Journal of Clinical Anesthesia (2011) **23**, 329–341

Journal of Clinical Anesthesia

Review article

Carcinoid syndrome and perioperative anesthetic considerations

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Received 10 February 2010; revised 7 December 2010; accepted 8 December 2010

Keywords:
Carcinoid syndrome;
Octreotide;
Serotonin

Abstract Carcinoid tumors are uncommon, slow-growing neoplasms. These tumors are capable of secreting numerous bioactive substances, which results in significant potential challenges in the management of patients afflicted with carcinoid syndrome. Over the past two decades, both surgical and medical therapeutic options have broadened, resulting in improved outcomes. The pathophysiology, clinical signs and symptoms, diagnosis, treatment options, and perioperative management, including anesthetic considerations, of carcinoid syndrome are presented.

1. Introduction

Carcinoid tumors are uncommon, but not rare, slow-growing neoplasms capable of metastasis. They originate from neuroendocrine cells and are capable of secreting bioactive substances, most importantly serotonin, histamine, and the kinin peptides [1-3]. If these substances reach the systemic circulation without first being metabolized by the liver, they are capable of producing carcinoid syndrome [1]. This syndrome may produce life-threatening perioperative hemodynamic instability. The syndrome most often occurs

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doi:10.1016/j.jclinane.2010.12.009

with primary tumors that do not drain into the portal system or with hepatic metastases (the most common site of metastasis) because they bypass metabolism in the liver [1]. The majority of these tumors are located in the gastrointestinal (GI) tract, most commonly in the appendix, rectum, and ileum [1]; however, they also may be found in the bronchial tree [1].

Improved tools have resulted in an increase in the diagnosis of carcinoid tumors [4]. Currently, the reported incidence is between 0.2 and 10/100,000 [1,4-6]. Autopsy results have shown incidental findings of carcinoid tumor to be as high as 8% [4], indicating that many of these tumors remain undiagnosed [7]. There is no difference in incidence with regard to either gender or race [1]. There is, however, a bimodal distribution with respect to age. Patients are typically diagnosed either between 25 and 45 years of age or over 60 years of age [1]. These tumors are sometimes found in children, most commonly in the appendix [8]. The 5-year survival rate is 80% overall, but ranges from 33% for patients with sigmoid colon tumors to 99% for those with tumors of the appendix. When distant metastases are present, the 5-year survival rate decreases to 18% to 19% [9,10]. With the introduction of octreotide in 1992, survival rates have improved significantly [10].

Table 1 Clinical presentation and incidence of Carcinoid syndrome

Location	Percentage of total	Incidence of metastases (%)	Incidence of Carcinoid syndrome (%)
Foregut			
esophagus	< 0.1	—	—
stomach	4.6	10	9.5
duodenum	2.0	—	3.4
pancreas	0.7	71.9	20
gallbladder	0.3	17.8	5
bronchus, lung, trachea	27.9	5.7	13
Midgut			
jejunum	1.8	58.4	9
ileum	14.9	58.4	9
Meckel's diverticulum	0.5	—	13
appendix	4.8	38.8	< 1
colon	8.6	51	5
liver	0.4	32.2	—
ovary	1.0	32	50
testis	< 0.1	—	50
Hindgut			
rectum	13.6	3.9	—

Modified from: Jensen RT: Endocrine tumors of the gastrointestinal tract and pancreas. In: Fauci AS, Braunwald E, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 17th edn. New York: McGraw-Hill Cos.; 2008. p. 2349.

2. Background

Although first reported in 1888, it was not until 1907 that Oberndorfer first described these tumors as "carcinoid" tumors [11]. They were described as slow-growing, small bowel tumors, capable of metastasis, with a generally favorable prognosis. More than 75% of carcinoid tumors originate in the GI tract [12-14]. The lung is the most common site outside of the GI tract in which carcinoid tumors are found (22% of distant metastases are found in the lung) [15,16]. Tumors also have been reported in the genitourinary tract, thyroid, breast [1], pancreas [17], thymus [18], and liver [19].

The extent of tumor burden is not necessarily related to the clinical course of the patient. Patients with a large tumor burden may remain asymptomatic for years, while some of those with only minimal disease, in the small bowel mesentery, for example, may have significant symptoms of carcinoid syndrome without any liver metastases [7,20-22]. Carcinoid syndrome is most often associated with ileal tumors with liver metastases that secrete mediators directly into the hepatic veins [19].

Carcinoid tumors traditionally have been classified by the embryonic site of origin of the tumor, eg, as foregut, midgut, or hindgut [4]. The site of origin affects the clinical presentation, secretion of vasoactive substances, signs and symptoms of carcinoid syndrome, and overall survival [23] (Table 1). Foregut carcinoids are found from the esophagus to the duodenum. Midgut carcinoids are found from the jejunum to mid-transverse colon, and are most likely to produce the classic carcinoid syndrome [24]. Hindgut tumors are found from the mid-transverse colon to the rectum [23,25], and usually do not present with carcinoid syndrome [24]. Hindgut carcinoids are more likely to present with GI bleeding [23]. There is another classification system which assigns the term "carcinoid tumor" only to midgut tumors, and "neuroendocrine tumor of the site of origin" to others [26].

Patients with carcinoid tumors also are at increased risk of having other co-existing tumors, frequently in the lung, esophagus, stomach, colon, prostate, and urinary tract [27]. The presence of an occult carcinoid tumor may become evident during surgery for a non-carcinoid tumor. Incidental findings of carcinoid tumor are often found in younger patients, 25 to 45 years of age, during appendectomy, trauma, or cesarean sections. In the older population, over 60 years of age, findings are often made during vascular surgery or transurethral resection of the prostate [1].

3. Signs and symptoms

Due to their slow growth, carcinoid tumors are usually asymptomatic and often produce only vague abdominal pain that is undiagnosed or misdiagnosed as irritable bowel

syndrome [28]. However, these non-secreting tumors may produce symptoms such as intestinal obstruction or hemoptysis [19]. Appendiceal carcinoids are usually found incidentally at appendectomy, whereas jejunoileal carcinoids are more likely to present with abdominal pain, obstruction, or signs of carcinoid syndrome [23]. Only 25% of carcinoid tumors actually produce mediators capable of causing symptoms of carcinoid syndrome [19]. Normally the release of vasoactive substances causes little if any symptoms because the liver is able rapidly to inactivate these substances [23]. With larger tumors, the liver's ability to inactivate these substances may be overwhelmed [19,29], and carcinoid syndrome results. Signs and symptoms of carcinoid syndrome develop only when neuropeptides and amine substances are released in their active form into the systemic circulation. These signs and symptoms often indicate the presence of hepatic, gonadal, bone, or pulmonary metastases, as substances produced in these sites bypass metabolism in the liver [4]. Primary tumors that do not drain into the portal circulation, such as bronchial, ovarian, or testicular tumors, are also capable of producing carcinoid syndrome [1].

Although 25% of tumors actively secrete substances capable of causing symptoms, less than 10% of people with a carcinoid tumor develop the classic carcinoid syndrome [24]. Carcinoid syndrome has a clinical spectrum that includes hypotension or hypertension, cutaneous flushing, bronchoconstriction, diarrhea, and carcinoid heart disease [4]. Clinical manifestations of carcinoid syndrome are listed in Table 2. The most common of these involve the vascular and GI systems. Episodic flushing of the head and neck is reported in about 94% of patients [1]. It presents with a classic distribution over the upper chest, neck, face, upper arms, and torso [19]. Labile blood pressure (BP) may be present, especially in severe cases of flushing; however, BP changes may not coincide with the flushing episodes. Diarrhea is the most common GI complaint [1]; it is reported in up to 78% of patients. It may vary from only a slight change in bowel habits to severe diarrhea with associated dehydration, hyponatremia, hypokalemia, hypochloremia, abdominal pain, and nausea [19]. Asthma rarely presents as the sole symptom of carcinoid syndrome, but mild wheezing is associated with flushing in about 19% of patients [19]. Cardiac involvement has been reported in more than half of the patients with carcinoid syndrome [30]. Cardiac lesions, if present, may result from the secretion of bioactive mediators and most often affect only the right side of the heart because of the ability of the lungs to clear the causative agents [1,19].

The classic carcinoid syndrome is characterized by episodic flushing, diarrhea, and wheezing but patients may also present with abdominal pain, right-sided heart disease, left-sided heart disease, and pellagra [31]. These symptoms may vary in intensity and display a paroxysmal onset [24]. Dizziness and wheezing may accompany this onset and may be associated with triggering agents such as stress, exercise, or certain foods high in serotonin (eg, bananas, alcohol, cheese, coffee) [1,19,28].

Table 2 Clinical manifestations of carcinoid syndrome

Sign/symptom	Frequency	Characteristics	Involved mediators
Flushing	85% - 90%	Foregut: long-lasting, purple face and neck. Midgut: short-lasting, pink/red. Severe flushing associated with hypotension and tachycardia	Kallikrein, 5-HTP, Histamine, substance P, Prostaglandins
GI hypermotility	70% - 80%	Secretory diarrhea, nausea, vomiting	Gastrin, 5-HTP, histamine, PGs, VIPs
Abdominal pain	35%	Progressive	Small bowel obstruction, hepatomegaly, ischemia
Heart failure			
right	30%	Dyspnea	5-HTP, substance P
left	10%		
Telangiectasia	25%	Face	Unknown
Bronchospasm	15%	Wheezing	Histamine, 5-HTP
Pellagra	5%	Dermatitis, diarrhea, dementia	Niacin deficiency

Modified from: Chang BB, Phan AT, Yao JC. Neuroendocrine carcinoma. In: Kantarjian HM, Wolff RA, Koller CA, editors. The M.D. Anderson Manual of Medical Oncology. New York: McGraw-Hill; 2006. p. 449-60.
GI = gastrointestinal; 5-HTP = 5-hydroxytryptophan; PGs = prostaglandins; VIPs = vasoactive intestinal peptides.

A life-threatening form of carcinoid syndrome, known as carcinoid crisis, is well described. Carcinoid crisis may be precipitated by physical manipulation of the tumor (including bedside palpation), chemical stimulation or tumor necrosis resulting from chemotherapy, and hepatic artery ligation or embolization [32]. It may occur spontaneously or during the induction of anesthesia. Clinical manifestations of carcinoid crisis include severe flushing with associated dramatic changes in BP, cardiac arrhythmias, bronchoconstriction, and mental status changes [33] (Table 2).

Since the introduction of octreotide as a therapeutic option, the prognosis has significantly improved. Nevertheless, carcinoid tumors may prove fatal for some patients. Death in these patients often results from pulmonary, cardiovascular, or hepatic involvement and dysfunction, rather than from carcinoid crisis [34]. Overall survival is significantly worse for patients with cardiac involvement, with median survival reported at approximately 1.6 years [34].

The presence of carcinoid heart disease or high levels of urinary 5-hydroxyindoleacetic acid (5-HIAA) also have been associated with an increase in postoperative complications [35]. The exact etiology of the cardiac lesions is unclear. Elevated levels of serotonin and tachykinin, in concert with endothelium and platelets, have been implicated in the development of valvulitis and fibroblast proliferation, resulting in the formation of carcinoid plaques that damage heart valves [31,34,36].

The classical presentation is a right-sided valvular lesion caused by fibrous tissue growth within the endocardium [23]. Because of retraction and fixation of the valves, tricuspid regurgitation is a nearly universal finding; however, tricuspid stenosis also may occur [29,34]. Pulmonary insufficiency and stenosis may be found as well [23]. In many patients, the structural valvular lesions will lead to symptomatic right-sided heart failure (edema, hepatomegaly, fatigue with exertion, and low cardiac output) [34]. Fibrous tissue growth, caused by carcinoid secretion of serotonin, also may interrupt electrical pathways, leading to arrhythmias [37]. In addition to right-sided lesions, cardiac involvement may include left-sided lesions, myocardial metastases, and pericardial effusions [34]. Less than 10% of patients with carcinoid heart disease have aortic or mitral insufficiency [38]. However, in at least one study, which was designed to assess cardiac function in patients with normal left ventricular ejection fraction via echocardiography, mitral, aortic, and tricuspid regurgitation were present [39].

If a bronchial tumor is present, left-sided heart lesions [19], pulmonary hypertension, and bronchospasm also may result [1]. The presence of left-sided lesions has led to the proposal that tachykinins are the causative agents in carcinoid-related fibrotic heart lesions [19]. However, treatment aimed at reducing the commonly measured urinary metabolite, HIAA, did not produce regression of the cardiac lesions [23].

4. Pathophysiology

Serotonin and histamine are significant causative agents in carcinoid syndrome; however, carcinoid tumors may produce an array of various vasoactive peptides, hormones, and other mediators, including tachykinins, bradykinins, motilin, prostaglandins, vasoactive intestinal peptide, and adrenocorticotrophic hormone [4,40-43]. Clinical manifestations may occur from the release of approximately 20 bioactive substances (Table 3). The range of various clinical presentations is explained by the specific mediators released and their interactions [19].

The three major substances released are serotonin, histamine, and the kinins [1]. Serotonin is synthesized from tryptophan via hydroxylation and decarboxylation [19]. Adrenergic stimulation causes the release of serotonin into the circulation. It is metabolized by aldehyde dehydrogenase and monoamine oxidase to 5-HIAA acid [1,19], which is excreted in the urine. Elevated levels of 5-HIAA are monitored in the urine as a marker of excess serotonin production and, therefore, the presence of a carcinoid tumor [1]. Serotonin synthesis normally uses only 1% of the body's supply of tryptophan, but this figure may be increased to as much as 60% [1].

Table 3 Bioactive substances

Serotonin	Kallikrein
Histamine	Prostaglandins
Bradykinin	Substance P
Insulin	Dopamine
Glucagon	Neuropeptide K
Catecholamines	Gastrin

Hypoproteinemia results from tryptophan depletion, which is an essential amino acid needed for the synthesis of serotonin, proteins, and nicotinic acid [44]. As a result, nicotinic acid production, which normally uses approximately 99% of tryptophan, may be reduced. This alteration of tryptophan metabolism results in hypoalbuminemia, decreased protein synthesis, and pellagra-like symptoms (eg, dermatitis, dementia, and diarrhea) [1,6] (Fig. 1).

Serotonin may cause vasoconstriction or vasodilation; thus, both hypertension and hypotension are possible [19]. At normal concentrations, serotonin does not affect cardiac function; however, the elevated levels seen in carcinoid syndrome may cause both inotropic and chronotropic responses [19]. This action is due in part to an indirect effect from the release of norepinephrine [45]. Elevated serotonin levels also result in increased gut motility and the secretion of water, sodium, chloride, and potassium by the small intestine [19]. Other effects attributed to elevated levels of serotonin are vomiting, bronchospasm, hyperglycemia, and prolonged drowsiness following emergence from anesthesia [19].

Histamine release is seen predominantly in patients with gastric or foregut carcinoids [19,46]. This may be due to the presence of histidine decarboxylase in normal gastric mucosa [47]. Histamine release is thought to be responsible for the bronchospasm seen in some carcinoid patients, and it also may be the cause of flushing [19]. However, this remains an area of controversy [19].

The kinins, especially bradykinin, also may be released by carcinoid tumors. Kinins are produced by the action of proteolytic enzymes, called kallikreins, on the inactive precursors of the kinins [19]. Lysosomal kallikrein release is triggered mainly by sympathetic stimulation [48]. When this action occurs, the newly produced bradykinin usually is rapidly broken down and removed from the circulation by plasma aminopeptidases and kinases [19]. When abnormally high amounts of bradykinin are released, the pathways become saturated, causing an exaggerated and prolonged effect from bradykinin [19]. The bradykinins produce profound vasomotor relaxation, causing severe hypotension

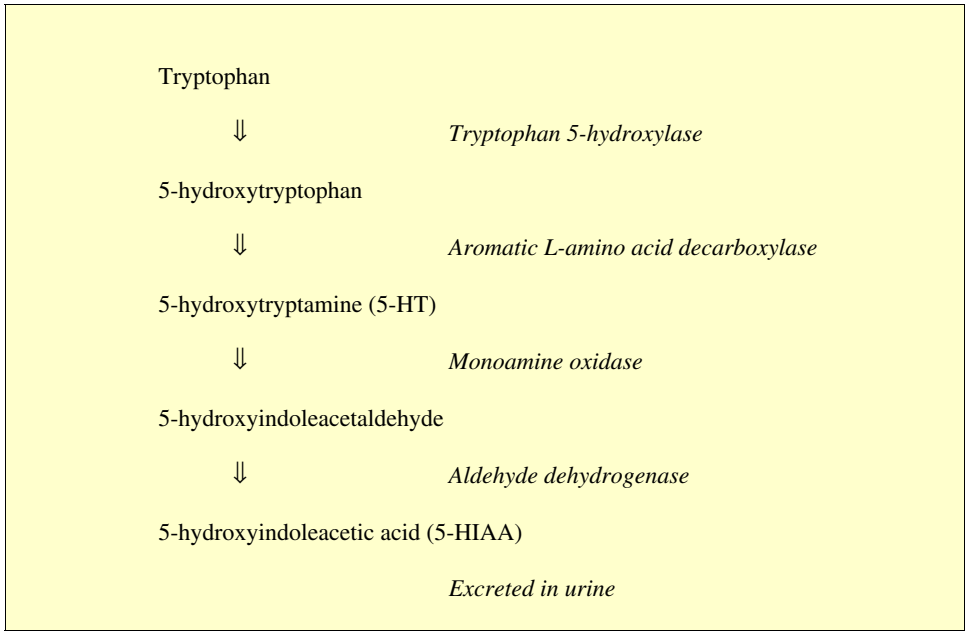

Fig. 1 Synthesis and metabolism of serotonin.

and flushing, probably via increased nitric oxide synthesis [4,49]. Bradykinin also causes bronchospasm, especially in known asthmatics, and frequently in the presence of cardiac disease [19].

Tachykinins are another group of kinin peptides that are thought to be associated with carcinoid syndrome [50]. This group of peptides (which includes neuropeptide K, neurokinin A, vasoactive intestinal peptide, and substance P), is derived from preprotachykinin [51]. Tachykinins are thought to be involved in the longer term cardiac effects of carcinoid syndrome. They also may be an active mediator responsible for flushing [19].

5. Diagnosis

Because the symptoms of carcinoid tumors are often nonspecific, there is frequently a delay in diagnosis, and metastatic spread at the time of diagnosis is common [23]. The clinical presentation of carcinoid tumors depends largely on whether the tumors are functional (mediator-secreting tumors) [6]. Patients with nonfunctional tumors, or in whom tumor mediators do not reach the circulation, usually present with pain, GI bleeding, or intestinal obstruction from the tumor [6]. Clinical features of carcinoid syndrome (eg, flushing, diarrhea, bronchoconstriction) typically are seen in patients with tumors that secrete mediators that bypass clearance in the liver.

For carcinoid patients, various imaging techniques, including endoscopy, endoscopic ultrasound, and video capsule endoscopy, may be used to locate the tumor [24]. Abdominal ultrasound, computed tomographic (CT) scans, magnetic resonance imaging (MRI), selective mesenteric angiography, and barium small bowel radiography are all used to identify the primary tumor and, if possible, any metastases [6,24]. Abdominal ultrasonography is quick and inexpensive, but it lacks reproducible sensitivity and specificity [52]. MRI has been particularly useful in evaluating lesions of the lung and liver [53].

Radiolabeled somatostatin analog scintigraphy is the current gold standard for confirming the location of functioning neuroendocrine tumor tissue [54]. However, initial attempts to use somatostatin analogs were complicated by difficulty associating the somatostatin analog with the isotope [52]. Bone scintigraphy is the main method of detecting bone metastases of neuroendocrine tumors, with detection rates reported to be above 90% [24].

Various localization studies also are used to identify primary and metastatic tumors [24]. Radiolabeled pentetreotide and octreotide bind to the same receptors, rendering pentetreotide an ideal compound for imaging tumors positive for somatostatin receptor subtypes 2 and 5 [55]. Test sensitivity is 80% to 90%, and metastatic lesions not found by conventional techniques often may be identified using this technique [56] (Table 3). Radiolabeled metaiodobenzylguanidine (MIBG), an amine precursor that is actively taken up by neuroendocrine tumors and stored in secretory granules, is not as effective as radiolabeled octreotide in the localization of tumors [57]. However, it causes targeted irradiation of the tumor and may be used as part of the therapy [58].

Positron emission tomography (PET) also may be used to localize carcinoid tumors. PET scanning is typically used for tumors that, unlike carcinoid tumors, are fast growing. However, by using a radiolabeled version of octreotide or a radiolabeled serotonin precursor, high detection rates are possible [59].

Serotonin is the most common mediator secreted by carcinoid tumors. As a result, the most common test used to diagnosis carcinoid tumors is the 24-hour urinary 5-HIAA assay [6], which monitors the metabolite of serotonin. Serotonin metabolism produces 5-HIAA, which is excreted in the urine [1]. Normal levels of 5-HIAA are less than 10 mg in a 24-hour urine sample. Levels greater than 25 mg per 24 hours have been considered diagnostic for carcinoid tumor [1]; however, up to 20% of carcinoid patients have normal urinary 5-HIAA levels [19,60,61]. During this test, patients must avoid serotonin-rich foods such as bananas, avocadoes, plums, tomatoes, pineapples, kiwis, eggplant, plantain, and walnuts [62].

Chromogranin A (CgA) is a protein found in most neuroendocrine cells and, when detected in plasma, it may be used as a general marker for carcinoid tumors, even those that are "nonfunctional" [24]. It is also often used as a marker for carcinoid tumor relapse [4]. CgA was elevated in 87% of midgut carcinoid tumors, whereas 5-HIAA was elevated in only 76% [24]. Plasma CgA levels are, however, nonspecific for carcinoids as these levels are elevated in other neuroendocrine tumors, as well as in liver failure, renal impairment, gastritis, and inflammatory bowel disease [63].

The pentagastrin challenge test may be used in conjunction with urinary 5-HIAA levels for diagnosis and treatment. This test utilizes the ability of gastrin to stimulate the release of other bioactive substances [1]. After a basal level of serotonin (5-HT) in the patient's blood is measured, pentagastrin is administered intravenously (IV). Serotonin levels are measured in blood samples drawn at one, two, and 5 minutes. A positive test produces increases in serotonin and substance P, but should not produce symptoms other than flushing [1]. These tests may be used to monitor disease progress [19] and the response to medical management.[1]

The definitive diagnosis of carcinoid heart disease is often difficult and cardiac symptoms usually do not appear until the later stages of the disease [34]. Physiologic changes resulting from carcinoid heart disease may not occur until late in the course of cardiac involvement; thus, detection of cardiac lesions requires a high index of suspicion. The duration of carcinoid syndrome alone cannot be used to distinguish which patients are likely to have cardiac involvement [23]. However, as expected, heart murmurs and dyspnea are more frequent in patients with carcinoid heart disease. Chest radiography and electrocardiography (ECG) are often nonspecific and, thus, in patients with known carcinoid heart disease, echocardiography is used to evaluate the severity of cardiac lesions [34] (Table 4). However, chest radiography and bronchoscopy are often useful in diagnosing patients with suspected bronchial carcinoids [6].

[1] Badola R. Preanesthetic assessment: the patient with carcinoid sysdrome. Anesthesiol News 1991;17:26-36.

Table 4 Findings in carcinoid heart disease

Electrocardiography	normal	31%
	ST-T wave abnormality	24%
	sinus tachycardia	13%
	low-voltage	10%
	right-axis deviation	9%
	primary A-V block	9%
Chest radiography	normal	46%
	cardiac enlargement	18%
	pleural effusion	11%
	pulmonary nodules	11%
	hepatomegaly	5%
	blunted costophrenic angle	5%

Modified from: Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. Circulation 1993;87:1188-96.

6. Treatment options

Although most carcinoids are slow growing, some may be very aggressive with widespread metastases. However, since the introduction of octreotide in the late 1980s, there has been a significant increase in survival [10].

The most effective treatment for carcinoid tumors is generally regarded as complete surgical excision of the tumor, often with partial bowel resection and mesenteric lymphadenectomy [4,23,64]. Surgery has the advantages of removing the primary lesion or metastatic lesions, with the intent of either curative or palliative treatment, thereby decreasing the levels of bioactive agents and improving symptoms [64,65] (Table 5).

Octreotide is commonly used to treat the symptoms of any residual tumor remaining after surgery [64]. Due to the slow growth of these tumors, the 5-year survival rate for tumor localized to the bowel wall is 60% to 70% [66]. The 5-year survival rate for patients with hepatic metastases decreases to 20% to 30%, with a mean survival of 8 years from the onset of symptoms [67]. Five-year survival following liver resection for carcinoid ranges from 47% to 82% [10,68]. However, the timing and efficacy of surgical interventions remain controversial [52]. Liver transplantation is performed only when the presence of extrahepatic metastases has been ruled out [64] and there is no evidence that it results in a survival benefit over nonsurgical treatments [52].

Hepatic carcinoid tumors receive their blood supply from the hepatic artery [52]. Hepatic artery occlusion by ligation, embolization, or transarterial chemoembolization (TACE), successfully reduces the size of hepatic metastases in 65% of patients (even without concurrent chemotherapy) [24,69]. When TACE is combined with chemotherapy, there is a reduction in tumor size in 78% of patients [70]. Cryoablation and radiofrequency ablation also have been reported but their efficacy has yet to be evaluated [25].

Table 5 Overview of patients with carcinoid syndrome

Diagnosis of carcinoid syndrome
• Cutaneous flushing of head, neck, and upper thorax
• Bronchoconstriction
• Hypotension
• Diarrhea
• ± Hypertension
• ± Carcinoid heart disease
Confirmation: > 30 mg of 5-HIAA per 24-hour urine sample (normal = 3 - 15 mg/24 hr)
Diagnosis of carcinoid heart disease
• Plaquelike deposits of fibrous tissue on right heart valvular cusps, atrium, and ventricle
• Tricuspid and/or pulmonary regurgitation
• Cardiac dysrhythmias
Confirmation: Two-dimensional echocardiography
Management
1. Perioperative blockade of serotonin receptors
2. Pay attention to procedures, treatments, and drugs that may stimulate release of vasoactive substances from tumor cells. These include:
◦ tumor-debulking surgery to reduce tumor size
◦ hepatic artery embolization to reduce tumor size
◦ biotherapy (eg, interferon for tumor shrinkage)
◦ chemotherapy for systemic spread
3. Treat effects of hormone release as necessary.
◦ long-acting somatostatin analogues (eg, octreotide), the mainstay of perioperative therapy
◦ anxiolytics to prevent stress-triggered release of serotonin
◦ H_1- and H_2-blockers to block the effects of histamine
◦ symptomatic therapy (eg, bronchodilators for wheezing)
◦ H_2-blockers, diphenhydramine, and steroids inhibit the action of bradykinin
◦ aprotinin (kallikrein inhibitor) to treat hypotension refractory to octreotide

Modified from: Ogunnaike BO, Whitten CW. Gastrointestinal disorders. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical Anesthesia. 6th edn. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 1221-9.

Pancreatic carcinoid tumor chemotherapy produces partial remission in up to 60% of patients, but midgut carcinoids are often resistant to standard chemotherapy, with a response rate of only 20% to 40% [24]. Chemotherapy may be more beneficial for poorly differentiated tumors or those resistant to standard therapy [24]. For these tumors, octreotide may be used to reduce tumor bulk and attenuate the release of bioactive substances [4].

Somatostatin analogs have become the mainstay of medical therapy, especially in patients whose disease is beyond resection with curative intent [52]. Somatostatin is a cyclic peptide present in two forms, somatostatin-14 and somatostatin-28. It inhibits GI motility, gastric acid production, pancreatic enzyme secretion, and bile and colonic fluid secretion [24]. It also inhibits insulin, glucagon, secretin, and vasoactive intestinal peptide secretion [71]. Its clinical use is limited by the requirement that somatostatin be administered by continuous IV infusion, as well as the frequency of postinfusion rebound hypersecretion [72].

At least 5 subtypes of somatostatin receptors have been identified [4]. These 5 somatostatin receptors, referred to as sst1 through sst5, have been described as G-protein coupled receptors. Of these receptors, most carcinoid tumors have a high concentration of type 2 receptors (sst2) [4]. Octreotide and another, less common somatostatin analog, lanreotide, do not bind receptor types sst1 and sst4 [24]. However, receptor types sst2, sst3, and sst5 display a high, low, and moderate affinity, respectively, for the somatostatin analogs [24]. The predominant expression of type 2 (sst2) somatostatin receptors forms the basis of the successful clinical use of octreotide [72], since it binds with the highest affinity to sst2 and sst5 receptors.

Octreotide may be administered by multiple subcutaneous or IV injections or subcutaneous or IV infusion [24]. Intravenous octreotide is very effective in treating carcinoid crisis [24]. There are now long-term reports indicating good compliance and symptomatic relief with both long-acting octreotide and lanreotide [52]. The slow-release formulation of octreotide, Sandostatin LAR, is administered in once-monthly intramuscular (IM) injections, and lanreotide can be administered every two weeks. These drugs control symptoms in 70% to 80% of patients, but tumor regression rates are much lower, less than 9% [73]. One recent randomized, placebo-controlled study showed that octreotide increased the time to tumor progression from 6 months to 14.3 months ($P = 0.000072$) [74].

Carcinoid tumors are generally resistant to radiotherapy; however, peptide receptor radionuclide therapy (prrt) has been introduced for nonoperable or metastasized tumors [24]. Because of the slow-growing nature of most carcinoid tumors, this type of targeted cytotoxic therapy may prove very useful [52]. The response rates have been variable, with patients usually achieving either tumor size reduction or biochemical stability [24]; more recent results have been encouraging with respect to tumor regression [24]. Although issues related to therapy include possible renal damage and the introduction of myeloproliferative disorders, this modality is becoming more accepted since the duration of the response is greater than two years [24]. New somatostatin analogs, new radionuclide compounds such as I-MIBG, and biologic compounds are currently in the development and testing phases as future therapies [24].

7. Perioperative management

The introduction of octreotide has rendered obsolete most of the literature concerning anesthesia prior to that time [4]. The primary goals during the perioperative period are to prevent the release of bioactive mediators by avoiding factors that trigger the release of these bioactive mediators, thereby avoiding carcinoid crisis. In the event that carcinoid

crisis develops, despite efforts to prevent it, preparations must be made for the management of such a crisis during all phases of the perioperative period [75].

Most patients with carcinoid tumors undergo general anesthesia because of the need to avoid the sympathectomy associated with neuraxial anesthesia; however, both epidural and spinal anesthesia have been used successfully in these patients [46]. Successful spinal anesthesia has been reported with the use of preoperative octreotide, fluids, and low-dose spinal anesthetic supplemented with low-dose intrathecal opioids [46].

8. Preoperative management

Preoperative assessment should include a history and physical examination that is focused on determining the presence and severity of any symptoms of carcinoid syndrome, such as flushing, diarrhea, bronchospasm, valvular heart disease, for example [19]. The presence of any triggering factors also should be determined. For known cases of carcinoid tumor, imaging studies and specific laboratory tests should be performed prior to scheduling for surgery. Laboratory tests should include the standard chemistry, blood count, liver function panel, blood glucose concentration, and ECG, as well as urinary 5-HIAA measurements [19]. A low threshold for further cardiac workup should be utilized since the reported incidence of cardiac involvement is as high as 50% to 60% [19]. Depending on the nature of the surgery, the presence of metastatic tumors may need to be determined [19]. In addition to CT scanning and MRI, radiolabeled octreotide may be used to locate tumors via a scintillation detector, since octreotide is taken up by most carcinoid tumors [76,77]. It is useful both preoperatively and postoperatively for both locating and then confirming removal of carcinoid tumors [19].

Preoperative therapy is aimed at optimization of the patient for surgery and providing relief of symptoms [19]. This may be achieved by antagonizing the mediators of carcinoid syndrome or by blocking their release [19]. Since its introduction, octreotide has become the mainstay of therapy. Fluid and electrolyte abnormalities may need to be corrected, especially in patients with a history of diarrhea. Alpha-agonists may be useful in reversing bronchospasm caused by histamine release, but adrenergic stimulation may cause further histamine release and may worsen the condition. For this reason, alpha-agonists should be used only after suppression therapy has failed [19].

Several drugs block the production, release, or action of mediators from these tumors. Of the mediators released from carcinoid tumors, the easiest to antagonize is histamine [19]. The effects of histamine are blocked by antihistamines such as chlorpheniramine, and histamine-2 blockers such as ranitidine [19]. Aprotinin, a kallikrein inhibitor, has been used to treat flushing associated with bradykinin production [19], but there are conflicting reports of its efficacy in treating perioperative hypotension [2,78].

Other agents also have been used in the perioperative management of carcinoid patients, including steroids, ketanserin, which blocks effects at 5-HT2 receptors, methylsergide, and cyproheptadine, which has anti-serotonin and antihistamine effects [19]. Several studies have been inconclusive regarding the effectiveness of pretreatment with these agents [29,79-81].

Somatostatin is a GI peptide that reduces the production and release of gastropancreatic hormones [19]. Somatostatin binding reduces the amount of serotonin released from tumor cells [61] and decreases the levels of 5-HIAA in urinary specimens [82]. Due to its short half-life of one to three minutes [1,19], somatostatin must be given by continuous infusion.

Octreotide is a synthetic analog of somatostatin that is resistant to degradation by serum peptidases, and thus has a longer half-life, 1.5 to 2 hours [24], when administered subcutaneously, and 50 minutes when given intravenously [1,83]. Octreotide blocks hormonal release and inhibits the action of circulating peptides by inhibiting either phosphatidylinositol [84] or adenylate cyclase [29]. Octreotide also inhibits insulin secretion in response to hyperglycemia. It has replaced nearly all other drugs as the drug of choice for treating carcinoid patients [46].

Intraoperative carcinoid events are difficult to predict; thus, no standard octreotide administration regimen is completely reliable and various recommendations have been proposed [46]. Octreotide is given subcutaneously for symptomatic relief [83] and for the prevention of perioperative hypotension [85]. A long-acting formulation of octreotide may be given in monthly injections. Following the initial dose, a concentration nadir is reached at one week and a higher plateau is reached at two weeks, which persists for subsequent injections [46]. Octreotide dosages of 50 to 200 μg IV are effective in rapidly reversing severe hypotension and bronchospasm [86]. It has been used successfully as an infusion of 50 μg/hr following induction during liver transplant for metastatic carcinoid tumor [32]. Octreotide used in combination with steroids or in diabetic patients may complicate glucose management [86]. The group at Louisiana State University (LSU) has used intraoperative infusions of octreotide of up to 500 μg/hr in over 300 major resective cases without crisis or untoward effect (unpublished data).

Chemotherapy also has been used to reduce tumor bulk and alleviate symptoms [87]. Surgery to debulk tumors decreases mediator release and improves symptoms [65,88].

9. Premedication

Premedication is focused on relieving symptoms and preparing for a potential carcinoid crisis [2]. All of the

patient's maintenance medications should be continued. Premedication with benzodiazepines and antihistamines is useful in decreasing anxiety and stress [19].

Octreotide is the most efficacious treatment for carcinoid syndrome, as it reduces symptoms in more than 70% of patients [89]. Various regimens for dosing octreotide have been reported. It has been suggested that subcutaneous octreotide 100 μg three times daily be given for two weeks prior to surgery and 100 μg again before induction to prevent mediator release [49]. Octreotide is also beneficial if it is given for only 24 hours prior to surgery. If it is discontinued postoperatively, it should be weaned over the first week [49]. The LSU group's regimen includes a continuous infusion of octreotide before anesthesia induction, which is weaned off over three days, aided by an immediate postoperative dose of depot octreotide (LAR).

Before octreotide was available, various combinations of drugs were administered with the goal of blocking the actions of the various substances often released [23]. These agents include methylsergide, ketanserin, cyproheptadine, steroids, diphenhydramine, and other antihistamines given in multiple combinations to inhibit the actions of the various mediators released by carcinoid tumors [79]. However, the efficacy of these agents in preventing intraoperative crisis proved unreliable [90].

10. Intraoperative management

10.1. Monitoring

Rapid changes in BP are often seen in carcinoid patients; therefore, in addition to standard monitors, invasive monitoring typically is required [91]. These monitors should be started before induction of anesthesia and continued into the postoperative period [19]. An arterial catheter is clearly indicated prior to the induction of anesthesia since the hypotension commonly seen with induction agents may trigger a carcinoid crisis. Increased bleeding also may be encountered, as abdominal carcinoids often have a rich vascular supply [88] and metastases may involve vessel-rich organs such as the liver [2]. Central venous pressure (CVP) may be very useful in these patients, especially during abdominal surgery for tumor resection [19]. CVP monitoring may help to exclude hypovolemia as a cause of hypotension and allow better attention and adjustment of fluid balance [19]. Normal responses to hypovolemia may be masked by the effect of vasoactive peptides released during handling of the tumor [19]. In patients with coexisting cardiac dysfunction, monitoring of left ventricular function with a pulmonary artery catheter may be useful; however, in patients with right-sided cardiac involvement or valvular disease, transesophageal echocardiography may be more beneficial [92]. Accurate airway pressure monitoring is necessary to rapidly detect the onset of bronchospasm [19]. Temperature monitoring and warming devices are also needed as these cases are often long, and hypothermia is a trigger of tumor mediator release [19].

10.2. Induction

Care should be taken on induction to avoid catecholamine release [75]. Propofol, thiopental sodium, and etomidate have been used to induce anesthesia; however, propofol has a more profound effect in suppressing the sympathetic response to intubation and thus may be the best induction agent in patients with carcinoid syndrome [93], as long as hypotension is avoided. Etomidate may have less effect on heart rate (HR) and BP, but may not suppress laryngeal reflexes [94]. The use of succinylcholine has been debated because increases in intraabdominal pressure from fasciculations may trigger mediator release; however, some researchers have not found any adverse effects with its use [32]. Opioids that are not associated with histamine release should be used. Furthermore, only nondepolarizing neuromuscular blocking agents that do not cause histamine release should be used [19]. Because of its cardiovascular stability, vecuronium is a good choice [95], and rocuronium is an effective alternative [19].

10.3. Maintenance

The most common anesthetic technique reported is the use of a balanced technique that incorporates positive pressure ventilation, an inhalation agent, a nondepolarizing neuromuscular blocking agent, and an opioid, most commonly fentanyl [19]. Propofol infusions also have been reported [96]. Inhalation agents with low blood-gas solubility such as desflurane are preferred [19], although all available inhalation agents have been used. Nitrous oxide also is safe [2]. A technique using high-dose opioids may be indicated as volatile anesthetics may cause myocardial depression and hypotension, resulting in release of tumor peptides [19]. As these patients often have chronic right ventricular (RV) valvular lesions and heart failure, one should avoid anesthetic factors that increase RV work with potential precipitation of acute RV failure. This includes hypoxemia, hypercarbia, and a light anesthetic plane.

Invasive BP monitoring and CVP monitoring may be required for early detection of hypotension [19]. Hypertension may be treated by increasing the depth of anesthesia, use of beta-blockers [2], or 5-HT2 receptor blockage with ketanserin [74] and/or octreotide to prevent peptide release [91]. Hypotension is potentially a much more serious problem since the drugs usually used to treat hypotension may make it worse by further stimulating the release of peptides [19]. This theory is controversial, however, as others have reported success with use of pressors with octreotide in carcinoid cardiac valvular surgery [97]. Fluid administration as tolerated and decreasing anesthetic depth

may be sufficient for mild hypotensive episodes. Boluses of IV octreotide up to 1.0 mg and hydrocortisone are often used to counteract "crisis"-induced hypotension. Hypotension tends to occur when large bulky hepatic metastases are manipulated. In the event of hemodynamic instability, it is important to have the surgeon stop operating until hemodynamic control is restored, as tumor manipulation may worsen the hypotension [19].

Epidural and spinal anesthesia have been used successfully in patients with carcinoid tumors undergoing non-carcinoid surgery [45,98]. Care must be taken to adequately evaluate and premedicate the patient as needed and to avoid the hypotension that commonly occurs with these techniques. As mentioned above, hypotension may trigger the release of tumor mediators and treatment with sympathomimetic agents may further trigger release of tumor mediators [19].

11. Postoperative management

In addition to the standard goals of postoperative care, these patients must continue to be monitored carefully for signs of tumor mediator release, especially since they may have a delayed recovery from anesthesia [99]. This may require placement in an intensive care or acute care unit. The effects of carcinoid tumor mediators may continue after tumor removal, and undetected metastases may still secrete peptides [19]. Patients with high serotonin levels are prone to a prolonged recovery period following general anesthesia. If patients have had palliative surgery or surgery unrelated to the tumor, then any remaining tumor may still secrete vasoactive mediators. Preoperative drug therapy such as octreotide should be continued and, if indicated, reduced slowly over the first week [19]. Fluids and electrolytes should be monitored since large fluid shifts may occur during some of these operations [85]. Analgesia to prevent excess sympathetic activity and stress is very important. Intravenous fentanyl has been used with good results [2], as well as epidural analgesia.

12. Perioperative complications

Perioperative complications are usually associated with intraoperative events. Complications may be associated with induction, intubation, or tumor manipulation; they also may occur at any time and without any provoking factor [19]. Early management is required to prevent progression to carcinoid crisis [43]. Cardiovascular instability is the most frequent complication but bronchospasm, flushing, and hyperglycemia have been reported [19]. Preoperative 5-HIAA levels are a good indicator of disease progression and severity but do not correlate with cardiovascular instability [2]. If flushing occurs, it should be considered a warning sign of potential cardiovascular instability [47]. Flushing typically responds to boluses of octreotide. Cardiovascular complications usually present as BP and HR instability rather than heart rhythm abnormalities [19].

Intravenous octreotide has become the treatment of choice, along with fluid administration, for hypotension in these patients [2]. As was mentioned earlier, the introduction of octreotide has rendered most of the older therapies obsolete. Octreotide corrects hypotension in as quickly as 15 seconds; however, in some instances BP may not recover until 10 minutes later [19]. Octreotide has been given subcutaneously or infused intravenously, usually at a concentration of 10 μg/mL until effect [19].

Other drugs have been reported with variable success, including vasopressin and angiotensin [19]. Aprotinin, a kallikrein cascade inhibitor, is effective in reducing the release of the kinin peptides [19], although this statement been disputed elsewhere in the literature [19].

Bronchospasm is less common than cardiovascular complications but it may be severe and resistant to treatment [48]. Beta-agonists may exacerbate the problem due to further tumor mediator release [19]. Octreotide is especially useful for bronchospasm that is resistant to other treatments [19]. Antihistamines as well as nebulized ipratropium have been used with good results [19]. Hyperglycemia resulting from elevated serotonin levels should be monitored and treated if necessary with an insulin infusion [19].

13. Summary

Carcinoid syndrome may cause serious problems for the anesthesia provider due to the nature and variability of the clinical manifestations of the syndrome and the perioperative complications often associated with it. Although it is not fully understood, there is a better understanding of the disease process than when it was first described. Severity of the symptoms does not reliably predict the severity of the perioperative complications. Urinary levels of 5-HIAA provide an indicator of disease progression but do not provide a reliable predictor of the type or severity of intraoperative response to tumor manipulation.

Octreotide has become the drug of choice in treating carcinoid patients and has largely replaced other drugs for the optimization, symptomatic control, and treatment of acute symptoms associated with carcinoid crisis. Anesthetic technique is focused on preventing carcinoid mediator release from stress caused by the induction of anesthesia, endotracheal intubation, and tumor manipulation during surgery. Drugs that are not commonly used in the operating room, such as octreotide, should be ordered, available, and administered in the room prior to induction. Invasive monitoring may allow rapid detection of hemodynamic changes and should be used since cardiovascular instability, most often hypotension, is common and may be sudden and severe.

Surgical management may provide curative resection of tumors in patients with well differentiated tumors less than

2.0 cm and with no evidence of spread or tumor invasion. Patients with early and correctable cardiac disease and those who require debulking or palliative resection also often undergo surgery. Durable and effective palliative surgery aimed at resection of the primary tumor and debulking of mesenteric and/or hepatic metastases, offers relief of symptoms, prevention of future complications such as obstruction and intestinal ischemia, and improved quality of life [28,65]. Patients with unresectable metastatic disease are often medically managed, frequently receiving liver-directed therapy, radiolabeled isotopes, chemoembolization, and sometimes chemotherapy [28]. Survival rates of patients having excision of gastric or appendiceal carcinoids approach those of the general population, as metastasis is unlikely [59].

Newer carcinoid tumor treatments have prolonged and improved the quality of life for carcinoid patients [100]. Successful anesthetic management of these patients requires preoperative optimization of the patient and good communication between the endocrinologist, anesthesiologist, and surgeon. Where indicated, such communication includes seeking advice from centers with expertise in managing this subgroup of patients.

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