Carcinoid Heart Disease: Impact of Pulmonary Valve Replacement in Right Ventricular Function and Remodeling

Heidi M. Connolly, MD; Hartzell V. Schaff, MD; Charles J. Mullany, MB, BS; Martin D. Abel, MD; Patricia A. Pellikka, MD

Background—Carcinoid heart disease characteristically affects tricuspid (TV) and pulmonary valves (PV), and TV replacement is helpful in selected patients. There is uncertainty, however, regarding optimal surgical management of PV regurgitation.

Methods and Results—We reviewed 22 patients having operation for carcinoid heart disease and compared those having TV and PV replacement (n=12), to those who underwent TV replacement and excision of the PV (n=10). Pre- and postoperative right ventricular (RV) size and dysfunction were assessed by consensus of 2 echocardiographers blinded to type of surgical treatment. RV dysfunction was graded as none (0), mild (1), moderate (2), or severe (3). RV size was graded as normal (0), or mild (1), moderate (2), or severe (3) enlargement. Preoperatively, RV size (2.2±0.8 [no PVR] versus 2.7±0.6 [with PVR], P=0.15), RV dysfunction (0.9±0.9 [no PVR] versus 1.4±0.7 [with PVR], P=0.14), and NYHA class were similar in the 2 groups. Postop RV size decreased inpatients with PVR, 2.7±0.6 to 1.7±1.0 (P=0.008), but did not change appreciably in those without PVR, 2.2±0.8 to 2.3±0.8 (P=0.67). There was no significant change in RV dysfunction after surgery, 1.4±0.7 to 1.8±0.9 with PVR (P=0.26) and 0.9±0.9 to 1.6±0.9 without PVR (P=0.07).

Conclusions—PV replacement appears to have a beneficial effect on RV size in patients after surgery for carcinoid heart disease. This may have important implications for RV remodeling after PV replacement. (Circulation. 2002;106[suppl I]:I-51-I-56.)

Key Words: valves ■ regurgitation ■ surgery ■ carcinoid

Carcinoid tumors arise in 1.2 to 2.1/100,000 people in the general population per year.1 Commonly, patients present with the carcinoid syndrome, which consists of flushing, gastrointestinal hypermotility and bronchospasm. The carcinoid syndrome is caused by the release of vasoactive substances, 1 of which is 5-hydroxytryptamine (serotonin). Diagnosis is confirmed by elevation of the by-product of serotonin metabolism, 5-hydroxy indole acetic acid (5-HIAA). The urinary 5-HIAA (24-hour collection) provides a reliable biological marker for the assessment of tumor activity and the response to therapy.2

Progress in the management of malignant carcinoid tumors and carcinoid syndrome has resulted in better patient survival. Treatment with the somatostatin analog, octreotide acetate (Sandostatin®) relieves symptoms in more than 70% of patients.3,4

Carcinoid heart disease is a major source of morbidity and mortality for patients with carcinoid syndrome and typically, leads to progressive dysfunction of the tricuspid and pulmonary valves. Patients present with symptoms of right heart failure. Tricuspid valve replacement provides good palliation in selected patients, but the best surgical approach to the pulmonary valve in patients with carcinoid heart disease remains uncertain. We hypothesized that pulmonary valve replacement may be beneficial for patients with carcinoid heart disease. In the present study, we analyzed the outcome of 22 surgical patients with carcinoid heart disease who had tricuspid valve replacement with or without pulmonary valve replacement.

Methods

Patients
This study was reviewed and approved by the Institutional Review Board of the Mayo Clinic.

Because of the known poor prognosis of patients with symptomatic carcinoid heart disease, patients were referred for cardiac surgery if they met the following criteria: (1) symptoms of right heart failure caused by carcinoid valvular involvement, (2) adequate control of systemic carcinoid symptoms with somatostatin or hepatic dearterialization (embolization or ligation of arterial supply to hepatic metastases), and (3) no other serious concurrent major medical illnesses.

Between 1987 and 2001, 82 patients underwent surgical treatment for carcinoid heart disease. Of these, 71 patients underwent tricuspid valve replacement and had a pulmonary valve procedure. Twelve patients died in the perioperative period (4 had pulmonary valve replacement).
replacement, 4 had pulmonary valve excision and enlargement of the right ventricular outflow tract, 2 had pulmonary valve excision alone and 2 had no procedure on the pulmonary valve. Pre- and postoperative echocardiographic studies were available for 22 patients; these comprise the group described here. Ten patients who underwent pulmonary valve excision were compared with 12 patients who had pulmonary valve replacement. Follow-up data were obtained by review of the medical records.

Clinical and Laboratory Findings
Preoperative evaluation included a complete history and physical examination, electrocardiography, chest radiography and determination of the urinary 5-HIAA levels in all patients. Coronary angiography was also performed in all patients.

Pre- and postoperative echocardiographic images were reviewed to assess pre- and post-operative right ventricular size and function. Right ventricular size and the degree of dysfunction were determined by consensus of 2 experienced echocardiographers who were blinded to type of surgical treatment. The right ventricular size and function was evaluated in 3 planes. Right ventricular dysfunction was graded as none (0), mild (1), moderate (2), or severe (3) reduction in systolic function. Right ventricular size was graded as normal (0), or mild (1), moderate (2), or severe (3) enlargement.⁵

Surgical Management
Treatment was not randomized. Initially, we reserved pulmonary valve replacement for those patients having severe right ventricular dysfunction who were undergoing tricuspid valve replacement. The smooth post-operative course in these patients in addition to the occasional persistence of right ventricular enlargement in patients who had isolated tricuspid valve replacement led us to use pulmonary valve replacement more liberally. Thus, the purpose of the present study was to compare clinical outcome and echocardiographic results of patients having tricuspid valve replacement with or without pulmonary valve replacement.

Anesthetic management combined high dose narcotic technique with fentanyl or sufentanil, with the volatile inhalational anesthetic, isoflurane, or enfurane.⁶⁻⁸ Hemodynamic monitoring included the use of a pulmonary artery catheter or a central venous catheter. Octreotide acetate was used liberally by intravenous administration any time the patient manifested flushing, unexplained hemodynamic lability, or unexplained volume loss during extracorporeal circulation. Intraoperative transesophageal echocardiography was employed in all patients to evaluate the results of the surgical procedure and to monitor ventricular and valve function.

Pathologic Findings
The surgical pathology reports were reviewed to assess the gross and microscopic pathology. Microscopic slides were prepared with the hematoxin-eosin, Masson trichrome, and Verhoff van Gieson stains.

Statistical Analysis
Data are expressed as mean ± SD. Comparison of group characteristics was performed by Fisher’s t test for nominal data. A probability of <0.05 was considered significant.

Results
Clinical and Diagnostic Data
All patients had the carcinoid syndrome with associated symptomatic valvular heart disease, median NYHA class 3 (range 2 to 4). Twelve patients, 7 men, 5 women, (patients 1 to 12, Table 1) mean age at operation 56 ± 12 years, who underwent tricuspid and pulmonary valve replacement were compared with 10 patients, 6 men, 4 women, (patients 13 to 22, Table 1) mean age at operation 59 ± 11 years, who underwent tricuspid valve replacement with pulmonary valve excision or pulmonary valve excision and outflow tract enlargement. The preoperative New York Heart Association functional class of the patients who had pulmonary valve replacement was similar to that of the patients who did not undergo pulmonary valve replacement, 3 ± 0.5 versus 3.3 ± 0.6, respectively.

The median interval from the diagnosis of carcinoid syndrome to the diagnosis of carcinoid heart disease was 15 months in patients who had pulmonary valvectomy and 20 months in patients who had pulmonary valve replacement. The median interval from diagnosis of carcinoid syndrome to cardiac operation was 24 months in patients who had pulmonary valvectomy and 34 months in patients who had pulmonary valve replacement (range 1 to 155 months).

All patients had urinary 5-HIAA measured before surgery. The mean preoperative 5-HIAA value for the 22 patients was 116 ± 70 mg per 24 hours (range 52 to 362, normal 0 to 6.0); 117 ± 81 in patients who had pulmonary valve replacement and 113 ± 50 in patients who had pulmonary valve excision. All patients were on somatostatin before operation and the usual initial dose was 150 micrograms administered subcutaneously every 8 hours, or 20 milligrams Sandostatin LAR® administered every 28 days. Increased dosages were administered for breakthrough symptoms or for the development of...

Echocardiographic Findings and Surgical Procedures in 22 Patients With Carcinoid Heart Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Operation</th>
<th>Preop Echo RV Size/Function</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>3/2</td>
<td>CE TVR, CE PVR</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>3/2</td>
<td>CE TVR, PV Homograft</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>3/2</td>
<td>CE TVR, CE PVR</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>3/2</td>
<td>CE TVR, PVR (SJ TVR, PVR removed)</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>3/2</td>
<td>SJ TVR, PV Homograft</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>3/1</td>
<td>CE TVR, CE PVR</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>3/2</td>
<td>SJ TVR, SJ PVR</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>2/1</td>
<td>SJ TVR, PV Homograft, SJ AVR, SJ MVR</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>2/1</td>
<td>SJ TVR, PV Homograft</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>1/0</td>
<td>CE TVR, CE PVR</td>
</tr>
<tr>
<td>11</td>
<td>46</td>
<td>3/1</td>
<td>CE TVR, CE PVR, PFO closed, CE MVR</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>2/1</td>
<td>CE TVR, CE PVR</td>
</tr>
<tr>
<td>13</td>
<td>52</td>
<td>1/0</td>
<td>SJ TVR, myocardial met removed</td>
</tr>
<tr>
<td>14</td>
<td>68</td>
<td>2/1</td>
<td>CE TVR</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>3/2</td>
<td>CE TVR, CABG, ASD closed, CE MVR</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>3/2</td>
<td>CE TVR</td>
</tr>
<tr>
<td>17</td>
<td>69</td>
<td>3/2</td>
<td>CE TVR, PFO closed</td>
</tr>
<tr>
<td>18</td>
<td>42</td>
<td>1/1</td>
<td>CE TVR, PFO closed</td>
</tr>
<tr>
<td>19</td>
<td>62</td>
<td>2/0</td>
<td>CE TVR</td>
</tr>
<tr>
<td>20</td>
<td>70</td>
<td>2/0</td>
<td>CE TVR, CABG</td>
</tr>
<tr>
<td>21</td>
<td>68</td>
<td>2/0</td>
<td>CE TVR</td>
</tr>
<tr>
<td>22</td>
<td>62</td>
<td>3/1</td>
<td>CE TVR, CABG</td>
</tr>
</tbody>
</table>

Preop = preoperative; RV = right ventricle; CE = Carpentier-Edwards; SJ = St. Jude; SE = Starr-Edwards; TVR = tricuspid valve replacement; PV = pulmonary valve; AVR = aortic valve replacement; MVR = mitral valve replacement; PVR = pulmonary valve replacement; PFO = patent foramen ovale; met = metastasis; CABG = coronary artery bypass graft surgery; ASD = atrial septal defect. 0 = none or normal; 1 = mild; 2 = moderate; 3 = severe.
tachyphylaxis. The mean somatostatin dose at the time of cardiac operation was 1040 micrograms per day (range 450 to 1500) for 5 patients on short acting therapy who had pulmonary valve replacement and 675 micrograms per day (range 450 to 1500) for 8 patients with pulmonary valvectomy. The long acting (Sandostatin LAR®) mean dose was 23 mg per 28 days (range 20 to 30 mg per 28 days). Sandostatin LAR® was used in 7 patients (58%) who had pulmonary valve replacement and 2 patients (20%) who had pulmonary valvectomy.

All patients had severe tricuspid valve regurgitation determined by preoperative echocardiography. The overall mean diastolic tricuspid valve gradient was 4.4±1.5 mm Hg and there was no difference in tricuspid valve mean gradient between patients with (4.2±1.3) and without (4.7±0.8) pulmonary valve replacement. Pulmonary valve regurgitation was considered moderate or greater in all patients by preoperative echocardiography. The average pulmonary valve peak gradient measured by echocardiography was 15±8 mm Hg (range 6 to 31) in patients who subsequently had pulmonary valve replacement, and 17±3 mm Hg (range 13 to 23) in patients who subsequently had pulmonary valvectomy (P=0.43). Associated mitral and aortic valve disease was present in 3 patients (patients 8, 11, and 15, Table 1).

Significant coronary artery disease (stenosis ≥50% diameter) was present in 3 patients preoperatively (patients 15, 20, 22, Table 1).

**Surgical Management**

The surgical procedures performed are shown in Table 1. All patients had tricuspid valve replacement because of severe tricuspid valve regurgitation (15 bioprostheses, 7 mechanical prostheses). Pulmonary valve replacement was performed in 12 patients for relief of right ventricular outflow tract obstruction and or management of pulmonary valve regurgitation (7 bioprosthetic, 1 mechanical, 4 homograft). Pulmonary valvectomy was performed in 10 patients. The pulmonary valve annulus was enlarged with pericardial patch to relieve anular narrowing in 3 patients.

Left-sided valve disease requiring surgery was present in 3 patients (patients 8, 11, and 15, Table 1); 2 patients had an intra-atrial communication (patient 11 and 15, Table 1) documented intraoperatively. A patent foramen ovale was also closed in 2 patients without left-sided valve disease. Mitral valve replacement was performed in 3 patients (2 bioprostheses, 1 mechanical prosthesis). Aortic valve replacement was performed in 1 patient (mechanical prosthesis). One patient (patient 8, Table 1) had all 4 valves replaced.

Simultaneous coronary artery bypass graft surgery was performed in 3 patients (patient 15, 20 and 22, Table 1). An intramyocardial carcinoid metastasis was removed from 1 patient (patient 13, Table 1). Additionally, 1 patient (patient 10, Table 1) had a papillary fibroelastoma removed from the aortic valve. The average cardiopulmonary bypass time was 108±37 minutes (range 68 to 173 minutes) in patients with pulmonary valve replacement compared with 96.3±48 (range 50 to 194) inpatients who had pulmonary valvectomy with or without annular enlargement (P=0.53).

Two patients had undergone cardiac surgery before referral to our Clinic. Patient 7 (Table 1) had surgical pulmonary valvectomy for symptomatic pulmonary valve stenosis and right heart failure at another institution before the diagnosis of carcinoid syndrome. He underwent tricuspid and pulmonary valve replacement 6 years later at Mayo Clinic. Another patient (patient 15, Table 1) had coronary artery bypass surgery at another institution 3 years before tricuspid valve replacement and pulmonary valvectomy.

Large doses of somatostatin were often required in the perioperative and postoperative periods. The average somatostatin dose administered during cardiac surgery among these 12 patients who received pulmonary valves was 1280±1674 mcg compared with 1598±1866 mcg for patients who did not receive pulmonary valves (P=0.55).

**Early Outcome**

The mean hospital stay among the patients who underwent pulmonary valve replacement was 11±9 days (range 5 to 39) compared with 8±3 days (range 6 to 14) for patients who had no pulmonary valve replacement (P=0.27). Three patients (patients 3, 4, and 12, Table 1), all with tricuspid and pulmonary valve replacement, required permanent pacemaker implantation for persistent postoperative heart block.

**Valve Pathology**

Pathological examination of the 22 tricuspid valves, 12 pulmonary valves, 3 mitral valves, and 1 aortic valve demonstrated gross thickening but no calcification. On microscopy, there was carcinoid plaque involving the tricuspid valve leaflets in all cases; in most patients, the tendinous cords and papillary muscles of the tricuspid valve also exhibited carcinoid plaque. All 3 mitral valve specimens showed carcinoid plaque involvement of both the leaflets and the tendinous cords. Carcinoid plaques were also seen in cusps of excised pulmonary valves and the aortic valve.

**Right Ventricular Size and Function**

Preoperatively, right ventricular size (2.7±0.6 versus 2.2±0.8, P=0.15), right ventricular dysfunction (1.4±0.7 versus 0.9±0.9, P=0.14), and NYHA class were similar in both groups. Postoperatively, echocardiographic examinations were performed on average 115±343 days for patients with pulmonary valve replacement versus 226±399 days for patients who did not have pulmonary valve replacement (P=0.49). Postoperative right ventricular size decreased in patients with pulmonary valve replacement, 2.7±0.6 to 1.7±1.0 (P=0.008), but did not change appreciably in patients who did not have pulmonary valve replacement, 2.2±0.8 to 2.3±0.8 (P=0.67) (Figure 1 to 3). Right ventricular dysfunction did not change significantly after surgery in either group, 1.4±0.7 to 1.8±0.9 (P=0.26) in patients with pulmonary valve replacement, and 0.9±0.9 to 1.6±0.9 (P=0.07) in patients with pulmonary valvectomy (Figure 4).

**Follow-Up Data**

Most patients (19/22, 86%) reported improvement in functional capacity after operation; median New York Heart Association functional class was 3 preoperatively versus 2.
postoperatively, $P=0.0008$ and was similar in the 2 groups (Figure 5). Two patients with pulmonary valve replacement (patients 4 and 9, Table 1) had little change in exercise capacity because of early prosthetic valve dysfunction, and both patients required reoperation; patient 9 developed severe homograft pulmonary stenosis 10 months after initial operation and patient 4 developed tricuspid and pulmonary prosthesis dysfunction 6 months after initial surgery. One additional patient (patient 16, Table 1) had no functional improvement after tricuspid valve replacement and pulmonary valve excision despite normal function of the tricuspid prosthesis.

Twelve patients were alive and had a mean follow up of 30 months (range 8 days to 118 months). Ten patients died after hospital dismissal, and average survival was 24 months, range 3 to 80 months (patients 2, 4, 8, 9, 13, 15, 16, 17, 19, and 22, Table 1). Late deaths were because of progression of metastatic carcinoid tumor in 8 patients (80%). Two deaths were cardiac, patient 4 had persistent heart failure symptoms and died 3 years after reoperation for prosthetic valve dysfunction and patient 9 died early after reoperation for prosthetic valve dysfunction.

**Discussion**

Patients with carcinoid heart disease typically present with symptoms of right-sided heart failure (hepatomegaly, edema, ascites, fatigue, and low cardiac output), and when symptoms are advanced (NYHA class 3 or 4), outlook is poor with an estimated survival of only 11 months.

Carcinoid heart disease is characterized histologically by diffuse collections of thick, pearly white plaque composed of smooth muscle cells called “myofibroblast.” These plaques are deposited on the endocardial surface of the right atrium and on the endocardial surfaces of the valves on the right side.
of the heart, resulting in characteristic pathologic and echocardiographic features, which include thickening and immobility of the tricuspid valve and pulmonary valve leaflets.\textsuperscript{11,12} Hepatic metastases allow large quantities of tumor products such as serotonin to reach the right heart without being inactivated.\textsuperscript{13,14} The relative sparing of the mitral and aortic valves in carcinoid heart disease is likely related to inactivation of the humoral substances by the lung. The mechanism of valve injury in carcinoid heart disease is not completely understood. It is known that blood levels of serotonin are higher among patients with valvular disease compared with carcinoid patients without cardiac involvement suggesting that serotonin contributes to the development of cardiac involvement.\textsuperscript{15,16}

The present study affirms the benefit of tricuspid valve replacement in patients with carcinoid heart disease and demonstrates several important points. First, functional improvement was noted in most of the surgical survivors. Secondly, pulmonary valve replacement appears to have an important impact on postoperative right ventricular size. Lastly, reoperation may be required for bioprosthetic valve degeneration in patients with carcinoid heart disease. The small patient population precludes definitive statements regarding specific types of valve prostheses.

Premature dysfunction with accelerated stenosis was noted in a homograft pulmonary prosthesis 10 months after implantation. Percutaneous valvuloplasty resulted in pulmonary artery rupture and emergency surgery was required. Pathology of the excised homograft demonstrated fibrosis of the valve cusps. In another patient, dysfunction of both tricuspid and pulmonary prostheses occurred 6 months after initial surgery and subsequent pacemaker implantation. At the time of reoperation the bioprosthetic tricuspid valve was replaced with a St. Jude prosthesis and the pulmonary prosthesis was removed and not replaced. Pathology of the explanted prostheses demonstrated no carcinoid plaque formation but extensive thrombosis of all valve pockets causing immobilization of the valve cusps. The mechanism of premature degeneration of tissue prostheses in patients with carcinoid heart disease is incompletely understood and requires additional investigation.

Surgical reports have largely recommended tricuspid valve replacement with a mechanical prosthesis for patients with carcinoid heart disease. This recommendation was based on the presumption that biological prostheses might be damaged by vasoactive tumor substances that affected the native valves, but accelerated degeneration of tissue valves in patients with carcinoid syndrome has not been clearly established.\textsuperscript{17–19} Further, this recommendation against the use of bioprostheses was made before the introduction of synthetic somatostatin and hepatic artery interruption, both of which may protect prosthetic valve tissue from the adverse effects of vasoactive peptides by decreasing the carcinoid activity. The choice of prosthetic valve type should be individualized but should include consideration of pulmonary valve replacement when pulmonary valve dysfunction is present.

Optimal timing of valve operation for carcinoid heart disease is difficult because patients may have considerable limitation because of their underlying disease and tumor burden. Indeed, in some patients it is difficult to determine how much the cardiac disease contributes to findings such as ascites and pleural effusions, complications that can also be because of advanced metastatic carcinoid tumor. Our assessment includes clinical examination, echocardiography, and functional evaluation by the treadmill exercise testing with oxygen consumption to provide objective assessment of the functional status. Currently, patients with carcinoid heart disease are referred for valve replacement when cardiac symptoms develop, when right ventricular size increases or function decreases, and when major hepatic resection of metastases is necessary and patients have elevated systemic venous pressure because of tricuspid or pulmonary valve dysfunction.

Our clinical experience and the data from this study suggest that tricuspid and pulmonary valve replacement should be considered when both valves are involved. It is true that many patients tolerate pulmonary regurgitation, but we have observed that patients who have a competent pulmonary valve have a much smoother postoperative recovery than do patients who have tricuspid valve replacement and pulmonary valvectomy. It appears that long-standing severe pulmonary valve regurgitation, as seen after pulmonary valvectomy, may have a detrimental effect on right ventricular remodeling. Indeed as seen in late follow up studies repaired tetralogy of Fallot, even patients with normal tricuspid valves who have pulmonary valve regurgitation can developed right ventricular enlargement and right heart failure.\textsuperscript{20}

The finding that right ventricular dysfunction persisted postoperatively both in patients with or without pulmonary valve replacement is not unexpected. As is true for mitral valve regurgitation and left ventricular ejection fraction, severe tricuspid valve regurgitation would be expected to lead to overestimation of right ventricular function as assessed by any ejection phase index. Similarly, correction of atrioventricular valve regurgitation would be expected to result in a decrease in early ejection phase indices of ventricular performance, and this is well documented in studies of mitral valve repair and replacement.\textsuperscript{21}

Conclusions

Carcinoid heart disease is an uncommon and complex form of valvular heart disease. Cardiac involvement is a major cause of morbidity and mortality and cardiac operation is the only definitive treatment. Despite metastatic disease that limits longevity, operative survivors in this series had functional improvement after valve surgery for carcinoid heart disease. Cardiac surgical intervention should be considered and individualized. Tricuspid and pulmonary valve replacement should be considered for patients with symptomatic carcinoid valvular heart disease affecting both right-sided valves.

References


Carcinoid Heart Disease: Impact of Pulmonary Valve Replacement in Right Ventricular Function and Remodeling
Heidi M. Connolly, Hartzell V. Schaff, Charles J. Mullany, Martin D. Abel and Patricia A. Pellikka

Circulation. 2002;106:I-51-I-56
doi: 10.1161/01.cir.0000032884.55215.87
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/106/12_suppl_1/I-51

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/