Morphology of Atrial Myocardial Extensions Into Human Caval Veins

A Postmortem Study in Patients With and Without Atrial Fibrillation

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Background—Atrial fibrillation (AF) may be triggered from arrhythmogenic foci originating from atrial muscular sleeves that extend into the pulmonary veins.1,2 Catheter ablation techniques aiming at electrical isolation of all pulmonary veins and/or at circumferential ablation around their ostia have been developed to treat AF.3,4 However, controversy still exists about the role of other locations of arrhythmogenic foci for triggering AF.5,6 Among them, the superior vena cava (SVC) appears to be a relatively frequent location,7–9 whereas the inferior vena cava (IVC) houses these foci only exceptionally.10,11

A great deal of evidence has accumulated that atrial fibrillation (AF) is frequently triggered from arrhythmogenic foci originating from atrial muscular sleeves that extend into the pulmonary veins.1,2 Catheter ablation techniques aiming at electrical isolation of all pulmonary veins and/or at circumferential ablation around their ostia have been developed to treat AF.3,4 However, controversy still exists about the role of other locations of arrhythmogenic foci for triggering AF.5,6 Among them, the superior vena cava (SVC) appears to be a relatively frequent location,7–9 whereas the inferior vena cava (IVC) houses these foci only exceptionally.10,11

Compared with numerous morphological studies on characteristics of atrial myocardium around the pulmonary veins,12–16 our knowledge about morphological characteristics of atrial myocardial extensions into human caval veins (CVs) is still limited.17,18 Because it may have practical implications for catheter ablation within the CVs, the goal of this study was to evaluate the presence, length, thickness, and arrangement of atrial myocardial fibers around CVs in autopsyed hearts from subjects with and without a history of AF.

Methods

A total of 25 human hearts obtained at autopsy were studied (15 from men; mean age, 65.5±12 years; range, 39 to 80 years). A cardiovascular cause of death was revealed in 11, malignancy in 1, bronchopneumonia in 1, respiratory failure in 3, septic shock in 2, hemorrhagic shock in 3, and brain death in 4 subjects. Underlying cardiovascular disease was diagnosed in 16 subjects. Atherosclerosis was found in 14 subjects, and 8 of them had predominant coronary artery disease. Arterial hypertension was known in 1 subject and cerebrovascular malformation in another. Heart failure was diagnosed before death in 11 subjects. Miscellaneous underlying diseases were found in the remaining subjects: 4 of them consisted of malignancies, 3 of liver cirrhosis, and 1 patient had peptic ulcer.

According to medical records, 7 subjects had a history of AF (group 1; 3 men; mean age, 67±10 years; range, 53 to 80 years). The remaining 18 subjects were without AF (group 2; 12 men; mean age, 70±13 years; range, 39 to 78 years). The heart was excised together with the SVC and the upper portion of the IVC (Figure 1). CVs were separated from the right atrium at the level of the junction determined macroscopically. The atriovenous junction for the SVC was defined at the level of the sulcus terminalis at the base of the appendage. The junction for the IVC was determined at the angle with the bottom of the atrium.16 This technique of sample collection was not intended to analyze the atriovenous junction in detail. In the...
last 8 subjects, we decided to harvest the atrial part of the junction as well and to analyze its transition into the myocar dial sleeve. All harvested CVs were cut longitudinally, spread flat, and fixed in formalin. Each vein was then cut into pieces both parallel and perpendicular to the long axis and processed routinely. A total number of 203 paraffin blocks (the minimum number of blocks per vein was 2, and the maximum number reached 6, with a mean of 4 blocks) were obtained. All sections (minimum of 2 sections per block; additional sections were cut whenever needed to assess continuous or discontinuous pattern) were cut by microtome and stained with hematoxylin-eosin stain, and if degenerative changes were present, with Masson’s trichrome stain. The presence of myocardial sleeves was evaluated in each section microscopically. Whenever myocardial extension was present, the maximum length was measured from the junction in parallel sections of tissue with a caliper (accuracy of 0.5 mm). Furthermore, myocardial thickness was measured at a distance of 1 cm from the ostium and at the point of maximum thickness, if different. In addition, continuity or discontinuity of myocardial sleeves in both the longitudinal and circular directions was assessed in each section. In addition, predominant myocardial fiber arrangement and regressive changes were evaluated. Regressive changes were described according to the following criteria: (1) hypertrophy, defined as myocyte enlargement with enlarged nuclei; (2) vacuolar degeneration, described as morphological reticulated pattern; and (3) fibrosis, characterized by replacement of solitary infarcted cells by fibrous noncontractile tissue.

Statistical Analysis
Data obtained from both groups of subjects are presented as the mean±SD. The differences between the 2 groups were analyzed by use of a nonparametric Mann-Whitney U test or χ² test, when appropriate. A probability value of P<0.05 was considered statistically significant.

Results
Myocardial sleeves were found around 38 of 50 (76%) CVs examined. All the myocardial extensions were localized on the outer side of the venous adventitia (Figure 2). In some cases, an interlayer of fatty or fibrofatty tissue was present between the atrial extension and the adventitia. Marked morphological heterogeneity of cardiomyocytes within the sleeves was noticed. However, no node-like cells or specialized cells forming discrete unsheathed tracts were observed.

In SVCs, atrial myocardial sleeves were found in 19 of 25 veins examined (76%). The maximum length extended up to 47 mm, and the average length was 13.7±13.9 mm. The maximum thickness reached 4 mm, and the average thickness was 1.2±1.0 mm. A comparison of characteristics of myocardial sleeves in both groups is presented in the Table. Analysis of the atrio caval junction suggested that in SVCs, the predominant pattern was continuous transition between right atrial myocardium and sleeve (4 of 5 subjects with present myocardial extensions) (Figure 3).

In AF patients, only 4 of 7 veins examined (57%) were surrounded by myocardial sleeves. The maximum length of myocardial sleeve in this subgroup was 10 mm, and the maximum thickness did not exceed 1 mm. A circular arrangement was revealed in all 4 veins. All but 1 sleeve showed a discontinuous pattern. Discontinuity was both circumferential and longitudinal in 2 subjects and circumferential only in 1 subject. Hypertrophic degenerative changes were observed in 1 vein and vacuolar degeneration in another. In subjects without AF, 15 of 18 veins (83%) contained myocardial fibers. The maximum length reached 47 mm, with a maximum thickness of 4 mm. Discontinuity was observed in 12 subjects (circumferential in 9 subjects and both longitudinal and circumferential in 3). The arrangement of myocardial fibers was circular in 4 and predominantly circular in another 8 subjects (Figure 4). A longitudinal course of the fibers was observed in 3 veins and an oblique pattern only in 2. Any degenerative changes were found in 7 subjects: fibrosis in 3, hypertrophy in 2, and vacuolar degeneration in 2 (Figure 2).

In IVCs, myocardial sleeves were also present in 19 of 25 subjects examined (76%). The sleeves reached a maximum length of 61 mm, and the average length was 14.6±16.7 mm. The maximum thickness was 3 mm, with an average thickness of 1.2±0.9 mm. In 3 subjects analyzed, we observed a discontinuous pattern of transition between the right atrium and IVC (Figure 3).

The Table shows a comparison of characteristics of myocardial sleeves in both groups. In AF patients, myocardial sleeves onto the IVC were found in 5 of 7 subjects (71%). The longest sleeve was 61 mm long, and the maximum thickness was 3 mm. The fiber arrangement was circular or predominantly circular in 4 subjects and longitudinal in 1. Two myocardial sleeves were arranged continuously, another 2 were discontinuous circumferentially, and 1 was discontinuous in both directions. Degenerative changes were present in 2 subjects and consisted of hypertrophy and vacuolar degen-
In subjects without AF, myocardial muscle was found in 14 of 18 veins (78%). The prevailing arrangement of myocardial fibers was circular or mostly circular (n/H11005 10); only 3 subjects showed a solely longitudinal course. The sleeves were discontinuous circumferentially in 6 subjects and continuous in another 7. One myocardial sleeve showed discontinuity in both the circular and longitudinal directions. Degenerative changes were diagnosed in 5 subjects (hypertrophy in 3, fibrosis in 1, and vacuolar degeneration in 1).

Discussion
To the best of our knowledge, this is the first study that compared morphological and morphometric characteristics of atrial myocardial extensions onto CVs in subjects with and without a history of AF. In addition, it appears to be the largest series analyzing the morphology of CVs in humans. Its major findings can be summarized as follows: (1) myocardial extensions were revealed in 76% of CVs and were equally frequent in the SVC and the IVC; (2) these extensions were localized on the outer side of venous adventitia in all subjects, and their maximum length reached up to 61 mm and maximum thickness up to 4 mm; (3) myocardial fibers in the sleeves were arranged predominantly circularly to the long axis of the vein and were frequently discontinuous; (4) no specialized conduction cells were observed; (5) degenerative changes were described in approximately one third of all myocardial extensions; (6) atriocaval junction assessment revealed a predominantly continuous pattern in the SVC in few subjects, whereas discontinuity was present in IVC; and (7) no major difference in characteristics of myocardial sleeves around the CVs was found between patients with and without a history of AF.

Comparison With Previous Studies
Thus far, relatively few studies have attempted to evaluate atrial activity within the CVs of different mammals. Lewis et al19 measured activation times within the SVC in dogs and demonstrated excitation 2 to 3 cm above the right atrium. Ito et al20 mapped the spread of atrial activation into the CVs of in vitro rabbit preparations. Compared with frequent activity to the upper limit of SVCs, the IVC was electrically silent except for a very short distance near its junction into the right atrium. Similar mapping findings were reported in dogs by Spach et al.17 Although these mapping studies did not reveal any evidence of electrical activity in the IVC, a morphological study by Nathan and Gloobe21 documented clearly the presence of myocardial sleeves on the IVC in various species and reported an average length ranging from 6 to 35 mm. This apparent discordance between mapping and morphological data may imply that although atrial myocardium is frequently present around mammal IVC, it is rarely electrically connected to the rest of the right atrium.

Figure 2. Low-magnification photomicrographs of myocardial sleeves (MS) and CVs. A, Around SVC (left) with transition (arrow) into right atrium (right). Mild fibrosis is apparent in region of transition, and circumferential arrangement of fibers behind ostium and more oblique course toward periphery of vein (hematoxylin-eosin; magnification \( \times 12.5 \); bar=2 mm). B, Around IVC from ostium (left) to periphery of vessel. More patchy arrangement of fibers is present (hematoxylin-eosin; magnification \( \times 12.5 \); bar=2 mm). C, Around SVC behind ostium (left) with both circular and oblique course of fibers (hematoxylin-eosin; magnification \( \times 12.5 \); bar=2 mm).

### Differences in the Length and Thickness of Myocardial Extensions Into Caval Veins

<table>
<thead>
<tr>
<th>Group</th>
<th>SVC MS Length</th>
<th>SVC MS Thickness</th>
<th>IVC MS Length</th>
<th>IVC MS Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.7±4.7</td>
<td>0.7±0.5</td>
<td>15.6±23.0</td>
<td>1.0±0.8</td>
</tr>
<tr>
<td>2</td>
<td>17.2±14.8</td>
<td>1.3±1.0</td>
<td>14.2±14.4</td>
<td>1.2±0.9</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

MS indicates myocardial sleeve.
The analysis of human data reveals a similar discordance between studies on mapping of electrical activity within the IVC and anatomic findings as seen in other mammals. Spach et al\textsuperscript{17} were able to map electrical activity during cardiac surgery 2 to 4 cm in all thoracic veins (ie, the SVC, coronary sinus, and pulmonary veins) except the IVC. In an attempt to find an alternative stimulation site for cardiac pacing, Zipes and Knope\textsuperscript{22} were able to stimulate atrium from the SVC but not from the IVC in 1 man who had undergone cardiac surgery in the past. Conversely, Jacomo et al\textsuperscript{23} described the presence of myocardial fibers in the IVC postmortem in 20 structurally normal adult hearts. Similarly, Hashizume et al\textsuperscript{18} in a morphological and morphometric study of 2 human autopsied hearts, revealed extensions up to 18 mm into the IVC.

The practice of catheter ablation has initiated more detailed mapping studies in both CVs. Tsai et al\textsuperscript{8} observed the origin of paroxysmal AF in 8 of 130 patients (6\%) within the SVC. The mean length of atrial extensions into the SVC in these patients as identified by electrophysiological mapping was 33±7 mm, ranging from 14 to 44 mm. More recently, the same group reported a series of 27 patients with AF-triggering foci within the IVC only sporadically.\textsuperscript{10,11} The reason for this difference is unknown. Embryologically, cardiomyocytes forming myocardial sleeves around both CVs are added to the primary heart tube at the venous pole from a similar source during the second wave of myocardium formation.\textsuperscript{25} However, it is unknown whether there is a difference between the 2 CVs in the presence of specialized conduction system cells. Isolation of 2 different types of cardiomyocytes from canine SVC by Chen et al\textsuperscript{26} may suggest that SVC could contain specialized cells that may be relevant in the genesis of AF. However, we failed to find any node-like cells or specialized cells in myocardial extensions around the SVC. This is in agreement with observations in 2 human hearts by Hashizume et al.\textsuperscript{18} It may reflect the limitations of light microscopy to detect specialized conduction cells, as emphasized by Perez-Lugones et

**Figure 3.** An example of photomicrographs of atrio caval junctions: SVC (A) and IVC (B). A, Continuous transition of right atrial (RA) myocardium into myocardial sleeve (MS) onto SVC. At level of ostium (#), myocardium consists of longitudinally arranged fiber stripes and moderate fibrosis (arrow). Myocardial sleeve is abundant in myocardial fibers that are arranged circularly (hematoxylin-eosin; magnification ×40; bar=1 mm). B, Discontinuous transition (arrow) of right atrial myocardium with significant fibrosis into myocardial sleeve onto IVC. Fibers of myocardial sleeve are arranged predominantly circularly; however, some fibers show longitudinal course. Fibrofatty interlayer separates CV and myocardial sleeve (hematoxylin-eosin; magnification ×40; bar=1 mm).

**Figure 4.** Photomicrographs showing degenerative changes within myocardial sleeves. A, SVC is separated from myocardial sleeve (MS) by sparse fibrous interlayer. Fibers are arranged either longitudinally or circularly. Blue color in trichrome staining emphasizes fibrosis between myocardial fibers (Masson's trichrome; magnification ×100; bar=200 μm). B, A detail of hypertrophic myocytes (arrow) in MS onto SVC with mixed oblique and circular arrangement of myocardial fibers (hematoxylin-eosin; magnification ×200; bar=100 μm). C, SVC is separated from MS by a fibrous interlayer. Heterogeneous fiber arrangement with significant vacuolar degeneration (arrows) is highlighted in this myocardial sleeve (hematoxylin-eosin; magnification ×40; bar=500 μm).
al. These authors described specialized conduction cells in human pulmonary veins by use of electron microscopy, even though several light-microscopy studies failed to do so. Conversely, myocardial cells with distinct properties for propagation of action potentials may not be distinguished from one another by ultrastructural morphology only. There is also no immunohistochemical marker available that could distinguish between working myocardium and human conduction system cells. Although Leu-7 is present in morphologically dynamic myocardial regions during heart ontogenesis and was hypothesized to correspond with abnormal atrial automaticity, we found its positivity in only 9.9% of sleeves onto pulmonary veins and no difference between groups with and without a history of AF.

In addition to focal mechanisms, some authors suggested reentry involving the SVC and/or upper part of the atrium, with fibrillatory conduction to the rest of the atrium. Liu et al. used noncontact mapping to reveal fractionated, low-amplitude signals suggesting electrical heterogeneity or anisotropic conduction properties of atrial myocardium within the SVC. Using high-resolution mapping, Shah et al. reported on a case of presumably circus movement reentry within the SVC, with marked slow and anisotropic conduction. Our data on structural heterogeneity of myocardial extensions may provide the basis for explanation of anisotropic conduction. Conversely, the finding of shorter myocardial extensions in the SVC in patients with AF does not suggest that these patients have more myocardium in the CVs to maintain AF.

In clinical practice, the distinction of focal source from localized reentry is not that important to abolish the arrhythmia, because complete electrical disconnection of the SVC can cure AF of either origin. Indeed, electrical isolation of the arrhythmogenic SVC has been suggested to treat AF originating from the SVC, using either circumferential ablation or interruption of preferential electrical connection. However, there is an increased risk of phrenic nerve palsy when ablating in this region, especially when radiofrequency current is applied to the posterolateral aspect of the right atrium/SVC. Our findings of frequent discontinuities and variability in arrangement of myocardial fibers in myocardial sleeves provide a potential explanation for preferential sites of conduction between the SVC and the atrium. The observed average thickness of the sleeve of approximately 1 mm explains the relatively high risk of damage to the phrenic nerve during circumferential disconnection. Therefore, it might be advisable to restrict application of radiofrequency energy only to sites of preferential conduction instead of anatomically guided circumferential disconnection. Pacing from an ablation catheter with high energy may help to identify high-risk sites with phrenic nerve capture.

**Study Limitations**

Unfortunately, the history of AF was available only from the clinical files available for the autopsy examination. Therefore, some data from a patient’s previous history could be missed. The number of AF patients in this study was small, and this might affect comparison with subjects without AF. Furthermore, measurements performed on autopsied heart may be influenced by postmortem dilatation of the musculature and/or shrinkage of tissues during formalin fixation and tissue processing. However, all postmortem studies face these study limitations. Because 3D reconstruction of the sleeves was not performed, it was impossible to describe the character of discontinuities of the myocardial sleeves around CVs in detail.

**Conclusions**

In conclusion, the present study demonstrates that atrial myocardial extensions into the CVs are present in the majority of human beings, both with and without a history of AF. One of the most important observations is the description of these extensions in the IVC with the same frequency as in the SVC. The arrangement, length, and thickness of myocardial sleeves onto the CVs vary among different individuals, and many of them contain degenerative changes.

**References**


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_Circulation_. 2004;110:483-488; originally published online July 26, 2004;
doi: 10.1161/01.CIR.0000137117.87589.88
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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