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Editorial

Pulmonary Vein Stenosis After Ablation: The Difference Between Clinical Symptoms and Imaging Findings, and the Importance of Definitions in This Context

Estenosis de vena pulmonar tras ablación: la distancia entre la clínica y los hallazgos de imagen y la importancia de las palabras en este contexto

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Pulmonary vein (PV) stenosis is a well-known complication of invasive therapy for atrial fibrillation, informally known as "PV ablation". This complication was detected in the early years after the introduction of the technique.[1] Pulmonary vein ablation was developed from the pathophysiological finding in some patients with paroxysmal atrial fibrillation that paroxysmal arrhythmias are triggered by high frequency electrical discharges.[2] This focal activity originates in striated muscle bands or sleeves in the last few centimeters before the PVs open into the left atrium and are connected to the latter through electrical excitation. Originally, cardiologists tried to ablate this electrical activity at the originating foci inside the PV.[2,3] This procedure resulted in a high incidence of PV stenosis, probably secondary to tissue retraction from the ablation site lesion.[3] In view of this common complication, together with the finding that arrhythmia mechanisms may also originate in the PV antrum, beyond the tubular portion of the PV,[4] the ablation approach was then changed with the aim of achieving electrical isolation of the PV by performing antral ablation,[5] thus isolating the PV from a distance. The wide diameter of the antrum prevents PV stenosis, even in the presence of scar retraction at the ablation sites. The adoption of this new ablation approach has drastically decreased symptomatic PV stenosis.[6]

However, there are still several lingering reasons for concern: *a)* the lack of controlled studies comparing different ablation approaches; *b)* some areas of the PV, such as the raphe that separates the left PVs from the left atrial appendage, make it impossible to perform PV ablation from a distance; *c)* the esophagus sometimes lies in close proximity to PVs on one side, and ablation has to be performed on the PV itself to avoid damaging the esophagus, and *d)* PV stenosis initially appeared to be confined to radiofrequency energy but has since been described with other forms of energy, suggesting that this complication can also occur with other ablation techniques.[7,8]

We therefore welcome any studies that investigate this problem rigorously and systematically and provide a more in-depth understanding of the topic. One such study, by Martín-Garre et al,[9] was published recently in *Revista Española de Cardiología*.

The study enrolled 80 consecutive patients with symptomatic, paroxysmal or persistent atrial fibrillation refractory to pharmacological treatment, who underwent radiofrequency PV ablation. All patients had a magnetic resonance imaging study before ablation and 3 months postprocedure. They all received targeted PV ostia ablation to achieve a bidirectional PV conduction block. Superoinferior and anteroposterior diameters and the cross-sectional area of the ostia were calculated from the morphological PV magnetic resonance imaging study. These PV measurements were compared at baseline and 3 months postablation to determine the incidence of stenosis. Out of a total of 322 analyzed veins, stenosis was observed in 24.2% (78 veins). Stenosis was mild in 84.6% (66 veins), moderate in 14.1% (11 veins), and severe in 1.3% (1 vein).[9]

Two variables showed a significant association with a higher risk of stenosis: the ostial cross-sectional area (odds ratio = 1.009; 95% confidence interval, 1.004-1.015; $P < .001$) and left inferior PV (odds ratio = 3.089; 95% confidence interval, 1.229-7.757; $P = .02$). Age (odds ratio = 1.033; 95% confidence interval, 0.998-1.068; $P = .06$) showed only a tendency to statistically significant association.[9]

We can conclude from this study that there is a high incidence of some degree of stenosis after PV ablation (24.4%), but that the incidence of severe stenosis is very low (1.3%) and that symptomatic stenosis is negligible (not a single case in 80 patients). It also appears that the risk of stenosis is higher in larger PVs and with left inferior PV involvement. Age is associated with a higher risk but does not attain statistical significance.

However, we believe that these conclusions should be qualified in the light of the following aspects:

1. Definition of PV stenosis: the most widely-accepted definition, as used in the consensus statement on ablation in atrial fibrillation,[10] is based on PV diameter reduction. Stenosis is categorized as mild if the reduction is $< 50\%$, moderate between 50% and 70%, and severe if it is $\geq 70\%$. However,

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Martin-Garre et al[9] used an absolute value as their threshold for PV stenosis, which was twice the standard deviation of intraobserver and interobserver variability. Since the standard deviation of these variabilities was 1.625 mm, PV stenosis was defined as any reduction in the PV diameter > 3.25 mm. Although this definition is flawless at a methodological level (any difference that is not due to a measurement error is due to the intervention itself), it is hard to compare the findings of this study with others, and, furthermore, it is far removed from clinical practice. The study has a very low rate of interobserver variability (the intraclass correlation coefficient was 0.96 for intraobserver reproducibility; standard deviation, 1.625 mm). This low variability means that small reductions in PV diameter were detected by the observer and defined as stenosis, leading to a high incidence (24.2%). This is not a criticism at all, because it shows that the experienced observers were able to detect very mild stenosis. However, incidence increases. Furthermore, to classify stenosis severity, Martín-Garre et al[9] use the ostial cross-sectional area, defining stenosis as mild, moderate, or severe by an area reduction of < 50%, 50% to 70% or > 70%, respectively. Again, although a classification by area reduction instead of diameter may be more correct (because PV ostia are elliptical), classification by area is not widely used and it exaggerates stenosis severity. For example, a 60% reduction in diameter (moderate) may be equivalent to an 84% reduction in area (severe). In fact, the single case of severe stenosis in this study could actually be classified as moderate, using Figure 3 in the article for reference.[9]

2. Time of measurement: since PV stenosis is a late-onset phenomenon after ablation, the time between ablation and the second magnetic resonance study (median, 95 days) may be too short, because stenosis can appear after 3 months. However, a study by Saad et al[6] found that only 4% of cases progressed from mild PV stenosis diagnosed at 3.5 months (7.7% of patients) to more severe stenosis at 6 and 12 months postablation. Only patients with some evidence of stenosis at 3.5 months showed stenosis later. Therefore, we believe that the timing of the second magnetic resonance imaging study was correct, and it is unlikely that more cases of stenosis or greater severity of observed cases would have been found if the second study had been performed later.
3. Adjustment of morphometric measurements for body surface area: none of the left atrium or PV measurements mentions an adjustment for body surface area. The study found larger ostia in men than in women ($P = .002$), as well as in patients with hypertension ($P = .05$), structural heart disease ($P = .03$), and with persistent atrial fibrillation ($P < .001$). The multivariable analysis showed that only left atrium size was an independent predictor of PV size. The authors did not mention body surface area as a confounding factor in the association between larger ostia in men than in women or in the association between left atrium size and PV ostia size.
4. Technical aspects of ablation: the study analyzed only clinical and anatomical characteristics as predictors of PV stenosis. It would have been interesting to analyze technical factors in the ablation procedure, such as the distance between lesions and the ostium, radiofrequency time and intensity, and operator experience. These variables have been analyzed in previous studies,[6,11] and not only are they determinants for stenosis risk, but they also have the advantage that they can be modified to prevent stenosis.
5. Stenosis predictors: it is interesting that, in general, veins with a larger diameter are at a higher risk of stenosis, but the left inferior PV, which has a smaller area than the others ($P < .001$), is the PV with the highest incidence of stenosis. The authors conclude that the elliptical shape of this vein may explain why more extensive lesions occur during ablation. Another reason could be that ablation is performed closer to the left inferior PV to avoid damaging the esophagus, and therefore the left inferior PV is a common location. One study analyzed esophageal temperature,[12] but Martín-Garre et al did not analyze this variable. The highest incidence of PV stenosis found in the left inferior PV in this study differs slightly from previous studies, which found a similar incidence in the left and right superior, and left inferior PVs.[13]
6. Number of stenosed PVs: this study does not mention the number of stenosed PVs per patient. In the event that 1 patient had several stenosed veins, this finding could suggest an individual susceptibility to PV stenosis after ablation, regardless of the PV diameter or anatomical position. The study by Saad et al[6] described a median of 2 stenosed veins per patient (range, 1–3) out of a total of 95 patients with PV stenosis.

Can we conclude that PV stenosis is a common clinical complication of PV ablation? Not at all. In the "Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation",[14] data were collected on 16 300 patients treated with PV ablation between 2003 and 2006. The survey found a 0.29% incidence of symptomatic, severe PV stenosis in these patients. One study of 500 consecutive patients at a single center found no cases at all of symptomatic PV stenosis.[15]

In view of the above, how can we explain the high incidence of PV stenosis reported by Martín-Garre et al? The key probably lies in the clinical insignificance of small or even moderate luminal narrowing, which will often be observed in meticulous and rigorous studies. Larger studies that were conducted before the era of PV ablation in the antrum (when the incidence of stenosis was higher) reported that some, but not all, patients with severe stenosis were symptomatic, especially if more than 1 PV was affected. Patients with mild or moderate stenosis remained asymptomatic and stenosis did not progress, suggesting that only severe stenosis is of clinical significance.[6] In short, there is a marked difference between clinical symptoms and findings in imaging studies. This explains why imaging studies are not systematically performed when patients are followed up after PV ablation,[10] and why they are restricted to patients with suspicious symptoms and those who need to undergo a second ablation procedure, despite there being an unknown number of patients with undetected mild and moderate PV stenosis.[15]

Finally, what information should we give our patients? The word stenosis describes the narrowing of a vessel, but it is generally understood to mean a clinical problem. The size of this problem is not clear, but the patient understands there is a problem, which might get worse. Since mild or moderate narrowing of PV lumen is unrelated to these connotations, we would prefer to restrict the use of the word stenosis to clinically significant scenarios and apply this definition when we inform our patients. Therefore, we should inform patients that PV stenosis is a possible and serious complication of PV ablation, but that current techniques mean that the incidence of PV stenosis is very low, below 0.5%.

We congratulate Martín-Garre and her colleagues for the systematic, millimetric method that they used to study the outcome of their clinical practice. Studies like this help us to gauge the quality of our daily work. We should also congratulate the authors for registering not a single case of symptomatic, severe PV stenosis in 80 consecutive cases. Fortunately, their findings confirm that PV ablation now carries a very low risk of symptomatic PV stenosis.

CONFLICTS OF INTEREST

None declared.

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