Coronary Arteriography in Long-Term Human Cardiac Transplantation Survivors

By James F. Silverman, M.D., Martin J. Lipton, M.D., Anthony Graham, M.D., Steve Harris, M.D., and Lewis Wexler, M.D.

SUMMARY
Coronary arterial lesions in survivors of cardiac transplantation result from accelerated coronary atherosclerosis. Clinical recognition of this event is difficult but essential for long-term management and prognostication. Coronary arteriography was performed on 30 occasions in a group of 16 patients 1-4 years after cardiac transplantation. Fifteen patients had normal coronary arteries at one year. Of 10 patients studied at two years, seven showed no change but three others revealed significant coronary arterial lesions which correlated well with clinical signs of coronary artery disease. These three patients subsequently died, two due to coronary artery disease, one due to infection. Three patients have remained normal at three years and one patient is normal at four years as evidenced on yearly coronary arteriograms. A postmortem examination of the patients who died with coronary artery disease confirmed the extent of the luminal narrowing due to atheromatous plaques superimposed on intimal lesions. Coronary arteriography has proven to be a safe, reliable method for assessing the coronary circulation of long-term cardiac transplant survivors.

Additional Indexing Words:
Coronary atherosclerosis

HUMAN CARDIAC TRANSPLANTATION has progressed from an early experimental phase to a stage of carefully controlled patient selection and continued management of long-term survivors. After overcoming the initial problems of devising a successful surgical technique that yielded a hemodynamically useful heart, attention was directed to solving the problem of acute and chronic rejection. The diagnosis of rejection is based on a combination of indirect indices of cardiac function as well as endomyocardial biopsy specimens, and can now be made with assurance in all but extremely unusual circumstances. The introduction of intermittent high dosage immunosuppressive therapy has resulted in successful reversal of over 95% of all rejection episodes, although opportunistic infections in the compromised host secondary to the immunologic change have remained a problem, especially in the long-term survivor. Over-all, survival in our series following transplantation is 43% at one year, 40% at two years and 26% at three years. If a patient survives the first three months following transplantation, his chance for living two years is 65%.

As experience with these long-term survivors increased, we became aware of the development of coronary ischemia as a late complication. Patients have died in our series from 5 months to 43 months following transplantation as a result of progressive accelerated atherosclerosis causing obliteration of major coronary artery lumina. Since the transplanted heart is denervated, patients do not experience anginal symptoms, though they may develop arrhythmias, positive exercise tests, or other electrocardiographic evidence of myocardial ischemia. In an attempt to uncover evidence of coronary artery narrowing in a grafted heart, we began a systematic program of patient follow-up.

Patient Studies
Each patient is seen on a twice weekly basis for the first two months following discharge. Studies are done, as shown in table 1, to detect signs of rejection or infection. Following this, the patient is seen at weekly intervals either at Stanford or, under supervision, by his local physician. At monthly intervals an exercise electrocardiogram is performed as well as Holter arrhythmia monitoring to detect signs of silent ischemia. Coronary arteriography is performed at yearly intervals in all long-term survivors and also in any patient who develops a positive exercise study. Serial lipoprotein analysis is performed at three month intervals to assess any aggrava-
**Table 1**

*Outpatient Cardiac Transplantation Follow-Up*

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<th>Weekly</th>
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<td>2. EKG (voltage, rhythm, conduction)</td>
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<td>2. Coronary arteriography</td>
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<tr>
<td>4. WBC, platelets and prothrombin time</td>
<td>4. Lipoprotein electrophoresis</td>
<td>a. special studies</td>
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<td>5. Electrolytes, liver function studies, glucose</td>
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Of this study group, 14 patients had normal hemodynamic studies and coronary arteriograms (table 2) at one year post-transplantation, 10 at 2 years, 5 at 3 years and 1 at 4 years. All surviving patients are clinically asymptomatic and lead active lives; three of these patients were reported in detail previously. The exercise electrocardiograms have remained normal and no arrhythmias have been detected. Serum cholesterol averages 300 mg% with triglyceride levels from 100-300 mg% at one year post-transplant in these patients. This is felt to be due, in part, to a long-term steroid effect. As a group, the long-term survivors without coronary artery disease have averaged 1.3 acute rejection episodes and of these 0.34 episodes were felt to be severe. Those with coronary artery disease have averaged 2.8 acute episodes of which 1.0 per patient was judged severe.

Three patients have developed signs of ischemia on exercise electrocardiogram. Coronary artery disease was confirmed by coronary arteriography in all instances.

**Case Reports**

S.C. was a 43-year-old male with a type II hyperlipidemia who underwent cardiac transplantation in February 1969 following an acute myocardial infarction complicated by cardiogenic shock. Following transplantation he had two severe rejection episodes within three weeks of surgery. He did well following this except for the development of steroid induced osteoporosis and an aggravation of his pre-existing lipid abnormality resulting in cholesterol levels of 400-425 mg%. At 27 months after transplantation, although asymptomatic, he developed a positive exercise test (fig. 1). Coronary arteriography (fig. 2) showed a totally blocked left circumflex coronary artery, an 80% proximal left anterior descending coronary artery obstruction, a small arterial venous fistula from a branch of the anterior descending artery, and diffuse narrowing of the right coronary artery. He was treated with anti-lipemic drugs and a rigid diet which resulted in a 30 pound weight loss. Despite this, he died suddenly 33 months following transplantation, presumably of an arrhythmia. At autopsy, severe atherosclerotic lesions of the three major coronary vessels were found (fig. 3). The gross and microscopic features were typical of those found previously in chronic cardiac allografts. Marked intimal proliferation was noted as well as intra and extracellular fat deposition.

C.S. was a 57-year-old male who underwent cardiac transplantation in October 1968 for intractable congestive heart failure following several myocardial infarctions. His postoperative course was complicated...
by a gram negative pneumonia which responded to treatment. He also developed episodes of sinus arrest 12 months following transplantation and had a permanent transvenous demand pacemaker inserted. He had two mild acute rejection episodes and one severe episode in the early postoperative period. In addition, he developed a type IV hyperlipidemia following transplantation which has been treated with diet. At 35 months post-transplantation he developed a positive exercise study. His coronary arteriogram showed significant narrowing of two diagonal branches of the left anterior descending coronary artery, significant left anterior descending narrowing, and diffuse irregularity of the circumflex artery (fig. 4).

P.B. was a 46-year-old male transplanted in May 1971 for inoperable coronary artery disease and congestive heart failure. He did well clinically for 1½ years. Cholesterol and triglyceride levels averaged 300 and 250 mg%. In June 1972, coronary arteriography was performed and was normal. Because of a positive treadmill test, repeat coronary arteriography was performed in February 1973 revealing several areas of luminal narrowing where normal coronary arteries were previously noted (fig. 5). A rejection episode occurred in September 1973; one month later the patient died from pneumonia. Postmortem studies of the coronary arteries revealed intimal hyperplasia with superimposed atherosclerotic vascular disease.

Discussion

Accelerated atherosclerosis appears to have been one of the major limiting factors to the long-term survival of some of the earlier patients in our cardiac transplant series. Factors that may predispose to its development may relate to the frequency and severity

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Figure 1

Upright exercise EKG. It is well demonstrated in all of the leads shown that the ST segments became markedly depressed after 10 minutes of exercise.

Figure 2

LAO projection of cine frame of left coronary artery injection. Black arrows point to totally blocked left circumflex coronary artery and 80% narrowed proximal left anterior descending artery.

Figure 3

Top) Gross specimens of proximal and distal left anterior descending coronary artery reveal a partial and complete plugging of the coronary artery lumen. Bottom) Microscopic section of the coronary artery revealing marked luminal narrowing.

Circulation, Volume 50, October 1974
The current immunosuppressant regimen for the long-term transplant survivor includes prednisone 0.25 to 0.5 mg/kg and azathioprine 2 to 3 mg/kg. In addition, dipyridamole 100 mg q.i.d. and warfarin sodium have been used in all patients since September 1969 in an attempt to prevent platelet aggregation and microthromboses. All patients are on low cholesterol, high polyunsaturated fat diets as well as active exercise programs to improve over-all physical condition and maintain ideal body weight.

The normal arteriograms seen in our recent patients up to four years after transplantation show that accelerated atherosclerosis is not an inevitable finding in all patients following transplantation (fig. 6). We believe that improved methods of early diagnosis and treatment of acute rejection episodes, rigid dietary and drug control of lipid abnormalities, as well as the use of dipyridamole and warfarin sodium, may be factors contributing to these improved results.

One further observation is worthy of mention. Coronary arteriography eight months after transplantation in one patient showed irregular luminal narrowings of the type usually associated with atherosclerosis. The patient has been maintained successfully on strict lipid control and the electrocardiogram and exercise tests have been normal. However, the donor heart had been obtained from a 42-year-old man. Because of the age of the donor, coronary arteriography had been performed prior to “death” and had demonstrated these same minor irregularities which did not compromise the lumen.

Figure 4
Patient C.S. Retouched LAO projection. Black arrows point to areas of narrowing in the left anterior descending and the left circumflex arteries.

Figure 5
There was no progression of disease over the eight month period of grafting. We now perform coronary arteriography routinely in prospective donors over the age of 35. Six of nine hearts studied for this reason were deemed unacceptable for transplantation because major abnormalities of the coronary arteries or left ventricular function were found.

Conclusion
Many important problems in the management of cardiac transplant patients are still unsolved. Therapy and prevention of the rejection phenomenon and control of opportunistic infections are examples. Coronary arteriography has proven to be a safe and useful technique for confirming and diagnosing graft atherosclerosis and for following serial changes in the coronary arteries of transplant patients. Current evidence indicates that coronary atherosclerosis may not be inevitable in the long-term transplant survivor if appropriate medical management and a careful dietary program are maintained.

References

Figure 6
Above) Lateral projection, left and right coronary injections, 1972, two years post-transplant. Below) Lateral projection, left and right coronary injection, 1974, four years post-transplant. Representative angiograms showing normal coronaries at 2 and 4 years post-cardiac transplantation.
10. Grieppe RB, Wexler L, Stinson EB, Dong E, Shumway NE: Coronary arteriography following cardiac transplantation. JAMA 221: 147, 1972
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Circulation. 1974;50:838-843
doi: 10.1161/01.CIR.50.4.838
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

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