THE OPERATION

A HUMAN CARDIAC TRANSPLANT: AN INTERIM REPORT OF A SUCCESSFUL OPERATION PERFORMED AT GROOTE SCHUUR HOSPITAL, CAPE TOWN

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On 3 December 1967, a heart from a cadaver was successfully transplanted into a 54-year-old man to replace a heart irreparably damaged by repeated myocardial infarction.

This achievement did not come as a surprise to the medical world. Steady progress towards this goal has been made by immunologists, biochemists, surgeons and specialists in other branches of medical science all over the world during the past decades to ensure that this, the ultimate in cardiac surgery, would be a success.

The dream of the ancients from time immemorial has been the junction of portions of different individuals, not only to counteract disease but also to combine the potentials of different species. This desire inspired the birth of many mythical creatures which were purported to have capabilities normally beyond the power of a single species. The modern world has inherited these dreams in the form of the sphinx, the mermaid and the chimerical forms of many heraldic beasts. Modern scientists have a more realistic approach and explored the possibility of treating certain diseases affecting specific organs by replacement of these organs with grafts.

The recent history of transplantation of the heart began with the experiments of Carrel and Guthrie in the early years of this century.[1,2] Gradually our knowledge increased and progress towards this goal continued through the years with the work of many other brilliant men[3-10] and, in particular, through the invaluable contributions of Shumway and his associates.[11-15]

Against the background of this research and with our own experience in the experimental laboratories, backed by the knowledge of the surgical management and postoperative care of patients undergoing major cardiac surgery, the time arrived when a cardiac transplant could be contemplated with hope of success.

PREPARATIONS FOR THE OPERATION

A patient was selected who was considered to have heart disease of such severity that no method of treatment short of cardiac transplantation could succeed. A suitable donor was obtained who had compatible red cell antigens and a similar leucocyte antigen pattern.

The donor was taken to the operating theatre on supportive therapy and the recipient was taken to the adjoining operating theatre. The donor was prepared for total cardiopulmonary bypass and a disposable oxygenator primed with Ringer's lactate solution was kept in readiness in this theatre. In the adjoining theatre, where the recipient had been placed, the DeWall-Lillehei pump oxygenator[16-19] was prepared and primed with fresh, citrated blood using haemodilution (2 parts blood: 1 part diluent consisting of 1,200 ml. 10% invert sugar in Ringer's lactate with 335 ml. THAM,* calcium 5 ml. of a 10% solution per pint of diluent and 15 ml. heparin).

*Trishydroxymethylaminomethane.

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As soon as it had become obvious that, despite therapy, death was imminent in the donor, the recipient was anaesthetized and the saphenous vein and common femoral artery were exposed through a right groin incision. The saphenous vein was cannulated and this cannula was used for intravenous fluid administration and venous monitoring. The heart of the recipient was exposed through a median sternotomy incision. The pericardium was opened and the superior and inferior venae cavae and ascending aorta were isolated and encircled with cotton tapes. A careful examination of the recipient's heart showed that no treatment other than transplantation could benefit the patient.

As soon as the donor had been certified dead (when the electrocardiogram had shown no activity for 5 minutes and there was absence of any spontaneous respiratory movements and absence of reflexes), a dose of 2 mg. heparin/kg. body-weight was injected intravenously. The donor's chest was then opened rapidly, using a median sternotomy, and the pericardium was split vertically. A catheter was connected to the arterial line of the oxygenator and was then inserted and secured in the ascending aorta. A single 5/16-in. cannula was inserted into the right atrium via the right atrial appendage for venous return to the oxygenator. Bypass and cooling were commenced in the donor. A vent was placed in the left ventricle, via its apex, and put onto slow suction to prevent distension of the atonic left ventricle. The flow rate was adjusted to 3·5 l./min. This general body cooling was continued until the mid-oesophageal temperature had dropped to 26°C, as the kidneys were also to be protected for use in a transplantation procedure in another hospital.

When the mid-oesophageal temperature had reached 26°C the aortic cannula was adjusted so that it pointed towards the aortic valve. The flow was reduced to 0·5 l./min. and the aorta was then cross-clamped so that only the myocardium of the donor's heart was perfused. The heart was cooled down to 16°C. Perfusion was discontinued and the heart was excised by dividing the aorta distal to the innominate artery, the inferior vena cava being transected on the diaphragm and the superior vena cava at the level of the azygos vein. The right and left pulmonary arteries were divided and the main pulmonary artery was freed. The left atrium was mobilized by dividing the 4 pulmonary veins. The heart was now free. The excision had taken 2 minutes.

The venous catheter in the donor heart was removed from the right atrium. The arterial cannula and left ventricular vent were disconnected from the heart-lung machine but were left in place as positioned in the heart. The heart was placed in a bowl containing Ringer's lactate solution at 10°C and was transferred to the adjacent theatre where, in the meantime, the recipient had been connected to the heart-lung machine.

Perfusion of the donor heart was recommenced immediately (0·4 l./min.) by connecting the arterial cannula to a coronary perfusion line, and as soon as the aorta had filled to displace the air, it was clamped distal to the perfusion cannula so that the coronary arteries would be perfused. The heart was vented continuously during this procedure, and a period of 4 min. had elapsed between cessation of perfusion in the first theatre and the resumption of cardiac perfusion in the second operating theatre.

After systemic heparinization of the recipient the cardiopulmonary bypass was commenced. The flow rate was 3·1./min. (1·8 l./sq.m. body-surface area/min.). Arterial return was through a 5·4-mm. ID metal cannula inserted into the right common femoral artery and venous return to the pump was performed by means of two 5/16-in. diameter cannulae inserted through the right atrial appendage into the superior and inferior venae cavae. During insertion of the cannula into the right common femoral artery, it was noticed that this vessel was atherosclerotic. After 7 min. of bypass it was noticed that the arterial line pressure had risen to over 300 mm.Hg. Accordingly, a 5·6-mm. ID cannula was inserted into the ascending aorta through a stab incision, controlled with a purse-string suture, and bypass was discontinued momentarily while the arterial line was disconnected and re-connected to the cannula in the ascending aorta.

Bypass was recommenced after 3 min., the flow now being increased to 4·2 l./min. (2·5 l./sq.m. body-surface area/min.) and cooling was continued until the patient's mid-oesophageal temperature had reached 30°C. The arterial line pressure was now 120 mm.Hg.

The patient's heart was excised after cross-clamping the aorta proximal to the aortic cannula. The aorta was transected immediately above the coronary ostia and the pulmonary artery divided immediately above the pulmonary valve ring. The ventricles were detached from the atria as near as possible to the atrioventricular groove. The atrial septum was divided as close to the ventricles as possible. The excision was performed in order to leave a cuff of left atrial wall surrounding the ostia of the pulmonary veins and to preserve the part of the right atrium carrying the venae cavae.

Transplantation of the Graft

The donor's heart was placed in the pericardial cavity; the coronary sinus blood was allowed to drip from the donor heart into the pericardial sac and was aspirated from here back to the pump. The bases of the left and right atria were prepared. The base of the left atrial wall around the 4 pulmonary veins was excised and the base of the right atrium was incised, an incision being made posteriorly from the orifice of the inferior vena cava to the orifice of the superior vena cava. It was evident that the portion of the left atrium of the patient's heart to which the donor heart would have to be anastomosed was too large. This area was thus plicated, tucking in the wall of the patient's left atrium both superiorly and inferiorly next to its junction with the interatrial septum.

The left atrium of the donor heart was first attached to the patient's left atrium by anastomosing the opening in the posterior wall of the donor's left atrium to the left atrial wall and septum of the patient's heart. This was done using double layers of 4-0 continuous silk. The right atrium was then anastomosed; the posterior opening in the donor's right atrium to the remaining right atrial wall and septum of the patient's heart. Throughout this period the vena-caval catheters were left in place as introduced, in the patient's right atrial appendage, and did not interfere with the anastomoses.

The donor's pulmonary artery was trimmed down to the required length and was anastomosed to the recipient's pulmonary artery using continuous 5-0 silk sutures, doubly sewn. Perfusion of the donor heart was discontinued. The aorta was cut to fit the patient's aorta and the anastomosis was completed with continuous 4-0 silk sutures, doubly sewn. The donor's left ventricle was vented throughout this procedure. The aortic clamp was released, permitting perfusion of the myocardium from the patient's aorta. The left ventricular apex was tilted up to allow air to escape from the left heart, and the right heart was needled in order to exclude all air from this chamber.

A pint of citrated blood was added to the perfusate after 50 min. of bypass and subsequently 2 further pints were added to the bypass machine, being reconstituted in the usual way by the addition of THAM, calcium and heparin. After completion of the aortic anastomosis, rewarming was commenced after 165 min. of total cardiopulmonary bypass and the flow was increased to 4·5 l./min. (2·7 l./sq.m./min.). After 184 min., partial bypass was commenced by withdrawing the caval cannulae into the atrium and removing the superior vena-caval catheter. With a mid-oesophageal temperature of 36°C and a rectal temperature of 31°C, after a total perfusion duration of 196 minutes, 35 joules of energy were applied to the heart from a DC defibrillator. The first shock was successful in restoring good coordinated ventricular contraction. The heart was beating at a rate of 120/min. in nodal rhythm. At this stage it had been without coronary perfusion for 7 min., at normothermia, and for 14 min. at 22°C, and it had been perfused artificially with the heart-lung machine for a total period of 117 min.

Rewarming was continued for a further 15 min., when an intravenous drip of isoprenaline hydrochloride was commenced, preparatory to discontinuing bypass. The left ventricular apex was tilted up again and the left ventricle was aspirated to remove all air. The left ventricular vent was removed and the opening in the apex was closed with purse-string silk sutures. One minute later bypass was discontinued.

The arterial line pressure was 65/50 mm.Hg and the venous pressure 6 cm. saline at this stage. The heart beat was not forcible and bypass was recommenced after a ½ min., being continued for a further 2 min. When the pump was stopped, the systemic pressure was 85/55 mm. Hg and the venous pressure was 8 cm. saline. One minute later the pump was again started and perfusion resumed for another 3 min. to further improve the heart beat. On discontinuing bypass, the systemic pressure was 95/70 mm.Hg, venous pressure 5 cm. saline, and cardiac contractions were satisfactory. Bypass was finally stopped 221 min. after commencement, with interruptions totalling 4½ min. The lowest mid-oesophageal temperature reached during the operation was 21·5°C.

Protamine sulphate was now administered by slow intravenous infusion, the dosage being calculated at 1·25 times the dosage of heparin administered before bypass. Haemostasis was excellent and no further sutures were required in any of the suture lines. The cannula in the ascending aorta was removed and the aorta repaired with 3-0 silk purse-string sutures. The recipient's atrial appendage was excised and the edges of the wound were closed with silk sutures.

After lavage of the pericardial sac with a warm, normal saline solution, the pericardium was closed with a continuous suture of chromic catgut around a size 20 F plastic catheter. A further chromic catgut suture re-united the 2 lobes of the thymus and a size 24 F plastic mediastinal drainage tube was inserted. Haemostasis of the divided sternum was achieved, and the sternum was approximated with interrupted stainless-steel wire binding, passed through the sternum with an awl. The divided linea alba was closed with interrupted sutures of monofilament nylon and the soft tissues anterior to the sternum were coapted with a running chromic catgut suture. A subcutaneous suture of plain catgut and a continuous skin suture of monofilament nylon completed the thoracotomy closure. The groin wound was closed with interrupted chromic catgut and monofilament nylon, without drainage.

A nasotracheal tube was inserted for maintenance of postoperative mechanical ventilation. The chest X-ray, electrocardiogram, arterial and venous pressures, urinary output and peripheral circulation were assessed and all were satisfactory. The patient was returned to the postoperative room.

POSTOPERATIVE CARE

The postoperative care of the patient was concentrated on:

1. Maintaining a satisfactory cardiac output.
2. Suppressing the immunologic reaction to the transplanted organ.
3. The prevention of infection.

Cardiac Output

The adequacy of the cardiac output was judged by monitoring the following parameters:

1. The systolic blood pressure, measured ¼-hourly by palpation distal to an arm-pressure cuff.
2. The venous pressure, measured by inferior vena caval cannulation, established at surgery and connected to a disposable venous-pressure set.
3. The rate and rhythm of the heart, by recording the peripheral pulse rate and by electrocardiographic monitoring. This apparatus displays a continuous trace of standard lead II and gives visual and audible signals of each R wave, and incorporates a heart-rate meter.
4. The volume of the peripheral pulses and the peripheral circulation, by palpation and inspection.
5. Renal function, by measuring the urinary output every 2 hours and by performing daily creatinine clearance studies.
6. The temperature is recorded ¼-hourly by means of an indwelling rectal probe.
7. Acid-base balance studies are performed by the Astrup method.
8. Serum electrolyte investigations performed twice daily in the first few days and subsequently once daily.

Any evidence of deterioration in the cardiac output is treated vigorously by correcting abnormalities in the acid-base balance or serum electrolytes. Maintenance of adequate cardiac function was ensured initially by intravenous administration of isoprenaline hydrochloride in accurately regulated dosage of a 1:400,000 solution in 5% dextrose in water. Tachycardia was treated by slow digitalization with digoxin.

Suppression of the Immunologic Reaction to the Transplanted Organ

The following parameters were studied to detect any evidence of threatened rejection of the heart:

(*a*) the leucocyte response in the blood stream,
(*b*) deterioration in cardiac output,
(*c*) change in the serum enzyme levels which could indicate myocardial damage,
(*d*) changes in the voltage of the R wave of the electrocardiograph.

Anticipated rejection was treated by the use of steroids, commencing on the day of operation with intravenous hydrocortisone 500 mg. administered over 24 hours, and in addition 60 mg. prednisone administered orally. The hydrocortisone dosage was gradually reduced by 100 mg. daily while the prednisone dosage was maintained at 60 mg./day. The heart was irradiated locally, using a 1 curie source of cobalt, starting with a dose of 100 rads. on day 3, then 85 rads. on day 4 and 200 rads. on days 5, 7 and 9, given in the Radiotherapy Department.

Initially, 150 mg. azathioprine was administered daily through a nasogastric tube; as soon as urinary function improved, this was increased to 200 mg.

Threatened rejection was treated by administration of 200 mg. prednisone and 200 μg. actinomycin C daily for 3 days. The dosage of prednisone was gradually reduced.

Prevention of Infection

As absolute sterility of the patient's environment is not possible, the following preventive measures were adopted.

1. Pre-operative Period

(*a*) *Patient.* The patient is washed daily with hexachlorophene soap. Swabs are taken from the skin, nose, throat, mouth and rectum and are examined for the possible presence of potential pathogens, especially yeasts, *Pseudomonas aeruginosa*, Klebsiella species, beta-haemolytic streptococci and staphylococci. Antibiotic sensitivities of these organisms are determined where possible. Any obvious septic lesion is treated vigorously.

(*b*) *Staff.* Nurses and medical staff who are to handle the patient postoperatively have swabs taken from the nose, mouth, throat and rectum for bacteriological examination to determine if they are carriers of any potential pathogens.

(*c*) *Room.* A room is set aside in the unit, which is then thoroughly cleaned in the following manner:

(*i*) gaseous disinfection under bacteriological control,
(*ii*) thorough washing of all walls and floor with a

phenolic disinfectant, using boiled cleaning utensils,
(*iii*) thorough washing of the bed with liberal amounts of the correctly diluted phenolic disinfectant,
(*iv*) autoclaving of the mattress which is then covered in plastic, and autoclaving of the pillows, and
(*v*) flushing of the wash-basin 3 times daily with a suitably diluted phenolic disinfectant.

(*d*) *Apparatus.* Any apparatus to be used near or on the patient is carefully checked for cleanliness. This applies particularly to the oxygen tent, the suction apparatus and the Bird respirator.

This apparatus is dismantled as completely as possible and thoroughly cleansed mechanically, then all parts which can be autoclaved or boiled are so treated. Parts which cannot be boiled or autoclaved are treated by gaseous disinfection, or a phenolic disinfectant. Particular attention is given to any humidifying unit. The water in this unit is changed daily and the water container is boiled at the end of each day, pre- and postoperatively.

2. *Postoperative Period*

The patient is transferred to the specially prepared room. All staff attending the patient wear caps, masks, canvas overshoes and sterile gown and gloves, as for any sterile procedure. After any form of attention to the patient, the gloved hands are rinsed in the iodopher disinfectant and dried on disposable paper towels.

The patient's sheets and cotton blanket are changed twice daily, taking due care not to disturb the air excessively while doing this. The floors are mopped twice daily with a phenolic disinfectant. The bedpan and urinal are stored in a phenolic disinfectant. They are rinsed in hot water and dried before use.

In addition the following measures are taken:

(*a*) *Patient.* Every second day, swabs for bacteriological examination are taken from the nose, throat, mouth and anus to assess the presence of potential pathogens, or a change in bacterial flora.

All venepunctures, intravenous therapy sites and injection sites are treated as for a sterile surgical procedure. Daily blood cultures are performed. Careful attention is given to the perineum and scrotal region. These areas are dusted daily with hexachlorophene and Mycostatin powder.

The minimal number of personnel attend the patient.

(*b*) *Staff.* Nose, throat, mouth and rectal swabs are taken for bacteriological investigations every week to assess the presence of any potential pathogens. Antibiotic treatment was introduced as required.

The diabetes was controlled as for any patient with diabetes who has undergone major surgery, by means of frequent testing of urine for sugar and ketone bodies, and regulating a dosage of soluble insulin accordingly. This aspect did not present any particular problems.

SUMMARY

The first human heart transplant is described. The steps leading up to this event are outlined briefly and the operative technique is detailed. The postoperative care of the patient following this successful operation is described.

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THE ACQUISITION OF HUMAN TISSUE FOR TRANSPLANTATION PURPOSES: LEGAL REQUIREMENTS IN SOUTH AFRICA

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Rapid advances in transplant immunology and surgery have resulted in an increasing demand for human tissue for scientific and therapeutic use. It is envisaged that this need will increase considerably in the future in the face of the increasing tempo of technological advances in this field of medical endeavour.

'Because it is desirable that the results of animal and laboratory experiments be applied to human beings to further scientific knowledge and to help the suffering of humanity, the World Medical Association (of which the Medical Association of South Africa is a member) has prepared recommendations as a guide to each doctor engaged in clinical research'.[1]

These recommendations draw a clear distinction between 'clinical research in which the aim is essentially therapeutic for a patient, and clinical research, the essential object of which is purely scientific, and without therapeutic value to the person subjected to research'.

PRINCIPLES RECOMMENDED BY THE WORLD MEDICAL ASSOCIATION

Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research, and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.