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Anesthesia for Major Operations on Patients Who Have Transplanted Hearts, A Review of 29 Cases

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The first human allograft cardiac transplant was carried out in December 1967. The first cardiac transplant at Stanford University was one month later in January 1968. From that period through August 1976, there have been 114 human allograft cardiac transplants performed on 109 patients at Stanford University. For patients who survive the critical first three postoperative months, the current one-, two- and three-year survival rates are 79, 65, and 50 per cent respectively. At the time of this writing, 44 patients who have undergone cardiac transplantation at Stanford University are still alive, with the longest living cardiac-transplanted patient surviving 77 months post-transplant.

Twenty of these cardiac transplant patients have had to undergo additional operations (table 1). There has been no published report of the anesthetic management of these patients. This report reviews the anesthetic management of these patients, and discusses the principal concerns of the anesthetist caring for such patients.

Review of Cases

Review of the charts of 20 patients who underwent general anesthesia following cardiac transplantation (table 1) revealed several interesting facts. Fifteen operations occurred in the first three months following transplantation, while 14 operations occurred 10 to 68 months after transplantation. As expected, the patients anesthetized within three months of transplantation underwent surgical procedures for the saving of life or limb. The four patients who died within a week of operation were in this group (table 2). Only one of these deaths was possibly related to anesthesia (difficulty placing a Robert-Shaw tube).

Prior to elective surgical procedures, the cardiac-transplanted patients had cardiovascular evaluation, including angiography, electrocardiography, and endomyocardiac biopsy to evaluate the status of the coronary arteries, the hemodynamic status, and the presence or absence of rejection.

Anesthetic management encompassed many techniques. Monitoring included measurement of mean arterial pressure and central venous pressure (CVP) in all major cases. CVP was usually maintained above 10 cm H_2O. Induction and maintenance of anesthesia varied and were tailored to the patients' needs. Induction agents included thiopental, diazepam, ketamine, and droperidol, with or without the narcotics morphine, fentanyl, or demerol. Inhalational agents used included nitrous oxide, methoxyflurane, halothane, and enflurane. Muscle relaxation was achieved with succinylcholine, *d*-tubocurarine, dimethylcurarine, or pancuronium. The most popular method employed was the use of nitrous oxide, narcotic, and relaxant with a low dose of an inhaled volatile anesthetic. Cardiovascular drugs used included atropine, isoproterenol, ephedrine, norepinephrine, dopamine, sodium nitroprusside, and thorazine. Except for atropine and pancuronium, discussed below, there was no unusual response to any of these agents. Excluding retransplantation and the patient who died on the operating table with a bronchopleural fistula, there was no episode of intraoperative hypotension or arrhythmia that could not be explained on the basis of acute blood loss or sepsis.

TABLE 1. Operative Procedures Requiring General Anesthesia in 20 Cardiac-transplanted Patients

Operation	Number of Cases	Time Following Cardiac Transplantation
Retransplantation	5	8 hours; 2, 2, 27, 66 months
Thoracotomy	3	1, 12, 25 days
Femoral-artery exploration	2	2, 29 days
Exploratory laparotomy*	7	4, 24, 30, 45 days 2, 2, 3 months
Wound debridements	5	10, 11, 16, 24, 24 months
Removal of infected pacemaker generator	1	15 months
LR ext. amps.	3	24, 48, 48 months
Total hip replacements	2	26, 26 months
Resection of abdominal aortic aneurysm	1	68 months
	29	

* Five perforated viscus, one abscess, one enterocolitis.

Discussion

Cardiac-transplanted patients present the anesthetist with challenging problems related to their complex drug therapy (table 3) and the pharmaco-

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TABLE 2. Deaths within Six Weeks Following General Anesthesia in Cardiac Transplantation Patients

Diagnosis	Procedure	Interval Following Transplantation	Time Following Procedure	Cause
Perforated sigmoid colon	Exploratory laparotomy	24 days	1 week	Gram-negative sepsis
Bronchopleural fistula	Thoracotomy	12 days	On table	Problem in placing Robert-Shaw tube; extensive pulmonary infarct and bronchopneumonia
Perforated esophagus	Exploratory laparotomy	2 weeks (following second cardiac transplantation)	1 day	*Candida* peritonitis
Perforated gastric ulcer	Exploratory laparotomy	1½ months	4 days	Hemorrhagic infarct; right upper lobe *Aspergillus* empyema; bronchial pneumonia

dynamics and hemodynamics of the denervated heart. The potential complications of immunosuppression, high-dose steroids, anticoagulation, and use of diuretics have been well described and are not elaborated upon here.

Infection causes the deaths of slightly more than half of all cardiac-transplanted patients, and the respiratory tract is the most common site of infection.[1] We, therefore, consider that the patient must be handled with sterile technique, including sterile placement of all intravascular lines, sterile handling of airway equipment, and keeping the patient's exposure to nonessential personnel to a minimum.

The potential cardiovascular problems presented by the cardiac-transplanted patient are: 1) the denervated heart responds to stress utilizing atypical adaptive mechanisms[2]; 2) there is an increase in arrythmias.[3] One result of cardiac transplantation is that the transplanted heart has two independently functioning sinoatrial nodes, one in the recipient atrium and one in the donor atrium.[4] Both can be recorded electrically. The recipient atrium remains innervated, but hemodynamically insignificant, while the donor atrium is denervated and is responsible for the electrophysiologic responses of the transplanted heart.[3] By using intra-atrial electrode monitoring of "p" waves arising from the recipient atrial remnant and from the donor atrium following amyl nitrate inhalation and administration of atropine,[4,5] it has been shown that there is no evidence for reinnervation of the transplanted human heart as long as 44 months after transplant[3] (recipient atrial rate increased while the donor atrial rate remained the same). In contrast, the transplanted canine heart does show signs of reinnervation as early as 140 days after transplant.[3] Thus, heart rate does not change following atropine,[4-6] nor would we expect to see a change with pancuronium, gallamine, neostigmine, or pyridostigmine (these patients showed no change in rate with intravenous administration of pancuronium, atropine or neostigmine).

TABLE 3. Drug Therapy after Cardiac Transplantation

Medication	Average Dose (mg) One Year Postoperatively[3]	Potential Problems
Prednisone	30	Osteoporosis, aseptic necrosis, gastric ulceration, cardiovascular collapse, infection
Azathioprine	175	Mild hepatic abnormalities, leukopenia, infection
or Cyclophosphamide	75	Granulocytopenia, thrombocytopenia, infection
Warfarin sodium	5–10	Bleeding
Dipyridamole	400	Increased bleeding tendency?
Diuretic agent	As needed	Hypokalemia, hypovolemia

There is no published study of the responses of the transplanted human heart to anesthetic and surgical stresses. However, exercise studies of patients one year and two years after transplantation using a ten-minute period of submaximal supine bicycle exercise revealed several interesting facts.[2] At rest, the intracardiac pressures were normal. The average heart rate was 90/min and did not show the usual respiratory variations. Cardiac output was lower than normal at rest and exercise, with the arteriovenous oxygen difference greater. With exercise, there was a gradual increase in heart rate throughout the exercise period, with prompt elevation of left ventricular end-diastolic pressure (average 10 torr) followed by a decrease during late exercise in some patients. There was a progressive increase in left ventricular systolic pressure through-

TABLE 4. Effects of Cardioactive Drugs on the Denervated Human Heart

Drug	Dosage (iv)	Chronotropy	Inotropy	Comment
Atropine[4,5,6]	1–2 mg	No effect	Not studied	Recipient atrial rate increased
Digoxin[8,9]	1.25 mg	No effect	+	No effect on A-V nodal refractory period
Glucagon[8]	4 mg	+	+	Effective even after digitalization; can overcome propranolol effects
Isoproterenol[6,8]	3.5 μg	+	+	Recipient atrial rate also increased; decrease in central blood pressure secondary to decreased peripheral vascular resistance
Norepinephrine[6]	4–8 μg/min over 10 minutes	+	Not studied	Recipient atrial rate decreased; increased systolic blood pressure; no signs of supersensitivity
Propranolol[6]	7 mg/10 min	–	Not studied	

out the first half of the exercise period. A continuously positive change in left ventricular rate of pressure change (dP/dt) throughout exercise was observed, with an average 44 per cent increase in stroke volume and an average 92 per cent increase in cardiac output. Of practical concern to the anesthetist is that the denervated heart responds to stress primarily by increasing stroke volume (Frank-Starling effect), compared with the normally innervated heart in which the increase in cardiac output is primarily due to an increase in heart rate with little change in stroke volume.[7] Also, of the primary determinants of cardiac output, *i.e.*, preload, afterload, heart rate, and contractile state, it is the latter that appears to be limiting.[2] The slow increase in heart rate is thought to be mostly secondary to increased circulating catecholamines.[2,5,7] Therefore, to avoid hypotension and maintain cardiac output during stress, an adequate preload must be available, in addition to the means to increase heart rate rapidly and also enhance contractile force. The anesthetist may wish to avoid direct myocardial depressant drugs.

Studies of various cardioactive drugs in the transplanted human heart reveal that the adrenergic receptors are intact and, contrary to earlier assumptions, there is no evidence that the receptors become supersensitive to exogenous catecholamines[6] (table 4). Of importance to the anesthetist is the fact that neither atropine nor digoxin alters heart rate,[8,9] and the denervated human heart responds to isoproterenol, glucagon, norepinephrine, and propranolol as does the innervated heart.[6,8] The reactions of the patients in our series to isoproterenol, atropine, and norepinephrine support these findings.

Arrhythmias, both atrial and ventricular, are common in the recently transplanted human heart, but decrease in the long-term cardiac-transplant survivors at rest and during exercise.[3] Electrical conduction from the atria to the ventricles is normal in denervated hearts.[4,7] Coronary arterial vascular resistance is independent of innervation and is responsive to changes in perfusion pressure, hypoxia and ischemia.[7] The suggested etiology for the arrhythmias includes local injury secondary to acute rejection, lack of normal vagal suppressant tone, and increased sensitivity to catecholamines.[3]

Cardiac arrhythmias have been treated successfully with antiarrhythmic drugs, including procainamide and quinidine, cardioversion (25–200 watt seconds for conversion of both atrial flutter and atrial fibrillation), and correction of the underlying rejection episode with large doses of immunosuppressive drugs[3] (plus antithymocyte globulin and heparin, when necessary[5]). The anesthetist should be alert to a potential increased incidence of both atrial and ventricular arrhythmias, especially when coronary-artery disease has developed, and be prepared to treat these arrhythmias.

In conclusion, we feel that the smooth anesthetic courses of most of these patients were achieved by a careful induction of anesthesia, with careful titration of anesthetic drugs and maintenance of an adequate intravascular volume (measured when indicated by central venous pressure). When hypotension or arrythmias do occur, the proper medications, fluids and cardioversion apparatus should be immediately available to correct the problem. With proper attention to these details, the cardiac-transplanted patient presents an acceptable anesthetic risk for surgery.

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Recognition Thresholds for Diethyl Ether and Halothane

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Operating room personnel are chronically exposed to anesthetic gases polluting their environment.[1–4] Some dangers of this exposure have been documented and published and efforts to scavenge the pollutants promoted.[5–7] Some investigators have suggested that inability to smell halothane indicates an efficient and safe scavenging system.[8] We created an apparatus for the production of trace concentrations of inhaled anesthetics with which to investigate whether halothane concentrations that are commonly found in the operating rooms and can significantly impair intellectual function are less than most people can detect by their sense of smell. We also established whether ether or halothane vapor is more easily detected by human olfaction.

METHODS

Generation of Traces of Inhalational Agents

1. The Long Calibrating Vapor Still. Air laden with vapor of halothane or diethyl ether was drawn slowly through a long coiled glass tube immersed in an ice and water bath. Anesthetic liquid condensed, leaving the vapor saturated at 0 C, at which temperature the calculated concentrations are 12.7 per cent halothane and 24 per cent ether.[9] Gas chromatographic analysis showed these concentrations to be reproducible to within 0.5 vol per cent.

2. The Diluting Tube (Figure 1). The concentrated vapor was discharged from a 50 ml glass syringe at a rate governed by a motorized syringe pump, through a 7-inch plastic connector and a 25-gauge needle soldered into the sealed end of a copper tube, 91 cm long and 3.8 cm in diameter. The vapor was diluted by compressed air injected tangentially into the same end of the tube, to encourage rotation and mixing. The injection ports were carefully adjusted prior to soldering to eliminate venturi-type effects on the flow from the syringe pump. The total gas flow was approximately 10 l/min as measured by a calibrated dry gas meter and the final concentration of vapor was calculated as follows:

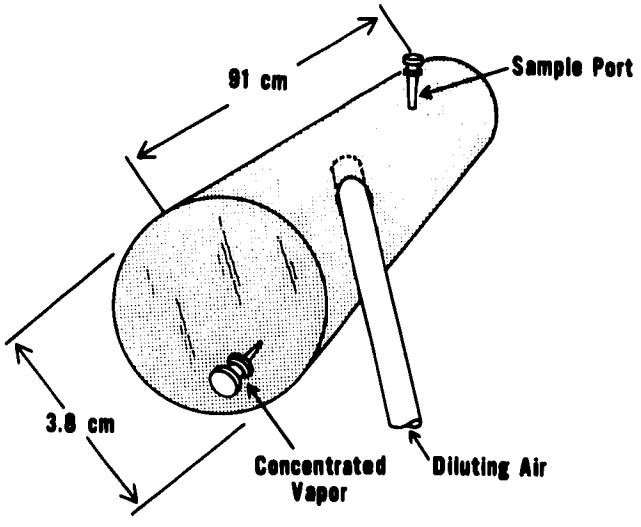

FIG. 1. Dilution tube for production of traces of volatile agents.

$$\text{Final concentration} = \text{syringe concentration} \times \frac{\text{syringe flow rate}}{\text{total gas flow}}$$

The concentrations of diluted vapor were measured by gas chromatography using a flame ionization detector. The barrel output was reproducible to within ±5 per cent and the concentrations produced were greater than predicted by a factor of 1.3 within the ranges used in this study. Such equipment requires calibration against known standards. The washout time—the time elapsing before vapor was undetectable by chromatography (0.1 ppm halothane) after the concentrated vapor input had been discontinued—was 15 seconds.

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