The Coronary Sinus Marshall Structure: from an Anatomical Ligament to an Arrhythmogenic Vein

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The original Marshall Plan was a foreign aid program of the United States to prevent the economic deterioration of Western European countries after the second world war, with a particular focus on Western Germany. The Marshall plan was launched in an historical speech by the Secretary of State, General George C. Marshall, on June 5, 1947 at Harvard University (1). Almost a century earlier, in 1850, the English surgeon John Marshall provided the description of a vestigial fold of connective tissue in the vicinity of the anterior coronary sinus venous system (2). While the postwar plan for foreign aid by George C. Marshall almost instantaneously achieved historical significance, the role of the invention by John Marshall took more than 150 years to become relevant in the clinical setting of cardiac arrhythmias. After experimental and clinical studies identified the arrhythmogenic potential of the ligament/vein of Marshall in different atrial arrhythmias (3-5), Valderrabano and co-workers first introduced in 2009 a systematic approach to target the

vein of Marshall (VOM) with ethanol infusion in order to induce a transmural necrosis in its neighboring, venous drained tissue (6). The Bordeaux Marshall plan for persistent atrial fibrillation (AF), implemented by Derval et al (7), provided an ablation approach consisting of VOM ethanol infusion combined with radiofrequency ablation for pulmonary vein isolation (PVI) and linear ablation at the mitral isthmus (including the coronary sinus, CS), left atrial (LA) roof and cavotricuspid isthmus. This strategy, based on systematically targeting anatomical structures rather than arrhythmia-related endpoints, achieved an impressive outcome with 89% of patients being free of arrhythmia recurrences after 1 year and up to 2 ablation procedures. However, the data need to be considered in the context that they derived from a single-center, single-cohort study (without a control group) performed by extremely experienced operators. It is again the credit of Valderrabano et al. (8) to provide high-quality data on VOM ethanol infusion in the setting of persistent AF: in a prospective, single-blinded, multi-center, randomized trial, the authors evaluated the effect of persistent AF ablation in conjunction with VOM ethanol infusion (VENUS trial). A large population of almost 350 patients with persistent AF (more than half of them with long-standing persistent AF) was randomized to undergo PVI plus atrial substrate ablation in conjunction with or without VOM ethanol infusion. Since a 15% failure rate at cannulating the VOM was expected, a 15% excess of patients randomized to the VOM group was designed per protocol. In contrast to the Bordeaux Marshall-Plan approach where a standardized AF ablation protocol was used, the strategy of persistent AF ablation beyond VOM ethanol infusion was left at the discretion of the operator including posterior wall isolation, mitral isthmus ablation and ablation of complex fractionated atrial electrograms. However, all patients underwent PVI. Freedom from atrial arrhythmias was higher in the VOM group (65% vs. 54% after multiple procedures).

The additional effect of VOM ablation can be explained by an enhanced atrial denervation, eradication of arrhythmogenic triggers, a higher rate of acute conduction block and lower rate of conduction recovery of the mitral isthmus (3, 8). However, the volume of atrial tissue (or even atrial mass, considering the transmurality of the lesion) and the distinct distribution of VOM ablation induced atrial low voltage areas may further beneficially impact long-term outcomes.

In the current issue of the journal, Kamakura and co-workers (9) provide a comprehensive analysis of the amount and distribution of low voltage atrial tissue induced exclusively by VOM ethanol infusion. In a total number of 114 patients undergoing de-novo ablation for persistent AF, a high-density CARTO map obtained by a multi-polar catheter (Pentaray, Biosense Webster) was created before and after the VOM procedure with a mean of more than 1.000 points. In all patients, VOM ethanol infusion was the first step of the procedure before any other ablation was performed. After the second map, the procedure was continued according to the Bordeaux Marshall plan approach with PVI, roof line, mitral-isthmus- and cavotricuspid isthmus ablation. With the aim to systematically describe the anatomical distribution of LOM ablation induced low voltage areas, the authors defined five different LA regions of which four were further subdivided, resulting in a total of 11 different segments mainly confined to the lateral and posterior LA. Interestingly, VOM ethanol infusion induced low voltage in almost all patients in two regions: the upper part of the mitral isthmus (PV site) and the anterior carina of the left PVs, thereby providing a distinct fingerprint of VOM ablation. However, an arborization with anastomosis to branches of posterior and roof veins was frequently observed, resulting in an expansion of low voltage into the respective areas in some but not all patients. Of note, the present study only comprised patients in whom a venous branch of the coronary sinus, angiographically considered to represent the VOM, was successfully cannulated. Of them, the LA appendage vein was actually treated inadvertently in three patients, however not resulting in LA appendage isolation in any of them. It is one of the most important findings of this study that successful VOM ethanol infusion in conjunction with radiofrequency ablation within the CS (in all patients) was able to achieve bidirectional block of the mitral isthmus in 97%, a result that virtually promise a guarantee of bidirectional block of the most challenging linear lesion in the human atria.

The strength of the presented study by Kamakura et al (9) is that it provides important new data on the distribution of lesion sets specifically induced by VOM ethanol infusion in a large cohort of patients with persistent AF. Moreover, the authors identified a distinct fingerprint lesion pattern of VOM ethanol infusion that is observed in almost all patients undergoing successful VOM ethanol infusion. Thus, it is important

to know what "ablation effect" on arrhythmias can actually be anticipated with this procedure since it adds another step of technical challenge to the complexity of persistent AF ablation. Nevertheless, whenever this fingerprint region needs to be treated in order to eliminate arrhythmogenic substrates of either AF or atrial tachycardias, successful VOM ethanol infusion obviously creates transmural lesions, evidenced by the highest rate of mitral isthmus block achievement ever reported. Furthermore, a higher long-term endurance of mitral isthmus block can be expected with VOM ablation since the most common part of mitral isthmus recovery was found to be located at the upper part of the line close to the LIPV (11), which represents the fingerprint area of VOM ethanol infusion.

The Bordeaux group again provides important new data and adds another piece to the puzzle elucidating the impact of VOM ethanol infusion on persistent AF ablation. However, the widespread clinical application of this procedure is still limited, not only because of its technical complexity. Therefore, some few aspects of the consequences of VOM ethanol infusion in the context of persistent AF ablation should be considered. First, the fingerprint area of VOM, or in other words, the upper mitral isthmus area anterior from the LIPV and posterior to the LA appendage, usually do not exhibit spontaneous or AF-induced low voltage areas (11). In contrast, the anterior LA is far more frequently affected by fibrotic alterations in persistent AF patients with the potential to represent an arrhythmogenic substrate of both, AF and atrial tachycardias (11). Thus, treating the anterior LA for arrhythmias in the presence of a complete mitral isthmus line after VOM ethanol infusion has a high risk to result in inadvertent LAA isolation, particularly in the presence of a complete roof block. Second, VOM ethanol infusion does not provide the avoidance of CS ablation with all its inherent risks. In the present study, all patients with bidirectional block required additional CS ablation since the VOM ethanol ablation area obviously not includes the musculature network of the CS itself. Third, the radiation exposure to the patient, especially when an additional CT scan is performed prior to the procedure in order to visualize the VOM, is markedly increased in a VOM procedure (8, 12). In our own clinical routine work, a persistent AF ablation procedure consisting of PVI and linear ablation at the LA anterior wall and roof habitually requires a mean of 2-3 minutes of fluoroscopy time (without pre-procedural imaging). And finally, VOM ethanol infusion is best performed as a four-hand procedure, especially in centers without high-volume experience in this approach. Again, the VOM ethanol infusion procedure is anything but a technically undemanding part of AF ablation, requiring experience in CS arborization variants as well as manual skills with a steerable sheath, angiography catheters, coronary guidewires and vascular balloon dilatation techniques.

Although VOM ethanol infusion appears to offer an attractive strategy to achieve transmural lesions at least in its fingerprint region, the above-mentioned aspects associated with the procedure claim appropriate consideration. Not surprisingly, persistent AF ablation yet remains a challenge to the clinical electrophysiologist, even in the aspect of selecting the most beneficial ablation procedure for the individual patient. However, having a fingerprint lesion pattern of VOM ethanol infusion, this new information can help to guide the decision to either start persistent AF substrate ablation with the ethanol syringe or a RF ablation catheter.

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