Thromboembolic Complications of Prosthetic Cardiac Valves

By Mohammed Akbarian, M.D., W. Gerald Austen, M.D., Peter M. Yurchak, M.D., and J. Gordon Scannell, M.D.

SUMMARY

Our experience with thromboembolism in 283 patients surviving at least 1 week following insertion of Starr-Edwards valves is reported here. Of these patients, 155 underwent aortic valve replacement, 21 had aortic valve replacement with mitral commissurotomy, 80 had mitral replacement, and 27 had both aortic and mitral valve replacement. Complete follow-up data were obtained on all patients, from 3 to 49 months following surgery (mean, 20 months).

Thromboembolic episodes developed in 68 of the 283 patients (24%). Seventeen of these 68 patients died (25%), three had serious neurological residual (4%), but the majority of survivors recovered completely.

Use of long-term anticoagulant therapy appeared to reduce incidence of embolic episodes only in patients with aortic valve replacement. Control of anticoagulant therapy (good, fair, or poor) bore no relationship to incidence of embolism within this group. Anticoagulant therapy in untreated patients with emboli reduced the incidence of subsequent thromboembolism. Hemorrhagic complications occurred in 23 patients (8%); one died.

Thromboembolism is a serious complication of prosthetic valves. Its incidence in some patients is reduced but not eliminated by anticoagulant therapy.

Additional Indexing Words:
Anticoagulant therapy  Starr-Edwards valve  Hemorrhagic complications
Aortic valve replacement  Mitral valve replacement  Mitral commissurotomy
Atrial fibrillation

Since the insertion of the first successful ball-valve prosthesis by Starr1 in 1960, over 20,000 Starr-Edwards valves have been placed in human hearts. Over the years, the operative mortality and morbidity of the insertion of this type of artificial valve in aortic and mitral positions have been reduced to an acceptable level. Systemic thromboembolism, however, remains a serious complication of prosthetic valve replacement. The purpose of this paper is to review our experience with postoperative thromboembolism and to examine factors bearing on its incidence following insertion of the Starr-Edwards valve in 283 patients.

Methods

The records of all patients who underwent aortic or mitral valve replacement*, or both, at the Massachusetts General Hospital from September 1961, to July 1966, were reviewed. In order to exclude the patients who died during surgery or in the immediate postoperative period, all patients who lived less than 1 week following surgery were excluded. None of these patients had died of thromboembolism.

There were 283 patients in the entire group. Type of surgery is given in table 1. Patients’

*Starr-Edwards prosthetic aortic valve, model no. 1000, was used through April 1966, model no. 1200 thereafter. Mitral valve, model no. 6000, was used throughout.

From the Departments of Medicine (Cardiac Unit) and Surgery, Harvard Medical School and the General Medical and Surgical Services, Massachusetts General Hospital, Boston, Massachusetts.

Work was supported in part by Grants HE-5196, HE-06664 (HEPP), HE-08021, and HE-08043 from the U. S. Public Health Service.
THROMBOEMBOLISM AND PROSTHETIC VALVES

Table 1

<table>
<thead>
<tr>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of surgery</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
</tr>
<tr>
<td>Aortic valve replacement and mitral split</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>Aortic and mitral valve replacement</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Ages ranged from 19 to 74 years (mean, 50 years). There were 161 men and 122 women in the group. The severity of their cardiac disability was classified according to the New York Heart Association Classification. Forty-seven patients were in class II (17%), 223, in class III (79%) and 13, in class IV (4%).

A total of 218 patients received anticoagulant therapy using either warfarin sodium orbishydroxycoumarin (Dicumarol). This therapy was started by the third postoperative day. The remaining 65 patients were not given anticoagulant therapy for various reasons. Some earlier patients were not given anticoagulant therapy because the frequency of thromboembolism was not appreciated at that time. Patients with active peptic ulcer, recent gastrointestinal bleeding, and patients judged incapable of following instructions did not receive anticoagulant therapy. Dosage of the anticoagulant was regulated by the results of prothrombin content determinations. They were carried out daily initially and subsequently at intervals of 1 to 4 weeks. The method for measurement of prothrombin time was the one-stage Quick prothrombin time test using a barium sulfate adsorbed plasma dilution curve. Prothrombin time was considered to be in the therapeutic range when it was 2 to 2½ times the control level in seconds or 10 to 30% of normal value when it was expressed in percentage.

In some patients, there was wide variability of prothrombin time values over the course of time. The relationship of adequacy of anticoagulant therapy (judged by consistency of test results) to thromboembolism was examined. Control of anticoagulant therapy was arbitrarily classified as poor, fair, or good depending on the extent of variations of prothrombin measurements. It was considered poor when less than 50% of the measured prothrombin tests were in the therapeutic range, fair when 50 to 75% of the prothrombin tests were in the therapeutic range, and good when more than 75% of prothrombin tests were in the therapeutic range.

For purposes of determining the incidence of thromboembolism, the time of its occurrence after surgery, and the effect of anticoagulant therapy, only the first embolic episode was counted when a patient had more than one episode. Subsequent embolic episodes were included in calculating the frequency of sites involved in thromboembolism. Residual disability of a cerebral embolic episode was classified as none, mild, or severe. Only patients with definite clinical or autopsy evidence of thromboembolism were considered as having embolic episodes. Clinical evidence of emboli included neurological deficit, flank pain, and hematuria, or acute occlusion of artery to a limb.

After discharge from the hospital, 138 patients (49%) were followed closely by one of the hospital cardiologists or cardiac fellows. The follow-up in this group was obtained both from the patients' records and directly from the physicians involved. The remainder of the patients were followed by their referring physicians. The follow-up in this group of patients was obtained through questionnaires or telephone conversations with the physicians or patients or by both means. Whenever a patient was hospitalized or died in another hospital, a summary of the hospital record and autopsy report were obtained if available. On all but one patient, follow-up information was obtained at least through October 1, 1966 (date of beginning this study). In many of them the follow-up extended an additional 6 months. The duration of follow-up ranged from 3 to 49 months (mean, 20 months).

Results

Thromboembolism developed in 68 patients (24%). The distribution of the embolic episodes among various surgical groups is shown in table 2. There is no statistical difference in

Table 2

<table>
<thead>
<tr>
<th>Embolic Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of valve</td>
</tr>
<tr>
<td>Aortic</td>
</tr>
<tr>
<td>Aortic and mitral</td>
</tr>
<tr>
<td>Mitral</td>
</tr>
<tr>
<td>Aortic and mitral</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXVII, May 1968
the incidence of thromboembolic complications among patients with various valves. Thromboembolism occurred more frequently among patients not receiving anticoagulant therapy, both in patients with aortic valve replacement (with or without mitral commissurotomy) and in patients with mitral valve replacement. The difference in incidence of thromboembolic complications between the group receiving anticoagulant therapy and the untreated group was highly significant \((P < 10^{-6})\). Embolic complications were seen in 29 of 52 untreated patients \((56\%)\) versus 16 of 124 treated patients \((13\%)\) with aortic valve replacement (including those with mitral commissurotomy). They occurred in three of 10 untreated patients \((30\%)\) versus 15 of 70 treated patients \((22\%)\) with mitral valve replacement. The great majority of patients with combined aortic and mitral valve replacement were given anticoagulant therapy; therefore, the number of untreated patients in this group was too small \((only three of 27\) to be compared with the treated group. The relationship of adequacy of control of anticoagulant therapy to thromboembolism is shown in table 3. Although there is a tendency to lower incidence of thromboembolism in patients with better control of therapy, this is not statistically significant.

Following the first thromboembolic episode in the initially untreated group, 23 patients were started on anticoagulant therapy \((20\) patients with aortic valve replacement, two with aortic valve replacement and mitral commissurotomy, and one with mitral valve replacement). This therapy appeared to reduce the incidence of subsequent thromboembolism during the ensuing 18 months of follow-up. Among the 20 patients with aortic valve replacement who were given anticoagulant therapy after the first episode of thromboembolism, three had a second embolic episode, an incidence of 15%. This is comparable to that of the group of patients with aortic valve replacement treated with anticoagulants from the time of their surgery.

Thromboembolism followed abrupt discontinuation of anticoagulant therapy in four patients, proving fatal in all of them. Three of these patients had aortic, and one had mitral, valve replacement. Anticoagulant therapy had been stopped in two patients because of bleeding \((hematuria, gastrointestinal bleeding)\) and in preparation for teeth extraction in another patient. The fourth patient had discontinued taking her anticoagulant drug on her own volition. Other patients may well have had anticoagulant therapy stopped temporarily for various surgical or dental procedures without suffering from embolic episodes, but their exact number is not known.

It is difficult to evaluate the effect of cardiac rhythm \((sinus rhythm versus atrial fibrillation)\)

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation of Embolism to Anticoagulant Therapy</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Type of valve</td>
</tr>
<tr>
<td>Aortic replacement (mitral valve included)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mitral replacement</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Aortic and mitral replacement</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
on the incidence of thromboembolism in the present series. This was because most of the patients with aortic valve replacement were in sinus rhythm and most of the patients with other types of valve replacement were in atrial fibrillation. As can be seen from table 4, the incidence of thromboembolism in patients with atrial fibrillation is similar to that of each corresponding group as a whole.

The most common vessels involved with thromboembolism were the cerebral (57 instances), followed by coronary (eight), renal (two), splenic (two), extremity (two), and retinal (one). In two patients with aortic valve replacement, extensive clot formation on the rim and struts of the prosthesis had made the ball valve almost immobile. Both died of intractable congestive failure.

Seventeen of the 68 patients with thromboembolism died as a result of the embolic episodes (25% of those who had emboli). This represents 24% of the late deaths for the entire group. Three patients had severe residual neurological damage (4%), and 14 patients had mild residual impairment of function (21%). Of those who survived the embolic episode, 34 (50%) were free of any residual defect.

Various hemorrhagic complications occurred in 23 patients (8%). Bleeding was a major complication in four patients (1%), requiring blood transfusion; it was fatal in one patient (0.4%). This patient died from massive intra-thoracic hemorrhage. The most common source of bleeding was the gastrointestinal tract (11 instances), followed by genitourinary tract (six instances), and skin (four instances). Bleeding complications occurred most commonly in patients with aortic valve replacement (16 patients or 10%).

**Discussion**

Late embolic problems following prosthetic valve replacement have been an important cause of disappointing late results. The incidence varies from series to series in the literature5-9 and has been related to such factors as site of the prosthesis, use of anticoagulants, cardiac rhythm, and duration of follow-up.

Of paramount importance in determining the incidence of systemic embolization in a study such as this is adequacy of follow-up and care taken to detect all instances of embolism. In the present series, we were able to account for almost 100% of the patients entering

### Table 4

**Relationship of Rhythm to Incidence of Embolism**

<table>
<thead>
<tr>
<th>Valve group</th>
<th>Rhythm</th>
<th>Total no.</th>
<th>Anticoagulant therapy</th>
<th>No. with embolism</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic replacement (155)</td>
<td>NSR</td>
<td>134</td>
<td>Yes: 89</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 45</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>AF</td>
<td>21</td>
<td>Yes: 17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 4</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Aortic replacement + mitral split (21)</td>
<td>NSR</td>
<td>7</td>
<td>Yes: 6</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>AF</td>
<td>14</td>
<td>Yes: 12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Mitral replacement (80)</td>
<td>NSR</td>
<td>16</td>
<td>Yes: 16</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>AF</td>
<td>64</td>
<td>Yes: 54</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 10</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Aortic + mitral replacement (27)</td>
<td>NSR</td>
<td>9</td>
<td>Yes: 9</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>AF</td>
<td>18</td>
<td>Yes: 15</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No: 3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: NSR = normal sinus rhythm; AF = atrial fibrillation.

*Circulation, Volume XXXVII, May 1968*
follow-up. Yet even the technique of close personal and questionnaire follow-up used here must have missed some minor embolic episodes. The site in which an embolus lodges largely determines its likelihood of being detected, and the brain is most likely to give signs of such an event. Only by close questioning of both patient and spouse can minor episodes of cerebral embolism be suspected. Even then, proof of these may be impossible, since signs clear rapidly. Organs other than the brain can tolerate an embolus without tell-tale symptoms. Yeh and associates\(^8\) cite the case of a patient with a prosthetic valve who died of unrelated causes and showed evidence at necropsy of embolism to many organs, quite unsuspected in life. Since we accepted as embolic episodes only those that could be diagnosed with certainty, the incidence given here is lower than the actual one. The same can doubtless be said for most such follow-up studies.

Most authors have reported the lowest incidence of embolism in patients with prosthetic valves in the aortic position. This has ranged from as low as zero\(^6\) to as high as 31\%.\(^5\) The overall incidence of embolism in patients with aortic valve replacement in our series was 25\%. However, this included a substantial number of patients (45 of 155) who were not initially given anticoagulant therapy. The incidence in those treated with anticoagulants from the outset was only 13\%. Most series have reported a higher incidence of embolism in patients with mitral valve prostheses, ranging from as low as 18\%\(^8\) to as high as 53\%;\(^6\) our incidence was 22\%. It is notable that the incidence for embolism in the small number of patients after double valve replacement has been close to that of patients with mitral prosthesis alone. The reason why incidence should not be additive is not clear.

Previously reported practices with respect to anticoagulant therapy following prosthetic valve insertion have differed widely from center to center. Some groups do not give anticoagulants at all,\(^7\) some give them to only "selected patients,"\(^6\) while others use them routinely and indefinitely in the absence of specific contraindications.\(^5, 8, 9\) In the present series, use of anticoagulants was definitely beneficial to those with aortic valve prostheses. There was a tendency to lower incidence of thromboembolism in patients with combined aortic and mitral replacement whose anticoagulant therapy was more adequately controlled. This is not statistically significant, but the number of patients involved is small, and a larger group might show clear-cut benefit. Anticoagulants did not appear to have any important protective effect on patients with mitral valve prostheses. When given to previously untreated patients with aortic prostheses following their first embolic episode, anticoagulants significantly reduced the incidence of further embolism. It is notable that anticoagulants were of benefit to the patients with aortic valve prostheses, whether control of therapy was good, fair, or poor. Adequacy of control of therapy bore no significant relation to freedom from embolic complications in any of the patient groups studied. This is in agreement with the experience of Yeh and associates\(^8\) and Duvoisin and associates\(^8\) with respect to patients with mitral replacement, but the latter observers found better protection in the aortic prosthesis group with more adequate control.

One must always weigh the risk from hemorrhagic complications in the balance when deciding on anticoagulant therapy, and our 8% incidence of serious complications is in agreement with that of Yeh and associates.\(^8\) It is our current practice to give anticoagulants routinely and indefinitely to all patients undergoing prosthetic valve insertion, unless specific contraindications exist.

The role of cardiac rhythm in production of embolic episodes is difficult to assess. A limitation imposed upon analysis in our series is the great tendency of patients with mitral valve disease to have atrial fibrillation, and for the great majority of patients with isolated aortic valve disease to have sinus rhythm.

The overall incidence of embolism following prosthetic valve insertion tends to increase with duration of follow-up (fig. 1). However, there appears to be some leveling-off at about 2 years of follow-up, as seen in our patients.
with aortic or mitral prostheses, and in patients of Duvoisin and associates with mitral prostheses. The central nervous system was the common site involved by thromboembolism, in agreement with the finding of other groups. Of interest is the fact that coronary artery embolism, an uncommon cause of myocardial infarction, has been reported in a number of patients with prosthetic valves. Thromboembolism was responsible for 17 deaths (25% of those who had emboli). Although 4% of patients with thromboembolism were left with severe residual defects and 21% had mild impairment of function, 50% recovered completely. The disputed efficacy of anticoagulants in preventing embolic complications has stimulated sustained interest in improved prosthetic design. Preliminary follow-up of patients with the newer model Starr-Edwards prostheses (no. 1200 aortic valve, no. 6120 mitral valve) suggests that embolism may be much less of a problem (and Starr, personal communication). The present study can serve as a basis for comparison with valve prosthesis of improved design in the future.

Acknowledgment
The authors wish to express their thanks to Misses Joan Sheahan, Kim Griswold, and Lynn Johnson for help in preparation of this manuscript.

References
4. Dyke, G. V., and Patterson, H. D.: Analysis of factorial arrangements when the data are proportions. Biometrics 8: 1, 1952.

Figure 1
Incidence of postoperative thromboembolism among various groups of patients.
Thromboembolic Complications of Prosthetic Cardiac Valves
MOHAMMED AKBARIAN, W. GERALD AUSTEN, PETER M. YURCHAK and J. GORDON SCANNELL

Circulation. 1968;37:826-831
doi: 10.1161/01.CIR.37.5.826
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 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/37/5/826

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/