Obesity and atrial fibrillation (AF) are 2 major growing epidemics associated with considerable morbidity and mortality in the American population and globally (1). Obesity is a risk factor for AF, as reported by the Framingham study, and is associated with a 50% increase in the risk of AF development (2,3). Further, obesity is associated with increased prevalence of hypertension, coronary artery disease, diabetes mellitus, obstructive sleep apnea, and congestive heart failure (4,5). These cardiovascular conditions, in turn, are known to contribute to the development of AF. The propensity of obese people to develop AF may be attributable to left ventricular (LV) diastolic dysfunction and left ventricular (LV) diastolic dysfunction and left
agents on hemodynamics, only desflurane was used for all general anesthesia. To minimize the effect of anesthetic Study protocol.

CATHETERIZATION. Selection of catheters was performed using the Conquest program (Somanetics, Troy, Michigan) for each patient. A 6-F catheter was advanced through the transseptal sheath and placed in the pulmonary veins, right atrium, right ventricle, and coronary sinus. A 10-F decapolar circular catheter was advanced through the transseptal sheath for mapping PV potentials. Intracardiac bipolar electrograms were displayed simultaneously on a multichannel recorder (Prucka Engineering, Houston, Texas). Patients received heparin before transseptal puncture and throughout the ablation procedure to maintain an activated clotting time of 300 to 400 s. The study protocol was then undertaken before the ablation.

HEMODYNAMIC STUDY. A high-fidelity 2-F Millar catheter was advanced to the LV via a long transseptal sheath and multipurpose catheter. LV and LA pressure recordings were measured simultaneously (via a saline-filled long transseptal sheath) and stored digitally for off-line analysis. The LV and LA pressures were measured during right atrial pacing at cycle lengths of 800 and 600 ms, and during AF. All pressure measurements were repeated 3 times and averaged. Left ventricular end-systolic pressure (LVESP), the peak rate of left ventricular pressure change (dP/dt), left ventricular relaxation indicated by tau (time constant of LV relaxation), and left ventricular end-diastolic pressure (LVEDP) were determined. Cardioversion was performed to resume sinus rhythm if the patient was in AF at the time of the study.

ECHOCARDIOGRAPHIC STUDY. Standard comprehensive echocardiography (Vivid 7, GE Medical Systems, Milwaukeee, Wisconsin) was performed simultaneously with the hemodynamic study. LV volume, LVEF, and left atrial volume index (LAVI) were assessed. Mitral inflow was obtained by pulsed-wave Doppler echocardiography with the sample volume between mitral leaflet tips during diastole, and mitral annulus velocities were obtained from the septal annulus by tissue Doppler imaging. LA strain was measured at LA septal and lateral segments during ventricular systole and diastole. All measurements were performed for 5 cardiac cycles and then averaged.

ELECTROPHYSIOLOGICAL STUDY. The effective refractory period (ERP) of the high right atrium, LA (distal coronary sinus), and proximal and distal left superior PV was measured by a programmed single extra stimulus (Fig. 1). The ERP was defined as the longest AA interval that failed to elicit tissue response. Electrical impulses of 2.0-ms duration at twice the pacing threshold were delivered at drive cycle lengths (S1) of 600 ms, 500 ms, and 400 ms, with premature (S2) stimulation in 10-ms decrements. The atrial extrastimuli were introduced following an 8-beat drive train. A 2-s pause was allowed between each drive train. Direct

Methods

Study patients. This single-center study enrolled 63 subjects who had highly symptomatic, drug-refractory AF and who underwent catheter-based radiofrequency PV isolation in the electrophysiology laboratory at the Mayo Clinic, Rochester, Minnesota, between June 2007 and September 2009. Body mass index (BMI) (weight in kilograms divided by the square of height in meters) was determined for all patients. Patients were categorized as normal (BMI < 25 kg/m²; n = 19) or obese (BMI ≥ 30 kg/m²; n = 44) at the time of ablation. Patients with BMI 25 to 29.9 kg/m² were excluded to allow comparison between the obese and those with truly normal body weights. Patients with a left ventricular ejection fraction (LVEF) < 50%, cardiomyopathy, valvular disease, congenital heart disease, or long-lasting AF with a duration of more than a year were excluded. This study was approved by the Mayo Clinic Institutional Review Board, and all patients signed informed consent.

All patients underwent clinical evaluation before ablation, which consisted of a detailed history and physical examination, a 12-lead electrocardiography, a 24-h Holter study, a chest multislice computed tomography, and transcranial and transesophageal echocardiography. All antiarrhythmic drugs were held for more than 5 half-lives. Amiodarone was discontinued 1 month before the procedure.

Study protocol. CATHETERIZATION. All patients received general anesthesia. To minimize the effect of anesthetic agents on hemodynamics, only desflurane was used for all study patients during the study. Fentanyl and midazolam were avoided until the study was complete.

Standard catheterization was performed by placing catheters (5- to 7-F) into the right ventricle, right atrium, coronary sinus, and His bundle region from the femoral veins and right internal jugular vein. LA access was achieved by a double transseptal puncture technique. A decapolar circular catheter (Lasso, Biosense Webster, Diamond Bar, California) was advanced through a transseptal sheath for mapping PV potentials. Intracardiac bipolar electrograms were displayed simultaneously on a multichannel recorder (Prucka Engineering, Houston, Texas). Patients received heparin before transseptal puncture and throughout the ablation procedure to maintain an activated clotting time of 300 to 400 s. The study protocol was then undertaken before the ablation.
current (DC) cardioversion was performed to restore sinus rhythm when AF was induced. The LA conduction time was determined as the traveling time from distal coronary sinus (CS) (pole 1, 2) to mid CS (pole 9, 10) by distal CS pacing. A 3.5-mm open, saline-irrigated ablation catheter (ThermoCool, Biosense Webster) was placed at the left superior PV ostium. The longitudinal PV conduction time was determined as the time interval from proximal to distal recording electrodes on the ablation catheter, during distal CS pacing. A 15-mm, 10-unipolar circular lasso catheter was placed at the orifice of the left superior PV. Circumferential PV ostial conduction was defined as the conduction time from lasso pole 1 to pole 6 with pacing from lasso pole 1 (one-half of lasso circle) (Fig. 1). All conduction times were measured at pacing cycle lengths of 600, 500, and 400 ms. Conduction velocity was then calculated (catheter electrode distance divided by conduction time). At the completion of the study, AF was induced by programmed LA stimulation from the CS with 2 extrastimuli and burst pacing to determine excitability of the atria.

PV AND LA 3-DIMENSIONAL MAPPING. A 3-dimensional electroanatomic mapping system (Carto XP Navigation System, Biosense Webster, or NAVX, St. Jude Medical, St. Paul, Minnesota) was used to create the anatomy of the 4 PV ostia. Thereafter, an LA activation map was created in sinus rhythm. The following electroanatomic features were collected to examine LA myocardial substrate: 1) median LA voltage; 2) LA volume; 3) the location and total area of electrically silent regions (scar), defined as absence of recordable activity or a bipolar voltage <0.05 mV; and 4) the location and total area of low-voltage regions that were defined as contiguous areas of bipolar voltage >0.05 and <0.5 mV.

Statistical analysis. Continuous variables are presented as mean ± SD. Patients were grouped according to BMI, and characteristics of the BMI groups were compared by using 2-sample Student t tests, or Wilcoxon rank sum tests, depending on the distribution of the data. Categorical variables were assessed with a chi-square test. Paired comparisons of continuous variables were accomplished with a paired t tests. Multivariate linear regression analysis was performed to evaluate whether hypertension, diabetes, and sleep apnea account for the difference between obese and normal BMI groups for each of the echocardiographic and electrophysiological outcomes. Values of p <0.05 were considered significant.

Results

Patient baseline characteristics. The study population consisted of 44 obese and 19 nonobese subjects. The mean age was 57 ± 10 years. Baseline patient characteristics are shown in Table 1. Obese patients had a higher waist/hip ratio (p = 0.02) and more prevalent hypertension and sleep apnea compared with normal BMI patients (68% vs. 32%, p = 0.007; 45% vs. 5%, p = 0.002, respectively). There was no significant difference in the incidence of persistent AF between the 2 groups (p = 0.11). In patients who presented in sinus rhythm, the interval between the last documented AF episode and the procedure was similar in the obese (31 ± 40 days) and normal BMI groups (32 ± 31 days, p = 0.73). The majority of patients (89%) had failed treatment with at least 1 antiarrhythmic agent. Before the procedure, 8 patients were taking amiodarone, which was discontinued in all patients (1 [5%] in the normal BMI group and 7 [13%] in the obese group, p = 0.42). The mean duration from stopping amiodarone to the procedure was 46 ± 29 days. More obese patients were taking statin drugs (36% vs. 5%, p = 0.01).

Of the 63 study patients, 52 were in sinus rhythm and 11 were in AF at the time of the ablation procedure. These 11 patients underwent DC cardioversion (2 in the normal BMI group and 9 in the obese group, 10.5% vs. 14.3%, p = 0.47) before the electrophysiology and hemodynamic studies. The presenting AF persisted for 75 ± 105 days in the normal BMI group and 130 ± 112 days (p = 0.59) in the obese group before cardioversion. The time from DC cardioversion to electrophysiology study was 32 ± 17 min and 49 ±
16 min (p = 0.37) in the normal BMI and obese groups, respectively.

Electrophysiological features in obese patients. At a pacing cycle length of 600 ms, the ERPs were significantly different among the right atrium, left atrium, proximal PV, and distal PV (p < 0.001) (Fig. 2). Comparison of ERPs in the right atrium, left atrium, and proximal and distal PV between normal BMI and obese patients is shown in Figure 3. At a 600-ms pacing cycle length, obese patients had shorter ERPs in the left atrium (233 ± 32 ms vs. 251 ± 25 ms, p = 0.04), proximal (207 ± 33 ms vs. 248 ± 34 ms, p < 0.001) and distal (193 ± 33 ms vs. 248 ± 44 ms, p < 0.001) PV than normal BMI patients. This difference is maintained at pacing cycle lengths of 500 ms and 400 ms in the PV. Figure 4 shows LA (A1 and A2), proximal PV (B1 and B2), and distal PV (C1 and C2) ERP for a patient with persistent AF and obesity.

The LA conduction velocities (1.24 ± 0.22 m/s vs. 1.18 ± 0.30 m/s, p = 0.48) and PV circumferential conduction time (23 ± 11 ms vs. 31 ± 30 ms, p = 0.12) were similar in normal BMI and obese patients. However, the longitudinal PV conduction velocity in obese patients was significantly slower than in normal BMI patients at pacing cycle lengths of 600 ms (0.78 ± 0.35 m/s vs. 1.11 ± 0.54 m/s, p = 0.05). Figure 5 shows an example of measurement for LA conduction time (Fig. 5A), longitudinal PV conduction time (Fig. 5B, from proximal to distal ablation catheter), and circumferential PV conduction time (Fig. 5C, from lasso catheter pole 1, 2 to 6, 7).

There was no difference in the mode of AF induction between obese and normal BMI patients. AF (sustained for more than 5 min) was induced by programmed extrastimuli in 26 patients (7 normal BMI, 19 obese, p = 0.78) and rapid atrial burst pacing in 16 patients (4 normal BMI, 12 obese, p = 0.75). After DC cardioversion, spontaneous AF recurred within 5 min in 6 normal BMI patients (32%) and 5 obese patients (11%) (p = 0.07) before the ablation.

A comparison of atrial electrical features by 3-dimensional mapping between normal BMI and obese patients is shown in Table 2. The LA activation time,
median voltage, and scar areas were similar between the 2 groups (p > 0.05).

**Hemodynamic features in obese patients.** The mean sinus cycle length was 965 ± 236 ms. When pacing at 800 ms and 600 ms as compared with sinus rhythm, the LVESP and maximum LV dP/dt increased (p < 0.01), minimum LV dP/dt and tau decreased (p < 0.01), and LVEDP was unchanged. Compared with the normal BMI patients, the obese patients had higher LVEDP and mean LA pressure in sinus rhythm, whereas LVESP and maximum LV dP/dt were not different (Fig. 6). During atrial pacing at 800 ms, 600 ms, and induced AF, the difference in LVEDP and mean LA pressure between the 2 groups was maintained. **Figure 7** shows simultaneous LV and LA pressure recordings in a patient with normal BMI (Fig. 7A) and a patient with obesity (Fig. 7B).

**Echocardiographic features in obese patients.** In sinus rhythm, LV end-diastolic and systolic volume indexes and LVEF were not different between normal BMI and obese patients. However, the LAVI at LV end-diastole (end of LA systole, p = 0.002) and LAVI pre-A (end of diastole, p = 0.006) were significantly higher in obese patients, resulting in a lower LA ejection fraction (p = 0.001) in obese patients compared with normal BMI patients. The E and A flow velocity, E/A ratio, deceleration time, LA septal E velocity, and E/E’ ratio were similar between the 2 groups. Compared with the normal BMI patients, obese patients had lower longitudinal LA strains (p < 0.001) (Table 3).

**Multivariate analysis for electrophysiological and hemodynamic features in obese patients.** Hypertension, diabetes, and obstructive sleep apnea were more frequently present in obese patients compared with normal BMI patients in this study. Multivariate linear regression modeling was performed to determine whether these clinical confounding factors affect the results. After adjustment for each of the individual factors, the differences between obese and nonobese groups continued to be significant in proximal and distal PV ERP, PV longitudinal conduction time, LAVI, LA strain, LVEDP, and LA mean pressure (all p < 0.05).

**Discussion**

**Main findings.** Obese patients with AF showed slower conduction from the left atrium entering the PV and a significantly shorter ERP in the left atrium and PV. However, no significant LA substrate scarring was identified by 3-dimensional mapping in obese and normal BMI patients. Obese patients had higher LA filling pressures and greater extent of LA remodeling with a higher LAVI and impaired LA contractility. This difference remains present after adjustment for the clinical confounding factors, including hypertension, sleep apnea, and diabetes, which are more prevalent in obese patients.

**Electrophysiological features predisposing to AF in obese patients.** There is increasing evidence that obesity is associated with greater prevalence of AF (11,12). At the Mayo Clinic, 40% of the patients who underwent PV isolation for symptomatic, drug-refractory AF were obese with a BMI ≥ 30 kg/m² (7). How obesity promotes AF is unclear. In this study, obese patients had central adipose deposition with increased waist/hip ratio, a 2-fold higher incidence of hypertension, and a 9-fold higher incidence of obstructive sleep apnea compared with normal BMI pa-
patients, similar to our previous reports and those from others (13,14).

We have noted that the ERPs were shortened in the order of right atrium, left atrium, proximal PV, and distal PV, consistent with the findings from other reports (15,16). Here, we report the novel finding that the ERPs in the proximal and distal PV in obese patients were substantially shorter than those in normal BMI patients. The shortened ERP in the PVs could be a potential mechanism of sustaining or perpetuating AF in obese patients. Conversely, AF may shorten the PV ERP, and hence, promote “AF begets AF.” Although the elapsed time of the last episode of AF prior to the study was 31 days on average in this study, and similar between obese and normal BMI groups, Rostock et al. (17) have shown evidence that a brief episode of AF shortens ERP and slows conduction of PV to a greater extent than the atria. Further, to investigate the mechanism of AF initiation by premature atrial contraction in the PV, Narayan et al. (18) made a novel finding that an action potential duration restitution slope >1 near the PVS enables single premature atrial beats to initiate AF in patients with paroxysmal AF. By contrast, marked activation delay near PVSs and flattened action potential duration restitution are the features of persistent AF (18). We could speculate that obese subjects may have the electrical substrate predisposing atria to fibrillation initiation in the PVSs (triggers) and prone to sustaining AF. The atrial ERPs were also shortened, though more modestly, in obese patients in our study. The longitudinal conduction velocity from left atrium to PV was slower in obese patients than that in normal BMI patients. The LA conduction velocity did not differ between the 2 groups. This observation was in agreement with the finding from electroanatomic mapping that only limited atrial pathological substrate (LA endocardial fibrosis or scarring) was present in both obese and normal BMI patients, despite the presence of hemodynamic stress with larger LA volume, depressed LA function, and impaired diastolic function in the obese group. The absence of extensive LA structural remodeling may be due to exclusion of patients with long-standing AF or structural heart diseases. However, a direction-dependent conduction abnormality was notable in patients with lone AF, but not in control subjects (19). AF

![ERP Measurement](image-url)
mechanisms other than myocardial fibrosis, such as autonomic imbalance and LA stretching, may contribute to the initiation of and perpetuation of AF. Indeed, using a stretch-related AF model in the sheep heart, Kalifa et al. (20) reported a positive correlation between intra-atrial pressure and the number of waves emanating from the left superior PV, but not from the LA free wall. A higher maximum dominant frequency in the LA superior PV junction, as compared with the LA free wall, was observed when measured LA pressure is increased above 10 cm H2O (20).

LV diastolic dysfunction and atrial structural remodeling in obese patients. A unique feature of our study is the simultaneous hemodynamic measurements by cardiac catheterization and noninvasive echocardiography to assess intracardiac pressures and LV systolic and diastolic function in the electrophysiology laboratory. LV contractility and systolic function in obese patients were comparable to those in normal BMI patients. However, the indexes of LV diastolic function, including the LV filling pressures (LVEDP and mean LA pressure) were significantly elevated in obese patients compared with normal BMI patients. Such differences were present during sinus rhythm and in AF. In addition, the LAVI at the end of LA diastole and systole, measured by 2-dimensional echocardiography, was higher and LA ejection fraction was lower in obese patients. Although the Doppler study did not show evidence of LV diastolic dysfunction, the findings of normal E/A ratio, E/E' ratio, and deceleration time in obese patients, the LA strain was reduced, consistent with impaired LA stretching and contraction in obese patients. A previous study has shown that a higher BMI was associated with elevated LV diastolic pressure after controlling for the end-diastolic volume (21). Elevated LV filling pressures stretch the left atrium and increase LA wall strain, leading to LA dilation.

LA dilation is associated with an increased risk of AF (3). In addition, the increased circulating volume (obliged by a larger body mass) may be a pathophysiological cause of atrial enlargement (5,22,23). The present study clearly showed significant elevation in LV diastolic pressure, mean LA pressure, and impaired LV relaxation in obese patients. These findings indicate that cardiac catheterization is more sensitive than Doppler techniques in detecting LV diastolic dysfunction. However, the major cardiac chamber of interest in obese patients appears to be the left atrium, where hemodynamics parameters, LA strain, and echographic measurements all indicate the presence of structural and functional impairments.

Table 2  Comparison of LA Substrate Between Normal BMI and Obese Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BMI &lt;25 kg/m² (n = 19)</th>
<th>BMI ≥30 kg/m² (n = 44)</th>
<th>Total (N = 63)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of LA mapping points</td>
<td>69.1 ± 17.5</td>
<td>67.1 ± 19.6</td>
<td>67.6 ± 18.9</td>
<td>0.76</td>
</tr>
<tr>
<td>LA activation time, ms</td>
<td>110.0 (106.0, 118.0)</td>
<td>120.0 (95.0, 135.0)</td>
<td>116.0 (98.0, 130.0)</td>
<td>0.51*</td>
</tr>
<tr>
<td>LA voltage, mV</td>
<td>1.3 (1.2, 1.9)</td>
<td>1.1 (0.6, 1.5)</td>
<td>1.2 (0.9, 1.5)</td>
<td>0.11*</td>
</tr>
<tr>
<td>Highest</td>
<td>6.1 ± 1.9</td>
<td>5.9 ± 2.8</td>
<td>6.0 ± 2.5</td>
<td>0.87</td>
</tr>
<tr>
<td>Lowest</td>
<td>0.1 (0.1, 0.3)</td>
<td>0.1 (0.1, 0.2)</td>
<td>0.1 (0.1, 0.2)</td>
<td>0.68*</td>
</tr>
<tr>
<td>Scar area (&lt;0.05 mV), cm²</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.0 (0.0, 0.0)</td>
<td>0.42*</td>
</tr>
<tr>
<td>Low-voltage area (&lt;0.5 mV), cm²</td>
<td>2.8 (0.0, 3.9)</td>
<td>2.5(0.0, 8.4)</td>
<td>2.5 (0.0, 5.6)</td>
<td>0.59*</td>
</tr>
</tbody>
</table>

Values are mean ± SD or median (quartile). *Rank sum test.
BMI = body mass index; LA = left atrial.
Study limitations. This is a study investigating obese patients undergoing catheter ablation for symptomatic AF. The patient population may not be representative of the epidemiological obese population with AF (e.g., those with AF without symptoms). This study did not include a control group of obese subjects without AF, which could provide additional information for the pathophysiology of AF in obesity. Only consented patients were enrolled; hence, patient selection bias could weaken the results. Some patients with persistent AF required DC cardioversion to provide measurements in sinus rhythm. Electrical remodeling or atrial mechanical stunning after cardioversion may affect the electrophysiological and hemodynamic results. However, the hemodynamic and echocardiographic measurements within each case were comparable. The collection of LA mapping points using electroanatomical mapping may...
not be sufficient to assess small area of atrial fibrosis. Because the PV ostial diameter may be variable in each patient, the measured circumferential PV conduction time could be falsely shortened by using a standard 15-mm lasso in those patients with small veins. Also, the difference in conduction velocity at a faster rate or shorter cycle length of 150 to 250 ms, typically seen in AF, was not determined in this study. Although LA pressure and volume overload were more apparent in the obese group, the changes in LA electrical remodeling is modest. No significant atrial scarring or impaired conduction velocity was noted in this study. Inclusion of patients with long-standing AF may provide further information.

Conclusions

To our knowledge, this is the first mechanistic study to characterize the electrophysiological, hemodynamic, and echocardiographic properties in obese patients with AF. Factors that contribute to the predisposition and perpetuation of AF in obese patients include shortened ERP, slowed conduction in the PV ostia, elevated LA filling pressure, LV diastolic dysfunction, impaired LA stretching and contraction, and enlarged LA volume. The mechanism that underlies atrial and PV electrophysiological remodeling from hemodynamic stress and predisposes obese patients to AF remains to be determined.

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REFERENCES


Key Words: atrial fibrillation • catheter ablation • electrophysiology • hemodynamics • obesity.