Morphology of Atrial Myocardium in Human Pulmonary Veins

A Postmortem Analysis in Patients With and Without Atrial Fibrillation

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OBJECTIVES	We report an in-depth postmortem morphologic analysis of atrial myocardium in human pulmonary veins (PVs) from patients with and without atrial fibrillation (AF).
BACKGROUND	Electrophysiologic studies established the critical role of PVs in the initiation of AF. To date, a paucity of data exists about PV morphology as an arrhythmogenic substrate.
METHODS	Longitudinal tissue-strips of PVs were excised and histologically analyzed from the distal part to just beyond the atriovenous junction in the left atrium from 20 patients, obtained at autopsy. Anatomical measurements, including diameters, lengths, and wall-thicknesses of PVs, obtained at autopsy, were made.
RESULTS	Histological analysis revealed extension of atrial myocardium into 89% of all PVs. Prevalence of myocardial extension was significantly higher in veins of 6 patients with compared with 14 patients without AF. Other significant differences in the histology of PVs between the two groups were a higher frequency of discontinuity and hypertrophy and a higher degree of fibrosis of the atrial myocardium in the PVs of patients with AF. A marked variation existed in anatomical dimensions of PVs, although no differences were observed between patients with or without AF.
CONCLUSIONS	Atrial myocardium was more often present in the PVs of patients with compared with patients without AF. In the first group, the atrial myocardium in the PVs was characterized by more severe discontinuity, hypertrophy, and fibrosis. A marked variation in anatomical dimensions of the PVs existed. (J Am Coll Cardiol 2003;42:1108–14) © 2003 by the American College of Cardiology Foundation

Animal and human histological studies of the pulmonary veins (PVs), which date back to the 19th century, have reported extension of atrial myocardium beyond the atriovenous junction (1–5). Clinical electrophysiologic studies have demonstrated that the PVs are of pathophysiologic importance and can play a critical role in the initiation of atrial fibrillation (AF) in some patients (6–11). These studies reported a prominent clustering of tachycardia foci within the PVs, especially the superior veins.

Because of the clinical importance of the PVs in the initiation of AF and the increasingly widespread application of catheter ablation techniques in these veins as a treatment for AF, we undertook this study to define more precisely the morphologic characteristics of the PVs and their left atrial junctions. Limited data concerning the histology of the extended atrial myocardium in the PVs are currently available in humans. Furthermore, only a paucity of data exists that compares the morphology of the pulmonary venous wall from patients with AF with patients without the arrhythmia. Therefore, we studied the postmortem histological morphology of the atrial myocardium in the PVs and compared this between both patient groups. Secondly, we measured various postmortem anatomical dimensions of the PVs of patients with and without AF before death.

METHODS

Study populations. Histological studies were performed in 20 human hearts obtained at autopsy. The clinical data of the 20 patients for the histology study are represented in Table 1. The average age of this group (7 female, 13 male) was 65.0 (± 19.8) years. A history of persistent AF was found in 6 of 20 patients. The average age of the patients with a history of AF (3 female, 3 male) was 75.2 (± 15.8) years. The average age of the patients without a history of AF (4 female, 10 male) was 60.6 (± 20.2) years. Anatomical measurements were made of PVs from 17 human hearts obtained at autopsy. The clinical characteristics are given in Table 2. The average age of the patients (5 female, 12 male) from which the veins were derived was 68.7 (± 12.4) years. According to their medical records, 5 of 17 patients had persistent AF before death. Patients who had undergone cardiac surgery or had involvement of the pulmonary hilar regions by malignancy were excluded from both study sets. The histology and the anatomy study were not carried out at the same time, but partially overlapped each other, which explains that both study groups do not consist of exactly the same patient population.

Histological analysis. The lungs and hearts of 20 patients were obtained at autopsy. The junctions of the PVs with the left atrium were marked with a thin line of Indian ink on the external surface using a micropipette. Longitudinal strips of

tissue, approximately 5-mm wide, were excised from the distal end of the PV in the lung to the left atrium just beyond the atriovenous junction. Sections of the anterior and posterior wall of all four PVs were taken, resulting in eight sections per patient. The tissue samples were immediately fixed in 10% neutral buffered formalin for more than 24 h. After standard tissue processing, the sections were embedded in paraffin and cut at 6 μm and stained with Masson's trichrome and immunohistochemically with monoclonal mouse anti-smooth muscle actin (SMA) (Sigma, St. Louis, Missouri; prediluted) and monoclonal mouse anti-cardiac troponin-T (Accurate Chemical & Scientific Corp., Westbury, New York; dilution: 1:50) in order to distinguish between smooth and atrial myocardial muscle, respectively. Incubation of antibodies was preceded by microwave pre-treatment. Before all staining procedures, paraffin sections were deparaffinized with xylene (2 × 5 min) and dehydrated with 100% ethanol (2 × 5 min) and 95% ethanol (2 × 5 min). The incubation time was 60 min for both antibodies. The secondary antibody used for the anti-SMA was a goat anti-mouse IgG (Sigma), and for anti-troponin-T it was a biotinylated broad spectrum IgG (Zymed, San Francisco, California). All staining was done by the Streptavidin-biotin complex (ABC) method, using diaminobenzidine for detection, and hematoxylin for counterstaining. All incubations were conducted at room temperature.

Extension of the atrial myocardium into the venous tissue was measured with a calibrated reticule in the lens of an Olympus (Model E600, Tokyo, Japan) microscope. The degree of fibrosis and hypertrophy of the atrial myocardium in the PVs was scored by visual assessment of the microscopic images. The degree of fibrosis was scored as 0 (no fibrosis), 1 (<50% of myocardium fibrotic), and 2 (>50% of myocardium fibrotic). Hypertrophy was scored as 0 (not present) or 1 (present). We typically looked at cellular and nuclear shape and size, in comparison with normal atrial cardiomyocytes, to assess hypertrophy by "visual means." It is something we do as a matter of routine on myocardial biopsy specimens and, as such, is subjective but nonetheless very reproducible. The whole sections were analyzed and scored at the same time by two investigators, using an octopus-microscope, in order to minimize intraobserver and interobserver variability.

Anatomical analysis. All measurements were made in freshly obtained unfixed autopsy specimens after removal of the epicardium. The superior-inferior diameters of the four PVs, that is, left superior pulmonary vein (LSPV), right superior pulmonary vein (RSPV), left inferior pulmonary vein (LIPV), and right inferior pulmonary vein (RIPV), were determined at the junction with the left atrium. The lengths of the four PVs were measured from the atriovenous junction until the total distal end in the lung hilus. The thicknesses of the PV walls were determined 1 cm proximal to the atriovenous junction at the anterior and posterior sites, the parts that were used for histological analysis as described in the preceding text, of the vein. The thickness of

Table 1. Patient Characteristics of Pulmonary Vein Histological Analysis

Patient #	Gender	Age (yrs)	AF	HTN	CAD	MI	VHD	CM	OHD	Cause of Death
1	F	66								Pneumonia
2	M	46	+	+			+			Subtotal pontine infarct
3	M	59		+						Hypoxic vasoconstriction
4	M	63								Pulmonary embolus
5	M	74	+	+	+	+				Acute respiratory distress syndrome
6	M	56								Pulmonary embolus
7	M	81		+	+					Congestive heart failure
8	M	72	+					+	+	Massive hepatic hematoma
9	M	82			+	+				Acute respiratory distress syndrome
10	M	56			+	+				Myocardial infarction
11	F	88	+	+	+		+			Pulmonary thromboembolism
12	F	88	+		+					Congestive heart failure
13	M	65								Hemoperitoneum
14	F	83	+							Metastatic breast carcinoma
15	M	79		+	+	+				Myocardial infarction
16	M	38								Intraperitoneal hemorrhage
17	F	82			+				+	Severe acute bronchopneumonia
18	M	17								Hemorrhagic bronchopneumonia
19	F	30		+						Pulmonary hypertension
20	F	75		+				+		Pulmonary embolus

AF = atrial fibrillation; CAD = coronary artery disease; CM = cardiomyopathy; HTN = hypertension; MI = myocardial infarction; OHD = other heart disease; VHD = valvular heart disease.

Table 2. Patient Characteristics of Pulmonary Vein Anatomical Analysis

#	Gender	Age (yrs)	AF	HTN	CAD	MI	VHD	CM	OHD	Cause of Death
1–12 Same patients as in Table 1										
13	M	77			+	+				Mesothelioma
14	F	75		+					+	Pneumonia
15	F	63								Ovarian cancer
16	M	53			+	+				Intrathoracic hemorrhage
17	M	69				+				Cerebrovascular accident

Abbreviations as in Table 1.

the left atrial wall was measured between the inferior PVs (posterior wall) and on the opposite site of the atrium (anterior wall), 2 cm above the mitral valve.

Statistical analysis. Student *t* test for unpaired data was used to evaluate the significance of differences in morphologic appearances of the PVs between the AF and the non-AF group. Results were expressed as mean ± standard error, and percentages and range. A value of $p < 0.05$ was considered statistically significant.

Ethics. The institutional review board approved the study, and the procedures followed during autopsy were in accordance with the institutional guidelines.

RESULTS

Histology. Extension of atrial myocardium into the pulmonary venous wall (Fig. 1) was found in 89% of the tissue samples, measuring an average length of 9.3 mm, following formalin fixation and tissue processing (Table 3). All four PVs of all 20 patients were analyzed. The average length of the myocardial sleeves into the LSPVs was 10.9 mm (range, 3.6 to 19.3 mm), into the RSPVs 10.3 mm (1.1 to 25.0 mm), into the LIPVs 8.5 mm (0.6 to 23.5 mm), and into the RIPVs 7.2 mm (1.88 to 17.0 mm). Myocardial extension was found in 100% of the PVs from patients with AF and 85% of the veins from patients without AF ($p < 0.05$). The average length of myocardial extension into the PVs of patients with AF was 10.4 (± 4.8) mm, and in patients without AF 8.7 (± 6.1) mm. Only in the LSPV specimens did the difference in length of myocardial extension reach significance, with a mean myocardial extension of 15.1 (± 3.8) mm in the AF group and 8.8 (± 3.6) mm in the non-AF group ($p < 0.05$).

The pulmonary venous myocardial extension appeared to be discontinuous in 54% of the histology sections (Fig. 2). There was a significant difference in the frequency of this finding between the AF group, where it was present in 71% of PV specimens, and the non-AF group, where it was present in 46% of the specimens.

The degree of fibrosis and the presence of hypertrophy were significantly different in the AF and non-AF groups. Figure 3 shows an example of myocardial fibrosis in the wall of a PV. The degree of intercellular fibrosis increased progressively in the PV from proximal to distal. Hypertrophic myocardial cells were present in the proximal as well as in the more peripheral site of the veins. The presence of fibrosis, discontinuous myocardium, and hypertrophy were not particularly related to one or more PVs, but equally existed in all four veins.

Using immunohistochemical methods, we found no difference between the staining patterns or staining intensity in the atrial myocardial components of the PVs in the two patient groups. The myocytes stained strongly for troponin-T (Fig. 4). The troponin-T staining identified the atrial myocytes in the PVs, while staining for SMA only stained the smooth muscle components of the PVs (Fig. 5). The staining pattern for the myocardial markers did not differ from that of myocytes of the atrium proper.

Transition from the atriovenous anatomical junction was characterized by gradual tapering of either tissue in each direction from the junction. In the PV wall, the myocardial sleeve was always external to the smooth muscle layer, in agreement with a recent study (12).

Recent electrophysiologic studies (6–11) have indicated that the superior PVs are more frequently involved in the initiation of AF than the inferior PVs. When comparing all

Table 3. Histological Analysis of Atrial Myocardium in Human PVs

Parameters	All (± SE)	AF Group (± SE)	Non-AF Group (± SE)	p Value
Mean extension of myocardium in all PVs (mm)	9.3 (± 5.7)	10.4 (± 4.8)	8.7 (± 6.1)	NS
Mean extension of myocardium in LSPVs (mm)	10.9 (± 4.7)	15.1 (± 3.8)	8.8 (± 3.6)	<0.05
Mean extension of myocardium in RSPVs (mm)	10.3 (± 7.7)	10.2 (± 6.4)	10.4 (± 8.7)	NS
Mean extension of myocardium in LIPVs (mm)	8.5 (± 5.3)	8.9 (± 1.8)	8.3 (± 6.6)	NS
Mean extension of myocardium in RIPVs (mm)	7.2 (± 4.1)	7.2 (± 2.4)	7.2 (± 4.9)	NS
Percentage PVs with myocardium extension	89.5	100	84.6	<0.05
Percentage PVs with discontinuous myocardium	53.9	70.8	46.2	<0.05
Percentage PVs with hypertrophic myocytes	47.9	79.2	32.7	<0.05
Degree of fibrosis of myocardium in PVs	1.08	1.58	0.84	<0.05

LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PV = pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.
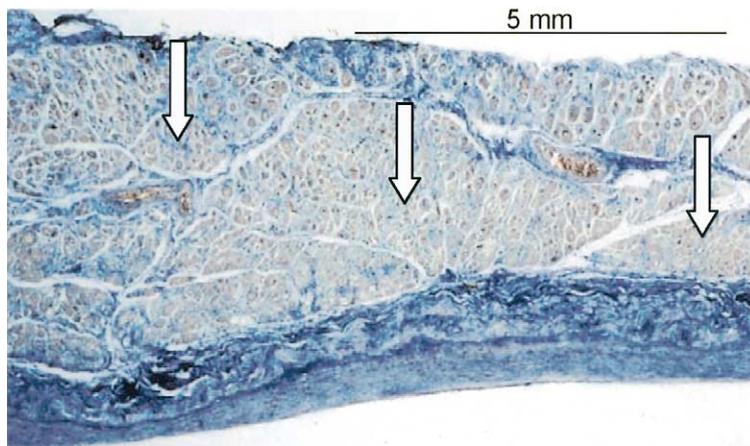
Figure 1. Extension of atrial myocardium **(red/brown; arrows),** stained with Masson's trichrome, in the wall of a human left superior pulmonary vein from a patient with atrial fibrillation. (Bottom side of figure represents luminal side of the vein.)

superior vein sections with inferior vein sections, the extension of atrial myocardium in the superior PVs was significantly longer than in the inferior veins. The superior veins had an average extension of 10.6 mm (range, 1.1 to 25.0 mm) versus an extension of 7.7 mm (range, 0.6 to 23.5 mm) in the inferior PVs ($p < 0.05$).

Anatomy. All four PVs of all 17 patients were anatomically analyzed (Table 4). As is evident from the morphometric data in Table 4, a marked variation was present in the various PV dimensions measured. Correction for heart weight did not influence the degree of variation. The mean diameter of the superior PVs was 17.7 mm and for the inferior PVs 16.5 mm. The diameter of the PVs ranged from 5 to 30 mm, whereas the length prior to bifurcation of the PVs ranged from 10 to 54 mm. The wall thickness of the PVs, presented as the mean of the anterior and the posterior sites measured, was almost uniformly thin (0.3 to 0.8 mm) in contrast to the wall thickness of the true atrium (0.6 to 2.6 mm). All these gross anatomical dimensions did not significantly differ between patients with and without AF before death. All patients had four PVs; no conjoined PV orifices were found.

DISCUSSION

Only a limited number of studies have previously reported the histological appearance of the extended atrial myocardium in human PVs. The present study describes the histological patterns of the pulmonary venous myocardium, which may provide insights into the pathophysiologic mechanisms underlying the arrythmogenicity of these structures. The key findings of the postmortem histological analysis include the following:

1) Atrial myocardium extended into 89% of all human PVs. Extension of atrial myocardium was more frequently present in the veins of the six patients with a history of AF compared with the 14 patients without a history of AF;

2) Significant differences in the histological appearance of the extended atrial myocardium between these two patient groups were a higher frequency of discontinuity, hypertrophy, and a higher degree of fibrosis of pulmonary venous myocardium of patients with compared with those without a history of AF before death;

Figure 2. Longitudinal section of a human left superior pulmonary vein from a patient with atrial fibrillation, showing discontinuous atrial myocardium **(arrows)** stained with cardiac troponin-T. (Bottom side of figure represents luminal side of the vein.)
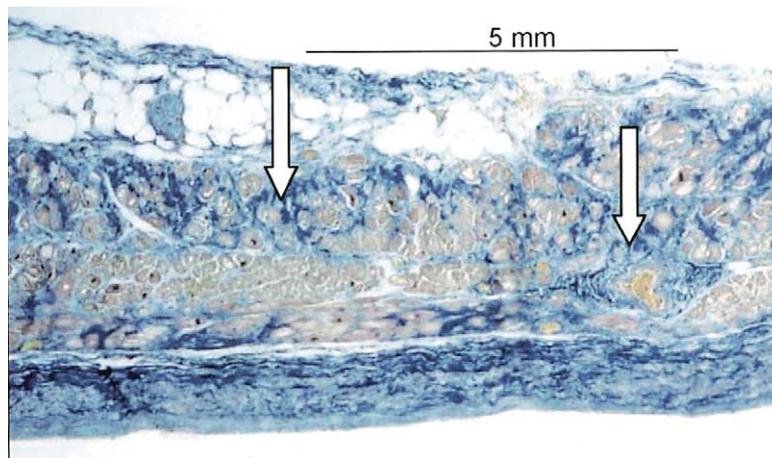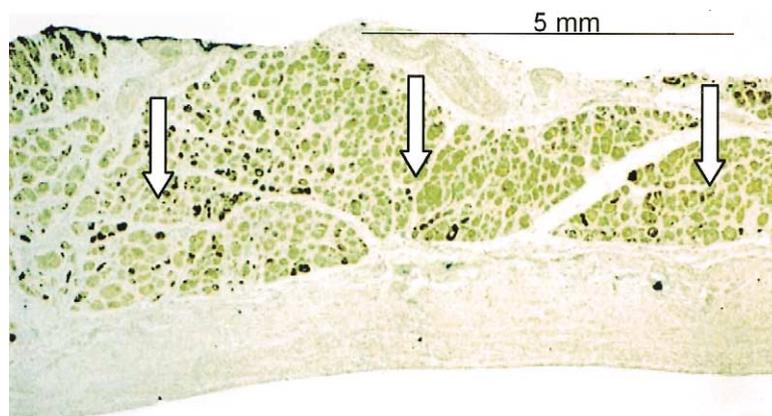
Figure 3. Longitudinal section of a human left superior pulmonary vein from a patient with atrial fibrillation, stained with Masson's trichrome, showing loosely coupled atrial cardiomyocytes **(red/brown)** with high degree (>50% of atrial myocardium) of intercellular fibrosis **(blue; arrows).** (Bottom side of figure represents luminal side of the vein.)

3) Immunohistochemical staining patterns did not differ between the myocytes in the PV wall and myocytes in the atrium proper nor between the patients with and those without a history of AF.

The findings of this study demonstrate that the left atrial myocardium extends for variable but significant distances into the PVs. The myocardium found to extend into the PVs demonstrated the immunohistochemical staining properties of true atrial myocardium and, thus, was in keeping with the hypothesis that such a myocardial investiture arises embryologically from outbudding of the proximal PVs from the atria. Interestingly, the extension of myocardium appeared to be most pronounced in the superior left PV, which in some clinical series has been found to be the most frequent site of focal triggers. The nature of the myocardium was different between the two patient groups, with hypertrophy and fibrosis being more common in the AF group. Increased fibrosis in the AF group may be entirely explained by the patients' age. Nonetheless, in the light of a recent canine experimental heart failure study (12), which showed increased atrial fibrosis in dogs that developed AF,

the presence of fibrosis raises the possibility of a pathophysiologic mechanism. It may be of relevance that the incidence of AF in the general population increases progressively with age, and fibrosis may provide a possible pathophysiologic link. Separation of the atrial myocardial bands (discontinuous myocardium) within the PVs was also found more frequently in the hearts of patients with AF. This finding may merely represent a normal anatomical variant or reflect increased stretch and size of the PVs. It is possible that this anatomical milieu, fibrosis and discontinuous myocardium, provides an arrhythmogenic substrate. Even mild amounts of fibrosis within the PVs may result in myocardial clusters, which are comparatively isolated. This may result in reduced myocyte coupling and reduced electrotonic inhibition, thus facilitating automaticity. The degree of intercellular fibrosis in our study increased progressively in the PV from proximal to distal such that the most distal myocytes were the most poorly coupled. This may, in part, explain why exit block is frequently encountered from single premature beats as well as from bursts of focal activity from within the PVs. The recording of discrete spike potentials and, at other sites,

Figure 4. Longitudinal section of a human left superior pulmonary vein from a patient with atrial fibrillation, with atrial myocardium stained with monoclonal mouse anti-cardiac troponin-T **(brown; arrows).** (Bottom side of figure represents luminal side of the vein.)
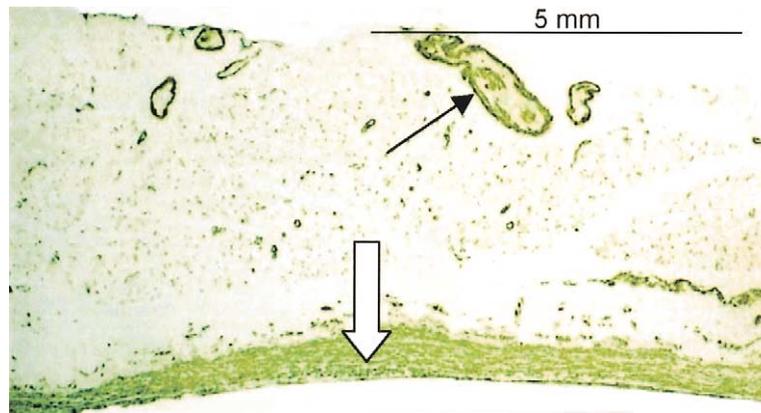
Figure 5. Same section as in Figure 4, now stained with monoclonal mouse anti-smooth muscle actin **(white arrow; black arrow** points to smooth muscle of vasa vasorum). The smooth muscle layer is always internal from the extended atrial myocardium. (Bottom side of figure represents luminal side of the vein.)

fractionated electrograms within a PV may be explained by isolated distal projections of myocytes and by poorly coupled myocardium at other sites, respectively. The combination of poorly coupled cells, fibrosis, and cellular hypertrophy may lead to slow conduction and, thereby, facilitate local re-entry within the PVs. Recently, a study in rats suggested the role of interstitial fibrosis and atrial cell hypertrophy contributing to the increase in atrial conduction slowing, conduction block, and inducible AF (13).

In a study published by Saito et al. (14), myocardial sleeves were recognized in 96 of 99 PVs (97%) examined, compared with 89% in our study. The prevalence of sleeves was comparable between patients with and those without AF in their study, whereas we found a statistically significant higher frequency of atrial myocardium in the PVs of patients with AF. The distances of the myocardial extension into the PVs in their study group were comparable with our measurements and in both studies more extensive in the superior than in the inferior PVs. Saito et al. (14) reported the same lengths of myocardial sleeves between patients with and without AF, where we found a significant difference in the average distance of the myocardial extension in the LSPVs, being longer in patients with AF. Also, in

contrast to our study, Saito and his colleagues reported no discontinuity of the extended atrial myocardium. Furthermore, Saito et al. (14) showed the existence of fibrous tissue in the distal part of the extended atrial myocardium. In our study this was found significantly more often present in AF patients compared with non-AF patients. Additionally, we noticed the presence of hypertrophic cardiomyocytes in the PVs, especially in those of patients with the atrial arrhythmia. Tagawa et al. (5) reported longer myocardial sleeves in the superior PVs compared with the inferior PVs as well. The distances of the sleeves in both inferior PVs reached a statistically significant difference comparing veins of patients with and without AF, being longer in the subjects with the arrhythmia. At the peripheral end, the investigators found less uniform myocytes and some fibrosis. In our study we found fibrosis also being present in the proximal part of the veins. The presence of hypertrophic myocytes and discontinuous myocardium was not reported in the Tagawa et al. (5) study.

The use of catheter ablation techniques for the treatment of focally triggered AF arising from the PVs is growing rapidly. The present study provides anatomical measurements, which should be instructive in the development of adequate catheter ablation procedures. There existed a marked variation in the anatomical dimensions of the PVs. These gross and variable anatomical measurements have implications for the development of new catheter ablation techniques. The gross anatomical variation of the PVs with respect to diameter and length suggests that circumferential isolation ablation systems should also be versatile with respect to inflation diameters and length of the inflated components, particularly if intended for deployment within the lumen of the vein itself as opposed to deployment outside the PV os against the posterior left atrial wall.

The finding that the PV wall is extremely thin (0.5 mm) in most patients also has significant implications. Inflation pressures used to deploy balloon-based systems within the PVs should be limited to reduce the risk of PV rupture as has occurred in early animal studies, or, alternatively,

Table 4. Anatomical Dimensions of Pulmonary Veins

Measurements	Mean (mm)	SE (mm)	Range (mm)
Diameter LSPV	17.9	3.2	11.1–23.4
Diameter RSPV	17.4	6.1	4.8–29.8
Diameter LIPV	16.7	3.7	9.7–21.8
Diameter RIPV	16.3	4.7	5.9–21.4
Length LSPV	40.0	7.6	25.5–53.6
Length RSPV	33.7	7.8	21.9–49.0
Length LIPV	36.2	5.7	30.6–52.5
Length RIPV	29.1	8.4	10.1–47.6
Thickness LSPV wall	0.54	0.16	0.3–0.8
Thickness RSPV wall	0.48	0.14	0.3–0.8
Thickness LIPV wall	0.49	0.15	0.3–0.7
Thickness RIPV wall	0.49	0.15	0.3–0.8
Thickness LA anterior wall	1.6	0.5	1.0–2.4
Thickness LA posterior wall	1.7	0.6	1.1–2.6

LA = left atrial. Other abbreviations as in Table 3.

intracardiac echocardiography should be used to match the size of the PV and maximal inflated balloon diameter. Secondly, the amount of radiofrequency power required to achieve a transmural lesion within the PVs should be significantly less than that used in the true atrium, where the wall is significantly thicker.

Study limitations. Assessment of the degree of fibrosis and myocyte hypertrophy in this study was done visually, although under the eye of an experienced cardiac pathologist and, therefore, subjective. The number of patients with AF in this autopsy study was small, and, as such, this study represents an initial step in the examination of PV morphology in patients who had AF. Although all the gross measurements were performed in fresh specimens, the extension of myocardium into the PVs was determined after formalin fixation and tissue processing. These procedures are well known to cause shrinkage of tissues, which is tissue-type–dependent (15,16). While the specific degree of shrinkage of the PVs is not established, the range of PV measurements in this autopsy study is consistent with the degree of variation we encounter on magnetic resonance imaging in vivo in patients undergoing PV isolation.

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