Recovery of Mitral Isthmus Conduction Leads to the Development of Macro-Reentrant Tachycardia after Left Atrial Linear Ablation for Atrial Fibrillation

Running title: Sawhney et al.; Recovery of mitral isthmus conduction

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Abstract:

Background - Left atrial linear ablation for atrial fibrillation (AF) may be proarrhythmic, leading to left atrial macro-reentrant tachycardia (LAT). Whether due to failure to achieve block initially or to recovery of conduction after ablation is unknown. This study was designed to evaluate the frequency of recovery of mitral isthmus (MI) conduction compared to cavo-tricuspid isthmus (CTI) conduction, and the relationship between recovery of MI conduction and post-ablation LAT.

Methods and Results - Of 163 patients with AF who underwent circumferential pulmonary vein ablation plus left atrial linear ablation, in whom MI and CTI ablation produced bidirectional conduction block, 52 underwent repeat ablation for recurrent atrial arrhythmias (AF and/or LAT). Of these 52 patients, coronary sinus ablation was required in 48 to achieve bidirectional MI block at the index ablation. During repeat ablation MI and CTI conduction was assessed in sinus rhythm. At repeat ablation, MI conduction had recovered in 38 of 52 patients, as compared to CTI conduction which recovered in only 12 of 52 patients (p=0.001). At repeat ablation, the recurrent clinical arrhythmia in 12 patients was MI dependent LAT. Recovery of MI conduction was associated with development of MI dependent LAT (p=0.01).

Conclusions - Despite using bidirectional conduction block as a procedural endpoint, recovery of MI conduction is common and may lead to LAT after left atrial linear ablation for AF. The reason for greater recovery of MI versus CTI conduction is unknown, but could be due to differences in isthmus anatomy or lower power used for ablation in the left versus right atrium.

Key words: atrial fibrillation, atypical atrial flutter, catheter ablation
Introduction

Although circumferential pulmonary vein ablation is commonly performed as an initial approach to atrial fibrillation (AF) ablation, and randomized trials have shown an improvement in AF ablation success rates with additional left atrial linear ablation at the left atrial (LA) roof or mitral isthmus (MI)\textsuperscript{1,2}, there has been growing concern about the potential proarrhythmic effect of left atrial linear ablation,\textsuperscript{3,4} particularly with regard to the occurrence of left atrial macro-reentrant tachycardia (LAT).

Ablation at the MI has been associated with atrial pro-arrhythmia, and occurrence of peri-mitral atrial flutter following AF ablation is reported to be higher in patients with previous MI ablation compared to those without\textsuperscript{5}. However, it is not clear if this is due to inability to achieve bidirectional conduction block at initial ablation, or due to recovery of MI conduction after ablation. The objective of this study was to evaluate the frequency of recovery of MI conduction after bi-directional block had been achieved during a prior ablation procedure, compared to the frequency of recovery of cavo-tricuspid isthmus (CTI) conduction, and to evaluate the relationship between recovery of MI conduction and post-ablation LAT.

Methods

Patient population

The study population consisted of 163 consecutive patients who underwent circumferential pulmonary vein ablation between January 2007 and January 2010 for paroxysmal or persistent AF, who also underwent additional left atrial linear ablation, including the MI and CTI, with documentation of bidirectional conduction block during their initial ablation procedure. Patients in whom bi-directional block could not be achieved were excluded from this analysis.
All patients had routine follow up in the Arrhythmia Clinic at the University of California San Diego Medical Center and underwent 7-10 days of mobile outpatient telemetry monitoring every 6 months to evaluate for arrhythmia recurrence.

Fifty-two of these 163 patients underwent a second procedure for recurrence of atrial arrhythmias (AF or LAT). At electrophysiology study, these patients were evaluated for recurrence of MI and CTI conduction and electro-anatomic mapping was performed of their spontaneous or pacing induced clinical arrhythmia to determine its mechanism. The Human Studies Committee at the University of California, San Diego approved the study protocol.

**Catheter placement for ablation**

Transseptal catheterization was performed using standard Brokenbrough needle technique with intracardiac ultrasound (ICE) and fluoroscopic guidance. Two 8 French SL1 transseptal sheaths were placed in the left atrium, through which an ablation catheter (Thermacool, Biosense-Webster, Inc., Diamond Bar, Ca, or Blazer, Boston Scientific, Inc., Natick, MA) and a circular twenty-pole Lasso™ catheter (Biosense Webster, Inc) were placed for mapping and ablation of the PVs and linear ablation. Prior to transseptal puncture, unfractionated heparin (10,000-15,000 Units) was administered as a bolus followed by a continuous intravenous infusion to maintain an ACT >350 seconds throughout the procedure, as measured every 15 minutes.

**Method for mitral isthmus and cavo tricuspid isthmus ablation**

A 3-dimentional CT image of the left atrium and pulmonary veins (PV) was imported and registered in the mapping system prior to ablation. (CARTO, Biosense Webster Inc., Diamond Bar, CA or ESI NavX, St. Jude Medical, St. Paul, MN). Radiofrequency energy was delivered in the left atrium with either a Thermocool™ irrigated tip catheter at 35 watts and maximum
temperature of 45º C, or with an 8 mm solid tip catheter at a maximum power of 50 watts and maximum temperature of 55º C for up to 30-120 seconds at each location (Stockert 70 RF, Biosense-Webster, Inc., Diamond Bar, CA or EPT-1000 Maestro, Boston Scientific, Inc., Natick, MA, radiofrequency generators, respectively). Initially, circumferential pulmonary vein ablation was performed around the pulmonary veins and the Lasso™ catheter was used to document PV isolation (entrance block), with additional segmental antral ablation performed as needed to ensure complete isolation of the PVs. Additional linear ablation was then performed by creating a line between the two circumferential ablations at the roof of the left atrium. Ablation was performed along the LA roof line until electrograms amplitude was <0.5 mV along the entire length of the line. A line was then created from the mitral valve annulus up to the left encircling lesion (MI line). Following linear ablation, pacing from the left atrial appendage and the proximal coronary sinus was performed to document bidirectional MI block. If block was not achieved, ablation was performed within the coronary sinus with the same power and temperature settings noted above until bidirectional MI block was achieved.

MI conduction was assessed during sinus rhythm by pacing at a cycle length of 600 msec or longer, from the left atrial appendage and proximal coronary sinus, while observing coronary sinus activation sequence, and activation times between the proximal coronary sinus and left atrial appendage, respectively. Lateral to medial MI conduction block was defined as reversal of the distal to proximal activation sequence observed during left atrial appendage pacing prior to ablation, to a proximal to distal activation sequence after ablation (Fig. 1A), with an associated prolongation of conduction time from pacing to recording site of 50% increase from baseline, or to ≥150 ms if baseline measurements were not made. Medial to lateral MI conduction block was defined as observation of similar activation times from the proximal coronary sinus pacing site to
the left atrial appendage (Fig. 1B), compared with the left atrial appendage pacing site to the proximal coronary sinus (Fig. 1A) after ablation. In addition, observation of widely spaced double potentials along the MI line during pacing from either site provided further confirmatory evidence of MI block. Persistence of MI block was confirmed for 30 minutes after initial documentation and after patients had been given isoproterenol at a dose of 20 mcg/min for 5 minutes.

Ablation of the cavo-tricuspid isthmus was then performed in all patients, with either a Thermocool™ catheter at a maximum power of 50 watts and maximum temperature of 45°C or with an 8 mm tip catheter at a maximum power of up to 80-100 watts and maximum temperature of 60°C, for up to 120 seconds during each energy application, until there was documentation of bidirectional CTI block demonstrated during pacing both medial and lateral to the ablation line, while evaluating activation sequence (contralateral descending wavefront), conduction time (>140 msec) and observing for widely spaced double potentials along the ablation line (in an analogous method to documenting mitral isthmus block).

**Repeat ablation procedures**

Repeat circumferential pulmonary vein ablation was performed initially if PV reconnection was observed during mapping with the Lasso™ catheter. Following repeat circumferential pulmonary vein ablation, if mapping still demonstrated incomplete PV isolation, additional segmental antral ablation was performed, as described above, to isolate the PVs. If patients presented in persistent AF that persisted after repeat PV isolation, they were externally cardioverted to NSR. In NSR, MI and CTI conduction was reassessed and if recovery of conduction was present, repeat ablation was performed as previously described, until bidirectional conduction block was achieved.
If patients presented in a stable atrial tachycardia, after registration of a 3D CT image, the tachycardia mechanism was evaluated by activation mapping (CARTO, Biosense Webster Inc., Diamond Bar, CA or ESI NavX, St. Jude Medical, St. Paul, MN). Mitral isthmus-dependent macro-reentrant AT was diagnosed by demonstrating the majority of the tachycardia cycle around the mitral annulus (clockwise or counter-clockwise) during 3D activation mapping, and the location of the reentrant circuit was confirmed with entrainment mapping at two separate sites within the circuit, demonstrating a corrected post-pacing interval (post-pacing interval – tachycardia cycle length) within 20 msec of the tachycardia cycle length. The critical isthmus within the reentrant circuit was then targeted for ablation until termination of the tachycardia was achieved.

Statistical Analysis

All continuous variables are reported as the mean±1 standard deviation and were compared using student’s t-test. Categorical variables were compared by chi-square or Fisher’s exact method, as appropriate. A two-tailed test with p<0.05 was considered statistically significant. Statistical analysis was performed using STATA software version 9.0 (STATA Inc. USA).

Results

Clinical Characteristics of the Patients Enrolled

The study population consisted of 52 out of 163 consecutive patients who demonstrated complete PV isolation as well as bidirectional MI and CTI conduction block during their initial ablation procedure and who subsequently underwent a second ablation procedure for recurrent arrhythmia. Mean age was 65±8 years, median duration of AF 8.5 years with the 25th and 75th
percentiles being 5 and 15.5 years respectively, mean ejection fraction 56±16%, and mean left atrial size 43±6 mm. Thirty-nine patients were male, and 40 had a diagnosis of hypertension (Table 1).

**Patterns of Atrial Arrhythmia Recurrence**

Of the 52 patients included in this analysis, 35 had recurrent AF and 17 had predominantly LAT. No patients presented with spontaneous recurrent CTI dependent flutter. Of the 17 LATs, 12 were mitral isthmus dependent.

**Recovery of Conduction**

At repeat EP study, recovery of conduction was seen in only 12 out of 52 patients (23.1%) at the CTI, but in 38 of 52 patients (73.1%) at the MI (p = 0.001). Recovery of MI conduction (Figure 2) was associated with the development of MI dependent LAT (p=0.01), with 12 of 38 patients in whom MI isthmus conduction recovered developing MI dependent LAT (Figure 3). In addition, 44 of the 52 (84%) patients undergoing repeat ablation demonstrated reconnection of one or more previously isolated PVs. There was no statistical difference between which PVs reconnected.

**Acute Outcome of Repeat Ablation**

Following repeat ablation, complete isolation of the PVs and bidirectional CTI block was achieved in all patients. However, bidirectional MI block was achieved in only 36 out of 38 patients at repeat ablation, with MI conduction delay in the remaining 2 patients (trans-isthmus conductions times <120 msec). Recurrent MI conduction was predominately epicardial, requiring coronary sinus ablation in 33 of the 38 patients to achieve bidirectional block.
Discussion

This study has demonstrated that like the PVs, where reconnection has been associated with recurrence of AF \textsuperscript{6,7}, recurrence of MI conduction is also associated with development of MI dependent LAT following initially successful ablation. When AF ablation employs circumferential pulmonary vein ablation plus left atrial linear ablation, LAT is relatively common, occurring in 10-30\% of patients during follow-up \textsuperscript{3,4,8}. LATs that develop after extensive linear ablation may negate any benefit with regard to reduction in recurrence rates of AF \textsuperscript{9}. The vast majority of the arrhythmias that occur after circumferential pulmonary vein ablation plus left atrial linear ablation are thought to be due to gaps in prior ablation lines that facilitate reentry \textsuperscript{3}. Whether these gaps are due to incomplete initial ablation or recovery of conduction has not been well characterized.

The MI line has been implicated in the development of post-ablation LAT and it has been shown that the incidence of peri-mitral atrial flutter is higher in patients in whom MI ablation was performed during AF ablation, than in those in whom it was not. \textsuperscript{5} These data suggest that MI ablation may facilitate development of mitral isthmus dependent LAT. This may be explained in part by inability to achieve MI block initially. Studies have shown that even with both endocardial and epicardial ablation, MI block may only be achieved in 82-89\% of cases, and failure to achieve bidirectional MI conduction block results in an increased rate of recurrence of MI dependent LAT \textsuperscript{5,10}. However, recovery of conduction has also been noted in some studies \textsuperscript{10,11} but has not been well characterized. By excluding patients in whom MI block could not be achieved at initial ablation, in the present study we were able to demonstrate that recovery of conduction across the MI is common and also correlates with the development of MI dependent LAT.
After initially achieving complete PV isolation, PV reconnection is commonly seen and has been implicated as a mechanism for AF recurrence\textsuperscript{6,7}. In this series of patients who underwent repeat EPS for recurrent arrhythmias, we saw recovery of PV conduction in 84% of patients, similar to other published data\textsuperscript{12}. We also saw a 22% rate of recovery of conduction across the CTI. This is similar to that seen in prior studies, such as that of Lo, et. al.\textsuperscript{13}, where it was reported that recovery of CTI conduction was associated with complex CTI anatomy, including pouches and longer isthmus length. What is novel in this series that has not been previously reported is the 71% frequency of recurrence of conduction across the MI despite using bi-directional block as a procedural end point. The reason for the higher incidence for recovery of conduction at the MI as compared to the CTI is not clear. Anatomy likely plays a significant role, but MI anatomy was not extensively evaluated in this study. Previous studies demonstrated that the shape and depth of the atrial myocardium vary greatly around the MI, and that the depth of the tissue may be the limiting factor in achieving and maintaining bidirectional block, with LA thickness along the course of the MI ranging between 1 and 8 mm\textsuperscript{14,15}. In addition, it has also recently been shown that when the circumflex coronary artery courses between the mitral isthmus and the coronary sinus there is a higher likelihood of failure to achieve mitral isthmus block\textsuperscript{16}. The circumflex coronary artery and the great cardiac vein both pass in close proximity to the MI and may act as a heat sink, preventing adequate tissue heating by radiofrequency delivery and preventing the development of a transmural lesion. This may be why in the majority of patients, recovery was felt to be in the epicardium with CS ablation required in 33 of 38 patients in this study to achieve bidirectional MI block at repeat ablation. It has been reported that a high percentage of patients who developed MI dependent LAT after ablation for AF, required ablation in the CS in order to achieve bidirectional MI block\textsuperscript{11}. The
importance of epicardial ablation in the coronary sinus has also been reported to be critical to the success of the surgical Maze procedure, where a 15% arrhythmia recurrence rate is seen if ablation in the coronary sinus is not performed as an adjunct to the endocardial mitral isthmus line.\textsuperscript{17}

In a porcine study, D’avila, et.al. reported that temporary displacement of the venous blood pool using an air-filled CS balloon promotes transmurality of MI ablation\textsuperscript{18}. Whether this technique would prevent late recovery of MI conduction after initial ablation remains to be seen. It was recently shown in humans that balloon occlusion of the CS during mitral isthmus ablation decreased ablation time and need for CS ablation to achieve block, supporting the hypothesis that “heat sink” is an obstacle to successful permanent MI ablation \textsuperscript{19}.

Another possible reason for the higher recovery rate of conduction at the MI as compared to the CTI, is failure to achieve transmural lesions due to the lower power settings used in the LA as compared to the RA, for safety reasons. Jaïs, et.al. reported cardiac tamponade in 4% of patients undergoing MI ablation for AF. In their study, cardiac tamponade occurred exclusively when they delivered power up to 50 watts endocardially \textsuperscript{2}. Currently most operators ablate in the LA endocardium at powers between 35-40 watts, as compared to the right atrium and CTI, where powers up to 50 Watts are more commonly used \textsuperscript{20}. In our series of patients, we routinely used higher powers for CTI ablation, up to 50 watts with irrigated catheters and up to 80-100 watts with large-tip non-irrigated catheters, as compared to MI ablation where powers were limited to 35-40 watts with irrigated tip catheters and 55 Watts with large-tip catheters.

These observations suggest that it might be prudent to evaluate mitral isthmus anatomy before MI ablation is performed, and is some patients it might be best to avoid MI ablation if possible. Further investigation is needed to better understand how to achieve transmural lesions
during linear ablation at the mitral isthmus. Using electrophysiologic endpoints alone might not be adequate for maintaining long term results as failure to achieve transmural lesions may lead to recovery of tissue conduction, which is associated with the development of LAT.

Conclusions

In this study we found that like PV reconnection, recovery of MI conduction after initially achieving bi-directional block, is common and is associated with the development of MI dependent LAT. The incidence of recovery of MI conduction is similar to that of PV reconnection after initially successful AF ablation, but significantly higher than the frequency of recovery of CTI conduction. The reasons for this are unclear, but may be due in part to differences in isthmus anatomy and ablation techniques, particularly power delivery. Using electrophysiologic endpoints alone might not be adequate for maintaining long term results as failure to achieve transmural lesions may lead to recovery of tissue conduction. Further investigation is needed in order to understand how to achieve transmural lesions during linear ablation at the mitral isthmus.

Limitations

The present study has several possible limitations: 1) This is a retrospective analysis and patients without recurrence of AF or LAT were not restudied. Therefore, the true incidence of recovery of conduction across the MI may not have been accurately estimated in all patients undergoing initial AF ablation. 2) The anatomy of the MI was not evaluated during this study to understand why there was such a high rate of recurrence of conduction following initially successful ablation. A more detailed assessment of MI anatomy and results of initial ablation
with intracardiac echocardiography (ICE), or other imaging modalities such as MRI, might provide insight into any anatomical influence on recovery of conduction. 3) MI Conduction was evaluated at pacing cycle lengths of 600 ms in most patients. Therefore, it is possible that residual conduction remained across the MI at longer cycle lengths and was missed.

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Conflict of Interest Disclosures: Dr. Sawhney has received speaking honorarium from Boehringer Ingelheim Pharmaceuticals. Modest.

References:


### Table 1. Baseline characteristics

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<td>Age (years)</td>
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<td>Male/Female</td>
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<tr>
<td>Persistent / Paroxysmal AF</td>
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<td>Median duration of AF (years)</td>
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<td>Hypertension</td>
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<td>LA size (mm)</td>
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<tr>
<td>LVEF (%)</td>
<td>56±16</td>
</tr>
<tr>
<td>Duration of follow-up (months)</td>
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<tr>
<td>Number of AA drugs tried per patient</td>
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<td>Class Ic antiarrhythmic</td>
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<td>Class III antiarrhythmic</td>
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<td>Amiodarone</td>
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AA = antiarrhythmic, AF = atrial fibrillation, LA = left atrial, LVEF = left ventricular ejection fraction, mm = millimeters
Figure Legends:

Figure 1: Demonstration of bidirectional MI conduction block at initial AF ablation. (A) Lateral to medial MI conduction block after ablation within the coronary sinus, observed during pacing (S) from the left atrial appendage at a cycle length of 800 msec. Note the change in coronary sinus activation sequence from distal-to-proximal to proximal-to-distal between the second and third paced beats. Also note that the left atrial appendage to proximal coronary sinus activation time (A) and proximal coronary sinus to left atrial appendage activation time (B) after MI ablation are equal (165 msec), during pacing from the left atrial appendage and proximal coronary sinus, respectively. This confirmed the presence of bi-directional MI conduction block. Abbreviations: I, aVF, V1; surface ECG leads, RFd&p; proximal and distal electrodes on the RF catheter positioned at the His bundle in (A) and at the lateral cavo-tricuspid isthmus in (B), CSP-d; proximal to distal coronary sinus electrograms, and PVd-p; proximal to distal electrograms on the PV loop catheter (Lasso®), S; stimulus artifact. (Adapted with permission from Anousheh, et.al. PACE 2010; 33:460–468)

Figure 2: Acute recovery of mitral isthmus conduction during an initial mitral isthmus ablation procedure demonstrated during pacing from the Lasso™ catheter in the left atrial appendage. Initially, conduction through the coronary sinus is observed going form proximal to distal with a trans-isthmus conduction time of 136 msec. However, with continued pacing there is recovery of conduction across the MI with a change in CS activation sequence to distal to proximal, and shortening of trans-isthmus conduction time to 98 msec. In the initial two paced beats of the tracing, there is delay in MI conduction, but in this case as the trans-isthmus conduction time is
relatively short at 136 msec, bidirectional block may not have been achieved prior to recovery of conduction.

**Figure 3:** Bar plot demonstrating the incidence of MI dependent LAT in patients by MI reconnection status. Recovery of MI conduction is associated with the development of MI dependent LAT.
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