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1 **Gaps after linear ablation of persistent atrial fibrillation**
2 **(Marshall-PLAN): clinical implication**

3
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13
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24

25 **ABSTRACT**

26 **Background**

27 Beyond pulmonary vein (PV) isolation, anatomic isthmuses transection is an adjunctive strategy for
28 persistent atrial fibrillation (AF). Data on the durability of multiple lines of block remain scarce.

29

30 **Objective**

31 To evaluate the impact of gaps within such a lesion set.

32

33 **Methods**

34 We followed 291 consecutive patients who underwent: (1) vein of Marshall ethanol infusion, (2) PV
35 isolation, and (3) mitral, cavotricuspid, and dome isthmuses transection. Dome transection relied on two
36 distinct strategies over time. A single roof line with touch-ups applied in case of gap demonstrated by
37 conventional maneuvers (*first leg*). An alternative floor line if the roof line exhibited a gap during high-
38 density mapping with careful electrogram reannotation (*second leg*).

39

40 **Results**

41 12-month sinus rhythm maintenance was 70% after 1 procedure, and 94% after 1 or 2 procedures. Event-
42 free survival after first procedure was lower in case of residual gaps within the lesion set (log
43 rank=0.004). Delayed gaps were found in 94% of second procedure performed in the 69 patients
44 relapsing despite complete lesion set with PV gaps increasing the risk of recurrence into AF (67% vs
45 34%; p=0.02), and anatomic isthmuses gaps supporting a majority of ATs (60%). Between *first leg* and
46 *second leg*, a significant decrease was found in roof lines considered blocked during first procedure
47 (99% vs 78%; p<0.001), and in delayed dome gaps observed during second procedure (68% vs 43%;
48 p=0.05).

49

50 **Conclusion**

51 Gaps are arrhythmogenic, and can be reduced by optimized ablation and assessment of lines of block.

52 Closing these gaps improves sinus rhythm maintenance.

53

54 **KEY WORDS**

55 Atrial fibrillation – Catheter ablation – Conduction block – Conduction gap – Pulmonary vein isolation

56 – Mitral line – Cavotricuspid line – Roof line – Floor line

57

58

59 **INTRODUCTION**

60 Beyond pulmonary vein (PV) isolation, considerable efforts have been invested in adjunctive ablation
61 strategies for persistent atrial fibrillation (AF). If durable, addition of anatomic lines of block has proved
62 more efficient than lone PV isolation.¹ Lesion durability may explain why surgical "cut-and-sew"
63 partition of the atria has consistently achieved outstanding long-term results.^{2,3} However, delayed gaps
64 across lines of block are still reported in the EP-laboratory despite systematic use of force sensing,
65 stability monitoring and higher power settings.^{4,7} Since 2018, our institution treats persistent AF patients
66 with a simplified version of the "Cox-maze" that includes vein of Marshall (VOM) ethanol infusion, PV
67 isolation and conduction block at the mitral, dome and cavotricuspid isthmuses.⁸ This "EP-maze" has
68 been developed with the aim of blocking anatomic structures that have been individually recognized as
69 important for AF initiation or maintenance, but thus far not collectively targeted in a systematic manner
70 that respects natural atrial activation.⁹ Little is known about the role of gaps within a lesion set made of
71 multiple lines of block performed in the EP-laboratory with optimized ablation tools. The present study
72 evaluates their clinical impact in a large series of patients.

73

74 **METHODS**

75 **Study population**

76 The study adhered to the guiding principles of the Helsinki Declaration, and was approved by our ethics
77 committee on human research. Consecutive patients were enrolled if they experienced recurrences after
78 first persistent AF ablation performed at our institute since January 2018. Exclusion criteria were: age
79 < 18 years, severe valvular disease, hypertrophic cardiomyopathy and history of atrial ablation.

80

81 **First ablation procedure**

82 *General principles*

83 All procedures were performed under conscious sedation with the CARTO-3 mapping system (Biosense
84 Webster, Diamond Bar, CA). Four catheters were used: (1) a decapolar catheter (Dynamic XT, Boston
85 scientific, MA) inside the lumen of the great cardiac vein and coronary sinus (GCV-CS set); (2) a

86 quadripolar catheter (Dynamic XT, Boston Scientific, MA) in the left atrial appendage (LAA); (3) a
87 multipolar catheter (Pentaray, Biosense Webster, CA) for mapping; and (4) a 3.5 mm irrigated-tip
88 catheter (ThermoCool SmartTouch SF, Biosense Webster, CA) for ablation. Point-by-point
89 radiofrequency was delivered with an interlesion distance ≤ 4 mm, a power-control mode, temperature
90 limited to 45°C, and normal saline irrigation (8-20 mL/min). Each RF application was delivered for 10-
91 30 seconds at a power of 20-25W inside the GCV-CS set, of 35-50W at the dome within the four PVs
92 ("posterior wall"), and of 40-50W elsewhere. Automated lesion annotation included a catheter stability
93 range of motion ≤ 2 mm for 4 seconds, and a minimum force ≥ 8 g for 70% of the time. Ablation catheter
94 stability was optimized using a steerable long sheath (Agilis, St Jude Medical). For all patients, the
95 lesion set, previously described as the "Marshall-PLAN", followed the same succession of steps: (1)
96 vein of Marshall (VOM) ethanol infusion that primarily aimed at facilitating mitral isthmus block; (2)
97 wide antral PV isolation; (3) mitral isthmus transection with a line joining the mitral annulus to the left
98 inferior PV; (4) cavotricuspid isthmus transection with a line joining the tricuspid annulus to the inferior
99 vena cava; and (5) dome isthmus transection with a line joining two contralateral PVs (**Figure 1A**).⁸
100 The respective endpoints were: (1) injecting 10 mL of absolute ethanol inside the VOM lumen; (2) exit
101 block when pacing the entire antral area with the ablation catheter; (3) mitral isthmus block, defined as
102 a homogeneous "proximal-to-distal" activation of the CS catheter and a "septal-to-lateral" activation of
103 the posterior LA during left atrial appendage (LAA) pacing; and (4) cavotricuspid isthmus block,
104 defined as a downward activation of the lateral wall of the right atrium (RA) with double potentials
105 along the line during proximal CS pacing.

106

107 *Specific considerations for dome transection*

108 Because of its superior position with respect to the chest, the anatomical isthmus between the two sets
109 of PVs is referred by anatomists as the "dome" rather than the "posterior wall" (PW). The latter
110 terminology is used for the area joining the lower border of the inferior PVs to the vestibule surrounding
111 the mitral annulus (**Figure 1A**). Our approach for its transection by one line of block significantly
112 changed over time. Before May 2019, one line was created only, and placed at the roof between the two

113 superior PVs. During this "single roof" *first leg*, roof line block was assessed by conventional maneuvers
114 during LAA pacing, and validated by a shortening of the delay from the pacing artefact to the
115 electrogram recorded by the ablation catheter which was gradually shifted down the dome and the true
116 PW. If not blocked after first pass, roof line touch-ups were performed by ablating at dome areas that
117 displayed the earliest electrograms just below the line, until reversal of the activation sequence was
118 achieved. Since May 2019, a second line could be created, and placed at the floor between the two
119 inferior PVs as recently described in detail.¹⁰ During this "roof-or-floor" *second leg*, careful electrogram
120 reannotation after high-density mapping of the dome during LAA pacing helped unmask residual
121 epicardial gaps across the roof line via the septopulmonary bundle. If not blocked after first pass, instead
122 of roof line touch-ups, an alternative floor line was created. Floor line block was validated by two
123 changes in CS and LAA activation while pacing with the ablation catheter below then above the floor
124 line: (1) an increase in CS activation delay becoming greater than the LAA one; and (2) a modification
125 of CS activation from a "bracket" to a "proximal-to-distal" pattern (**Figure 1B**). Of note, two reasons
126 led us to create the floor line in case of failed roof line only: (1) our endpoint was dome isthmus
127 transection, and not dome area isolation; and (2) limiting the risk of esophageal injury, given its
128 proximity to the lower portion of the dome.

129

130 **Follow-up**

131 Antiarrhythmic medications were continued for 1-month post-ablation. Follow-up at 3, 6 and 12 months
132 comprised 12-lead ECG and 24-hour Holter recording. Recurrence was defined as documented episode
133 of AF or stable atrial tachycardia (AT) lasting ≥ 30 seconds after a 1 month blanking period. Beyond
134 this blanking period, repeat ablation procedures were recommended in case of recurrence, be the patient
135 symptomatic or not.

136

137 **Second ablation procedure**

138 All second procedures followed the same general principles than the first procedure. At the beginning,
139 sinus rhythm was restored by mean of electrical cardioversion in case of AF, or after ablation of any

140 stable AT. In the latter case, a conduction gap across the initial lesion set was systematically targeted if
141 it supported AT circuit. Then, conduction block of the multiple lines of the lesion set was assessed as
142 described above, and gaps were systematically closed.

143

144 **Statistical analysis**

145 Continuous variables are presented as mean \pm standard deviation and compared using a Student's t-tests
146 or Mann-Whitney *U* tests, as appropriate. Categorical variables are presented as number (%) and were
147 compared using chi-squared tests. Kaplan-Meier analysis and log-rank tests were used to assess
148 arrhythmia-free survival rates. A p-value of <0.05 was considered statistically significant. All analyses
149 were performed using the Statistical Package for Social Studies (IBM, Armonk, NY).

150

151 **RESULTS**

152 **First procedure**

153 Baseline characteristics of the 291 consecutive persistent AF patients with first ablation procedure are
154 summarized in **Table 1**. The Marshall-PLAN lesion set could not be achieved in 23 patients (8%), due
155 to VOM ethanol infusion failure in 8 patients, residual mitral isthmus gap in 7 patients and residual
156 dome gap in 8 patients. In these 23 patients, sinus rhythm maintenance at 12 months was 48%, while it
157 reached 72% in the 268 patients with a complete Marshall-PLAN lesion set (**Figure 2A**). Dome
158 transection was performed according to the "single roof" *first leg* approach in 92 patients (32%), and the
159 "roof-or-floor" *second leg* approach in 199 patients (68%). The number of lines considered blocked at
160 the dome was: (1) 91 roof lines (99%) during *first leg*; and (2) 155 roof lines (78%) and 37 floor lines
161 (84%) during *second leg*. The rate of roof line considered blocked decreased between *first leg* and *second*
162 *leg* [91/92 (99%) vs 155/199 (78%); $p < 0.001$], while the rate of dome considered blocked did not differ
163 [91/92 (99%) vs 192/199 (96%); $p = 0.44$] (**Figure 2B**).

164

165 **Second procedure**

166 A second procedure was performed in 69 of the 75 patients with recurrence despite complete lesion set
167 achieved during the first procedure. Recurrence type was AF in 36 patients (52%), and stable AT in 33
168 patients (48%). The clinical AT was ongoing and mapped at the time of the second procedure in 20
169 patients (61%). For the latter, gaps within the Marshall-PLAN lesion set supported 65% of clinical ATs:
170 7 perimitral flutters (35%), 4 roof-dependent flutters (20%), 1 perivenous flutter (5%), and 1 common
171 flutter (5%). All 7 remaining ATs (35%) were anterior reentries. Delayed gaps were observed in the
172 Marshall-PLAN lesion set in 65 patients (94%), including 21 patients in one step only and 44 patients
173 in multiple steps. No significant difference was found in the recurrence mode [AT in 12/21 (57%) vs
174 19/44 (43%); $p = 0.29$]. PV gaps, but not anatomic isthmuses gaps, were more frequent in AF patients
175 than in AT patients [25/36 (69%) vs 14/33 (42%); $p = 0.02$] (**Figure 3A**). As a corollary, AF recurrence
176 is 1.7 fold more frequent in patients with PV gaps rather than without [25/39 (64%) vs 11/30 (37%); p
177 = 0.02]. The rate of delayed roof gaps [23/34 (68%) vs 11/26 (42%); $p = 0.05$] and dome gaps [23/34
178 (68%) vs 15/35 (43%); $p = 0.04$] decreased between *first leg* and *second leg* (**Figure 3B**). All delayed
179 gaps found in the 65 patients could be closed during second procedure. Among the remaining 4 patients
180 without delayed gaps at the beginning of second procedure, ablation was performed at the LA anterior
181 wall in 1 patient, and at the RA in 3 patients. A second procedure was performed in 10 of the 12 patients
182 with recurrence and an incomplete lesion set at the end of first procedure. Among these 10 patients, all
183 delayed gaps could be closed, except one mitral isthmus gap in a patient for whom VOM ethanol
184 infusion systematically failed. Sinus rhythm maintenance rate for all 291 patients was 70% after one
185 procedure for a mean follow-up of 12.1 ± 7.6 months, and was 94% after one or two procedures for a
186 mean follow-up of 12.5 ± 8.1 months. The Kaplan-Meier curves show that event-free survival between
187 the 268 patients with a complete lesion set and the 23 patients with an incomplete lesion set at the end
188 of first procedure significantly differed after one procedure (log rank = 0.004), but did not after one or
189 two procedures (log rank = 0.33) (**Figure 4**).

190

191 **DISCUSSION**

192 This study evaluated the role of gaps within a lesion set based on lines of block for persistent AF
193 treatment. Several findings confirm that atrial partition must be perfectly blocked to be fully effective:
194 (1) recurrence is more frequent when first procedure ends up with an incomplete lesion set; (2) delayed
195 gaps are almost universal during a second procedure after recurrence; (3) among patients with recurrent
196 atrial arrhythmias, PV gaps confer a nearly two-fold increase in risk of having AF recurrence; (4)
197 anatomic isthmuses gaps support a majority of ATs recurrence; and (5) a repeat ablation closing these
198 gaps improves sinus rhythm maintenance. Two findings specifically related to dome transection show
199 that both assessment modality and ablation strategy affect line durability: (1) a more challenging
200 assessment of the roof line leads to lower rate of block validation, but more durable roof block; and (2)
201 systematic shift to floor line creation instead of touch-ups ablation of roof line gaps ensures more durable
202 dome transection.

203

204 **Importance of linear conduction block**

205 The medical literature has long provided reports questioning the benefit of achieving conduction block
206 when creating linear lesions.^{11,12} Regarding a key target like the PVs, the "substrate modulation" concept
207 has even been opposed to the "anatomic isolation" principle.¹³ To address this question, Kuck et al
208 compared sinus rhythm maintenance after PV encirclement with strict conduction block or with
209 intentional residual gaps in a multicentric randomized trial, and demonstrated that the isolation strategy
210 was superior.¹⁴ Based on a more extended linear lesion set, our work not only found the same negative
211 impact of residual gaps – although unintentional in the present study – on recurrence, but also shed lights
212 on the specific role of their distribution. Hence, PVs gaps clearly favor the fibrillatory process with a
213 higher risk of recurrence in AF when present, and anatomic isthmuses gaps support a majority (60%) of
214 stable reentries mapped during second ablation procedure. Whether these stable ATs proceed from the
215 proarrhythmic effect of gaps or would occur without any line is still a matter of debate. We recently
216 showed that *de novo* creation of all three anatomic lines (mitral, cavotricuspid, roof) was required in >
217 80% of patients to treat the succession of circuits observed after a first procedure based on electrical
218 substrate ablation strategy without line creation.¹⁵ Although not closing this debate, the present data are

219 encouraging since clinical ATs found after a first procedure based on the Marshall-PLAN strategy
220 proved easy both to diagnose with ready mapping, and to treat by discrete touch-ups ablation. The
221 Marshall-PLAN can be viewed as a simplified version of the historical Maze III. In 1995, Cox et al
222 described their third iteration of atrial partition for persistent AF treatment.² With this approach, the
223 Mayo Clinic reported a sinus rhythm maintenance of 85% at 5 years.³ However, inability to replicate
224 these outstanding results in the EP laboratory raised the problem of the comparative durability of
225 standard ablation versus "cut-and-sew" technique. Although biased by the fact that we only reevaluated
226 patients having arrhythmia recurrence, the present work points out the poor durability of lines created
227 in the EP laboratory at first attempt. Data on the durability of LA partition are in fact relatively scarce.
228 In 2005, Gaita et al surgically treated persistent AF patients undergoing valve repair or replacement with
229 anatomic lines of block encircling the two antra and transecting the dome and mitral isthmuses.¹ They
230 reported an overall block durability of 65% during systematic electrophysiological study at 3-month. In
231 2017, Mujovic et al translated the same lesion set from the operatory room to the EP-laboratory with
232 mixed success.¹⁶ They found a much lower block durability of 28% only during systematic
233 electrophysiological study at 3-month. Of interest, both teams showed that delayed gaps were
234 significantly predictive of atrial arrhythmia recurrence within or after the blanking period. In the present
235 study, we found that recurrence rate was higher in case of incomplete lesion set at the end of first
236 procedure, that delayed gaps were almost universal during second procedure warranted by arrhythmia
237 recurrence, and that sinus rhythm maintenance was higher after closing these gaps. All together, these
238 findings highlight the importance of judging an anatomic lesion set once lines are definitely blocked, all
239 the more if block durability seems achievable at the cost of one repeat procedure. Although
240 disappointing at first glance, these delayed gaps constitute readily identifiable targets which improve
241 sinus rhythm maintenance once closed. In other words, one key benefit of a challenging but well-defined
242 lesion set from the start of first procedure is to facilitate the strategy adopted during repeat procedures.

243

244 **Improvement in linear conduction block**

245 Delayed gap despite acute block proves that both contiguity and transmural-ity of linear lesions are
246 difficult to maintain over time. By favoring close core lesion creation, 3D-mapping systems have helped
247 improve contiguity. However, the reason why lesion depth theoretically achieved with actual ablation
248 settings would not encompass atrial thickness reported by anatomists was not clear.^{5,17} In this respect,
249 fat insulating property may play a key role, as reflected by the recent shift we made in roof line
250 ablation.¹⁰ Observation of fat infiltration within the upper dome suggests that subepicardial layers may
251 be protected against radiofrequency at the level of the roof line. This led us to not only modify the
252 ablation strategy with an alternative floor line at the lower dome likely to be less infiltrated by fat, but
253 also to reappraise roof line block validation with criteria revealing unsuspected epicardial gaps. This
254 more practical transection of the dome where it is easier to achieve – be it with a roof line or a floor line
255 – recently proved effective in the acute phase. The present data further show that dome transection is
256 significantly more durable with this new strategy (*second leg*), instead of insisting on a challenging roof
257 line (*first leg*). Three reasons may explain why the *first leg* strategy for dome transection was less durable
258 than the *second leg* strategy despite similar acute success. First, the need for roof line touch-ups reflected
259 tissue refractoriness to radiofrequency with associated risk of reconnection. Second, validation criteria
260 facilitating the diagnosis of epicardial gap were not used yet. Third, extensive "touch-ups" ablation
261 below the roof line could disrupt dome activation and thus complicate the interpretation. The two latter
262 pitfalls suggest that a substantial amount of delayed gaps observed after the *first leg* strategy may just
263 have been unidentified acute gaps across roof lines wrongly considered blocked. This point is critical as
264 it may explain why the *first leg* strategy resulted in a higher rate of roof line deemed blocked at the end
265 of first procedure, but a higher rate of delayed gaps revealed by the use of the new validation criteria
266 during second procedure. Similar roof and floor lines durability found during *second leg* strategy does
267 not conflict recent report by Markman et al on rarer reconnection across the floor line.¹⁸ Indeed, they
268 systematically created the two lines since they aimed at a "box" isolation of the dome, whereas we did
269 not insist on a failed roof line and directly switched to a floor line as we aimed at single transection of
270 the dome. With our approach, the pretest probability for block durability *de facto* differed between the
271 two lines. The reason why the roof line would be more difficult to block than the floor line may be the

272 greater amount of fat infiltration at the higher portion of the dome.¹⁰ Of interest, difficulty encountered
273 in durable mitral line block may also proceed from fat infiltration within the complex architecture of the
274 mitral isthmus. In this respect, Valderrabano et al have made a critical step forward by performing VOM
275 ethanol infusion.¹⁹ Beyond its positive impact on sinus rhythm maintenance, this innovative technique
276 has been proved to decrease the rate of acute and delayed gaps across the mitral line, while meeting
277 safety principle.²⁰⁻²³ Similarly, the present data on the dome confirm that optimizing strategies in light
278 of anatomic considerations help increase block durability.

279

280 **Limitations**

281 First, this study is limited by its single-arm and non-randomized designed. However, consecutive
282 patients were prospectively enrolled, treated with a standardized ablation strategy with clear predefined
283 efficacy endpoints during follow-up. Second, reassessment of delayed gaps was not performed in a
284 systematic fashion for all 291 patients, limiting durability estimates to the subset of patients with atrial
285 arrhythmia recurrences.

286

287 **CONCLUSION**

288 Conduction gaps across a linear lesion set created for persistent AF treatment have an influence on both
289 the likelihood and the mode of arrhythmia recurrence. A second ablation procedure that targets and
290 closes these gaps improves sinus rhythm maintenance. Optimizing assessment modality and ablation
291 strategy of lines of block is critical to increase their durability.

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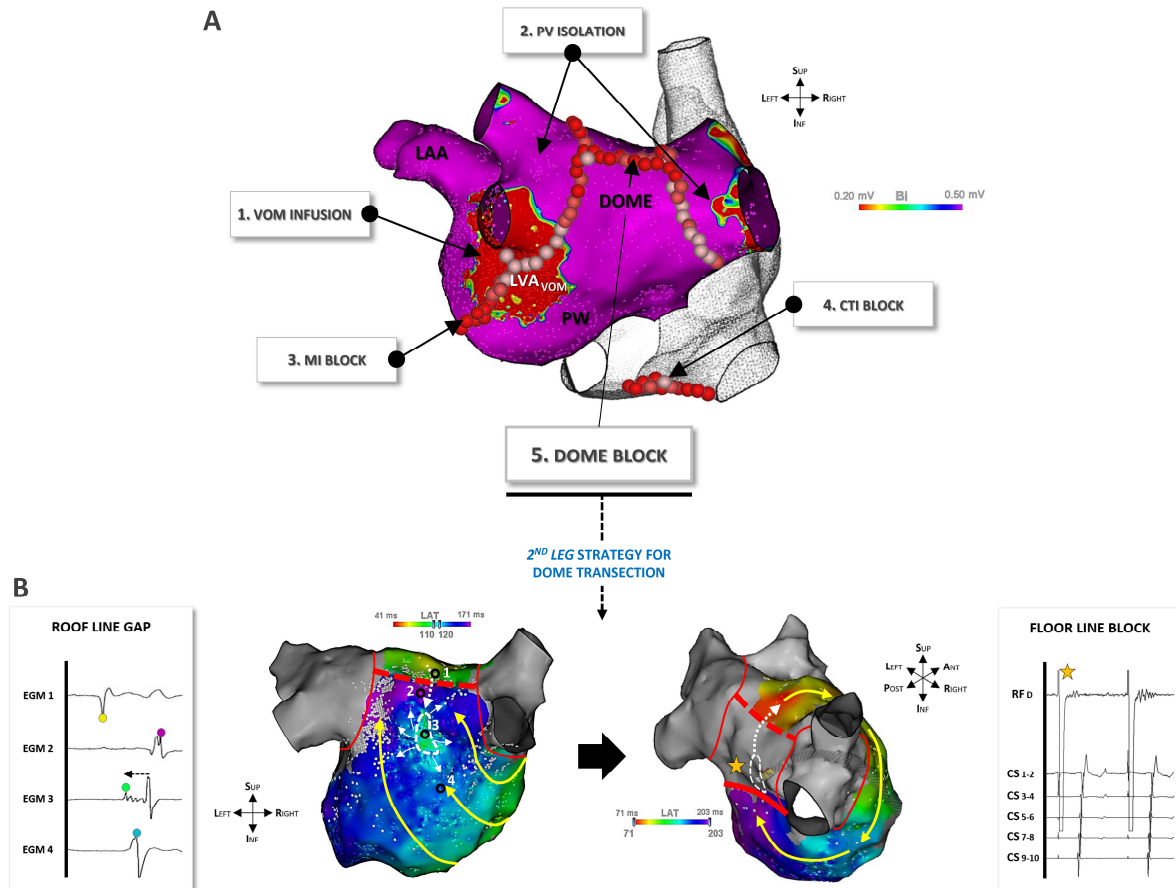
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404

405 **FIGURES**

406

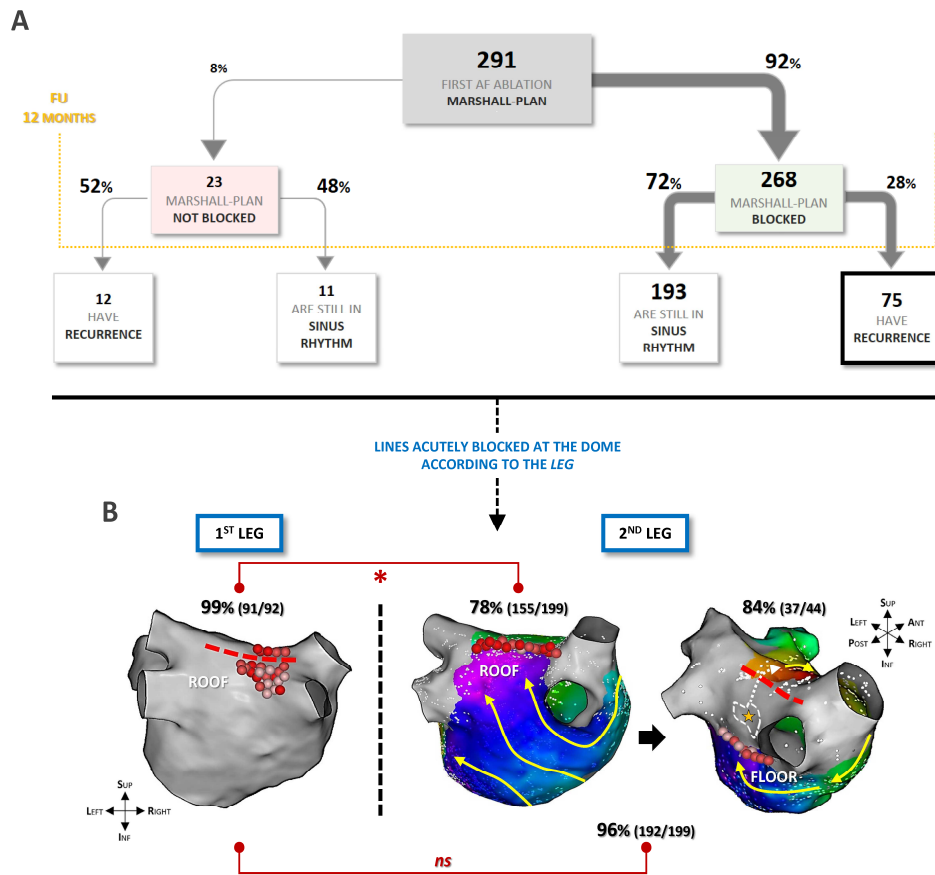


407

408 **Figure 1 - Marshall-PLAN lesion set**

409 **A:** Successive steps of the Marshall-PLAN are depicted on LA (voltage) and RA (mesh) maps shown
410 in posterior view. **B:** Specific focus on the *second leg* strategy for dome transection, with a representative
411 example of a failed roof line. The left panel shows high-density LA activation map during LAA pacing.
412 An epicardial gap (*dotted white arrow*) bypasses the roof line (*dashed red line*) via the SPB, resulting
413 in a focal dome activation while the endocardial activation (*yellow arrows*) courses around the right
414 PVs. Among four points of interest just above the line (1), just below the line (2), at the dome
415 breakthrough (3), and at the posterior wall (4), manual reannotation of the local activation time of point
416 3 to the earliest potential reveals (*dotted black arrow*) early activation of the SPB. The right panel shows
417 high-density LA activation map while pacing above the floor line (*solid red line*) in the same patient.

418 Unidirectional activation around the right PVs (*yellow arrows*) confirms that the floor line is blocked
419 and requires an epicardial bypass (*dotted white arrow*) of the roof line. This results in a delayed
420 "proximal-to-distal" activation of the CS. See reference 9 for further details. LA: left atrium; RA: right
421 atrium; LAA: left atrial appendage; SPB: septopulmonary bundle; VOM: vein of Marshall; PV:
422 pulmonary vein, MI: mitral isthmus; CTI: cavotricuspid isthmus; CS: coronary sinus; PW: posterior
423 wall.
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426 **Figure 2 - First procedure data**

427 Data of the 291 persistent AF patients who underwent their first ablation procedure based on the

428 Marshall-PLAN lesion set. Statistical comparisons are reported in red with an asterisk when significant,

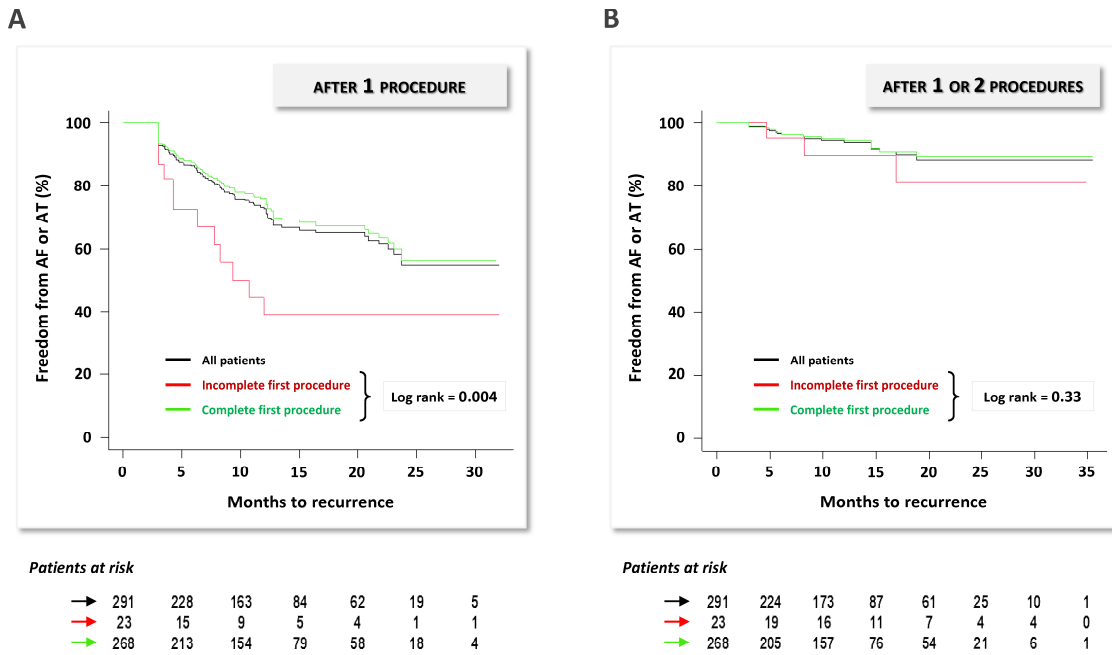
429 or with the acronym "ns" when not. **A:** They were classified according to the lesion set status at the end

430 of the procedure (complete or incomplete), and then followed for a mean of 12 months to evaluate

431 arrhythmia recurrence. **B:** Specific focus on dome transection. The rate of lines considered blocked is

432 reported according to the strategy used (*first leg* or *second leg*).

433



445

446 **Figure 4 - Sinus rhythm maintenance**

447 Kaplan-Meier event-free (no AF or AT) survival curves. Color code as follows: *green line* for the 268
 448 patients with complete lesion set at the end of first procedure, *red line* for the 23 patients with incomplete
 449 lesion set at the end of first procedure, and *black line* for all 291 patients. **A:** After 1 ablation procedure.

450 **B:** After 1 or 2 ablation procedures.

451

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455 **TABLE**

456 **Table 1.** Patient characteristics

Variable	Value
Age, <i>years</i>	64.1 ± 9.5
Male	226 (78)
Left ventricle ejection fraction, %	55.2 ± 11.4
Body mass index, <i>kg/m²</i>	28.4 ± 4.8
CHADS ₂ score	1.8 ± 1.3
Hypertension	149 (51)
Diabetes mellitus	32 (11)
Heart failure	57 (20)
Stroke	22 (8)

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