Shifting Paradigms in the Pathophysiology and Treatment of Carcinoid Crisis

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ABSTRACT Carcinoid crisis is a potentially fatal condition characterized by various symptoms, including hemodynamic instability, flushing, and diarrhea. The incidence of carcinoid crisis is unknown, in part due to inconsistency in definitions across studies. Triggers of carcinoid crisis include general anesthesia and surgical procedures, but drug-induced and spontaneous cases have also been reported. Patients with neuroendocrine tumors (NETs) and carcinoid syndrome are at risk for carcinoid crisis. The pathophysiology of carcinoid crisis has been attributed to secretion of bioactive substances, such as serotonin, histamine, bradykinin, and kallikrein by NETs. The somatostatin analog octreotide has been considered the standard of care for carcinoid crisis due to its inhibitory effect on hormone release and relatively fast resolution of carcinoid crisis symptoms in several case studies. However, octreotide’s efficacy in the treatment of carcinoid crisis has been questioned. This is due to a lack of a common definition for carcinoid crisis, the heterogeneity in clinical presentation, the paucity of prospective studies assessing octreotide efficacy in carcinoid crisis, and the lack of understanding of the pathophysiology of carcinoid crisis. These issues challenge the classical physiologic model of carcinoid crisis and its common etiology with carcinoid syndrome and raise questions regarding the utility of somatostatin analogs in its treatment. As surgical procedures and invasive liver-directed therapies remain important treatment modalities in patients with NETs, the pathophysiology of carcinoid crisis, potential benefits of octreotide, and efficacy of alternative treatment modalities must be studied prospectively to develop an effective evidence-based treatment strategy for carcinoid crisis.

Well-differentiated neuroendocrine tumors (NETs) are slow-growing and are commonly found in the tubular digestive tract, pulmonary system, and pancreas.1 Despite their indolent nature, NETs frequently metastasize.2 Although well-differentiated NETs are uncommon, their incidence and prevalence have increased substantially over the past two decades. In a retrospective, population-based study of the Surveillance, Epidemiology, and End Results Program database, the annual age-adjusted incidence of NETs increased from 1.09/100,000 persons to 6.98/100,000 persons between 1973 and 2012.3 The relatively high prevalence of NETs may be in part due to a longer life expectancy in patients with metastatic well-differentiated NETs versus most other metastatic malignancies. In contrast to other cancer subtypes (e.g., adenocarcinoma), patients with widespread disease often achieve survival beyond 5–10 years,3 emphasizing the importance of understanding and treating symptoms associated with metastatic disease.

Carcinoid syndrome is characterized by cutaneous flushing, abdominal pain, diarrhea, and bronchospasm and is estimated to affect 19% of patients with NETs at the time of diagnosis.4,5 The incidence of carcinoid syndrome is heterogeneous among different NET subtypes, with the
highest rates seen in patients with small-bowel NETs (32.4%) and metastatic pulmonary NETs (7.6–38%) and a lower rate in colorectal NETs (11.5%). The symptoms of carcinoid syndrome are thought to be the effects of tumor-elaborated bioactive substances into the systemic circulation. This may occur spontaneously or in the context of stress-induced catecholamine release. It is commonly, in the treatment of carcinoid syndrome. Recent Octreotide and lanreotide are two examples of SSAs used targeting somatostatin receptor-expressing tumor cells and emitting radionuclide (e.g., yttrium-90, lutetium-177) to drain into the systemic circulation, thus bypassing the portovenous system and metabolism of their secreted products by the liver.

The association between flushing, tissue fibrosis, and metastatic gastrointestinal NETs was initially suggested in the late 1920s and 1930s, but it was not until the 1950s that the symptoms of carcinoid syndrome were associated with elevated levels of serotonin and its urinary metabolite 5-hydroxyindoleacetic acid (5-HIAA). Serotonin production in pancreatic neuroendocrine tumors (PNETs) associated with carcinoid syndrome is not well studied, although one retrospective series noted that 42% of patients who underwent resection for their PNET had elevated serotonin or urinary 5-HIAA. Only 29% of those patients had symptoms suggestive of carcinoid syndrome. Following these reports, other bioactive and vasoactive amines have been implicated in carcinoid syndrome. Elevated histamine levels were observed in patients with midgut NETs and carcinoid syndrome during flushing. Similarly, high levels of kallikrein and bradykinin have been detected in the blood of some patients with carcinoid syndrome during episodes of adrenaline- and epinephrine-induced flushing, respectively.

Somatostatin analogs (SSAs) are the foundation of carcinoid syndrome management. Somatostatin is a naturally occurring peptide hormone secreted by the D cells of the pylorus, duodenum, and pancreas that inhibits the secretion of a number of gastrointestinal hormones and decreases the rate of gastric and small-bowel motility. Octreotide and lanreotide are two examples of SSAs used in the treatment of carcinoid syndrome. Recent prospective studies have demonstrated the efficacy of both intermediate-acting (i.e., administered 2–3 times daily) and long-acting (i.e., administered monthly) SSAs in decreasing the number of episodes per day of abdominal pain, diarrhea, bloating, and flushing in patients with NETs and carcinoid syndrome.

Peptide receptor radionuclide therapy (PRRT) utilizes a radiopharmaceutical consisting of an SSA linked to a β-emitting radionuclide (e.g., yttrium-90, lutetium-177) to target somatostatin receptor-expressing tumor cells and deliver a potent dose of radiation. Given its efficacy as an agent of nonsurgical cytoreduction, PRRT has ameliorated refractory carcinoid syndrome symptoms in several studies, but data are limited and it is unclear whether PRRT demonstrates long-term efficacy in controlling carcinoid syndrome. However, PRRT has been reported to cause flares of carcinoid syndrome in high-risk patients.

As with PRRT, surgical cytoreduction and/or hepatic artery embolization (HAE) of liver metastases have also been shown to effectively ameliorate symptoms of carcinoid syndrome. Impressively, Que et al. reported symptomatic response in 90.4% of patients undergoing resection for neuroendocrine liver metastases. The mean duration of response was 19.2 months. A recent multi-institutional study of 139 patients with preoperative carcinoid syndrome showed that 22.7% of patients who underwent a noncurative cytoreductive operation achieved symptomatic relief. In the literature, symptomatic response rates of 60–70% and more than 50% were reported for patients receiving SSAs and PRRT, respectively.

Carcinoid crisis is a feared and potentially fatal complication when patients with NETs and metastatic disease are undergoing invasive procedures, including PRRT in rare cases. The presentation of carcinoid crisis can be dramatic and features prolonged hemodynamic instability with or without the symptoms of carcinoid syndrome (e.g., flushing, diarrhea, bronchoconstriction with wheezing, cardiac arrhythmias). Beyond the initial episode, those experiencing crisis are at increased risk for major postoperative complications, such as acute renal injury, myocardial infarction, stroke, and hepatic dysfunction. Although symptoms of carcinoid crisis are more severe than those of carcinoid syndrome, it has been assumed that the risk factors and underlying physiologic mechanisms for both are similar. Current treatment of both carcinoid crisis and carcinoid syndrome relies on the use of SSAs. Patients deemed to be at high risk for carcinoid crisis are often administered prophylactic perioperative infusions of octreotide or preoperative treatment with a long-acting SSA, although the evidence for that practice is very limited. Acute episodes of hemodynamic instability that are refractory to standard resuscitative measures are treated with bolus injections of octreotide.

Appropriate management of these patients mandates a cohesive and proactive approach to carcinoid crisis. Definitive action toward this goal has been hampered because of the lack of consensus in the literature of the definition of carcinoid crisis and identification of patients at greatest risk. Furthermore, consensus is lacking on whether the underlying mechanism of carcinoid crisis mimics that of carcinoid syndrome and therefore whether SSAs are...
efficacious in the prevention and treatment of carcinoid crisis.12,47,55 Here, we review the literature on carcinoid crisis and reconcile the historical understanding of this phenomenon with recent studies challenging the classical paradigms concerning pathophysiology and optimal treatment of carcinoid crisis. The issue of definition and patient identification is explored as we attempt to recognize the patient populations at greatest risk for carcinoid crisis. The evolution of octreotide use as the standard management of carcinoid crisis and evaluation of the current studies that question its efficacy are discussed.

CARCINOID CRISIS: A HISTORICAL PERSPECTIVE

Carcinoid syndrome was first described by Åke Thorson and colleagues in 1954. In this initial report, 16 patients with metastatic neuroendocrine cancer presented with signs and symptoms, including frequent watery stools, peculiar patchy flushing, unusual attacks of bronchial asthma, and valvular pulmonary stenosis with tricuspid regurgitation. These symptoms were assumed to be initiated by the carcinoid tumors, as previous animal studies had found that injection of serotonin had caused similar symptoms. Interestingly, these authors may have reported one of the earliest cases of carcinoid crisis in a patient with metastatic disease from an ileal NET who died after a cardiac catheterization procedure.17 It would take a decade before the term “carcinoid crisis” would come to represent acute episodes of hemodynamic instability in patients with NETs, as proposed by Kahil et al.9

These early reports provided the observational evidence that underlies our current assumptions about the etiology, pathophysiology, and treatment of carcinoid syndrome and crisis. Documented triggers of carcinoid crisis include anesthesia; surgical procedures; certain medications; PRRT; chemotherapy; liver-directed therapy, such as HAE or ablation of metastases; and different forms of tumor manipulation, including liver palpation or biopsy.7,40,48,58–71 However, a recent retrospective study of 106 needle biopsies of lung and liver lesions in patients with NETs reported no instances of carcinoid crisis.72 Another retrospective report from the same institution found that among 17 patients undergoing catheter ablation for cardiac arrhythmia, one patient had carcinoid crisis.73 Rarely, noninvasive procedures have been associated with crises, including mammography.74 It is thought that patients at greatest risk for developing carcinoid crisis are those with carcinoid syndrome, given the similarities in symptomatology and treatment. However, carcinoid crisis is also observed in patients without a history of carcinoid syndrome.55 In that subset of patients, risk factors such as the presence of hepatic metastases, an overall high tumor burden, elevated levels of 5-HIAA, and plasma serotonin have been cited.12,40,47

The heterogeneity in symptoms and risk factors has meant that no consensus has been reached on the definition of carcinoid crisis. As seen in many studies, diagnosis can be variable.75 Table 1 presents a subset of studies that have provided various definitions of carcinoid crisis, ranging from a clinical documentation of occurrence by any treating physician to sudden or abrupt onset of signs, including flushing and hypotension. Differentiating the hemodynamic instability of carcinoid crisis from the instability associated with preoperative volume status, patient comorbidities, hemorrhage, induction of general anesthesia, compression of the inferior vena cava, or tumor manipulation can be difficult, especially when attempted retrospectively. The univariate analysis of a prospective case series of patients undergoing resection for their lung or gastrointestinal NET (71% with liver metastases, 74% with carcinoid syndrome) showed that patients who suffered an intraoperative carcinoid crisis had a statistically significant greater recorded blood loss (P = 0.005), a longer duration of anesthesia (P = 0.001), and a greater reported rate of preoperative symptoms compared with those who did not experience an intraoperative crisis.53

Without a standard definition of carcinoid crisis, defining its true prevalence is impossible, and reported rates vary widely between groups.53,55,76–78 In 2018, a retrospective series published by the Mayo Clinic in Rochester, Minnesota, found that none of the 169 patients with lung or gastrointestinal NETs who underwent a total of 196 operations for their hepatic metastases experienced an episode of carcinoid crisis.76 Fouché et al. also reported an incidence of 0% in a retrospective study of 81 patients who had undergone resection of small-bowel NETs.77 However, Woltering et al. reported an incidence of 3.4% in their retrospective study of 150 patients who underwent 179 cytoreductive surgeries for metastatic small-bowel NETs.78 A second study by Woltering et al. reported their experience with 800 patients undergoing 1001 cytoreductive operations. Among these patients, 61% reported symptoms of carcinoid syndrome and 73% received SSA therapy prior to resection. Carcinoid crisis was documented in 12 (1%) procedures.70 When studied prospectively, Condron et al. reported that 30–35% of the patients undergoing an abdominal operation for NETs in their two single-center studies experienced an intraoperative crisis.53,55

Thorson and Kahil assumed that carcinoid syndrome and carcinoid crisis were attributable to elevated levels of serotonin, given that the effects of serotonin were consistent with those observed in patients with carcinoid syndrome and because symptomatic improvement occurred when affected patients were treated with an
antiserotonin. Further implicating serotonin as a mediator of carcinoid crisis were subsequent reports and case studies describing elevated urinary 5-HIAA levels in patients following carcinoid crisis.\textsuperscript{59,64,80} Hormonal mediators other than serotonin are also secreted by NETs. Factors such as histamine, bradykinin, dopamine, and norepinephrine, have been reported.\textsuperscript{11,20,52,81,82} The temporal association between these elaborated factors and episodes of crisis, as well as the known function of these amines in other contexts, suggested their possible role in carcinoid crisis and began to influence efforts in the prevention and management of crisis.\textsuperscript{52,83,84} For example, carcinoid crisis refractory to antiserotonin and antihistamine therapies was reported to be reversed with methylene blue, an inhibitor of bradykinin-mediated nitric oxide release, in a Canadian case study.\textsuperscript{83} In 1989, surgeons in New Zealand reported a case of a woman with a lung NET who developed a hypertensive episode of carcinoid crisis that subsided following administration of ketanserin, an antiserotonin agent.\textsuperscript{84} These observations informed the classical model regarding the pathophysiology of carcinoid crisis, in which serotonin and other bioactive substances precipitate the signs and symptoms of carcinoid crisis (Fig. 1).

As evidence mounted implicating serotonin as the primary mediator of carcinoid crisis, some practitioners began to avoid using selective serotonin reuptake inhibitors (SSRIs) in patients with NETs.\textsuperscript{85} However, a retrospective study of 92 patients with NETs, 17% with carcinoid syndrome, failed to detect a single case of carcinoid crisis attributed to SSRI use and suggested that these drugs did not raise any safety concerns in patients with NETs.\textsuperscript{86} Catecholamines were thought to stimulate secretion of serotonin from NETs and trigger carcinoid crisis,\textsuperscript{52,87} thus treatment with catecholamines for hypotension (e.g., epinephrine) was discouraged.\textsuperscript{52,60} Stenzel et al. described a patient with a small intestinal NET and liver metastases who experienced carcinoid crisis with symptoms that included hypertension and bloody diarrhea after PRRT. In addition to elevated plasma chromogranin A levels, the patient had high plasma catecholamine levels. In this case, the authors attributed carcinoid crisis to elevated catecholamine levels because 5-HIAA levels were elevated but

### TABLE 1 Definitions of carcinoid crisis in the literature

| Reference | Definition of intraoperative carcinoid crisis |
|-----------|---------------------------------------------|
| Massimino et al. [54] | Prolonged hypotension (SBP \( \leq 80 \) mm Hg for \( \geq 10 \) min) or report of hemodynamic instability, including hypotension, sustained hypertension, or tachycardia, not attributed to acute blood loss or other obvious causes by the attending anesthesiologist or surgeon |
| Condron et al. [53] | Significant hemodynamic instability (SBP < 80 or > 180 mm Hg, heart rate > 120 BPM, display of physiology expected to cause end organ dysfunction [i.e., ventricular arrhythmias or bronchospasm causing difficulty with ventilation]) not attributable to other factors, such as significant blood loss or compression of the inferior vena cava |
| Woltering et al. [78] | Incidence of prolonged hypotension (SBP < 80 mm Hg for > 10 min) |
| Fouché et al. [77] | Intraoperative hemodynamic instability (e.g., hypertension, hypotension, tachycardia) |
| Kinney et al. [76] | Sudden or abrupt onset of \( \geq 2 \) of the following: Flushing or urticaria not explained by allergic reaction Bronchospasm or bronchodilator administration Hypotension (SBP < 80 mm Hg >10 min and treated with pressors) not explained by volume status or hemorrhage Dysrhythmia not explained by volume status or hemorrhage Tachycardia of \( \geq 120 \) BPM |
| Condron et al. [55] | Clinically important hemodynamic instability (SBP < 80 or > 180 mm Hg, heart rate > 120 BPM, display of physiology expected to cause end organ dysfunction) not attributable to other factors, such as substantial blood loss or compression of the inferior vena cava |
| Kwon et al. [75] | Subjective clinical documentation of occurrence by any treating physician, including the anesthesiologist, surgeon, or interventional radiologist |

BP, blood pressure; BPM, beats per min; SBP, systolic blood pressure.
stable.52 In another study, a patient with a metastatic ileal NET became profoundly hypotensive after induction of general anesthesia and developed ventricular tachycardia following epinephrine administration. Hypotension resolved following treatment with a somatostatin receptor antagonist. The authors theorized that epinephrine had stimulated further mediator release, which was then mitigated by the SSA.60

Taken together, these studies suggest that a number of factors may be responsible for the wide variety of symptoms observed during a crisis — in particular, serotonin and histamine release.9,17,84,88,89 Therefore, the main goal of carcinoid crisis treatment has been to prevent the release of bioactive molecules from NETs.47,89

**EVOLUTION OF OCTREOTIDE USE FOR THE TREATMENT OF CARCINOID CRISIS**

The rationale for using octreotide in carcinoid crisis was its phenotypic similarity to carcinoid syndrome, the assumption that the two shared etiologic mechanisms, and the documented efficacy of octreotide in lowering plasma and urinary levels of factors thought to cause the symptoms of carcinoid syndrome.5,9,55,90,91 A study of 20 patients with midgut NETs and liver metastases demonstrated that octreotide had a favorable safety profile, decreased urinary 5-HIAA excretion by 26%, and reduced the intensity of flushing episodes.31 In vitro, octreotide reduced intracellular and extracellular levels of serotonin and 5-HIAA in midgut NET cultures. Compared with controls, extracellular serotonin and 5-HIAA levels were significantly reduced by 44% ± 6% and 17% ± 3%, respectively (P < 0.05).92 This supported the rationale that octreotide was likely the optimal treatment for carcinoid crisis.

Prior to FDA approval in 1988, octreotide was restricted to compassionate use.40,93,94 However, Kvols et al. reported one of the first instances that octreotide was used as a rescue treatment of intraoperative carcinoid crisis in 1985. After reporting the rapid resolution of carcinoid crisis symptoms following octreotide administration, the authors proposed that octreotide should be readily available for emergency use in patients with carcinoid syndrome who are undergoing resection.90 After 1988, octreotide utilization greatly increased, and it was widely recommended for use in carcinoid crisis based on studies that demonstrated reductions in serotonin levels and symptoms following its administration.40,90,91,93–95

Not long after octreotide was first used as a rescue agent, its use as a prophylactic agent for carcinoid crisis was reported by Roy et al. In that 1987 article, a patient with a metastatic NET and a documented history of carcinoid syndrome suffered an episode of hemodynamic instability in the preoperative holding area that was not controlled with anxiolytics and antihypertensives. Ten days after the addition of thrice-daily 100 l g subcutaneous octreotide to her treatment regimen, her plasma levels of gastrin, pancreatic polypeptide, and urinary 5-HIAA were substantially decreased compared with pretreatment levels, and she remained stable throughout the case.96

More recent studies describe routine use of octreotide for both the prevention and emergency treatment of carcinoid crisis (Table 2).53–55,61,76,78,80,97–101 In 2001, Kinney et al. retrospectively reported their experience using octreotide in 119 patients undergoing abdominal operations for their metastatic NETs. In this group, six patients received only preoperative octreotide and of these, one (17%) experienced intraoperative complications defined as flushing, dysrhythmia, bronchospasm, hypertension,
| Reference       | Type of study | Patients                                                                 | Octreotide dosage                                      | Results                                                                                                                                 |
|-----------------|---------------|---------------------------------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Massimino et al. [54] | Retrospective | Patients who had undergone abdominal operations for gastrointestinal NETs (N=97) | 500 µg IV prophylactically (median)                      | No statistically significant correlations between carcinoid syndrome and intraoperative complications or carcinoid crisis              |
| Guo et al. [56] | Systematic review | Patients who had experienced carcinoid crisis and received treatment with SSAs (octreotide, lanreotide, or pasireotide; N=53) | –                                                       | Risk of perioperative carcinoid crisis was not affected by prophylactic SSA treatment                                                |
| Condron et al. [53] | Prospective | Patients who had undergone operations with continuous octreotide infusions (N=127; 71% had liver metastases, 74% had carcinoid syndrome) | 500 µg IV preoperative bolus followed by intraoperative infusion at a rate of 500 µg/hour | Incidence of intraoperative crisis: 30%                                                                                              |
| Wollering et al. [78] | Retrospective | Patients who had undergone 179 surgeries for stage IV, small-bowel NETs (N=150) | 500 µg/hour IV infusion preoperatively, intraoperatively, and postoperatively | Incidence of intraoperative crisis: 3.4% (6/179)                                                                                     |
| Fouché et al. [77] | Retrospective | Patients who had undergone resection of small-bowel NETs (N=81; 72.8% had hepatic metastases, 60.5% had carcinoid syndrome) | 40 or 80 µg/hour IV infusion before surgery and continued intraoperative and postoperative at the same doses | No intraoperative crisis occurred during the study                                                                                   |
| Kinney et al. [76] | Retrospective | Patients who had undergone partial hepatic resection for metastatic NETs (N=169) | 500 µg IV or SC preoperatively and/or 500 µg IV intraoperatively (median) | No documented cases of carcinoid crisis (0.0%; 95% confidence interval: 0.0–2.2%)                                                   |

IV, intravenous; NET, neuroendocrine tumor; SC, subcutaneous; SSA, somatostatin analog.
acidosis, hypotension, or need for vasopressor support. Of the 45 patients who received octreotide during their operation, none experienced intraoperative complications compared with 8/73 (11%) patients who did not receive octreotide. Based on these findings, Kinney et al. concluded that intraoperative octreotide use was associated with a decreased frequency of intraoperative complications.

In 2016, Woltering et al. retrospectively described a protocol that consisted of continuous IV octreotide 500 μg/h preoperatively, intraoperatively, and postoperatively. In this group of 179 patients, review of the medical record uncovered six (3.4%) likely cases of carcinoid crisis, leading the authors to conclude that prophylactic treatment with octreotide was beneficial for patients undergoing extensive surgical procedures for midgut and foregut NETs. As of 2016, the ENETS guidelines suggested a preoperative 250- to 500-μg IV bolus of octreotide followed by intraoperative infusion at a rate of 500 μg/h. Of the 127 patients who underwent a total of 150 abdominal operations, 30% were identified as having suffered an episode of crisis. Based on these results, the authors announced at the Annual Meeting of the American Association of Endocrine Surgeons that they would no longer use prophylactic infusions of octreotide for patients with NETs, as their study did not demonstrate its efficacy in preventing episodes of crisis.

As with the conflicting conclusions between single-institution studies, societal guidelines also differ in their suggestion for the management of carcinoid crisis. In 2013, the North American Neuroendocrine Tumor Society (NANETS) guidelines suggested a preoperative 250- to 500-μg IV bolus of octreotide for patients with a history of carcinoid syndrome undergoing resection of their primary gastrointestinal NET. Additional boluses were to be made available throughout the procedure. Just four years later, the NANETS guidelines on the surgical management of small-bowel NETs removed specific guidance on perioperative octreotide dosing and acknowledged that preoperative administration of octreotide and/or continuous infusion of octreotide may not prevent carcinoid crisis. They acknowledged that the risk of harm following administration of preoperative or perioperative octreotide is minimal but cautioned against relying on octreotide to prevent carcinoid crisis or reduce the severity of such crises and recommended that patients with refractory hypotension be treated with vasopressors. The NANETS guidelines for the surgical management of pancreatic neuroendocrine tumors most recently suggest that patients should undergo preoperative testing and perioperative monitoring as appropriate for their endocrine syndrome, including consideration of SSAs. However, they continue on to state that “the role of SSAs for the intraoperative prevention of carcinoid crisis in patients with pancreatic neuroendocrine tumors remains undefined.” The European Neuroendocrine Tumor Society (ENETS) published consensus guidelines in 2017 addressing perioperative therapy of patients with small intestinal NETs that recommended perioperative prophylaxis with IV octreotide at 50–100 μg/h for 12 h prior to induction of anesthesia. In patients with carcinoid syndrome, the use of doses up to 500 μg/h was permitted in cases of carcinoid crisis with hypotension. In contrast to the NANETS guidelines published in the same year, the ENETS authors concluded that “although octreotide is of proven value in preventing and treating carcinoid crisis, the current literature relies on small sample size studies and relatively low quality of data”. Most recently, the 2020 European Society of Medical Oncology guidelines did not address the question of whether perioperative prophylaxis was recommended prior to resection or procedures.

The lack of a standard definition of carcinoid crisis, the difficulty capturing the intraoperative factors that contribute to hemodynamic instability (i.e., hemorrhage), and the variability of patient response to treatment with octreotide during a crisis have led to difficulty in creating a standard prophylactic or rescue dosing regimen using octreotide. Octreotide dosing regimens vary widely throughout the literature and there is no consensus as to whether IV or subcutaneous administration is preferred. Prophylactic infusions are initiated at doses ranging from 25 μg/h up to 1500 μg/h, and then usually titrated off over the postoperative 24 h. Selection of the starting dose is often surgeon-dependent. The favorable safety profile of octreotide allows for high doses to be administered, although there is no evidence that higher doses are necessarily better. A periprocedural protocol at Mayo Clinic recommends 200 μg subcutaneous octreotide prior to minor procedures with an additional 50–100 μg octreotide as needed for flushing or hypotension, but this protocol is not routinely used for all patients. For major procedures, 200–500 μg subcutaneous preprocedural octreotide can be considered with an infusion of 100–200 μg/h during and after the operation. Additional octreotide IV boluses up to 1000 μg, fluids, and vasopressors can be administered as needed for treatment of hypotension. Importantly, periprocedural octreotide use is not supported by robust data, no randomized trial data exist, and practice patterns vary widely across institutions. For instance, no standard periprocedural protocol has been established at the University of Texas MD Anderson Cancer Center, but refractory hypotension is treated with vasopressors and octreotide IV boluses as needed per NANETS guidelines.
First line use of vasopressors is supported by the suggestion by Condron et al. that carcinoid crisis is most consistent with a form of distributive shock.\textsuperscript{55}

**OCTREOTIDE: A VALID TREATMENT FOR THE MANAGEMENT OF CARCINOID CRISIS?**

Octreotide is considered the standard of care for carcinoid crisis, but questions remain about its efficacy. First, definitions of the term “carcinoid crisis” vary across studies and have shifted over time. Several recent definitions of carcinoid crisis are provided in Table 1. The lack of a universal definition for carcinoid crisis may be partly due to heterogeneity in clinical presentation, as symptoms (e.g., flushing, bronchospasm) may not always occur during carcinoid crisis.\textsuperscript{71} This heterogeneity underscores the difficulty that clinicians have encountered in precisely defining patients at risk for carcinoid crisis.

The lack of specific hemodynamic criteria for carcinoid crisis has further complicated the identification of carcinoid crisis cases, many of which have been confirmed not because they met predefined hemodynamic parameters but because there appeared to be no other plausible explanation for symptom onset. Fouché et al. defined intraoperative carcinoid crisis as hemodynamic changes $\geq 40\%$ that are not explained by surgical or anesthetic management, \textsuperscript{77} and other recent studies have defined carcinoid crisis as hemodynamic instability not attributable to other factors.\textsuperscript{53,55,76,78} Therefore, confirming a case of carcinoid crisis can be subjective.

In addition, the pathophysiology of carcinoid crisis is not well understood.\textsuperscript{53,55} Given the similarities in symptoms between carcinoid syndrome and carcinoid crisis, it has been postulated that they share the same etiology.\textsuperscript{5,7,78} However, this hypothesis has not been proven and may hinder further investigation into the underlying mechanisms of carcinoid crisis. Only one prospective study (Condron et al., 2016) has assessed the efficacy of octreotide for the treatment of carcinoid crisis.\textsuperscript{53} Most studies that have recommended octreotide for the treatment of carcinoid crisis have been retrospective.\textsuperscript{60,76,78,90,93,96}

**NEW PERSPECTIVES REGARDING PATHOPHYSIOLOGY AND TREATMENT PARADIGMS OF CARCINOID CRISIS**

Although carcinoid crisis has been attributed to the release of bioactive molecules (e.g., serotonin, histamine) from NETs,\textsuperscript{106} this notion was challenged by a recent study by Condron et al. that assessed hemodynamic parameters and hormone levels in patients at high risk for carcinoid crisis. In a 2-year prospective study of 46 patients with small-bowel or lung NETs who received octreotide preoperatively, there were no differences in serotonin, histamine, bradykinin, or kallikrein levels between preincision, mid-crisis, and closing timepoints. Linear regression analyses showed positive correlations between preincision serotonin levels and the mid-crisis cardiac index ($r = 0.73, P = 0.017$) and cardiac output ($r = 0.61, P = 0.017$), and a negative correlation with mid-crisis systemic vascular resistance ($r = -0.61, P = 0.015$). In addition, linear regression analyses showed positive correlations between mid-crisis serotonin levels and mid-crisis cardiac index ($r = 0.56, P = 0.030$) and cardiac output ($r = 0.53, P = 0.043$), and a negative correlation between mid-crisis serotonin levels and mid-crisis systemic vascular resistance ($r = -0.54, P = 0.039$). Taken together, these results suggest that although there was no substantial release of serotonin, histamine, bradykinin, or kallikrein during carcinoid crisis, serotonin may partly contribute to carcinoid crisis and its severity given that preincision levels were substantially elevated.\textsuperscript{55}

The role of catecholamines in carcinoid crisis has been questioned. Epinephrine, a nonselective adrenergic agonist, has been shown to induce flushing in patients with carcinoid crisis. Given its action on $\beta_2$ receptors, there was concern that its administration during a carcinoid crisis to correct hemodynamic instability could trigger a secondary carcinoid crisis by inducing paradoxical hypotension. However, this phenomenon was not seen in a recent study investigating this question. In a retrospective study of anesthesia records for 56 patients with NETs who received vasopressor treatment for hypotension and had at least one declared intraoperative carcinoid crisis event, there was no significant difference in the incidence of paradoxical hypotension ($P = 0.242$), crisis duration ($P = 0.257$), or the postoperative complication rate ($P = 0.896$) with $\beta$-adrenergic agonists (i.e., ephedrine, norepinephrine, or epinephrine) compared with non-$\beta$-adrenergic agonists. Furthermore, no significant linear associations were found in percentage decreases in mean arterial pressure with increasing doses of ephedrine or epinephrine upon dose-response curve analysis ($r^2 = 0.003, P = 0.780$; and $r^2 = 0.006, P = 0.661$, respectively). Although conclusions are constrained by the retrospective nature and small sample size of the study, these findings suggest that $\beta$-adrenergic agonists should be considered for the treatment of refractory hypotension in patients with carcinoid syndrome if phenylephrine and vasopressin are ineffective.\textsuperscript{107}

Other studies have shown that octreotide administration may not be required to manage hemodynamic instability associated with carcinoid crisis. A retrospective study of 161 patients with neuroendocrine tumors undergoing 98 ablation procedures and 207 HAE procedures showed that...
Elevated serotonin levels are associated with carcinoid crisis risk and severity. Although serotonin has not been demonstrated to directly cause carcinoid crisis, it is possible that serotonin may exert its effects indirectly by inducing the release of vasoactive substances, including interleukin-6 and other cytokines. Condron et al. demonstrated elevated preincision levels of serotonin in patients diagnosed with intraoperative carcinoid crisis. Targeting serotonin production may therefore be a viable treatment strategy for assessment in clinical trials. One potential treatment option for investigation would be telotristat ethyl, a tryptophan hydroxylase inhibitor that is approved for the treatment of diarrhea associated with carcinoid syndrome in combination with SSA therapy in adults inadequately controlled by SSA therapy. Telotristat ethyl has demonstrated efficacy in decreasing urinary 5-HIAA levels, and mean number of bowel movements per day in patients with carcinoid syndrome. Future studies are needed to understand the possible contribution of cytokines and other factors on carcinoid crisis, as well to assess the potential clinical benefit of telotristat ethyl and other agents in patients experiencing or at risk of carcinoid crisis.

**CONCLUSION**

Much remains unknown about the pathophysiology of carcinoid syndrome and carcinoid crisis, although a recent prospective study has challenged the historical perspective that carcinoid crisis is precipitated by the bioactive molecules produced by the tumor. To our knowledge, no new treatment modalities have been developed for carcinoid crisis. Although octreotide has appeared to resolve some cases of carcinoid crisis and is currently recommended in consensus guidelines, the lack of high-quality data from randomized controlled trials and inconsistency of efficacy across available reports have impeded the establishment of evidence-based guidelines for its use.

Recent studies investigating the pathophysiology of carcinoid crisis and efficacy of octreotide suggest that octreotide may not prevent carcinoid crisis and other treatment options should be considered. In addition, the use of catecholamines, particularly beta-adrenergic vasopressors, does not appear to cause or worsen carcinoid crisis, and the use of such drugs should not be withheld in cases of hypotension because prompt therapy with vasopressors and IV fluids may successfully shorten carcinoid crisis and reduce postoperative complications.

Further clinical and biochemical characterization of the pathophysiology of carcinoid crisis, in addition to rigorous study of the benefits of octreotide and the efficacy of alternative treatment modalities are warranted to develop an effective evidence-based treatment strategy for clinicians as they care for patients who are either at risk of, or experiencing, carcinoid crisis.

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