Management of patients undergoing multivalvular surgery for carcinoid heart disease: the role of the anaesthetist

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Background. The management of patients with carcinoid heart disease poses two major challenges for the anaesthetist: carcinoid crisis and low cardiac output secondary to right ventricular (RV) failure. Carcinoid crises may be precipitated by the administration of catecholamines and histamine-releasing drugs.

Methods. We analysed a series of 11 patients [six males, median (range) age 60 (42–73) yr] with severe symptomatic carcinoid heart disease who underwent multivalve surgery (right-sided valves, n=8; right- and left-sided valves, n=3) between 2001 and 2007.

Results. All patients received octreotide intraoperatively [650 (300–1050) μg] to prevent carcinoid symptoms and vasoplegia. Those patients on a greater preoperative octreotide regime required additional intraoperative octreotide [median (range) dose 320 (300–850) vs 750 (650–1050) μg]. Similarly, the use of greater doses of aprotinin (>5 KIU) was associated with greater requirements for octreotide [475 (300–700) vs 750 (320–1050) μg] and higher glucose levels (>8.5 mmol litre–1). Catecholamines were generally required in those patients who presented with a worse New York Heart Association functional class. Overall mortality was 18% (n=2) and only one episode of mild intraoperative carcinoid crisis was observed.

Conclusions. Carcinoid crisis and RV failure still remain the primary challenges for the anaesthesiologist while managing patients with carcinoid heart disease. Our study supports the administration of catecholamines to wean patients off cardiopulmonary bypass, particularly in the presence of myocardial dysfunction. Those patients on higher octreotide dosages may require close intraoperative glucose monitoring. Despite high operative mortality, surgical outcome has been improved potentially due to earlier patient referral and better perioperative management.

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Carcinoid tumours are rare slow-growing tumours derived from enterochromaffin cells that make up the APUD (amine precursor and decarboxylation) system. They are most commonly located in the gastrointestinal tract and the bronchopulmonary system. The incidence of carcinoid tumours ranges from 3 to 4 per 100 000 yr in the USA.1 At the time of diagnosis, 20–30% of patients present with disseminated disease and consequent malignant carcinoid syndrome defined by cutaneous flushing (90%), gastrointestinal hypermotility (70%), heart involvement (30%), and bronchospasm (15%).1 The term carcinoid heart disease is used to describe the severe fibrotic endocardial plaqing resulting form elevated blood concentrations of vasoactive substances such as 5-hydroxytryptamine (serotonin), histamine, tachykinins, prostaglandins, and possibly other growth factors released from the tumour.2 Structural changes in cardiac valve leaflet architecture leading to pathological valve function occur in more than 50% of patients with secondary hepatic metastases.3 This fibrous reaction particularly involves the right-sided valves,
extending towards the subvalvular apparatus including the chordae tendineae and papillary muscles (Fig. 1). Left-sided involvement is rare and mostly observed in the presence of an interatrial shunt, endobronchial tumour localization, and high tumour activity.4 In patients with carcinoid heart disease, advanced lesions, and severe valvular dysfunction, surgical therapy seems to be the only definitive treatment option available to improve both the quality of life and survival.5 6

Carcinoid heart disease poses two distinct challenges for the anaesthetist during the perioperative period: carcinoid crisis and low cardiac output syndrome secondary to right ventricular (RV) failure. Carcinoid crisis, characterized by flushing, hypotension, and bronchospasm,7 may be precipitated by the administration of catecholamines and histamine-releasing drugs used routinely in the anaesthetic management of patients presenting for cardiac surgery.8–10 Although the use of the somatostatin analogue octreotide has been shown to stabilize haemodynamic variables during the perioperative period, it remains clinically challenging to differentiate between hypotension due to a carcinoid crisis as opposed to low cardiac output syndrome secondary to myocardial dysfunction.11

We report our operative experience and outcome in the management of 11 patients with carcinoid heart disease who underwent multivalvular surgery. We also analyse the impact of vasoactive drugs in triggering a carcinoid crisis leading to haemodynamic instability and a need for additional intraoperative octreotide administration.

Methods

We retrospectively analysed a series of 11 patients with severe symptomatic carcinoid heart disease who underwent multivalvular surgery at our institution between January 2001 and December 2007. The protocol was approved by our local institutional review board (IRB). The approval included a waiver of informed consent.

Data collection

Data collection was performed prospectively. Clinical variables were entered into the New York State Department of Health (NYSDH, State Cardiac Advisory Committee) data registry. The NYSDH data registry is a mandatory verified peer-reviewed data collection system, which includes all cardiac surgery procedures in New York state. Anaesthetic data were extracted from an information management system used intraoperatively (CompuRecord, Philips Medical, Andover, MA, USA) which includes variables such as anaesthetic technique, haemodynamic course, timing, and dosage of all administered medications, including antifibrinolytics and vasoactive drugs and also blood products transfused (red blood cells, cryoprecipitate, fresh frozen plasma, platelets, plasmalyte, and albumin). Additionally, a thorough medical chart review was performed to obtain all tumour-related variables. Follow-up survival information was obtained by postoperative visits and by cross-matching the patient’s social security number with a web-based death index (http://ssdi.rootsweb.com/).
Preoperative workup

All patients underwent preoperative evaluation including measurements of urine 5-hydroxyindoleacetic acid (5-HIAA), blood serotonin, chromogranin A, and other chemical markers. Valve morphology and function were assessed first with transthoracic (TTE) and if necessary by subsequent transoesophageal (TOE) echocardiography. The severity of valvular regurgitation, as determined by Doppler echocardiography, was graded on a scale from 1+ to 4+ (1+, mild; 2+, moderate; 3+, moderately severe; and 4+, severe). Mean and peak transvalvular gradients were also measured to grade the degree of valvular stenosis. RV and left ventricular functions were also assessed. Cardiologists experienced in echocardiography interpreted the preoperative TTE/TOE investigations. Cardiac catheterization was performed in all patients.

Anaesthetic management

A balanced anaesthetic technique was used in all cases. Before securing the airway with a standard tracheal tube, general anaesthesia was induced with etomidate and maintained with isoflurane. Fentanyl or sufentanil, midazolam, and vecuronium or rocuronium were used. The doses administered were at the discretion of the consultant anaesthetist. Patient monitoring included standard ASA monitors, an indwelling radial arterial catheter, and a pulmonary artery catheter inserted through the right internal jugular vein and TOE for intraoperative assessment of valve and ventricular function.

A precise anaesthetic care protocol was applied to avoid carcinoid crisis. A pre-emptive infusion of octreotide at 50–100 μg h⁻¹ was started in the holding area before insertion of the arterial catheter and then continued throughout the case. During induction, an additional bolus of 50–100 μg was given. Additionally, octreotide was administered intermittently throughout the procedure as bolus injections of 20–100 μg to patients with carcinoid symptoms or unexplained decline in venous return during cardiopulmonary bypass (CPB). The infusion of octreotide was increased to a maximum dose of 300 μg h⁻¹ if required.

Vasoactive medications were used, when necessary, to wean patients off CPB providing a carcinoid crisis was not the cause of systemic vasoplegia. Medications included phenylephrine in incremental doses (40–100 μg) and calcium chloride as a single bolus dose (500–1500 mg) with the aim to normalize the concentration of ionized calcium. When additional inotropic support was needed, catecholamine infusions were given in patients with severe ventricular dysfunction and as rescue therapy for those patients who presented with refractory hypotension.

Antifibrinolytic therapy consisted of the administration of aprotinin (Trasylol®) to all patients except to those patients with severe renal dysfunction defined as a creatinine >221 μmol litre⁻¹. These patients received epsilon-aminocaproic acid (EACA, Amicar®). Throughout the study period from 2000 to 2006, aprotinin was administered according to the Hammersmith protocol. We gave a loading dose of 2 million kallikrein inhibitory units (KIU) i.v. over a 30 min time period. After completion of the loading dose, a maintenance dose of 500 000 KIU h⁻¹ was started and continued until the surgical procedure was finished. In addition, 2 million KIU were added to the CPB circuit prime. EACA 150 mg kg⁻¹ was administered as a bolus over 30 min, followed by a continuous infusion of 15 mg kg⁻¹ min⁻¹. No EACA was added to the CPB circuit prime. The infusion was continued until the end of surgery.

The heparin dosage required for adequate anticoagulation for CPB was calculated by the heparin dose–response method to maintain the patient’s activated clotting time ≥480 s with a heparin level at or greater than 200 U kg⁻¹, or more specifically 2.7 U ml⁻¹ circulating volume. Additionally, 10 000 U of heparin was added to the pump prime. After the completion of CPB, heparin was reversed with protamine sulphate. The protamine dose was calculated based on the heparin dose and was 0.015 mg U⁻¹ of heparin. After the administration of protamine, blood products (packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate) were given as necessary to correct coagulopathy.

Our standard postoperative pain management protocol included the administration of parenteral opioids such as fentanyl or morphine and non-steroidal anti-inflammatory drugs such as ketorolac tromethamine. Patients who continued complaining of pain received a patient-controlled analgesia pump with one of the aforementioned opioids. In our centre, it is not a departmental policy for cardiac surgical patients to receive thoracic epidural catheters after operation.

Statement of responsibility

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agreed to the manuscript as written.

Results

Patient characteristics

Characteristics of 11 patients are summarized in Table 1. The median (range) age of the patients was 60 (42–73) yr and five patients were female. Congestive heart failure with New York Heart Association (NYHA) functional class III or IV was present in all patients. Symptoms of severe right-sided heart failure were observed in six patients. Additional preoperative comorbidity included hypertension (n=5), hepatic failure (n=3), renal failure (n=2), and peripheral vascular disease (n=1).
Echocardiography findings

Two-dimensional and Doppler echocardiography revealed restricted leaflet motion during diastole (Carpentier’s functional classification type IIIa) of the tricuspid valve (TV) in all patients. Tricuspid leaflets were heavily thickened and retracted resulting in severe valve regurgitation. Four patients had associated moderate or severe tricuspid stenosis with a median (range) peak gradient of 11 (10–13) mm Hg. Pulmonary valve (PV) lesions were also present in 10 patients with significantly thickened and retracted leaflets leading to combined pulmonary regurgitation and stenosis. The median (range) PV peak gradient was 51 (40–75) mm Hg.

Left-sided valvular disease was noted in three patients with type IIIa mitral valve (MV) dysfunction due to leaflet thickening/retraction, and also chordal fusion and shortening. Mitral regurgitation was graded as moderate to severe in all patients. No patient presented with mitral stenosis. One patient presented with moderate aortic valve regurgitation. A patent foramen ovale (PFO) was noted in three patients (patient’s number 2, 6, and 8 in Table 2). Visual qualitative RV function assessed by TOE revealed mild, moderate, and severe RV dysfunction before surgery in one, four, and six patients, respectively.

Anaesthesia

As noted above, anaesthesia was induced with etomidate and maintained with isoflurane. Other anaesthetic drugs were administered as follows: fentanyl median (range) dose 2000 (500–2500) μg or sufentanil 250 (250–500) μg, midazolam 10 (4–20) mg, and neuromuscular blocking agents to facilitate tracheal intubation including vecuronium 15 (3–26) mg or rocuronium 65 (48–80) mg.

Intraoperative variables

Surgical procedures and perioperative variables are reported in Table 2. All patients were treated with octreotide before operation. Nine patients were on an octreotide protocol consisting of the administration of 30 mg (n=6) or 60 mg (n=3) of long-acting octreotide monthly, whereas two patients were taking 1000 and 2000 μg of s.c. octreotide daily, respectively. Intraoperatively, octreotide was administered to all patients with a median (range) dose of 650 μg (300–1050). Those patients who were on a higher octreotide regime (60 mg monthly or 2000 μg daily) required additional intraoperative octreotide administration [320 (300–850) vs 750 (650–1050) μg]. Furthermore, patients in whom peak glucose levels were ≥8.3 mmol litre⁻¹ required greater doses of octreotide [310 (300–600) vs 750 (650–1050) μg]. Three patients required an intraoperative insulin infusion.

Ninety per cent of patients (n=10) were given vasoactive medications. Calcium was administered to eight patients, phenylephrine to six, epinephrine to five, and dopamine to two patients. Ten patients required two or more vasoactive medications. Administration of catecholamines was different between patients with congestive heart failure in NYHA functional class IV (n=3) as opposed to patients in NYHA functional class III (n=4).

Ten patients received aprotinin intraoperatively whereas only one patient was given EACA. The four patients who were given increased amounts of aprotinin (>5 million KIU) mostly due to longer surgical procedures also required higher dosages of octreotide [475 (300–700) vs 750 (320–1050) μg].

Ten patients required blood product administration. Packed red blood cells were transfused to seven patients (range 1–4 units), platelets to six patients (range 4–6 units), and fresh frozen plasma to three patients (3–6 units). Total transfusion requirements were higher in five patients with longer (>200 min) CPB times [3 (1–5) vs 5 (2–14) units], but no differences were found when itemizing transfusion requirements (RBC vs non-RBC).

Surgical outcome

Surgical outcome is detailed in Table 3. Intraoperatively, one patient had a mild carcinoid crisis (patient number 1) during the fourth hour of anaesthesia, presenting with...
Table 2 Intraoperative variables. A, arterial; AV, aortic valve; Ca, calcium; CPB, cardiopulmonary bypass time; CV, central venous; EACA, epsilon-aminocaproic acid; MV, mitral valve; P, repair; PA, pulmonary artery; PFOC, patent foramen ovale closure; PV, pulmonic valve; R, replacement; TV, tricuspid valve; X-clamp, aortic cross-clamp time

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<th>Short-acting opioids</th>
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<th>Vasoactive medications</th>
<th>Antifibrinolytic therapy</th>
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Discussion

Cardiac tumors secrete large amounts of biogenic amines, peptides, and other vasoactive substances, which serotonin is the most prominent. Serotonin produced by the carcinoid tumor is transported to the liver through the portal vein, metabolized to 5-HIAA, and excreted in the urine. Most often, a carcinoid crisis is precipitated by an intravenous injection of serotonin.

Follow-up was complete for all patients. All nine discharged patients were alive at a median (range) follow-up of 21 (4–75) months. Five patients were classified as NYHA class I and four patients as NYHA class II. Ten patients had been treated with octreotide (30–60 mg monthly, n = 7; 1000 μg every n = 2, and calcium channel blockers (n = 6), angiotensin-converting enzyme inhibitors (n = 3), and betablockers (n = 5). Echocardiographic findings at follow-up are reported in Table 3. Medians and values are presented in Table 3. Echocardiographic findings at follow-up are reported in Table 3.

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or indirectly trigger a carcinoid crisis. Several factors have been shown to mediate the release of peptides from carcinoid tumours, such as emotional stress, hypercapnia, hypothermia, hypotension (which all have the potential to release catecholamines), histamine-releasing medications, and hypertension, which releases bradykinin. Recom-
mendations for the use of certain anaesthetic drugs are based mostly on anecdotal but logical experiences reported in the literature. Drugs that are considered capable of triggering the release of mediators include long-acting opioids, specifically meperidine and morphine, histamine-releasing neuromuscular relaxants, and also catecholamines. Although histamine release is most likely to occur in the presence of a gastric carcinoid tumour, drugs with potential to release histamine such as thiopental, atracurium, succinylocholine, meperidine, or morphine are best avoided. The anxiolytic properties of benzodiazepines make this class of drug very useful since emotional stress is an important factor in the development of carcinoid crises.

In our experience, anaesthetic induction can be accomplished safely with etomidate and muscle relaxation achieved with rocuronium or vecuronium. Short-acting synthetic opioids such as fentanyl or sufentanil are also safe.

Administration of antifibrinolytics
Aprotinin has been shown to reduce platelet activation on bypass, to decrease the activation threshold of the clotting factor cascade, and to prevent fibrinolysis. Although the efficacy of aprotinin has been reported with variable results in the setting of carcinoid syndrome, it has been traditionally used to inhibit kallikrein peptide released by the tumour, thus reducing the risk of hypotension and intraoperative bleeding. EACA has been used as an inhibitor of carcinoid hormones when aprotinin was not available. Previous studies have documented the beneficial effects of EACA on facial oedema during cardiac surgery, but aprotinin is still considered a more potent and effective inhibitor of kallikrein. In our series, those patients who were given higher amounts of aprotinin mostly due to longer operation times also required higher dosages of octreotide. Our finding is consistent with previously reported results from the Mayo Clinic. Weingarten and colleagues, in the only contemporary series on anaesthetic management of patients undergoing cardiac surgery for carcinoid heart disease, showed that the use of aprotinin correlated with an increased intraoperative requirement of octreotide. This observation, and the fact that aprotinin failed to prevent carcinoid symptoms after catecholamine administration as documented in classic studies, led us to suppose that there might be no need to administer further kallikrein inhibitors to block carcinoid burden. Furthermore, recent publications have corroborated that in addition to previously

### Table 3 Surgical outcome and follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Major complications</th>
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Octreotide represents the pillar of treatment for patients with carcinoid syndrome and has replaced nearly all previously used drugs such as ketanserin, methysergide, and cyproheptadine as the drug of choice for any carcinoid event. It has been shown to be the most effective treatment for the deleterious cardiovascular and pulmonary effects of serotonin and bradykinin, preventing their release from carcinoid cells and subsequently reducing symptoms in more than 70% of patients. Octreotide may be administered i.v., i.m., or by s.c. depot, and daily octreotide therapy usually ranges from 100 to 600 μg in two to four separated doses. Intraoperatively, it is usually given as an infusion (50–100 μg h⁻¹), using i.v. boluses, should a carcinoid crisis occur. However, treatment of patients with octreotide raises several issues, particularly with respect to glucose metabolism. Octreotide is a somatostatin analogue that is known to suppress several hormones, including insulin. Therefore, its use in combination with steroids in obese or non-insulin-dependent diabetic patients mandates close monitoring of glucose concentrations throughout the surgical procedure. In line with these considerations, a notable finding in our study was the association of significantly elevated glucose levels with greater doses of octreotide.
reported renal and vascular damage, aprotinin administration is linked to a significant increase in hospital and long-term mortality among cardiac surgical patients when compared with recipients of EACA, particularly in those undergoing coronary artery bypass grafting. These findings support the use of alternative and safer generic medications such as EACA or tranexamic acid in this patient population. Consequently, we have restricted the routine use of aprotinin during cardiac surgery.

**Intraoperative hypotension and vasoactive medication**

Haemodynamic instability in patients with carcinoid disease may be directly related to the tumour activity, to severe ventricular failure, and to functional changes after CPB. If hypotension in the setting of a carcinoid crisis is not responsive to the standard management of optimal volume replacement, correction of electrolyte abnormalities and octreotide administration, more effective vasoactive agents may be considered. In this scenario, calcium and catecholamines such as dopamine provide additional inotropic action to achieve an immediate reaction in response to myocardial depression. Historically, it has been taught that catecholamines trigger release of kallikrein from the tumour, which in turn leads to bradykinin formation causing vasodilation, increased capillary permeability, and bronchial constriction. Therefore, its use has been avoided due to a paradoxical hypotensive effect. In our series, all patients received vasoactive medications. Seven patients required the administration of catecholamines. Their use was not associated with higher requirements of octreotide, potentially indicating stable carcinoid tumour activity and secretion. Previous publications have also reported the safety of vasopressors and inotrope administration in patients with carcinoid heart disease, particularly in the presence of primary myocardial depression. With the availability of octreotide, the historical recommendation to avoid these agents is no longer valid.

**RV dysfunction in patients with carcinoid heart disease**

Elevated blood concentrations of vasoactive substances such as serotonin lead to a severe fibrotic endocardial plauking mostly involving the surface of the right-sided chambers and valves. As a consequence of these structural changes, there is a characteristic restrictive filling pattern due to reduced myocardial compliance and subsequent diminished ventricular diastolic volume with near-normal systolic function. Additionally, the tricuspid and PVs appear echocardiographically thickened, retracted, and locked in a semi-open position during both phases of the cardiac cycle (Carpentier’s type IIIa dysfunction) which results in progressive RV volume overload and further RV diastolic pressure elevation.

Intuitively, carcinoid heart disease should be classified as a restrictive cardiomyopathy resulting in diastolic dysfunction. Unfortunately, a review of the most recent literature reveals no study specifically examining the incidence or degree of diastolic dysfunction in this patient population. Without doubt, right-sided heart failure can be documented clinically and represents the most common indication for surgery among patients with carcinoid heart disease. However, although classic Doppler-derived parameters to assess LV diastolic dysfunction (transmitral flow velocities and pulmonary vein flow velocities) have been widely developed and validated, modern emerging concepts of characterizing RV diastolic function (e.g. strain and strain rate) are still under review for accuracy and validation and have yet to be utilized in this particular patient population. Consequently, we were not able to evaluate our patient population for diastolic dysfunction.

Systolic function of the right ventricle appears initially normal, yet may be misleading. The afterload reduced state seen in patients with long-standing insufficient atrioventricular valves could lead to an overestimation of true systolic function. In addition, the echocardiographer is confronted with the difficulty of quantifying RV function.

**Mortality and morbidity**

During the last decades, advances in medical therapy with somatostatin analogues and more effective oncological therapies for tumour metastases have resulted in better control of carcinoid symptoms and potentially improved survival. Consequently, right-sided valvular disease has become a major source of morbidity and mortality.

Owing to the rarity of the disease, limited information is available regarding the outcome of multivascular surgery in patients with carcinoid heart disease. Knot-Craig and colleagues reported one of the first case series with 10 patients who mostly underwent right-sided valve surgery with an operative mortality of 10%. Later on in 1995, Robiolio and colleagues published a series of nine patients undergoing right-sided valve replacement with a high operative mortality of 63%. In the same year, Connolly and colleagues reported nine operative deaths (35%) in a surgical series of 26 patients. More recently, Moller and colleagues updated the Mayo Clinic’s experience and showed that despite high postoperative mortality (16%), a trend towards improved surgical outcome was achieved. Similar to these studies, we report two operative deaths among 11 patients (18%), both of which highlight the challenges (vasoplegia and right heart failure) associated with cardiac surgery in this patient population. No major postoperative complications occurred in the remaining nine patients. Furthermore, with the meticulous application of our perioperative protocol of octreotide administration, we only observed one episode of carcinoid crisis (9%).
Others have reported perioperative coagulopathy as a major source of mortality and morbidity among carcinoid heart disease patients undergoing cardiac surgery.\(^5\)\(^3\)\(^1\) This complication was mostly observed in elderly patients, particularly in those with an abnormal liver profile. In a more recent study, Connolly and colleagues\(^6\) reported a lower incidence of this complication that was comparable with that observed in our series. The trend towards the reduction of postoperative bleeding in these patients is probably related to the advances in perioperative management and surgical techniques. As mentioned previously, all patients except for one receiving aprotinin intraoperatively. We believe that the systematic use of this drug, which is a potent antifibrinolytic agent, may have contributed in significantly reducing the incidence of bleeding.

**Limitations**

The retrospective observational nature of the study may lead to conclusions necessarily limited in their application. Additionally, the small sample size of the study population prevents us from evaluating any independent casual relationship between medications or risk factors and operative complications.

**Conclusions**

Carcinoid crisis and low cardiac output syndrome secondary to RV failure still remain the primary challenges that the anaesthetist is confronted with while managing patients with carcinoid heart disease. Our study findings further support the administration of supportive catecholamines to weak patients off CPB, particularly in the setting of hypotension due to myocardial dysfunction rather than carcinoid crisis. Those patients on a greater dose of octreotide before operation may require greater intraoperative octreotide dosages, which may require close monitoring of glucose levels. Finally, despite high operative mortality, a trend towards improved surgical outcome in patients with carcinoid heart disease has been achieved potentially due to earlier patient referral and better perioperative management.

**References**

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625


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