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ELECTROPHYSIOLOGICAL DIFFERENCES BETWEEN THE EPICARDIUM AND THE ENDOCARDIUM OF THE LEFT ATRIUM

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Abstract

Background—Electrophysiological properties of the atrial endocardium compared to epicardium are not well understood. The purpose of this study was to compare the electrophysiological properties and vulnerability to arrhythmia induction from these regions.

Methods and Results—Transseptal endocardial and percutaneous epicardial mapping was performed in a porcine model (n=7). Two opposing 4 mm electrophysiological catheters were positioned endocardially and epicardially. A circular mapping catheter (CMC) was positioned at the ostium of the common inferior pulmonary vein (CIPV) recording left atrial (LA)-PV potentials. Endocardial and epicardial ERPs at 2 basic cycle lengths (CL) of 600ms and 400ms were recorded from 4 anatomic locations (CIPV, LA appendage, right superior PV and LA posterior wall). Atrial repetitive response (ARR) induction was also tested from endocardial and epicardial sites. Overall, 254 ERP measurements (mean 36.3/animal) and 84 induction attempts (mean 12/animal) were performed. The ERP was significantly shorter in the epicardium compared to the endocardium at basic CL of 400 ms (p=0.006) but not at CL of 600 ms (p=0.2). In addition only the epicardium, demonstrated ERP shortening when the CL of the basic drive was shortened (p=0.03). ARR could be induced more often from the epicardium (p=0.002) and fibrillatory activity with epicardial/endocardial dissociation was recorded (n=3). Also, the earliest PV activation site on the CMC was noted to be different in 16.5% of cases during epicardial and endocardial pacing.

Conclusion—The electrophysiological characteristics of the atrial epicardium are different from the endocardium with a shorter ERP and more frequent ARR induction by programmed stimulation.

Keywords

Animal Studies; Electrophysiology-Clinical

Several human and animal model studies have highlighted the importance of atrial and pulmonary veins (PVs) electrophysiological characteristics in both paroxysmal and persistent atrial fibrillation (AF).¹⁻⁵ These include: shortened atrial effective refractory period (AERP) at baseline and in response to tachycardia,¹ delayed recovery of tachycardia induced ERP shortening in the left atrium (LA)⁴ and AERP heterogeneity.² PVs in patients

with AF demonstrate shorter ERP and more frequent decremental conduction compared to control subjects.⁵

Significant electrophysiological differences contributing to arrhythmogenicity have been noted between the epicardial and endocardial regions of the right atrium and PVs in isolated atrial preparations.⁶⁻⁸ Electrical dissociation between the epicardium and endocardium during AF have been described in an isolated canine right atrium⁹ and also in mapping studies of goats and dogs with persistent AF.^{10, 11} Furthermore, there is data to suggest that the epicardium may be a potential source of triggers for atrial fibrillation¹² and connections between the PVs and the LA may be situated epicardially.^{13, 14} Differences in electrophysiological properties between the epicardial and endocardial atrial surfaces in the innervated beating heart have not been systematically characterized.

With increasing interest in epicardial AF ablation,¹⁵⁻¹⁷ the aim of the current study was to systematically compare electrophysiological characteristics between the endocardial and epicardial regions of the left atrium in a porcine model.

METHODS

This protocol was approved by the UCLA Animal Research Committee and was performed according to institutional guidelines.

Animals and initial preparation

Seven pigs weighing 35-48 kg were anesthetized with 1.4mg/kg Telazol (intramuscularly), and then intubated. Ventilation was maintained via endotracheal tube and mechanical ventilator (Summit Medical, Bend, OR); general anesthesia was achieved with inhaled 1.5% to 2.5% isoflurane. Two femoral venous and one arterial sheath (for arterial pressure monitoring) were placed using modified Seldinger technique.

Epicardial access was obtained via subxiphoid puncture using a Tuohy needle as previously described.¹⁸ An 8 French sheath (SL0, St. Jude Medical, Minnetonka MN) or an 8.5 French deflectable sheath (Agilis™, St. Jude Medical, Inc.) was advanced over a guide wire into the pericardial space. After administration of systemic intravenous heparin, transseptal puncture was performed to advance an 8 French SL0 sheath (St. Jude, Minnetonka MN) into the LA. A circular mapping catheter (CMC) (Optima™, St. Jude Medical, Inc, Minnetonka, MN.) was advanced to the LA through the transseptal SL0 sheath. A 4 mm steerable electrophysiological catheter (St. Jude Medical, Minnetonka, MN) was placed in the epicardial space through the epicardial sheath and an identical catheter was placed at the left atrium (advanced through the intraatrial septum beside the SL0 sheath).

Pacing protocol

Surface 12 lead Electrocardiogram (ECG) and local EGMs from the CMC and electrophysiological (EP) catheters were recorded continuously (filter at 30 to 500 Hz) and analyzed offline at 400 mm/sec speed using the GE Cardiolab recording system (Milwaukee, WI, USA). The CMC catheter was positioned at the ostium of the common inferior pulmonary vein (CIPV) recording circular LA/PV electrograms. The EP catheters were positioned endocardially and epicardially in 4 anatomical locations: CIPV, left atrial appendage (LAA), left atrial posterior wall (LAPW) and the right superior pulmonary vein (RSPV). In each anatomical location the endocardial and epicardial catheters were placed in the closest proximity on LAO, RAO and AP projections giving a fluoroscopic appearance of “kissing catheters” (Figure 1).

At each site stimuli were delivered at 2-ms duration at 1.5 the diastolic threshold from the endocardial and epicardial catheters. After a basic drive train (CL of 600 and then 400 ms) of 8 stimuli a single extrastimulus was delivered and decremented in steps of 10 ms until the ERP was reached. The following parameters were measured: (1) AERP: which was defined as the longest S1 to S2 interval without an A2. (2) The transmural conduction time from epicardial and endocardial pacing was defined as the interval from the pacing stimulus artifact in 1 catheter to the beginning of local EGM of the opposing catheter. Transmural conduction was measured at the basic drive CL (S1) and the shortest conducting S2. (3) Activation pattern at the CMC (located at the os of the CIPV) during endocardial and epicardial pacing. (4) Local EGM characteristics including duration, amplitude and fractionations. (i) Duration was defined as the time from the earliest local electrical activity to the point of final return to baseline. (ii) Amplitude was the voltage difference between highest and lowest deflections of each EGM. (iii) Fractionations were defined as the number of deflections (the number of turning points, positive to negative direction or vice versa) in each EGM.

Atrial repetitive response induction

At 84 sites, both epicardial and endocardial (mean 12/per animal), we tried to induce atrial repetitive response (ARR) using the following protocol: the atrium was paced at a cycle length of 400 ms (8 beats) and then an extrastimulus was delivered and decremented in steps of 10 ms until reaching tissue refractoriness. If ARR was not induced the protocol was repeated with S2 set at the shortest conducting interval and adding another extrastimulus decremented in steps of 10 ms. The protocol was repeated up to a maximum of 4 extra stimuli (S5). ARR was defined as at least 10 consecutive irregular beats with a mean cycle length less than 220 ms.

Locations where ARR induction was attempted were compared in terms of: Location, ERP, local EGM characteristics, and transmural conduction at basic cycle length of 400 ms and at the last conducted extrastimulus.

Correlation between Endocardial and Epicardial Activation

In order to define whether local wave activation of the ARR at the 2 opposing catheters (epicardial and endocardial) is associated or dissociated, timing (Tepi and Tendo in msec) of each of the first 8 beats (B_{1-8}) was measured (from the last pacing stimulus to the beginning of local EGM). If the activation recorded at the 2 catheters is associated, the interval between each beat on the endocardium and epicardium (Δ Tepi- Tendo) should remain constant and the SD of this difference SD(Δ Tepi- Tendo of beats 1-8 [B_{1-8}]) should approach 0 (see supplemental figure, examples A and B). However, if the epicardial and endocardial activation is dissociated, the interval between each beat on the endocardium and epicardium should not remain constant and the SD of this difference SD (Δ Tepi- Tendo of beats 1-8 [B_{1-8}]) should be >0 (see supplemental figure, example C).

Statistical analysis

Continuous variables are expressed as mean $\pm$ SE. Mean ERP of the endocardium and epicardium at 2 basic CL drives of 600 and 400 ms were compared using the 2 by 2 mixed effects ANOVA model (with location and basic CL drive as the fixed effects and animal as the random effect), this model takes into account that observations within the same animal are not independent. A secondary analysis using the 1-way mixed effects ANOVA model (with location as the fixed effect and animal as the random effect) compared changes in ERP (Basic CL of 600 - 400 ms) between the two heart surfaces. A 2 by 2 mixed effects ANOVA model was used to compare mean transmural conduction. Oneway mixed effects ANOVA was used to compare mean EGM characteristics. To assess regional ERP differences

between the two heart surfaces, we used the 4 by 2 mixed effects ANOVA (with region and location (epi vs. endo) as fixed effects and animal as the random effect). For comparison between points with and without ARR induction similar models were used as applicable.

As ARR were induced multiple times in each animal (repeated measures), the percentage of observations with induced ARR between the epicardium and endocardium were compared using the general estimating equations method (GEE) which takes into account that observations within the same animal are not independent. The percentage with induced ARR in each heart surface and the corresponding odds ratio (OR) and the p-values are reported.

Results

A total of 254 ERP measurements were obtained (mean 36.3/ per animal) equally divided between the epicardium and endocardium. The thresholds for stimulation of the epicardium and endocardium were $2.6 \pm 0.19V$ and $3.2 \pm 0.19V$ respectively, with a mean difference of $0.58 \pm 0.23V$ ($p=0.01$). Eighty four, 52, 68 and 50 ERP measurements were made in the CIPV, LAA, LAPW and RSPV respectively. The ERP was significantly shorter in the epicardium at a basic CL drive of 400 ms ($p=0.006$) but not at 600 ms ($p=0.2$) (Figure 2A, Table 1). Subdividing the ERP at 400 ms according to regions, epicardial ERP was significantly shorter at the RSPV (mean difference 34.6 ± 13.9 , $p=0.01$) and marginally shorter at the LAA (mean difference 26 ± 14 , $p=0.05$), but not in the CIPV (mean difference 5 ± 11 , $p=0.6$) or LAPW (mean difference 17 ± 12 , $p=0.15$). Significant shortening of ERP from basic drive of 600 compared to 400 was evident only in the epicardium ($p=0.03$ for epi, 0.48 for endo).

Transmural conduction

Transmural conduction at the 2 drive CL and the shortest conducted S2 were similar when epicardial and endocardial pacing were compared (Table 1). There was no difference in the conduction time from epicardial and endocardial catheters to the earliest CMC activation, either during the basic drive of 600 ms or 400 ms or during S2 (data not shown, $p=NS$ for all).

Local EGM characteristics

The duration, fractionation and amplitude of EGMs recorded from the epicardium and endocardium were not significantly different (Table 1).

ARR induction

The protocol for ARR induction was conducted 84 times (mean 12 times/per animal). ARR was induced more frequently from the epicardium (37.7%, 95% CI: 19-60.8%) compared to the endocardium (10.8%, 95% CI: 5.7-19.3%) with odds ratio for induction from the epicardium compared to the endocardium of 5.01 (95% CI: 1.8-13.9), $p=0.002$. Comparison of sites in which ARR could be induced to places where it could not be induced is presented in Table 2. ERP was significantly shorter at sites in which ARR could be induced (Figure 2B). Other parameters including transmural conduction and EGM characteristics were not different between sites with and without ARR induction (Table 2).

ARR characteristics

Observing the induced ARR recordings (ARR lasted up to 22 seconds) we identified an epicardial to endocardial local wave dissociation in 3 out of the 19 locations (Figure 3). The SD ($[T_{\text{epi}} - T_{\text{endo}}] B_{1-8}$) of these 3 ARR were 44, 49 and 60 ms. Whereas, the SD ($[T_{\text{epi}} - T_{\text{endo}}] B_{1-8}$) of all the other induced ARR was less than 17ms.

Pulmonary Vein Activation

Observing the earliest PV activation on the CMC from 218 pacings, (in one pig LA to PV conduction was not collected) during the shortest conducting S2 from epicardial and endocardial pacing we could identify different earliest activation in 16.5 % of the pacing points (Figure 4). In the majority of points (93.5%) LA ERP was reached before LA-PV ERP (i.e. LA to PV conduction block). However, in 7 pacing regions in 5 animals we could identify the LA-PV ERP. In 2 points LA-PV ERP was similar from epicardial and endocardial pacing, in 3 we could see LA-PV ERP only during epicardial pacing as we reached the LA ERP at a longer S2 interval from endocardial pacing. On 2 occasions the LA-PV ERP was different from epicardial and endocardial pacing (shorter in 1 animal from epicardial and the other from endocardial pacing by 50 and 70 ms respectively) (Figure 5).

DISCUSSION

Major Findings

The major findings of our study are: (i) the atrial epicardium has a shorter ERP compared to the endocardium (at a CL of 400ms) (ii) ARR was more frequently induced when stimulating the epicardium compared to the endocardium and (iii) epicardial ERP showed a greater response to shortening of the basic drive cycle length suggesting different restitution characteristics. This is the first study to our knowledge that has systematically compared atrial endocardial and epicardial electrophysiological properties in the innervated beating heart.

Differences in Excitability between the Epicardium and Endocardium

We found that the ERP in the atrial epicardium was significantly shorter by a mean of 19 ms compared to the endocardium at the shorter basic drive cycle. Similar findings of transmural heterogeneous distribution of repolarization have been suggested in previous studies in the PV, right atrium and also in the ventricles.^{6-8,19} One study which focused on the PVs demonstrated that epicardial PV action potential duration (APD) was shorter than the endocardial PV APD, however systematic epicardial vs. endocardial mapping was confined only to the PVs and not the LA as in our study.⁶ In another study which was performed on strips of right atrial free wall, the basic APD in the endocardium was longer than the epicardium.⁷ Adding acetylcholine to the atrial preparations shortened APD in both surfaces with a more prominent effect seen in the endocardium. The parasympathetic ganglia are located within the subepicardial connective tissue and the authors speculated that different distribution of muscarinic receptors or acetylcholine affected ion channels could potentially have accounted for this difference. However, the effect on APD in the innervated heart has not yet been determined. Our study systematically compared the LA endocardial and epicardial electrophysiological properties and in contrast to previous ex vivo studies it was undertaken in a close chest innervated beating heart.

Several different animal models are used experimentally for creating the substrate for AF.²⁰⁻²¹ Some of them cause LA structural changes with conduction slowing^{22, 23} while others cause atrial electrical remodeling with ERP shortening.^{20, 21} Continuous atrial pacing, a known AF induction model, can cause all these changes over time.^{20, 21} During pacing, ERP shortens and AF vulnerability increases. The mechanism behind these electrophysiological changes is probably related to Ca^{++} overload and corresponding changes in ion channel activity that leads to shortened action potential and refractoriness.¹ Recently, it was shown that some of these changes may also be attributed acutely to the effect of the intrinsic cardiac autonomic nervous system, located epicardially in fat pads, with local release of autonomic neurotransmitters, particularly acetylcholine.²⁴⁻²⁶ Our findings of shorter ERP and more frequent ARR induction from the epicardium may be

related to a higher basic influence of the intrinsic cardiac autonomic nervous system on the epicardium, perhaps due to anatomical proximity. Also, excitation of nerves can not be completely excluded. However, it should be noted that the mechanism of shortened ERP in the epicardium was not explored in this study.

However, our findings suggest that the epicardium due to its shorter ERP at 400ms drive CL may have important arrhythmogenic properties, especially in arrhythmia initiation before continuous tachycardia causes atrial electrical remodeling. Thus a short coupled atrial premature beat or a train of rapid firing from a focal trigger (such as a pulmonary vein) can find the atrial epicardium but not endocardium excitable and may initiate AF. The arrhythmogenic properties of the epicardium are further supported by animal models of AF induction like sterile pericarditis^{27, 28} and clinically by the high incidence of post cardiac surgery and pericarditis related AF¹.

Willems et al²⁹ demonstrated that continuous epicardial pacing increases AF inducibility compared to endocardial pacing. In their study the ERP (which was measured only endocardially in the HRA and at one basic CL) shortened after pacing, however there was no difference between epicardial and endocardial pacing. Two possible explanations for these findings include: (1) This study involved chronic pacing in contrast to our acute study and (2) the ERP was only measure endocardially, thus the possibility of differential influence on epicardial ERP was not tested.

Differences in Activation between the Epicardium and Endocardium

Another notable finding in our study was that fibrillatory activity on the epicardium and endocardium could be dissociated. A finding which has previously been reported.⁹⁻¹¹ This finding implies that each layer can potentially maintain AF separately; therefore, interpreting the AF initiation and cycle length pattern may not be applicable to both atrial surfaces. In addition, if a non transmural lesion is created during ablation,³⁰ the tachycardia may continue unaffected. In AF ablation especially in persistent AF decreasing functional atrial mass decreases the likelihood of maintaining AF, the epicardial surface should be regarded as part of this mass.³¹

Pulmonary Vein Activation

Finally, we demonstrated that the CMC recordings may show different activation pattern during epicardial and endocardial pacing and that LA-PV ERP may also be different. These findings imply that electrical impulses initiated in the epicardium or endocardium may use different fibers in terms of their precise anatomic location and EP properties. A recent anatomical histological study, demonstrated that 27% of myocardial strands cross the interpulmonary isthmus subepicardially and 20% cross at both the epicardial and subendocardial layers.¹³ In addition, the possibility of recurrence of PV to LA electrical conduction after endocardial PV isolation due to epicardial fibers has been described.¹⁴

Clinical implications

Endocardial AF ablation has a high success rate especially for paroxysmal AF. However, the results are less favorable for persistent AF and also in a subgroup of paroxysmal AF patients. One possible cause of procedural failure are non-transmural lesions. Our findings suggest that observing the substrate from the endocardium may not reflect the electrical activity in the epicardium. The atrial epicardium was shown be a potential source of both triggers for atrial fibrillation¹² as well as a possible area of connection between the PVs and the LA.^{13, 14} Therefore in challenging AF ablation cases an epicardial or hybrid epicardial/endocardial mapping and ablation may be needed.

Limitations

This is an acute study (in normal animals) to explore the basic electrophysiological properties of the atrial endocardium and epicardium. Whether our results can be extrapolated to humans with structural LA changes or persistent AF is not known. Further study is needed to explore the epicardial and endocardial changes in ERP over time in advanced LA disease.

Pacing thresholds differed between the endocardium and epicardium. However, pacing output was adjusted to 1.5 times threshold at each point.

In addition, as this was an acute model, we could induce ARR of up to 22 seconds duration and not sustained AF. However it has been shown that this correlates with atrial vulnerability for AF.³²

Lastly, while the term transmural conduction time was used by us, this only represents the conduction time between opposing catheters and does not account for factors such as anisotropy, preferential passes and the potential of activation to travel along one surface prior to transmural conduction.

Conclusion

The atrial epicardium has a shorter ERP compared to the endocardium and induction of arrhythmias is more frequent from this surface. Fibrillatory wave activity and LA to PV connections may also be different on both atrial sides. These findings may have relevance to epicardial AF catheter ablation especially in challenging recurrent cases. The basis for shorter ERPs in the atrial epicardium deserves further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Nattel S. New ideas about atrial fibrillation 50 years on. *Nature*. 2002; 415:219–26. [PubMed: 11805846]
2. Fareh S, Villemaine C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. *Circulation*. 1998; 98:2202–9. [PubMed: 9815876]
3. Kanagaratnam P, Kojodjojo P, Peters NS. Electrophysiological abnormalities occur prior to the development of clinical episodes of atrial fibrillation: observations from human epicardial mapping. *Pacing Clin Electrophysiol*. 2008; 31:443–53. [PubMed: 18373763]
4. Lee SH, Lin FY, Yu WC, Cheng JJ, Kuan P, Hung CR, Chang MS, Chen SA. Regional differences in the recovery course of tachycardia-induced changes of atrial electrophysiological properties. *Circulation*. 1999; 99:1255–64. [PubMed: 10069796]
5. Jaïs P, Hocini M, Macle L, Choi KJ, Deisenhofer I, Weerasooriya R, Shah DC, Garrigue S, Raybaud F, Scavee C, Le Metayer P, Clémenty J, Haïssaguerre M. Distinctive electrophysiological properties of pulmonary veins in patients with atrial fibrillation. *Circulation*. 2002; 106(19):2479–85. [PubMed: 12417546]

6. Arora R, Verheule S, Scott L, Navarrete A, Katari V, Wilson E, Vaz D, Olgin JE. Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. *Circulation*. 2003; 107(13):1816–21. [PubMed: 12665495]
7. Anyukhovsky EP, Rosenshtraukh LV. Electrophysiological responses of canine atrial endocardium and epicardium to acetylcholine and 4-aminopyridine. *Cardiovasc Res*. 1999; 43:364–70. [PubMed: 10536666]
8. Burashnikov A, Mannava S, Antzelevitch C. Transmembrane action potential heterogeneity in the canine isolated arterially perfused right atrium: effect of IKr and IKur/Ito block. *Am J Physiol Heart Circ Physiol*. 2004; 286:H2393–400. [PubMed: 15148061]
9. Schuessler RB, Kawamoto T, Hand DE, Mitsuno M, Bromberg BI, Cox JL, Boineau JP. Simultaneous epicardial and endocardial activation sequence mapping in the isolated canine right atrium. *Circulation*. 1993; 88:250–63. [PubMed: 8319340]
10. Eckstein J, Verheule S, de Groot NM, Allesie M, Schotten U. Mechanisms of perpetuation of atrial fibrillation in chronically dilated atria. *Prog Biophys Mol Biol*. 2008; 97:435–51. [PubMed: 18378284]
11. Everett, THt; Wilson, EE.; Hulley, GS.; Olgin, JE. Transmural characteristics of atrial fibrillation in canine models of structural and electrical atrial remodeling assessed by simultaneous epicardial and endocardial mapping. *Heart Rhythm*. 2010; 7:506–17. [PubMed: 20184976]
12. Yamada T, Murakami Y, Okada T, Yoshida N, Ninomiya Y, Toyama J, Yoshida Y, Tsuboi N, Inden Y, Hirai M, Murohara T, McElderry HT, Epstein AE, Plumb VJ, Kay GN. Non-pulmonary vein epicardial foci of atrial fibrillation identified in the left atrium after pulmonary vein isolation. *Pacing Clin Electrophysiol*. 2007; 30:1323–30. [PubMed: 17976093]
13. Cabrera JA, Ho SY, Climent V, Fuertes B, Murillo M, Sanchez-Quintana D. Morphological evidence of muscular connections between contiguous pulmonary venous orifices: relevance of the interpulmonary isthmus for catheter ablation in atrial fibrillation. *Heart Rhythm*. 2009; 6:1192–8. [PubMed: 19632632]
14. Matsuo S, Yamane T, Tokuda M, Kanzaki Y, Inada K, Shibayama K, Miyanaga S, Date T, Miyazaki H, Abe K, Sugimoto K, Yoshimura M. The dormant epicardial reconnection of pulmonary vein: an unusual cause of recurrent atrial fibrillation after pulmonary vein isolation. *Pacing Clin Electrophysiol*. 2008; 31:920–4. [PubMed: 18684294]
15. Shivkumar K. Percutaneous epicardial ablation of atrial fibrillation. *Heart Rhythm*. 2008; 5:152–4. [PubMed: 18053771]
16. Buch E, Shivkumar K. Epicardial catheter ablation of atrial fibrillation. *Minerva Med*. 2009; 100:151–7. [PubMed: 19390501]
17. Pak HN, Hwang C, Lim HE, Kim JS, Kim YH. Hybrid epicardial and endocardial ablation of persistent or permanent atrial fibrillation: a new approach for difficult cases. *J Cardiovasc Electrophysiol*. 2007; 18:917–23. [PubMed: 17573836]
18. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. *J Cardiovasc Electrophysiol*. 1996; 7:531–6. [PubMed: 8743758]
19. Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, Di Diego JM, Gintant GA, Liu DW. Heterogeneity within the ventricular wall. *Electrophysiology and pharmacology of epicardial, endocardial, and M cells*. *Circ Res*. 1991; 69:1427–49. [PubMed: 1659499]
20. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation*. 1995; 91:1588–95. [PubMed: 7867201]
21. Wijffels MC, Kirchhof CJ, Dorland R, Allesie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995; 92:1954–68. [PubMed: 7671380]
22. Verheule S, Wilson E, Banthia S, Everett TH 4th, Shanbhag S, Sih HJ, Olgin J. Direction-dependent conduction abnormalities in a canine model of atrial fibrillation due to chronic atrial dilatation. *Am J Physiol Heart Circ Physiol*. 2004; 287:H634–44. [PubMed: 15031120]
23. Verheule S, Wilson E, Everett Tt, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. *Circulation*. 2003; 107:2615–22. [PubMed: 12732604]

24. Lu Z, Scherlag BJ, Lin J, Niu G, Fung KM, Zhao L, Ghias M, Jackman WM, Lazzara R, Jiang H, Po SS. Atrial fibrillation begets atrial fibrillation: autonomic mechanism for atrial electrical remodeling induced by short-term rapid atrial pacing. *Circ Arrhythm Electrophysiol.* 2008; 1:184–92. [PubMed: 19808412]
25. Olgin JE, Sih HJ, Hanish S, Jayachandran JV, Wu J, Zheng QH, Winkle W, Mulholland GK, Zipes DP, Hutchins G. Heterogeneous atrial denervation creates substrate for sustained atrial fibrillation. *Circulation.* 1998; 98:2608–14. [PubMed: 9843470]
26. Sharifov OF, Fedorov VV, Beloshapko GG, Glukhov AV, Yushmanova AV, Rosenshtraukh LV. Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs. *J Am Coll Cardiol.* 2004; 43:483–90. [PubMed: 15013134]
27. Schoels W, Restivo M, Caref EB, Gough WB, el-Sherif N. Circus movement atrial flutter in canine sterile pericarditis model. Activation patterns during entrainment and termination of single-loop reentry in vivo. *Circulation.* 1991; 83:1716–30. [PubMed: 2022026]
28. Kumagai K, Khrestian C, Waldo AL. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. *Circulation.* 1997; 95:511–21. [PubMed: 9008471]
29. Willems R, Holemans P, Ector H, Sipido KR, Van de Werf F, Heidbuchel H. Mind the model: effect of instrumentation on inducibility of atrial fibrillation in a sheep model. *J Cardiovasc Electrophysiol.* 2002; 13:62–7. [PubMed: 11843485]
30. Schuessler RB, Lee AM, Melby SJ, Voeller RK, Gaynor SL, Sakamoto S-I, Damiano RJ Jr. Animal studies of epicardial atrial ablation. *Heart Rhythm.* 2009; 6:S41–S45.
31. Asirvatham SJ. The isolated appendage: a new victim of collateral damage during atrial fibrillation ablation? *Heart Rhythm.* 2010; 7:181–3. [PubMed: 20129294]
32. Tsuneda T, Yamashita T, Kato T, Sekiguchi A, Sagara K, Sawada H, Aizawa T, Fu LT, Fujiki A, Inoue H. Deficiency of testosterone associates with the substrate of atrial fibrillation in the rat model. *J Cardiovasc Electrophysiol.* 2009; 20:1055–60. [PubMed: 19460074]

FIGURE 1.

Representative example of catheter positioning in the left atrial appendage (LAA) (upper panel) and right superior pulmonary vein (RSPV) (lower panel): For pacing and ERP measurements LA endocardial and epicardial catheters were placed in the closest proximity on LAO, RAO and AP projections in 4 anatomical locations (Common inferior PV (CIPV), LAA, RSPV and LA posterior wall) giving a fluoroscopic appearance of “kissing catheters”. The circular mapping catheter was positioned throughout the study at the os of the CIPV. CMC=circular mapping catheter, EPI=epicardial catheter, END=endocardial catheter

FIGURE 2.

A. Epicardial and endocardial ERP at basic CL of 600 and 400 ms B. ERP in atrial repetitive response (ARR) induced and non-induced points. Epicardial ERP at basic drive of 400 ms was shorter than endocardial ERP and ERP was shorter in ARR induced points compared to non induced. *p values for 2A: epi 600 vs. endo 600=0.2, epi 600 vs. epi 400=0.03, epi 400 vs. endo 400=0.006, endo 600 vs. endo 400=0.48. ^ p values for 2B: ARR induced 600 vs. not induced 600<0.0001, ARR induced 400 vs. not induced 400<0.0001.

FIGURE 3.

Example of epicardial to endocardial local fibrillatory wave dissociation. Panel A: Sinus rhythm, Panel B: Atrial repetitive response (ARR) induction. ARR was induced during epicardial pacing with 4 extrastimuli 400/200/150/140 (last 3 extrastimuli shown). The timings of epicardial and endocardial activation from the last pacing stimulus are presented as well as the difference in timings ($\Delta T_{\text{epi-Tendo}}$). As shown epicardial activation precedes endocardial activation in beats 1-5 and follows endocardial activation in beats 6-8. The standard deviation of the $\Delta T_{\text{epi-Tendo}}$ is 44.2.

FIGURE 4.

Different circular mapping catheter activation pattern (ls1-ls10) during endocardial (upper panel) and epicardial pacing (lower panel), (Paper speed of 100 mm/s-left, paper speed of 400 mm/s-right). During endocardial pacing (600/200ms) earliest activation is seen on ls9 which is before ls10 and ls1 is also activated early (arrows). However, during epicardial pacing (600/200ms) ls10 is before ls9 and ls1 is activated late.

FIGURE 5.

Different LA-PV ERP (LA to PV conduction block) of 50 ms during epicardial and endocardial pacing. Panel A- epicardial pacing at 400/280 ms, 400/270 ms and 400/260 ms is shown. At 400/280- there is epicardial to endocardial activation (red arrow) as well as LA to PV activation (PV potentials (PVP) are marked with black arrows). At 400/270 ms we can see transmural conduction (red arrow) and PVP (black arrows), however the activation pattern is different. At 400/260 ms there is still epicardial to endocardial activation (red arrow) however we reached the LA PV ERP. On the circular mapping catheter as we can see LA potentials without PVP (blue arrows). Panel B- On endocardial pacing at 400/220 ms there is endocardial to epicardial conduction (red arrow) as well as LA to PV conduction (PVP marked with black arrows). At 400/210 ms transmural conduction is present (red arrow) however we reached LA PV ERP (blue arrows).

Table 1

Electrophysiological Characteristics

	Epicardium	Endocardium	P value
ERP (ms)			
S1-600 ms	208±14	217±14	0.20
S1-400 ms	194±14	212±14	0.006
Δ ERP shortening [§]	15±4	4±4	0.016
Transmural conduction			
Basic drive 600 ms (S1)	19.3±3.2*	22.5±3.2**	0.15
(S2)	32.8±4.4*	36.2±4.4**	0.29
Basic drive 400 ms (S1)	20.3±3.2*	23.0±3.2**	0.23
(S2)	36.8±4.4*	35.4±4.4**	0.66
EGM characteristics			
Duration (ms)	50.9±2	52.8±2	0.24
Fractionations	6.9±0.2	6.9±0.2	0.95
Amplitude (mV)	2±0.3	2.2±0.3	0.09

ERP= effective refractory period, Δ=delta.

* epi to endo

** endo to epi

[§]ERP at basic drive of 600 – 400

Table 2

	ARR induced (n=19)	ARR not induced (n=65)	P value
Epi/Endo (%)	15/4 (37.7/10.8)	27/38 (63.3/89.2)	0.002
ERP			
S1-600 ms	181±14	217±13	<0.0001
S1-400 ms	166 ±14	209±13	<0.0001
Δ ERP shortening [§]	16±8	9±5	0.42
Transmural conduction (ms)			
Basic drive (400 ms) [*]	22.7±3.3	23.8±1.9	0.78
Maximal [*]	52±8.2	39.9±5.2	0.18
EGM characteristics			
Duration (ms)	49.2±2.7	48.6±1.9	0.82
Fractionations	6.9±0.4	6.6±0.2	0.49
Amplitude (mV)	2.3±0.4	1.9±0.3	0.34

ARR= atrial repetitive response, ERP= effective refractory period, Δ=delta.

^{*} transmural= either epi to endo or endo to epi conduction.

[§]ERP at basic drive of 600 – 400