including the left atrial roof, floor and ridge. Most of the EGMs at the reconnection sites involved highly fractionated deflections (Figure 1&3).

Lesion Set Parameters in Association with AEPVRs

Univariate analysis of the lesion set parameters showed the patients with AEPVR had a lower impedance drop (P =0.013) including the regional impedance drop on the posterior wall (P =0.009), lower AI in the whole left atrium (P =0.039) and the posterior wall AI(P =0.005) compared to the patients without AEPVR. Among patients with PVR, AEPVR group had a lower inter-lesion distance (P =0.003) and a slightly lower contact force (P =0.057) compared to Gap group (Supplementary Table 1).

Multivariable logistic regression models were then performed which were adjusted for all variables showing statistical difference in univariate analysis or of vital importance in clinical practice. As results, lower left atrium diameter (P <0.001), lower impedance drop (P =0.039) and AI (P =0.028) on the posterior wall were significantly associated with the presence of AEPVR. In patients with PVR, only a lower inter-lesion distance was independent predictor of AEPVR (P =0.045)(Table 3).

The ROC analysis was then performed to evaluate the performances between different prediction index, which demonstrated that the above-mentioned integrated prediction model for AEPVR containing multiple indicators had a larger area under curve (AUC=0.790) than single index including impedance drop, AI and contact force. So was the model established to predict AEPVR in patients with acute PVR, which also had the largest AUC of 0.786 (Figure 5).

Ablation of AEPVR

AEPVR ablation was successfully achieved in all patients, radiofrequency directly applied at the distal insertion sites eliminated 30/32 AEPVRs. In 2 patients showing widely spread connections, ablation targeting proximal sites were successful. Bidirectional PV-left atrium block was confirmed in all subjects.

Follow-up

355 patients completed 1-year follow-up with overall success rate of 78.0%. The success rate of AEPVR group did not show statistical difference to the controls (71.9% vs. 78.7%, P =0.374) and Gap group (71.9% vs.

78.3%, P =0.756).

Discussion

Major Findings

We have the following major findings in the study: (1) Epicardial fibers was responsible for over half of the acute PVR in this study, which required a longer waiting period than endocardial gap. (2) Two typical distribution patterns of AEPVR were discovered, including epicardial reconnection over the ablation line on the posterior wall, and late manifestation of ICB conduction. (3) AEPVR demonstrated similar characteristics as delayed epicardial PVR in repeat procedures. (4) Presence of AEPVR was significantly associated with multiple ablation parameters.

The Prevalence of Epicardial Reconnection Phenomenon in Acute PVR

The influence of epicardial myofibers on PV isolation were studied in recent years[8-11]. The prevalence of remaining epicardial connections after completed circular ablation could be up to 22%[9-11, 14]. Residual epicardial connections could also be observed in repeat procedures[9], suggesting that the restoration of epicardial PV conduction with long-term endocardial block could be a common phenomenon, which worth more attention for timely identification and intervention. Acute PVR used to be considered as a similar concept with conduction gap[15, 16]. In this study however, we found the proportion of AEPVR higher than endocardial conduction gap as the type of PVR, based on our ablation protocols.

Characteristics and Possible Mechanisms of AEPVR

The distal insertion sites of AEPVR were mostly discovered between the ipsilateral PVs. The connection on the left atrial posterior wall traversed over the prior lesion, suggesting endocardial block with epicardial sparing. According to the anatomical literature, the interpulmonary area is covered with the thickest myocardium around PVs composed of overlapping layers of differently aligned fibers[17,18]. Myocardial strands here cross commonly in an oblique direction before connected to the longitudinally descending fibers on the posterior wall[19, 20], compatible with the mapping results in our study (Graphical Abstract). The subjects in AEPVR group had a smaller atrial size and a shorter DAT, indicating an earlier disease stage which may be associated with healthier myocardium which required higher energy to create transmural lesion. Although the presence of residual epicardial connection was reported mainly associated with anatomical issues[9-11], we have found multiple ablation parameters in relation to AEPVR. In multivariable analysis, the presence of AEPVR was generally associated with a lower energy output and tissue response reflected by AI and impedance drop, respectively. It was further validated by the integrated model in ROC containing multiple parameters which showed the best predictive ability for AEPVR. The relative inadequate energy applied at the posterior wall could be explained by the inevitable concerns of complication e.g., esophageal damage, gastric immobility, and cardiac tamponade[21,22](Figure 4A).

Besides the failure to create durable transmural lesion, another possible mechanism could be the delayed manifestation of a secondary connection after the preferential conduction was blocked. This was especially suitable to explain the reconnection between the right anterior carina and right atrium, which was not affected by prior circumferential ablation and also commonly present in the repeat procedures (Supplementary Figure 2 & Supplementary Video 1). The mechanism was similar to the late presence of an additional accessory pathway (AP) found after successful ablation of the first AP[23]. The anterior carina was preferentially activated by the wavefront from Bachmann bundle or fossa ovalis[24]. ICB conduction could be only revealed until the rest pathways are blocked. When it played the role of an AP with delayed appearance, it could be left unnoticed without sufficient waiting time and detailed remapping (Supplementary Figure 1).

Difference between Epicardial and Gap Conduction in Acute PVR

AEPVR could be considered as an intermediate state of lesion formation between durable isolation and endocardial conduction gap. The 2 types of PVR can be distinguished by remapping the regions of PVs and the antrum. Compared to AEPVR mostly at interpulmonary regions, the endocardial or transmural

reconnections were distributed widely in almost all segments along the ablation circle. The typical characteristics of endocardial gap was the near-field EGMs present at the prior lesion with fractionation. Although there were multiple factors in terms of ablation parameters associated with AEPVR in the whole cohort, inter-lesion distance was the only factor showing difference between endocardial gap and AEPVR in our study, suggesting its tendency to impact the endocardium.

Clinical Implication

AEPVR had the similar distribution and EGM characteristics as late epicardial PVR found in repeat procedures which was considered arrhythmogenic, indicating their common mechanism and the role in AF recurrence. The potential benefit of treating AEPVRs was reflected by the outcome showing no statistical difference between AEPVR and Control groups. According to the analysis, it is necessary to take the anatomic characteristics and multiple ablation-related parameters e.g., AI, impedance drop, inter-lesion distance into comprehensive consideration when evaluating the possibility of AEPVR. Although the duration for post-ablation waiting has been questioned[25], we recommend a 40-minute waiting period given the longer time for AEPVR to appear, especially when energy delivery has to be limited on the posterior wall. Based on the possibility late manifestation of ICB conduction, reconnection from the right carina to right atrium should be excluded after the observation period even in the absence of residual potentials when the circular ablation is completed.

Limitations

The results of this study was from a single-center experience. The prevalence and location of AEPVR could be influenced by some operator-related factors. Reconnection time might be slightly overestimated based on our approach with 2 catheters to monitor all PVs.

Conclusion

Epicardial reconnection accounted for the majority of acute PVR in this study, which had difference to endocardial gap in observation time, distribution and EGMs and showed similarity to epicardial PVR in repeat procedures. Presence of AEPVR was independently associated with a smaller left atrium and multiple ablation parameters, which could be explained by nondurable transmural lesion or late manifestation of non-preferential conduction. A sufficient waiting period with detailed mapping for AEPVR is of vital importance to achieve durable isolation.

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Figure legend

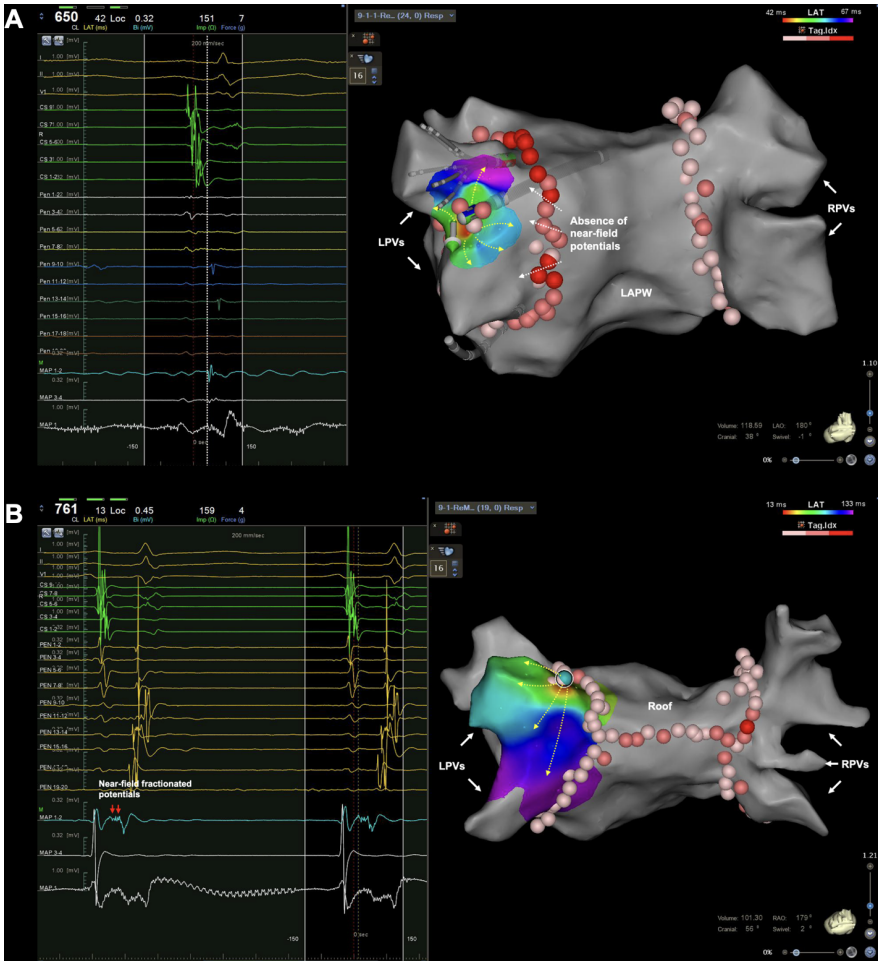
Figure 1 Illustration of AEPVR and Endocardial Conduction Gap. A: A patient showing AEPVR 35 minutes after first-pass isolation. The earliest distal activation site was located at posterior PV antrum, 18.6mm distant from the prior ablation line without near-field electrograms along the lesion. A centrifugal activation pattern within the circle was demonstrated. B: A patient showing PVR due to endocardial gap at the roof of LPV present 22 minutes after first-pass isolation. Electrograms at the breakthrough site (cyan dot) demonstrated near-field fractionated potentials preceding PV potentials. AEPVR=acute epicardial pulmonary vein reconnection; LAPW=left atrial posterior wall; LPV=left pulmonary vein; RPV=right pulmonary vein.

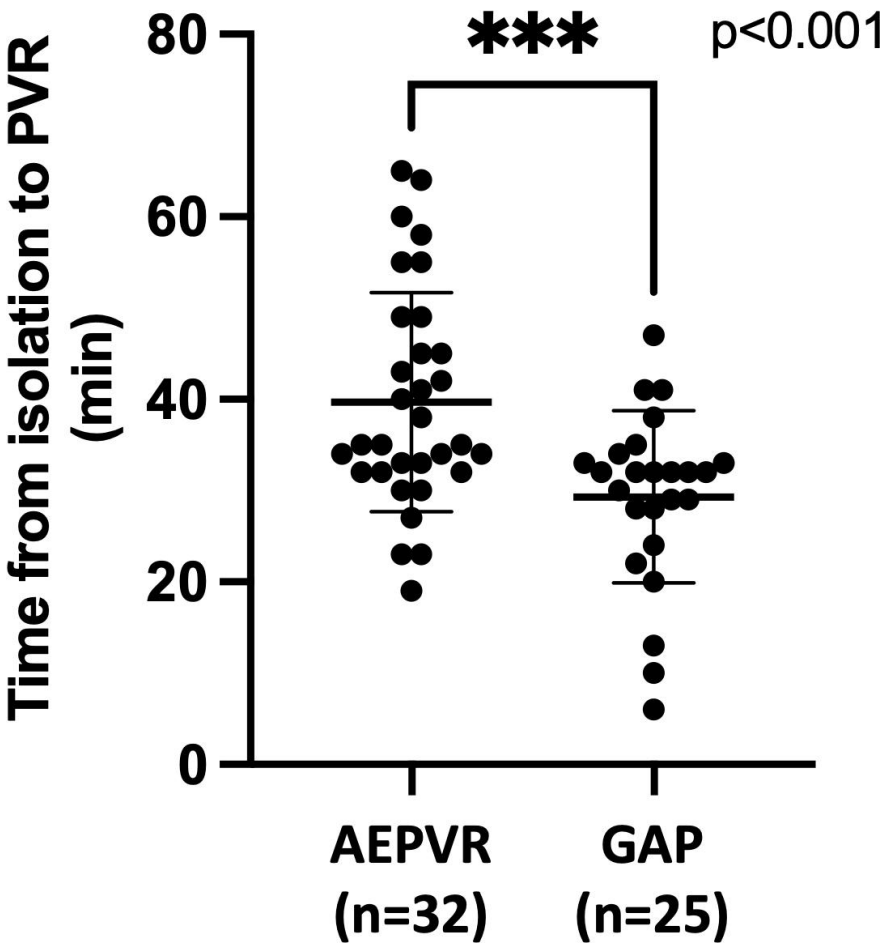
Figure 2 Observation Time before PVR in the Groups of AEPVR and Gap. Scatter plot showed that AEPVR required longer waiting period (40.3±11.9 vs. 29.3±9.4 minutes, P <0.001) than endocardial gap, counted from the time of PV isolation to the identification of PVR. AEPVR=acute epicardial pulmonary vein reconnection.

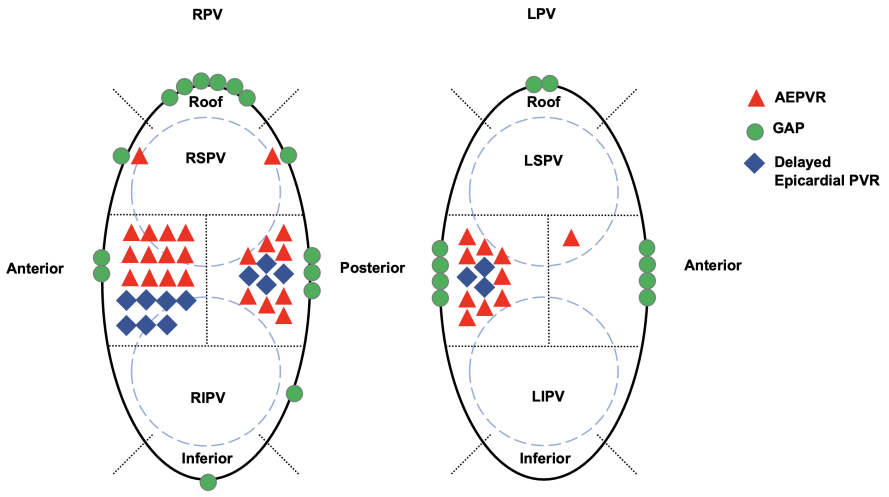
Figure 3 Distribution of AEPVR, Endocardial Gap and Delayed Epicardial PVR. Most AEPVR and late epicardial PVR found in repeat procedures were located at interpulmonary isthmus of PVs, while endocardial gaps were widely distributed around the circle. AEPVR=acute epicardial pulmonary vein reconnection; LIPV=left inferior pulmonary vein; LSPV=left superior pulmonary vein; RIPV=right inferior pulmonary vein; RSPV=right superior pulmonary vein.

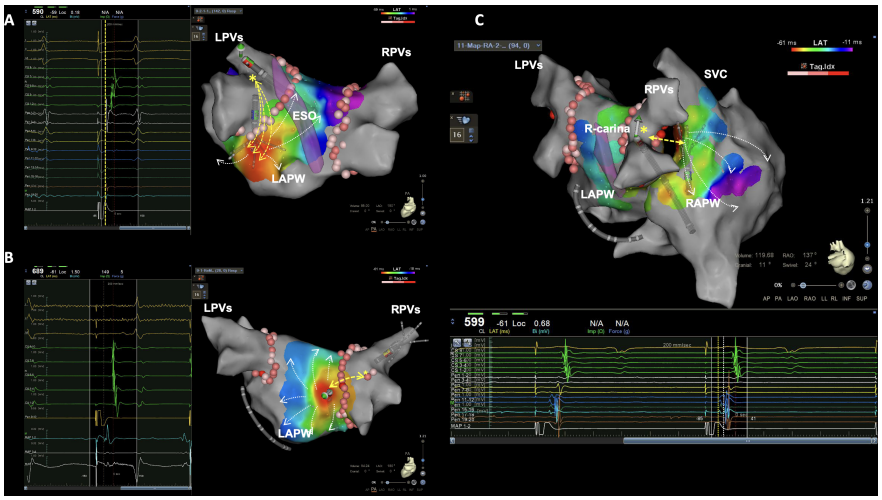
Figure 4 Localization of Proximal Insertion Sites of AEPVR with PV Pacing. A: During PV pacing in a patient showing AEPVR at left posterior PV antrum, the proximal insertion site were mapped and located at inferior posterior wall with a diffuse activation pattern based on the nearly identical timing in a small area (yellow dotted line). Also note the intracardiac echocardiographic contour of esophagus was in close proximity to the left PV antrum. B: AEPVR at right posterior PV antrum was connected to the posterior wall in a slightly oblique direction with localized activation pattern at the proximal end; C: Pacing at the right anterior carina with low output demonstrated earliest activation on the posterior wall of the right atrium where double potentials were shown. The near-field right atrial potentials (white dotted line) were preceded by the far-field PV potentials (yellow dotted line). The asterisks showed the earliest distal insertion mapped within PVs during sinus rhythm. AEPVR=acute epicardial pulmonary vein reconnection; ESO=esophagus; LAPW=left atrial posterior wall; LPV=left pulmonary vein; RAPW=right atrial posterior wall; RPV=right pulmonary vein; SVC=superior vena cava.

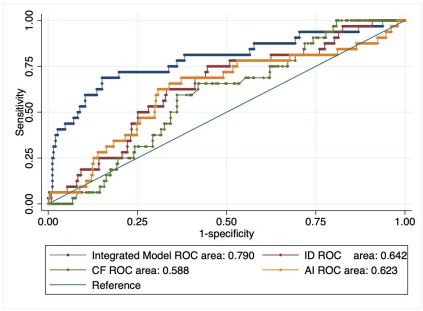
Figure 5 ROC Analysis of Different Prediction Indexes to Predict AEPVR. The integrated model containing multiple lesion set parameters had the largest AUC for predicting the presence of AEPVR both in the whole cohort (A) and in patients with acute PVR (B). AEPVR=acute epicardial pulmonary vein reconnection; AI=ablation index; CF=contact force; ID=impedance drop; ROC= receiver operating characteristic.

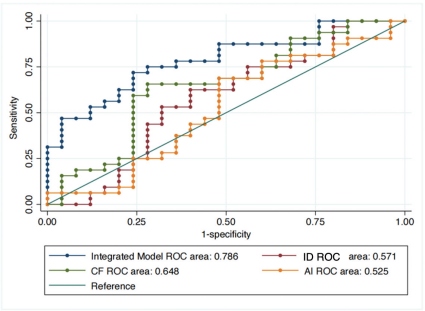












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