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Research Article

A Model Incorporating Left Ventricular Impedance Index may be Explanatory for Late Pulmonary Vein Isolation Failure

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Abstract

Objective: To study the influence of a flow-based Impedance Index to attempt to explain the persistent late failure rate of Pulmonary Vein Isolation (PVI) in patients with Atrial Fibrillation (AF).

Background: We recently described a flow-based Impedance Index for left ventricular ejection into the aorta and noted an association with Major Adverse Cardiovascular Event Rate (MACE). While the Impedance Index is not routinely measured in PVI patients it approximates to measures derivable from the left ventricular ejection fraction (EF). We sought to assess the Impedance Index's influence on PVI failure rate in combination with indices of left atrial size.

Methods: In AF patients (n=100) undergoing a Cardiovascular Magnetic Resonance (CMR) imaging examination prior to undergoing PVI we assessed baseline characteristics for their influence on the PVI failure rate at 3-12 months. Uni-variable and multi-variable binary logistic models were performed to find predictors of the PVI failure rate at follow-up.

Results: All patients underwent PVI and CMR imaging. A total of 26 (26%) patients had late AF recurrence at 3-12 months follow-up. Multi-variable models that predicted PVI failure were: 1) the baseline Impedance Index and LA volume index ($p<0.05$) and 2) the baseline Impedance Index and the degree of mitral valve regurgitation (MR) ($p<0.001$). While the Impedance Index was derived from EF, EF per se was not a predictor of PVI failure ($p=0.28$).

Conclusions: We have provided evidence of the influence of a flow-based Impedance Index on the PVI late failure rate which is significant and remains explanatory when adjusting for measures of atrial size, MR grade and LA volume index. Direct measure of the Impedance Index was not available here and was derived from EF measures. Further work is needed to directly measure the Impedance Index in a PVI population and determine the mechanism for the influence on PVI failure, which may lead to modification of the ablation procedure to improve the success rate.

Keywords: Atrial fibrillation, Cardiovascular magnetic resonance imaging, Impedance, Pulmonary vein isolation

Background

Pulmonary Vein Isolation (PVI) is currently widely used for treating patients with Atrial Fibrillation (AF) who are drug and\or cardioversion resistant [1,2]. The procedure is predicated on the belief that the pulmonary veins are the initiating source of electrical activity that disrupts normal sinus rhythm [3]. The procedure usually uses radiofrequency or cryo-energy to electrically isolate the Left Atrium (LA) from the pulmonary veins. Much research has been conducted on the procedure to improve its implementation and achieve the desired outcome of preventing recurrence. However, a high rate of recurrence remains problematic following PVI, and typically multiple procedures may be required to restore Normal Sinus Rhythm (NSR) [4,5].

Recurrence is usually classified according to the time window at which it manifests. Early recurrence is classified as being within the first three months after ablation. This is usually regarded as a ′blanking period during which ultimate success is not evaluated. It is typically explained by the ongoing active inflammatory process [6]. Late recurrence is classified as being 3-12 months after the procedure and usually understood in terms of healing and reconnection of the previously disconnected atrial tissue which allows the abnormal electrical activity from the pulmonary veins to activate systolic contraction. The current understanding is that gaps in the line of ablation may exist or there was a failure to produce completely transmural lesions during the procedure. Both of these causes can go undetected at the time of the initial procedure. However, reconnection could theoretically also result from tissue remodeling or via additional conduits such as the ligament of Marshall [7]. Very late recurrence after one-year post procedure is thought to be related

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to age, gender, hypertension, high cholesterol, diabetes, very large LA (>45mm^2), AF type (persistent) and other well-recognized patient and cardiac conditions [8]. For both late and very late recurrence, many predictors were studied, mainly addressing the LA conditions and volumetrics, Mitral Regurgitation (MR), early recurrence, general patient factors such as obesity and metabolic syndrome and procedural characteristics including duration and technique [9,10]. To date, however, no satisfactory explanation has been advanced despite much effort from multiple investigations globally. Thus, an enhanced rationale for the mechanism of PVI failure would have natural value and potentially point towards an ablation-based solution.

Despite the pulmonary veins being the main source of rhythm disruption and the main target of the procedure [3], relatively few studies have focused on the pulmonary veins themselves as a predictor of recurrence. Recently we presented results of a systematic study of the dimensions of the PVs pre and post procedure and related them to the late failure rate of the procedure [11]. However, during that investigation the factors studied did not reveal any significant relation to outcome. In other independent work from our lab, we identified an Impedance Index that describes the degree of matching between left ventricular ejection and the aortic outflow tract [12]. This flow-based Impedance Index was derived from aortic flow characteristics and naturally relates to the ejection fraction, since EF is also a measure of efficiency. However, unlike EF, the flow-based Impedance Index exhibited a distinct periodic variation over the EF axis with a periodicity of approximately 10 EF points. Thus, unlike the uniformly varying EF variable, the Impedance Index varies in a predictable cyclic manner. While not an exact match, the Impedance Index approximates to the integer value of the EF value when discarding the EF decade (e.g. for an EF of 46 the Impedance index is 6, and similarly for an EF of 56, the Impedance Index is 6). Shoucri has shown that EF does not uniquely define a patient's hemodynamic condition, but that it is often used as a surrogate, as is the case here [13]. In the original description of this phenomenon we showed that the occurrence of MACE exhibited a periodic variation with EF that was consistent with the Impedance Index description, even for patients with EF in the normal range. Here we investigate whether this phenomenon influences the late success rate of pulmonary vein isolation for treatment of atrial fibrillation patients.

Hypothesis

We hypothesize that late recurrence of AF after the PVI procedure is influenced by indices of LA size and the flow-based Impedance Index.

Methods

The study was approved by the IRB (No. 4889, Title "Assessment of pulmonary vein anatomy, left atrial appendage anatomy, left atrial thrombus left and right atrial metrics, left and right ventricular metrics in patients with atrial fibrillation pre-and post-pulmonary vein isolation and surgical Maze procedures using cardiovascular magnetic resonance (CMR) imaging). The study population was retrospectively selected from all patients undergoing PVI who received a CMR imaging study pre and post PVI between the dates of July 2007 to September 2011. Of the 123 patients in our database, 100 (81%) had follow-up data at the late period between 3 and 12 months. Follow-up consisted of two 24hour Holter Monitors, and failure was the occurrence of at least one documented episode of AF between 3 and 12 months, either on Holter or EKG. The CMR protocol was previously described; in brief the acquisition consisted of two long-axis cine images of the LV obtained with steady-state free precession imaging and a 3D angiographic view of the left atrium with gadolinium contrast [11]. However, the study protocol for pre and post PVI CMR scans did not include either the aortic flow measurements required to calculate the flow-based Impedance Index or the contiguous short axis set from which LVEF is calculated via the classic MRI technique using Simpson`s rule. We derived an LVEF index using systolic to diastolic changes in long axis LV diameters and major axis (Quinones Equation) [14].

$$\left(LVEF = K + 100\frac{LVEDD^2 - LVESD^2}{LVEDD^2}\right) \text{[eq-1]}$$

Where LV is the left ventricle, EDD is end diastolic dimension, ESD is end systolic dimension, and K is a correction for apical contraction (+10% Normal apex; +5% Hypokinetic apex, +0% Akinetic apex, -5% Dyskinetic apex and -10% Apical aneurysm). Here, the pre procedure Impedance Index was taken as the value of EF when discarding the decade of EF (e.g. an EF of 56 becomes an Impedance Index of 6). This resulted in an Impedance Index ranging from 0 to 9. To reduce the influence of noise in the analysis we formed a Reduced Impedance Index (RII) by grouping values as five pairs (9 and 0 = RII 0, 1 and 2 = RII 1, etc.). Note that Impedance Index values 9 and 0 are adjacent due to the cyclic nature of the Index. Additionally, for graphical illustration purposes we also formed a Reduced Impedance Cycle, approximating three equal size groups (9, 0, 1 = 0; 2, 3, 4 = 1 and 5, 6, 7, 8, = 2). A variable representing EF decade was formed (e.g. an EF of 56 becomes EF decade 50). The degree of mitral valve regurgitation (MR) was qualitatively assessed from the two and four chamber views, and graded as absent, mild, moderate or severe (0-3, respectively). The LA volume was measured from the 3D angiographic data [11,15] and the index formed by dividing by body surface area. The recurrence of late PVI was coded as 0 or 1 and binary logistic regression modeling was performed to identify individual and combinations of variables that were predictive of the PVI failure rate, with $p<0.05$ being the level of significance for inclusion of variables in each model.

Results

All 100 patients with AF and follow-up data (71% male) successfully underwent PVI with 74 (74%) responders and 26 (26%) non responders at follow-up. A total of 100 LA dimensions and volume were successfully measured and the degree of MR was evaluable in 80 patients (80%). Demographic data including age, BSA and antiarrhythmic therapies were similar between the groups, Table 1.

When entered into a uni-variable binary logistic regression model, the Reduced Impedance Cycle was found to be a significant predictor ($p<0.05$) with a negative coefficient, indicating that as the Reduced Impedance Cycle increased, the failure rate decreased. The observed PVI failure rate resolved along the Reduced Impedance Index axis is shown in Figure 1. The degree of MR pre PVI was also a significant uni-variable predictor ($p<0.01$), with failure rate

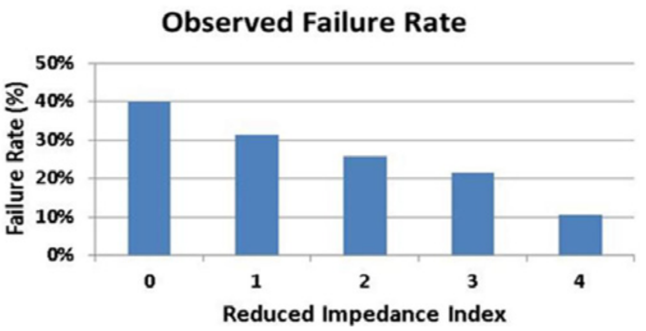

Figure 1: The observed PVI failure rate organized by the Reduced Impedance Index (i.e. 5 groups formed by combining two adjacent Impedance Index values). Binary logistic regression predication modeling of the PVI failure rate organized by the Reduced Impedance Index was significant ($p<0.05$)

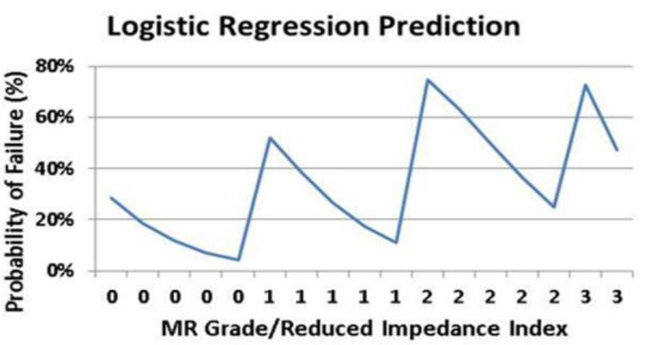

Figure 2: Binary logistic regression predication of PVI failure rate organized by mitral valve regurgitation (0 to 3), with the Reduced Impedance Index varying from 0 to 4 for each MR grade (values not shown).

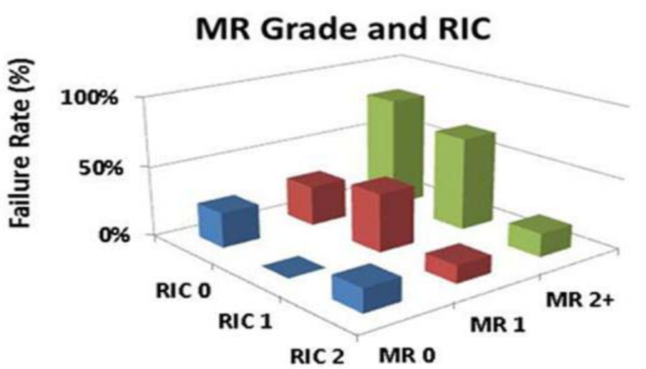

Figure 3: The PVI failure rate plotted against mitral regurgitation (MR) grade, with 2+ indicating grade 2 and above are combined, vs. the Reduced Impedance Cycle (RIC) (grouped into approximate to three equal groups).

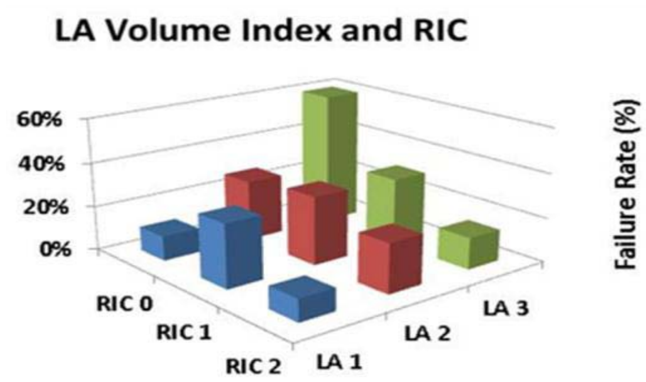

Figure 4: The PVI failure rate plotted against left atrial (LA) volume index (split into approximately equal groups ranging from LA 1 at the lower range to LA 3 at the upper range), vs. the Reduced Impedance Cycle (also grouped into approximate to three equal groups).

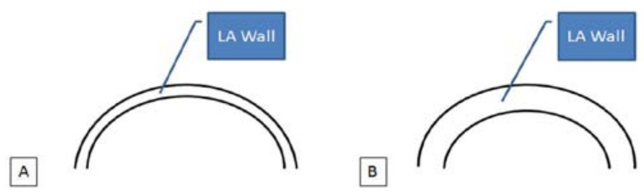

Figure 5: Hypothetical representation of the left atrial (LA) wall thickness: Idealized depiction of A) Left atria in Impedance Index position 0, exhibiting high stretch correlating with more Afib recurrence. B) Left atria in Impedance Index position 9 exhibiting low stretch correlating with less Afib recurrence.

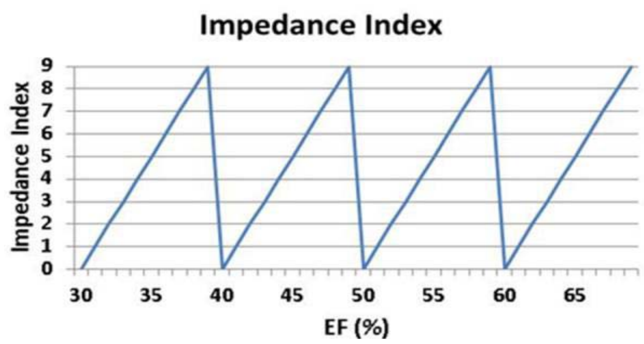

Figure 6: An idealized depiction of the cyclic nature of the Impedance Index over the ejection fraction (EF) axis. Note the sudden discontinuity of the Impedance Index at each cycle repeat point.

increasing with increasing MR degree as expected. Other variables that did not reach significance in uni-variable modeling included EF decade, which strongly trended towards significance ($p=0.07$), LA volume index, which trended towards significance ($p=0.1$) while LVEF was not significant and did not trend ($p=0.28$). Of interest the model coefficient for EF decade was positive, indicating that as EF decade increased, the failure rate also increased. Two multi-variable models were formed that predicted PVI failure rate. The model with the higher level of significance ($p<0.01$) incorporated the degree of MR and the Reduced Impedance Index, with predictive equation

(Failure Rate = -0.92 – 0.55 RII + 1.001 * MR grade pre) [eq-2]

The second model, with lower significance ($p<0.05$), incorporated the LA volume index and the Reduced Impedance Cycle, with predictive equation

(Failure Rate = -1.77 – 0.44 RII + 0.013 * LA vol index pre) [eq-3]

The effect size for each variable was derived from odds ratio multiplied by the range of each variable in this data set, Table 2. The model predicted failure rate for MR grade and Reduce Impedance Index are shown in Figure 2. A graphical representation of the observed PVI failure rate for MR and the Reduced Impedance Cycle

Table 1: Base line characteristics.

Variable	Full population	Responders	Non-responders	P value R vs. NR
Age (years) (mean ± SD)	58.8±19.1	58.9±9.2	58.3±9.8	0.77
Weight (lb) (mean ± SD)	212.9±94	214±36.8	209.4±40.2	0.59
Height (inches) (mean ± SD)	69.6±11.3	69.6±4.1	69.5±4.0	0.91
Body surface area (m2) (mean ± SD)	2.2±0.7	2.2±0.2	2.1±0.2	0.59
Males (%)	71	73	65	0.5
DM (%)	14	16.2	7.7	0.3
HTN (%)	49	48.6	50	0.9
Chronic chest diseases (OSAS, asthma, COPD) (%)	18	16.2	23	0.3
Dyslipidemia (%)	41	40.5	42.3	0.8
Thyroid disease (hyper & hypo) (%)	13	10.8	19.2	0.7
Persistent AF (%)	52	52.7	50	0.8
Paroxysmal AF (%)	48	47.3	50	
Mitral regurgitation: Grade:				
0 (none)%	45	53	23	0.01
1 (mild)%	34	33	36	0.76
2 (moderate)%	18	12	32	0.03
3 (severe)%	3	2	9	0.12
LA volume index:	105±34	61±18	67±18	0.11

DM, diabetes mellitus; HTN, hypertension; OSAS, obstructive sleep apnea syndrome; COPD, chronic obstructive airway disease; AF, atrial fibrillation; LA, left atrium.

Table 2: Binary logistic regression model parameters.

Model	OR (95% CI)	Effect Size	P value
MR & RII			
MR	2.72 (1.42-5.21)	5.16	0.002
RII	0.58 (0.37-0.90)	2.9	0.02
LAi & RII			0.01
LAi	1.01 (1.000-1.02)	2.62	0.049
RII	0.64 (0.45-0.92)	2.19	0.02

Summary parameters for multi-variable models of PVI failure rate, where OR is odds ratio, Effect Size is the OR multiplied by the range of the variable, MR is mitral regurgitation grade, RII is the Reduced Impedance Index, and LAi is the left atrial index.

is show in Figure 3, and a similar plot of observed failure rate for the LA volume index and Reduced Impedance Cycle in Figure 4.

Discussion

It was previously appreciated that increasingly higher failure rates of PVI are associated with increasing severity of mitral valve regurgitation and higher LA volume index values [16]. The unique finding here is that a recently described Impedance Index adds to the predictive value of each of these established variables. While not directly measured in this cohort, the Impedance Index approximately follows the EF integer values within each EF decade, and is thus cyclic over multiple EF decades. This formed the motivation to approximate the Impedance Index from measures of EF.

In the literature, EF was not generally found to show a significant effect on AF ablation outcomes. A meta-analysis published in 2018 [17] investigating the relationship between EF and AF recurrence showed no direct relationship following catheter ablation. It was concluded that this lack of association was possibly because of publication bias, and further studies should be performed to explore the mechanisms underlying AF recurrence. Here we separately analyzed the influence of two EF components 1) EF decade and 2) EF integer when discarding EF decade, with the latter approximating to the Impedance Index based on our prior reported work [12]. In the binary logistic regression model, EF decade strongly trended to predict failure rate (p=0.07) and the model coefficient was positive, indicating that for increasing decade of EF the failure rate increased. In contrast, in the binary logistic model of Reduced Impedance Index the coefficient was negative, indicating that for increasing Reduced Impedance Index the failure decreased, approximately ranging from 40% to 10% over the full range of Impedance Index, Figure 1. Thus, the competing influences of increasing EF decade and increasing Impedance Index within each decade tend to cancel each other's influence on PVI failure rate. Consequently, when linearly ordering data by EF, its influence on the PVI failure rate showed no systematic relationship. Thus, our data is in agreement with the literature that consistently indicates the lack of predictive value of EF. Prior to the introduction of the flow-based Impedance Index there would have been no expectation of counter influences of EF components, and thus it was unlikely to be investigated previously.

The electrical reconnection between the LA and the pulmonary veins is currently the most accepted explanation for late recurrence of AF. Despite advancements in ablation technology such as contact force sensing and cryoballoon technology, electrical reconnection is frequently observed [18]. Recently, Nery et al analyzed the relationship between PV reconnection and freedom from AF in a meta-analysis that included studies using radiofrequency ablation, cryoballoon ablation, and laser balloon ablation [19]. Among patients with and without AF recurrence, 86% and 59% had at least 1 PV reconnection, respectively. The average follow-up period of studies included in this meta-analysis was 8±10 months and broadly corresponds to the late and very late follow-up period. Beyond adding to the prognostic value of the likelihood of PVI failure, knowledge of the Impedance Index may indicate the nature of the ablation failure mode, and ultimately may allow changes to be made to the ablation treatment based on knowledge of the Impedance Index. In the description of the flow-based Impedance index we noted that over multiple patients, as the Impedance Index decreased, the aortic diameter progressively increased. We speculate that these cyclic changes in aortic diameter may also be experienced by other cardiovascular system structures, including the left atrium. In the event that the origin of these changes is related to the degree of stretch of the cardiovascular structures, it is consistent with the atria being in a high stretch state at the lowest level of Impedance Index and in a low stretch state at the upper extent of the Impedance Index, Figure 5. A higher stretch condition is associated with a high propensity for AF [20]. Further, we demonstrated that the LA volume index and Reduced Impedance Index formed a significant model of failure rate. The interpretation is that the "stretch" component is independent of the "natural" LA volume, Figure 4 and Table 2. While not significant here, we anticipate that within each grade of MR severity (equation 2), differentiation would be achieved over the LA volume index and Impedance Index axes (equation 3), with the hierarchy in use of formulas being MR grade followed by LA volume index. Further studies are required to verify if this is the case and whether increasing the power or duration in proportion to the Impedance Index would be more effective in safely producing a more consistent transmural scarring.

Here we showed that severity of MR was highly predictive of the failure rate, Figure 2. From Table 2 we see that the for each grade change of MR severity the failure rate increases by a factor of 2.7, while for each increase in Reduced Impedance Index the failure rate decreases by a factor of 1.7 (inverse of the OR). Thus, within each MR severity grade the failure rate over the full range of Impedance Index varies by a factor of 2.9. As an example of the implications of this, consider that patients with MR grade 0 at the lowest Impedance Index value will have a comparable expected failure rate to patients with MR grade 2 at the highest Impedance Index value, Figure 2. While the degree of MR that the patient presents with is generally beyond the control of the physician, if the PVI procedure was conducted such that the influence of the Impedance Index was effectively neutralized, the overall failure rate could be dramatically reduced, even for patients with severe MR.

Research is ongoing into the ideal duration and power of Radiofrequency (RF) ablation, with investigations incorporating approaches such as a short duration and high power or a long duration with low power to achieve the best outcome with the lowest complication rate and shortest procedural times [21,22]. Here we demonstrated the influence of an index of LV-aortic impedance, using an abstraction of EF employed as a surrogate for the Impedance Index. Ideally the flow-based Index would be directly measured from the flow conditions at the aortic outflow tract. These direct measurements are expected to more strongly represent the cyclic influence of the Impedance Index. However, if they are to be used to guide the PVI procedure the accuracy of measuring the Impedance Index would have to be approximately an order of magnitude better than current methods of measuring LVEF. There are two features of the flow-based Impedance index that may provide the necessary accuracy: 1) While the Impedance Index is periodic over EF, it does not smoothly vary over the axis; instead the Impedance Index is strikingly discontinuous at the repeat points, Figure 6. For example, as the Impedance Index approaches its lowest value at one end of a cycle, it suddenly transitions to its highest value in the adjacent cycle. Thus, unlike smoothly varying physiologic variables, identifying the beginning and end of each Impedance Index cycle is unambiguous. A physiologic reason for this is that a key component of the Impedance Index is the average aortic blood flow velocity. At the low end of the Impedance Index cycle, the average velocity approaches zero, and physiologically cannot go below this value. Thus, a yet to be determined change takes place in the cardiovascular system that transitions the system to the next cycle, corresponding to the highest Impedance Index value, with the associated high aortic blood flow velocities.

The search for refined or new approaches to improve success rates in performing PVI has progressed over many years with improvements in mapping and ablation technique being realized. However, the persistent high failure rate indicates that a new paradigm may be needed to better direct these advances. For many years, LVEF, being a measure of ventricular-vascular coupling, was regarded as a key physiologic variable to guide therapies, and currently, thresholds of LVEF are regarded as being the main guidance to administering certain therapies. However, the value of LVEF in guiding therapies has been eroded as increasingly; some diseases show no real relationship with EF [23,24]. We note that the flow-based Impedance Index is directly measured at the interface between the LV and the arterial system and thus may be of primary importance. In contrast, LVEF is measured remotely from the aorta and only directly assesses one component of the system. Here we showed that even a crude derivation of the Impedance Index from EF had a major influence on the PVI failure rate, Figure 1. Thus, the intuition that impedance is a key variable is likely correct, but the underlying periodic nature of impedance was not previously recognized. Further investigations are needed to determine if the Impedance Index can be measured with sufficient accuracy to not just better prognosticate, but to potentially guide conduct of the ablation approaches to achieve better outcomes.

Limitations

A number of limitations are noted. As stated, the Impedance Index was not directly measured, but only approximated from the EF. The flow data required to calculate the Impedance Index can be obtained from a single view through the ascending aorta, but currently, this is not routinely performed in patients being assess for PVI, although it adds no more than a few minutes to the conventional pre procedural cardiac MRI examination. Advances in performing PVI procedures have been realized since the data for this series was obtained. However, we note that the late failure rate remains high despite these recent advances. It remains a speculation that the observed changes in aortic diameter with Impedance Index are also experienced by the left atrium. It is possible that some other phenomena are responsible for the variation in PVI failure rate. It is possible that the PVI procedure cannot be effectively guided by knowledge of the Impedance Index, and thus further work is needed to determine if this is the case. Here, EF was measured from long-axis CMR images, as opposed to the more accurate short axis images which would allow outlining of endocardial boundaries.

Conclusion

In patients undergoing a clinically indicated PVI procedure we have presented indirect evidence of the influence of an Impedance Index on the late failure rate. The Impedance Index is approximately cyclic over each decade of EF. The failure rate is highest at the lowest Impedance Index value, where the atria is postulated to undergo the highest amount of stretch, and consequently be inherently more prone to AF. The low Impedance Index position is associated with the lowest success rate and its influence is additive to mitral valve regurgitation grade and the LA volume index. Further studies are required to directly measure the Impedance Index and assess its success in predicting PVI failure rate. Prior to conducting those studies, this work serves as the first step in this process.

Acknowledgements and Disclosures

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Conflict of Interest Disclosures: None.

Ethical statement: The study was approved by the Institutional Review Board to be conducted as a retrospective study of patient data. All patients provided a written consent for the MRI examinations, PVI procedures and for their anonymized data to be used in clinical research.

Footnote Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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