Observations during Anesthesia for Cardiac Homotransplantation in Ten Patients

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Observations made during the anesthetic management of ten cardiac transplantations in man have been summarized. Hypotension, serious arrhythmias or circulatory failure occurred in seven recipients during anesthesia and before transplantation. Hypotension and cardiac dilatation followed transplantation in nine recipients and was dramatically reversed, initially by calcium chloride and finally by digitalis. Early cardiac failure was attributed to acute denervation of the heart. Two recipients were given a second anesthetic two to three weeks after transplantation. The anticipated depression of the denervated heart by general anesthesia was not observed.

With each day of continued survival of the patient who received the human cardiac transplant in the operation performed by C. W. Barnard on January 2, 1968, transplantation of the human heart becomes less of an experimental procedure. The steadily increasing success of the operation, indicated by the growing number of survivors, suggests that this operation will be undertaken therapeutically more frequently and widely in the near future. For this reason, we are reporting our experiences in the anesthetic management of ten cardiac transplants performed by D. A. Cooley between May 2, 1968 and August 19, 1968. Although the sole purpose of these operations was therapeutic, it was possible to observe the response of the denervated transplanted heart to anesthetics and to drugs used in association with anesthesia. Some data related to these operations have already been recorded. Detailed clinical observations, immunologic aspects and developments during convalescence will be reported by others who participated.

Management of Recipients

All recipients were totally incapacitated by cardiac disease despite full medical therapy. No lesser operation was considered to have therapeutic value. Most recipients had coronary artery disease with previous infarctions and diffuse myocardial fibrosis (table 1). Since the availability of donors was unpredictable, operations were done on an emergent basis. Three recipients received no preanesthetic medication. Seven received meperidine, 25–75 mg, and scopolamine, 0.2–0.3 mg, intramuscularly an hour before anesthesia. The anesthesia apparatus was clean but not sterile. Anesthesia was induced with 0.2 per cent thiopental by infusion after a radial arterial cannula, an intravenous cannula and needle electrocardiographic (ECG) leads were inserted under local anesthesia. After the patient lost consciousness, 50 per cent nitrous oxide in oxygen was administered by mask. The trachea was intubated after intravenous administration of 100 mg succinylcholine. In recipients whose heart rates were less than 90 beats/min atropine, 0.2 mg, was given intravenously before succinylcholine. Anesthesia was continued with nitrous oxide and oxygen, supplemented by 0.5–1.5 per cent halothane in four recipients and by 10–20 mg doses of meperidine in six recipients. When muscle tone returned, d-tubocurarine, and, in two recipients, gallamine as well, was given in doses sufficient to permit continuous control of respiration. Electroencephalographic (EEG) leads and a nasogastric tube were in-
serrated at this time. Nitrous oxide was discontinued after the thorax was open.

As could be expected from the severity of the cardiac disease, circulatory problems were encountered in seven of the ten recipients during induction of anesthesia or before the start of cardiopulmonary bypass. Three recipients developed hypotension (less than 60 mm Hg systolic) without bradycardia, at least once. Each time, hypotension was corrected by 0.1 mg phenylephrine injected intravenously. Bradycardia (less than 50 beats/min) with hypotension developed in Recipient 4 after induction of anesthesia and was corrected by 0.4 mg atropine injected intravenously. An episode of ventricular tachycardia and hypotension appeared in Recipient 6 after intubation of the trachea. This was converted to sinus rhythm by two doses of 80 mg lidocaine administered intravenously. Before operation recipient 9 received lidocaine by continuous intravenous infusion to control frequent attacks of paroxysmal atrial tachycardia. Although the infusion was continued during induction of anesthesia, atrial tachycardia with a 1:1 ventricular response and severe hypotension occurred after intubation of the trachea and again just before cardiopulmonary bypass. The first episode was reverted with closed-chest massage; the second persisted until cardiopulmonary bypass was instituted. Recipient 3 had been in intractable congestive cardiac failure before operation and had had cardiac arrest with successful resuscitation seven hours earlier. After median sternotomy, profound hypotension and bradycardia occurred and did not respond to isoproterenol, atropine or calcium chloride. Cardiopulmonary bypass, therefore, was instituted rapidly, and electroencephalographic activity reappeared within five minutes.

Cardiopulmonary bypass was performed using a disposable bubble oxygenator primed with 20–25 ml/kg of 5 per cent dextrose in water to which 25 mg/l heparin had been added. Patients were given 3 mg/kg heparin and d-tubocurarine, 6–9 mg, before bypass. Oxygen without carbon dioxide or volatile anesthetic was used to oxygenate the blood. Anesthesia was maintained with 50–100 mg doses of thiopental given into the oxygenator reservoir when needed as indicated by movement or by an awake EEG pattern. A heat exchanger was used to maintain normothermia; esophageal temperature remained about 94.5 F during bypass. During the perfusion (table 1), 500 ml or less of priming solution were added to the oxygenator when needed to maintain an adequate level in the reservoir. No other drugs were given. Blood pressure dur-

<table>
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<th>Operation</th>
<th>Recipient</th>
<th>Donor</th>
<th>Etiology of Brain Damage</th>
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<tbody>
<tr>
<td>1</td>
<td>47 M</td>
<td>149</td>
<td>Rheumatic (calcific multivalvular)</td>
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<tr>
<td>2</td>
<td>48 M</td>
<td>168</td>
<td>Coronary</td>
</tr>
<tr>
<td>3</td>
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<td>54 M</td>
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<td>6</td>
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<td>130</td>
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<td>7</td>
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<tr>
<td>8</td>
<td>49 F</td>
<td>151</td>
<td>Coronary</td>
</tr>
<tr>
<td>9</td>
<td>51 F</td>
<td>40</td>
<td>Congenital (endocardial fibroelastosis)</td>
</tr>
<tr>
<td>10</td>
<td>50 M</td>
<td>160</td>
<td>Coronary</td>
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Table 1.
Fig. 1. Lead II electrocardiograms. A. During excision of heart of Recipient 2. Large irregular ventricular complexes were evoked by manipulation of the heart during removal. Once excised, only P waves at a rate of 140 appeared from the recipient’s SA node, which was left in situ. B. During implantation of the donor heart in Recipient 5. The donor heart had just been placed in the recipient’s chest and suturing of the left atrium had begun. Ventricular complexes of the donor heart appear randomly among the persisting P waves of the recipient’s SA node.

ing bypass ranged from 35 to 100 mm Hg, but most commonly remained between 40 and 60 mm Hg. Urinary output continued during perfusion.

The recipient’s sinoatrial node at the atrial caval junction was not removed upon excision of the heart.1 P waves, therefore, continued to appear on the ECG after excision (fig. 1A). In some recipients, ventricular complexes arising from the donor heart appeared on the ECG immediately after its placement in the recipient’s chest (fig. 1B). Since the donor heart was neither cooled nor perfused, these complexes disappeared as operation progressed. The voltage of the recipient’s P wave tended to decrease with time.

When the donor heart had been sutured in place and the air removed from the left side of the heart by needle and syringe, the aortic clamp was removed and coronary perfusion begun. In six recipients ventricular fibrillation promptly followed coronary perfusion. In these, 100 mg lidocaine and 44 meq NaHCO3 were injected into the oxygenator and coronary perfusion was continued for an additional 1–2 minutes. In three recipients 0.02 mg isoproterenol or 0.01 mg epinephrine was also given to increase the rate of fibrillation. All six recipients were then defibrillated with a single direct shock of 40–60 watt sec. In Recipient 1, atrial fibrillation with a ventricular rate of 120 beats/min followed ventricular defibrillation; the fibrillation was converted to normal sinus rhythm with a second shock. After defibrillation, the transplanted hearts beat vigorously at rates of 110–150 beats/min, with initial blood pressures of 80/40 mm Hg which rose to 135/90 mm Hg. Blood was added from the oxygenator to maintain systolic blood pressures no higher than 100 mm Hg in order to limit bleeding.

In the four recipients who did not develop ventricular fibrillation, a similar pattern of recovery followed bypass. Initial contractions were slow and feeble but increased in rate and vigor with continuing coronary perfusion. In view of the duration of cardiac ischemia, all were given 44 meq of NaHCO3 empirically into the oxygenator during this period. The patients were also given isoproterenol, 0.1–0.2 mg, to increase the rate and contractile force of the implanted heart. Full recovery of the heart after reinstatement of coronary perfusion
required only two to four minutes, after which time heart rates ranged from 110–120 beats/min and blood pressures from 80/55 to 110/75 mm Hg. All blood and priming solutions were then returned to recipients at rates which maintained systolic pressure at approximately 100 mm Hg. After the venous cannula had been removed, protamine, 4.5 mg/kg, was given slowly, intravenously.

Ten to 30 minutes after completion of cardiopulmonary bypass and complete resuscitation of the transplanted heart, all patients except the child (Recipient 9) developed at least one episode of progressive hypotension without change in heart rate. This was not the result of blood loss, drugs or manipulation of the heart, and was associated with loss of vigor of cardiac contraction and seeming cardiac dilatation. In the three recipients monitored during operation, central venous pressure rose from less than 10 mm Hg to 18–25 mm Hg during hypotension. In the first recipient, who had three such episodes, hypotension was reversed dramatically each time by intravenous administration of 0.3–0.5 gm calcium chloride. Three similar episodes occurred in the early postoperative period, but did not recur after digitalis had been administered. Two similar episodes occurred in Recipient 2, and did not recur after digitalis was given in the early postoperative period. After three episodes of hypotension were corrected by calcium chloride in Recipient 3, 0.5 mg digoxin followed in five minutes by 0.25 mg digoxin was given intravenously 30 minutes after bypass. This promptly stabilized blood pressure and decreased venous pressure. All subsequent adult patients behaved in a similar fashion. All received from one to five doses of calcium chloride, 0.3–0.5 mg, intravenously, which effectively corrected hypotension. All were then given digoxin (0.5–0.75 mg) before the end of operation. Heart rates tended to decrease by 10–20 beats/min after digoxin but remained rapid (90–140 beats/min) with an atrial rhythm. Since the sinoatrial node of the donor was transplanted with the heart, the recipient now possessed two sinoatrial nodes, which at times produced two P waves on the ECG (fig. 2).

![Fig. 2](image_url)

**Fig. 2.** Lead II electrocardiograms showing two sets of P waves after implantation of the donor heart. A. Recipient 2, ventricular rate 120 beats/min approximately 15 minutes after implantation. B. Recipient 6, ventricular rate 90 beats/min approximately 60 minutes after implantation. The P wave of the donor heart is well seen in A, with P waves of the recipient's SA node appearing at different positions within the QRS complex. The rates of the two pacemakers are only slightly different. In B the two pacemakers are more out of phase, with the recipient's SA node beating at approximately 150 beats/min. The absence of atrial fibrillation was confirmed by inspection of the heart.
During operation, adult recipients received an average of 1,150 ml stored citrated blood (range 0-3,000 ml), 1,500 ml 5 per cent dextrose in lactated Ringer’s solution (range 1,000-3,000 ml) and 1,500 ml 5 per cent dextrose in water (range 1,000-2,200 ml) used to prime the oxygenator.Recipient 9, a child, received no blood, 500 ml 5 per cent dextrose in lactated Ringer’s solution and 600 ml dextrose-in-water prime. No attempt was made to antagonize d-tubocurarine at the end of operation, and endotracheal tubes were left in place. Recipients were taken to a sterile operating room for continued care, and ventilation was assisted or controlled with a sterile Bennett or Bird ventilator. The intra-arterial cannula was left in place for one to two days to monitor blood pressure and blood gases. A right atrial catheter was inserted through the subclavian vein to monitor central venous pressure, and surface ECG electrodes were attached. Recipients responded to pain and voice approximately three hours after operation (range zero to nine hours). Endotracheal tubes were removed approximately 14 hours after operation (range three to 36 hours). No recipient had a tracheostomy.

The immediate postoperative courses of all recipients were remarkably benign. Recipient 2, whose low prothrombin time was not corrected preoperatively, bled moderately after operation and was given 250 ml fresh frozen plasma. He died 52 hours after operation of a rapidly developing leukopenia and overwhelming pneumonia secondary to an adverse reaction to immunosuppressive therapy. Recipient 3, who was moribund preoperatively, improved dramatically after operation. He was responsive six hours after operation, but ventilatory assistance through an endotracheal tube was continued for 36 hours. After extubation he continued to improve until mesenteric thrombosis, renal and hepatic failure led to death on the seventh postoperative day. Recipient 9 died on eighth postoperative day from homograft rejection. Recipient 8 died approximately two months after operation from bleeding gastrointestinal ulcers, thrombocytopenia and sepsis. The other six recipients have recovered and two are currently working full-time in the community.

Management of Donors

Donors were examined by consultants, including a neurologist, and were judged to have irreversible massive brain damage or “cerebral death” on the basis of history, neurologic examination and the electroencephalogram. Brain damage had been caused by trauma in four, cerebral hemorrhage in four, and anoxia following circulatory arrest secondary to non-cardiac disease in two (table 1). The intervals between brain injury and transplantation varied from nine hours to four days. When brought to the operating room, all donors were flaccid, apneic and breathing was mechanically controlled via an endotracheal tube. All were receiving continuous infusions of vaspressors (metaraminol, nor-epinephrine or phenylephrine), which maintained blood pressures between 65/30 and 90/60 mm Hg with heart rates of 100-150 beats/min. In the operating room oxygen was administered while an intraarterial cannula was introduced and EEG and ECG leads were attached. In all instances the EEG trace from bilateral frontoparietal leads was isoelectric with ECG artifacts appearing at amplifications of 20-50 Mv/cm. The EEG did not change during incision of the skin. No respiratory movements occurred when ventilation was interrupted for periods as long as ten minutes. Pupils were widely dilated, without motion or response to light. No pharyngeal, corneal or cough reflex was present in any donor. One donor had premature ventricular contractions and another nodal tachycardia, probably secondary to the high doses of vaspressors. After the donor was surgically prepared, heparin, 3 mg/kg, was given intravenously and the vaspressor infusion adjusted in an attempt to excise the donor’s heart simultaneously with excision of the recipient’s heart. Three donors required resuscitative measures (closed-chest compression, sodium bicarbonate, isoproterenol, or vaspressor by injection) to prevent premature circulatory failure. When vaspessor infusion was discontinued, circulatory failure progressed slowly and excision of the donor heart was begun when systolic blood pressure fell below 50 mm Hg. Succinylcholine was administered to the first two
donors to prevent the anticipated agonal diaphragmatic contractions. This was found to be unnecessary in all but one of the subsequent donors. Diaphragmatic contractions were feeble, if they occurred at all. The donor heart was not cooled or perfused after excision, but was immediately transported to the recipient for implantation. An attempt to relate vasopressor therapy, heart rate and rhythm of the donor heart to rate and rhythm after implantation in the recipient was not successful. All but one donor had sinus rhythms with rates greater than 100 beats/min, and the rate remained rapid after implantation.

Response of the Denervated Heart to Drugs

Two recipients were given a second general anesthetic for which gas-sterilized equipment was used. Recipient 1 required repair of a sternal dehiscence 15 days after transplantation. He was given no preanesthetic drugs. Anesthesia was induced with 50 per cent cyclopropane and maintained with 20–30 per cent cyclopropane in a partial rebreathing system with CO₂ absorption. Before anesthesia, the blood pressure was 110/60 mm Hg. During anesthesia, which lasted 65 minutes, blood pressure remained 100–110 mm Hg systolic, 50–60 mm Hg diastolic. Heart rate varied between 110 and 120 beats/min, with sinus rhythm. To prevent respiratory movement, succinylcholine, 100 mg, was administered intravenously after 30 minutes of anesthesia and respiration was controlled. Neither succinylcholine nor positive pressure altered blood pressure or heart rate. Emergence was prompt and uneventful.

Recipient 6 developed atrial fibrillation on the seventeenth postoperative day. The next day, without preanesthetic medication, he was given 250 mg 2 per cent thiopental in 50–100 mg increments and 50 per cent nitrous oxide in oxygen for cardioversion. Intra-arterial pressure and ECG were monitored. Before anesthesia, blood pressure ranged from 110 to 130 mm Hg systolic and from 75 to 90 mm Hg diastolic, with a ventricular rate of 120 beats /min. After thiopental the blood pressure decreased to 105–120 mm Hg systolic, 75–85 mm Hg diastolic. Ventricular rate increased to 130–135 beats/min. After one external shock, sinus rhythm was restored, with a rate of 80–90 beats/min without change in the range of blood pressure. Atrial fibrillation did not recur.

Three recipients were given 0.6 mg atropine intravenously shortly before the end of operation in an attempt to alter the rate of the recipient's own sinoatrial node so that two P waves might be seen on the ECG. Atropine had no effect on the rate of the transplanted heart and did not elicit a second P wave. In another recipient, neostigmine, 1.5 mg, was given for the same purpose without apparent effect. Recipient 3 had persistent atrial tachycardia postoperatively, with a rate of 130–130 beats/min. On the fourth postoperative day he was given 2.5 mg neostigmine without atropine; this did not change the heart rate.

During the period from the end of cardiopulmonary bypass to the end of operation, recipients received at various times one or more of the following drugs: calcium chloride, isoproterenol, epinephrine, lidocaine, digoxin, halothane, nitrous oxide, and meperidine. These were given in doses usually used for patients undergoing other types of heart operations requiring cardiopulmonary bypass. In no instance was there evidence of an increased or decreased sensitivity of the heart in response to these drugs.

Discussion

From this limited experience two observations have special significance. First, cardiac dilatation and hypotension corrected by digitalis occurred shortly after cardiac implantation despite prior digitalis therapy of the recipient. Second, marked sensitivity to the cardiac depressant effects of cyclopropane and thiopental did not occur two to three weeks after transplantation in two recipients.

The dramatic reversal of hypotension and cardiac dilatation by calcium chloride in the first recipient suggested that cardiac performance would improve with digitalis, since calcium and digitalis have similar positive inotropic effects on the ventricle. This observation was confirmed in subsequent recipients, all of whom received digitalis. The etiology of this apparent early cardiac failure is not
clear. Willman et al.\textsuperscript{4} noted cardiac dilatation with elevated right atrial pressure early after autotransplantation of dog hearts, and reported that treatment with digitalis was necessary for survival. Somewhat similar observations were made by Smith et al.,\textsuperscript{5} who reported the effects of ouabain on normal and autotransplanted dog hearts. Although the autotransplanted hearts were capable of adequate function without treatment after reimplantation, they noted that right atrial pressure was 18.3 mm Hg in the autotransplants, compared with 8.0 mm Hg in controls, three to five days after operation. The hemodynamic responses to ouabain differed in the two groups, but ouabain toxicity was the same. Both groups of investigators suggested that denervation was responsible for the mild heart failure. Since only one recipient in our group had pulmonary hypertension and only two had systemic hypertension, it is unlikely that outflow resistance caused ventricular dilatation. It is more likely that tonic sympathetic stimulation of the ventricles is as important in man as in the dog and that acute denervation leads to cardiac dilatation.

The important role of the autonomic nervous system in circulatory homeostasis during ether anesthesia was well demonstrated by Brewster et al.;\textsuperscript{6} during cyclopropane anesthesia by Price et al.\textsuperscript{7} From these studies and the observed effects of general anesthetics on the isolated perfused heart,\textsuperscript{8} we anticipated early and significant cardiac depression of the transplanted heart by thiopental and cyclopropane. This did not occur in the two recipients who received a second anesthetic. Several circumstances may have prevented the anticipated cardiac depression. In addition to omission of preanesthetic drugs, both anesthetics were administered slowly and in small doses. Both patients were on full maintenance doses of digitalis. It is possible that some epinephrine was released from the adrenal medulla and sustained the contractile force of the heart. It is also possible that norepinephrine was released from the large sympathetic plexuses in the lung and diffused into the heart. Antagonism of the direct myocardial effects of the anesthetic could have been achieved by small amounts of catecholamines, since cardiac stores certainly would have been depleted two weeks after transplantation. Hypersensitivity with an exaggerated response to norepinephrine and epinephrine has been shown to occur in the autotransplanted dog three weeks after operation.\textsuperscript{9} Sympathoadrenal stimulation with release of small amounts of catecholamines, therefore, could account for the absence of severe myocardial depression.

References