Surgery 165 (2019) 158–165

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Adrenal & Neuroendocrine

A prospective study of the pathophysiology of carcinoid crisis ☆

Mary E. Condron, MD[a], Nora E. Jameson, MS[a], Kristen E. Limbach, MD[a], Ann E. Bingham, MD[b], Valerie A. Sera, MD[b], Ryan B. Anderson, MD, PhD[b], Katie J. Schenning, MD[b], Shaun Yockelson, MD[b], Izumi Harukuni, MD[b], Edward A. Kahl, MD[b], Elizabeth Dewey, MS[a], SuEllen J. Pommier, PhD[a], Rodney F. Pommier, MD[a,*]

[a] Division of Surgical Oncology, Oregon Health & Science University, Portland
[b] Department of Anesthesiology & Perioperative Medicine, Oregon Health & Science University, Portland

ARTICLE INFO

Article history:
Accepted 3 April 2018
Available online 8 November 2018

ABSTRACT

Background: Sudden massive release of serotonin, histamine, kallikrein, and bradykinin is postulated to cause an intraoperative carcinoid crisis. The exact roles of each of these possible agents, however, remain unknown. Optimal treatment will require an improved understanding of the pathophysiology of the carcinoid crisis.

Methods: Carcinoid patients with liver metastases undergoing elective abdominal operations were studied prospectively, using intraoperative, transesophageal echocardiography, pulmonary artery catheterization, and intraoperative blood collection. Serotonin, histamine, kallikrein, and bradykinin levels were analyzed by enzyme-linked immunosorbent assay.

Results: Of 46 patients studied, 16 had intraoperative hypotensive crises. Preincision serotonin levels were greater in patients who had crises (1,064 vs 453 ng/mL, $P = .0064$). Preincision hormone profiles were otherwise diverse. Cardiac function on transesophageal echocardiography during the crisis was normal, but intracardiac hypovolemia was observed consistently. Pulmonary artery pressure decreased during crises ($P = .025$). Linear regression of preincision serotonin levels showed a positive relationship with mid-crisis cardiac index ($r = 0.73$, $P = .017$) and a negative relationship with systemic vascular resistance ($r = -0.61$, $P = .015$). There were no statistically significant increases of serotonin, histamine, kallikrein, or bradykinin levels during the crises.

Conclusion: The pathophysiology of carcinoid crisis appears consistent with distributive shock. Hormonal secretion from carcinoid tumors varies widely, but increased preincision serotonin levels correlate with crises and with hemodynamic parameters during the crises. Statistically significant increases of serotonin, histamine, kallikrein, or bradykinin during the crises were not observed.

Background

Carcinoid tumors are rare neuroendocrine tumors (2.5 to 5 individuals per 100,000 persons per year in the United States) that most often arise from the midgut.[1] They are known for their peculiar behavior and their ability to secrete an array of hormones, including serotonin, histamine, tachykinins, and bradykinin.[1,2] Secretion of these hormones by the tumor is believed to be responsible for carcinoid syndrome, which is characterized by flushing, abdominal pain, and diarrhea.[1–4] An equally complex, but acutely life-threatening feature of carcinoid disease is intraoperative carcinoid crisis. This scenario is characterized by the abrupt onset of hemodynamic instability, sometimes accompanied by characteristics of carcinoid syndrome, that can result in cardiovascular collapse and death.[3,5] Case reports and small studies have suggested that physiologic stress or direct tumor manipulation may initiate these crises.[3,6,7] The pathophysiology of carcinoid crisis is hypothesized to be attributable to a sudden, massive release of the aforementioned vasoactive hormones mediated by catecholamines.[3,8] This hypothesis, however, remains unproven. Early reports of a carcinoid crisis assumed it to be a severe form of carcinoid syndrome,[3] and consequently, the theories of the underlying mechanisms of the crisis appear to be extrapolated from what is understood of carcinoid syndrome from early investigations.[8–12]

☆ Presented at the 2018 Annual Meeting of the American Association of Endocrine Surgeons.

* Corresponding author: Department of Surgery, Division of Surgical Oncology, Oregon Health & Science University, Mail Code L619, 3181 SW Sam Jackson Park Road, Portland, OR 97239.
E-mail address: pommierr@ohsu.edu (R.F. Pommier).

https://doi.org/10.1016/j.surg.2018.04.093
0039-6060/

Hemodynamic instability from an intraoperative crisis presents a difficult and dangerous clinical problem. The profound hypotension that often accompanies such a crisis can cause hypoperfusion of vital organs, which can result in stroke, myocardial infarction, acute kidney injury, and liver damage, among other complications. It is therefore, not surprising that patients whose crises cause greater than 10 minutes of hypotension are at a greater risk of major postoperative complications.[13,14] Effective prophylaxis and treatment strategies, however, have remained elusive.

Determination of proper pharmacologic intervention, let alone prophylaxis, for a carcinoid crisis has been hampered by the lack of understanding of the underlying pathophysiology. Possible hormonally driven mechanisms include cardiac failure or cardiogenic shock, increased pulmonary vascular resistance impeding cardiac output,[15,16] and peripheral vasodilation.[12,17] There is one case report known to us that provides echocardiographic data during a carcinoid crisis, but it was limited by the absence of precrisis evaluation and by concomitant atrial flutter.[18] In an attempt to determine the pathophysiology of and hormones responsible for carcinoid crisis, we prospectively studied hemodynamic parameters and serum levels of hormones historically thought to be the most likely triggers of carcinoid crisis[3,8–12] during operations performed on patients at high risk for a crisis.

Methods

Approval for this study was obtained from the Oregon Health & Science University Institutional Review Board (Portland). Patients were eligible for inclusion if they had a small bowel or lung primary carcinoid tumor, were at increased risk of a carcinoid crisis because of the documented presence of hepatic metastases,[14] and were undergoing elective abdominal operation with the principal investigator (R.F.P.). Patients with carcinoid heart disease were excluded. Informed consent was obtained from eligible patients. Patient demographics, details of operative procedures, anesthesia, and postoperative course were obtained via review of the electronic medical record and electronic anesthesia record. The latter record documented vital-sign data with time-stamped, 1-minute resolution. The volume of liver metastases was measured using the arterial phase of preoperative computed tomography or magnetic resonance imaging of the liver. All data collection and storage were compliant with the Health Insurance Portability and Accountability Act of 1996.

All patients were treated with octreotide long-acting repeatable (LAR) at 30 mg—with exceptions of 3 patients who received 20 mg and 1 who received 10 mg—and had long-established control of symptoms on those doses. No patients missed a dose within 28 days of their operation. All patients received a loading dose of 500 mcg of intravenous octreotide before induction of anesthesia. After induction, a continuous infusion of 500 mcg of octreotide per hour was given until the end of the operation. Perioperative transesophageal echocardiography (TEE) was performed by TEE-credentialed attending anesthesiologists. Standard echocardiography views were recorded before incision, before closing, and during any crises that were declared. TEE studies were then analyzed post-hoc, using dedicated, vendor-independent, speckle tracking software (EchoInsite Right Ventricle Software Suite, Epsilon Imaging, MI).

A percutaneous pulmonary artery catheter was inserted via an internal jugular vein. Measurements of cardiac index, cardiac output, pulmonary artery pressure, systemic vascular resistance, and central venous pressure were recorded before incision, before closing, and during any crises that were declared. Peripheral blood samples for hormone assays were drawn before incision, before closing, and during any crises that were declared. Blood samples were frozen, stored, and batched for enzyme-linked immunosorbent assay (ELISA) analysis of serotonin, histamine, kallikrein, and bradykinin levels. ELISA analysis was performed using the following commercially available kits according to the manufacturer's instructions:

- Serotonin ELISA kit (Enzo Life Sciences, Inc, Farmingdale, NY, USA).
- Abnova Histamine ELISA kit (Abnova Corporation, Taipei City, Taiwan).
- Human Kallikrein 5 Quantikine ELISA kit (R&D systems, Minneapolis, MN, USA).
- Human Bradykinin EIA kit (Innovative Research, Novi, MI, USA).

An intraoperative carcinoid crisis was defined as a clinically important hemodynamic instability not attributable to other factors, such as substantial blood loss or compression of the inferior vena cava. Hemodynamic instability was considered clinically important if the systolic blood pressure was <80 or >180 mmHg, if the heart rate was greater than 120 beats per min, or if the patient was displaying physiology that, if sustained, would be expected to cause end organ dysfunction, such as ventricular arrhythmias or bronchospasm causing difficulty with ventilation. Consensus of the surgeon and attending anesthesiologist was necessary to declare a crisis.

Differences in patient characteristics were evaluated with independent sample t tests, χ^2 analysis, or the Fisher's exact test. Univariate analyses of risk factors for intraoperative carcinoid hemodynamic events and for major postoperative complications informed the construction of a multivariate logistic regression model for the risk of intraoperative crisis. The Hosmer and Lemeshow variable reduction methods were used to find the most parsimonious model. Likelihood ratio tests evaluated model fit. Differences in hormone levels and hemodynamic parameters at preincision, mid-crisis, and closing time points were evaluated with paired t tests. The association between hormone levels and hemodynamic parameters was evaluated with the Pearson correlation coefficient. Linear regression of hormone levels at each of the three time points studied and hemodynamic parameters was performed using IBM SPSS Statistics for Windows, v 24.0 (IBM, Armonk, NY). The level of significance was set at $P \leq .05$.

Results

A total of 46 patients were studied between 2015 and 2017, of whom 28 were women. Mean age was 63 years. A total of 40 patients (87%) had a small bowel primary, and 30 (65%) had carcinoid syndrome. Thirty-one patients had mesenteric metastases (67%), and 9 had carcinomatosis (13%). The most common procedures performed during the operation were debulking of hepatic metastases (80%), prophylactic cholecystectomy (76.%), resection of a mesenteric nodal mass (50%), and resection of small bowel primary (48%). The majority of patients had more than 1 procedure during their operation. Mean duration of anesthesia was 349 minutes (range 208–543 minutes), and mean estimated blood loss was 621 mL (range 20–3,500 mL). Median duration of hospital stay was 8 days (interquartile range 7—9 days). A total of 41 patients (89%) had an epidural placed preoperatively, but none had medications infused via the epidural during the operation. Twenty-two patients (48%) had postoperative complications, of which 8 had Clavien-Dindo class III-IV complications (Table 1).[19]

A total of 16 patients (35%) had an intraoperative hypotensive carcinoid crisis declared. Mean crisis duration was 8.1 minutes (range 3–17 minutes). Comparison of characteristics among patients who had an intraoperative crisis and those who did not (Table 2) revealed no differences among the parameters studied. There was no difference between groups in the overall rate of postoperative complications.

Table 1
Postoperative complications of patients grouped by incidence of intraoperative carcinoid crisis

Complication	Without crisis N (%)	With crisis N (%)	Clavien-Dindo classification
Dysthrythmia	2	1	II
Hemorrhage requiring transfusion	1	2 (13)	II-IIIb
Surgical site event	3 (10)	3 (19)	I-IIIb
Intra-abdominal abscess	4	1	IIIa
Anastomotic leak	0	1	IVb
Acute kidney injury	1	1	I
Urinary tract infection	2	0	II
Clostridium difficile infection	0	3 (19)	II
Pneumonia	1	0	II
Decompensated liver failure	0	1	IVb
Return to the operating room	2	1	IIIb

Note: Patients without crisis N = 30, and patients with crisis N = 16. Some patients with and without crisis had more than one complication.

Table 2
Patient Characteristics Grouped by Incidence of Intraoperative Carcinoid Crisis

	No Crisis (N=30)			Intraoperative Crisis (N=16)			
	N (%)	Mean	SD	N(%)	Mean	SD	*p*-value
Age at operation (years)		63.3	9.4		62.1	8.1	0.652
Female sex	16 (53.3)			12 (75)			0.152
Presence of carcinoid syndrome	19 (63.3)			11 (68.8)			0.713
Operative procedures							
Hepatic debulking	25 (83.3)			12 (75)			0.497
Prophylactic cholecystectomy	22 (73.3)			13 (81.3)			0.549
Resection of primary tumor	14 (46.7)			10 (62.5)			0.306
Resection of mesenteric nodal mass	16 (53.3)			7 (43.8)			0.536
Combination of above procedures	26 (86.7)			14 (87.5)			0.936
Volume of hepatic metastases on preoperative CT or MRI (cm^3)		34.3	62.3		83.2	109.7	0.059
Estimated volume debulked (cm^3)		21.5	40.2		29.7	32.2	0.484
Duration anesthesia (min)		340.6	72.4		363.3	71.4	0.314
Estimated blood loss (mL)		619.0	722.3		625.0	440.5	0.976
Hospital length of stay (days)		8.4	4.3		11.6	11.9	0.315
Any postoperative complication	14 (46.7)			8 (50.0)			0.829
Clavien-Dindo class I-II complications	8 (26.7)			6 (37.5)			0.447
Clavien-Dindo class III-IV complications	6 (20.0)			2 (12.5)			0.523
Dose of octreotide LAR at time of operation (mg)		28.5	3.7		28.7	5.2	0.912
Duration of treatment with long acting somatostatin analogue prior to operation (months)		16.6	31.5		14.6	31.3	0.832

Note. SD=standard deviation, CT = computed tomography, MRI = magnetic resonance imaging, LAR = long acting repeatable. *P*-values reported from χ^2 analysis and independent sample t-tests. $P \leq 0.05$ considered significant.

TEE data

All measured echocardiographic parameters were within the normal ranges at the preincision and closing time points in all patients. The TEE during the crisis also showed echocardiographic parameters were within the normal ranges and not different from preincision or closing values (Table 3). There were no differences in preincision and the closing TEE parameters between patients who did and did not have a crisis (Table 4), but intracardiac hypovolemia was consistently observed during the crisis.

Hemodynamic data

All patients had an increase in cardiac index (2.5 vs 3.4 L/min/m^2, $P < .001$) and a decrease in systemic vascular resistance (1,261 vs 946 dyn•s•cm^{-5}, $P < .001$) from preincision to closing time points. There were no changes in mean pulmonary artery pressure in patients who did not have an intraoperative carcinoid crisis; in contrast, patients who had an intraoperative carcinoid crisis demonstrated a decrease in mean pulmonary artery pressure at the time of crisis compared with mean preincision pressure (16.5 mmHg vs 18.9 mmHg, $P = .025$). Systemic vascular resistance also decreased during the crisis (1,412 vs 1,030 dyn•s•cm^{-5}, $P = .011$), but this value was not different from systemic vascular resistance during closing (1,028 vs 928 dyn•s•cm^{-5}, $P = .217$; Table 3). Comparison of hemodynamic parameters at both preincision and closing time points between patients with and without crisis revealed no differences, except for closing central venous pressure, which was less in patients who had a crisis (8.2 vs 11.0 mmHg, $P = .019$) (Table 4).

Hormone data

Preincision hormone profiles among the individual patients were markedly diverse. Comparison of preincision hormone levels between patients who had an intraoperative carcinoid crisis and those who did not showed greater levels of serotonin in those who had had a crisis (1,064 vs 453 ng/mL, $P = .006$). There were no other differences in the preincision levels of the other 3 hormones studied. In a best-fit, multivariate logistic regression model of the preincision hormone levels, as well as operative and demographic variables associated with a crisis, only the preincision serotonin level remained associated with development of crisis (odds ratio [OR] 1.10, $P = .015$, 95% confidence interval [CI] 1.02–1.19) (Table 5).

Comparison of mean hormone levels between preincision and mid-crisis time points revealed no differences in serotonin (1,064 vs 910 ng/mL, $P = .295$), histamine (1.07 vs 0.52 pg/mL, $P = .158$), kallikrein (37.6 vs 32.5 pg/mL, $P = .467$), or bradykinin levels (334

Table 3
Comparison of transesophageal echocardiographic and hemodynamic parameters in patients with intraoperative carcinoid crisis at preincision, mid-crisis, and closing time points

	Preincision			Mid-crisis			Closing			Preincision versus mid-crisis *P* value	Mid-crisis versus closing *P* value
	N	Mean	SD	N	Mean	SD	N	Mean	SD		
RV PLSS (%)	10	−23.4	4.4	10	−22.2	4.8	9	−23.2	5.0	.423	.687
RV TAPSE (cm)	10	1.6	0.3	10	1.5	0.3	9	1.7	0.6	.175	.193
LV GLS (%)	11	−21.2	3.7	11	−21.3	4.7	10	−22.0	3.1	.917	.608
LV EF (%)	11	57.5	6.3	11	55.5	6.9	10	55.3	6.2	.377	.965
MAP (mmHg)	15	80.9	14	15	62.0	9.6	15	73.7	11	< .001*	.010*
HR (bpm)	15	64.1	13	15	70.3	15.3	15	82.1	18	.071	.005*
CI (L/min/m^2)	15	2.53	0.6	15	2.47	0.6	15	3.47	0.8	.635	< .001*
CO (L/min)	15	4.7	1.3	15	4.7	1.3	15	6.5	2.0	.683	< .001*
SVR (dyn•s•cm^{-5})	14	1412	574	14	1030	350	14	928	307	.011*	.217
Mean PAP (mmHg)	15	18.9	4.0	15	16.5	2.1	15	18.8	4.3	.025*	.012*
CVP (mmHg)	15	11.0	5.4	15	8.0	2.6	15	7.9	2.1	.060	.845

Note: *P* values reported from paired *t* tests. $P \leq .05$ considered significant.
* $P \leq .05$.*SD*, standard deviation; *RV*, right ventricle; *PLSS*, peak longitudinal systolic strain; *TAPSE*, tricuspid annular plane systolic excursion; *LV*, left ventricle; *GLS*, global longitudinal strain; *EF*, ejection fraction; *MAP*, mean arterial pressure; *HR*, heart rate; *CI*, cardiac index; *CO*, cardiac output; *SVR*, systemic vascular resistance; *PAP*, pulmonary artery pressure; *CVP*, central venous pressure.

Table 4
Comparison of transesophageal echocardiographic and hemodynamic parameters in patients with and without intraoperative carcinoid crisis

	No crisis			Intraoperative crisis			*P* value
	N	Mean	SD	N	Mean	SD	
Preincision RV PLSS (%)	26	−22.0	3.2	14	−22.9	4.7	.530
Preincision RV TAPSE (cm)	26	1.82	0.4	14	1.68	0.4	.227
Preincision LV GLS (%)	27	−21.1	3.6	14	−20.9	3.3	.895
Preincision LV EF (%)	26	50.7	16.5	14	55.4	7.2	.315
Preincision MAP (mmHg)	29	81.6	17.8	15	80.9	13.9	.720
Preincision HR (bpm)	29	67.1	12.2	15	64.1	12.5	.447
Preincision CI (L/min/m^2)	29	2.50	0.35	15	2.53	0.62	.889
Preincision CO (L/min)	29	4.79	0.75	15	4.74	1.34	.865
Preincision SVR (dyn•s•cm^{-5})	28	1185	284	14	1412	574	.183
Preincision mean PAP (mmHg)	30	20.2	6.47	16	17.8	6.1	.217
Preincision CVP (mmHg)	29	11.2	4.8	16	11.1	5.3	.144
Mean mid-crisis RV PLSS (%)	0	—	—	10	−22.2	4.8	—
Mean mid-crisis RV TAPSE (cm)	0	—	—	10	1.5	0.3	—
Mean mid-crisis LV GLS (%)	0	—	—	11	−21.4	4.7	—
Mean mid-crisis LV EF (%)	0	—	—	11	55.5	7.0	—
Mean mid-crisis MAP (mmHg)	0	—	—	15	62.0	9.6	—
Mean mid-crisis HR (bpm)	0	—	—	15	70.3	15.3	—
Mean mid-crisis CI (L/min/m^2)	0	—	—	15	2.5	0.6	—
Mean mid-crisis CO (L/min)	0	—	—	15	4.7	1.3	—
Mean mid-crisis SVR (dyn•s•cm^{-5})	0	—	—	15	1028	337.4	—
Mean mid-crisis mean PAP (mmHg)	0	—	—	15	16.5	2.1	—
Mean mid-crisis CVP (mmHg)	0	—	—	15	8.0	2.6	—
Closing RV PLSS(%)	21	−22.9	4.0	11	−23.7	4.0	.585
Closing RV TAPSE(cm)	21	1.8	0.4	11	1.7	0.5	.510
Closing LV GLS(%)	21	−22.0	3.1	11	−21.7	3.1	.756
Closing LV EF(%)	21	54.8	10.0	11	54.8	6.1	.987
Closing MAP (mmHg)	29	83.6	17.6	15	73.7	11.2	.054
Closing HR (bpm)	29	79.8	17.4	15	82.1	18.4	.689
Closing CI (L/min/m^2)	29	3.4	0.8	15	3.5	0.8	.781
Closing CO (L/min)	29	6.4	1.5	15	6.5	2.0	.819
Closing SVR (dyn•s•cm^{-5})	29	944	240.3	15	928	307.2	.842
Closing mean PAP (mmHg)	29	20.9	6.1	15	18.7	4.3	.228
Closing CVP (mmHg)	30	11.0	3.9	16	8.3	2.7	.019

Note: N = 46. *P* values reported from independent sample *t* tests. $P \leq .05$ is considered significant.
SD, standard deviation; *RV*, right ventricle; *PLSS*, peak longitudinal systolic strain; *TAPSE*, tricuspid annular plane systolic excursion; *LV*, left ventricle; *GLS*, global longitudinal strain; *EF*, ejection fraction; *MAP*, mean arterial pressure; *HR*, heart rate; *CI*, cardiac index; *CO*, cardiac output; *SVR*, systemic vascular resistance; *PAP*, pulmonary artery pressure; *CVP*, central venous pressure.

vs 311 ng/mL, $P = .869$) (Fig. 1). Similarly, there were no differences between the mid-crisis and closing time points in the levels of any of the 4 hormones studied. Patients both with and without crisis had decreases from preincision to closing time points in kallikrein levels (47.7 vs 29.8 pg/mL, $P = .001$) and bradykinin levels (300 vs 139 ng/mL, $P = .002$) (Fig. 1).

Correlations between hormone levels and hemodynamic parameters

Linear regression revealed relationships between preincision serotonin levels and the mid-crisis cardiac index ($r = 0.73$, $P = .017$) (Fig. 2) and cardiac output ($r = 0.61$, $P = .017$) (Fig. 3), as well as a negative relationship with mid-crisis systemic vascular resistance ($r = -0.61$, $P = .015$) (Fig. 4). Linear regression also showed a

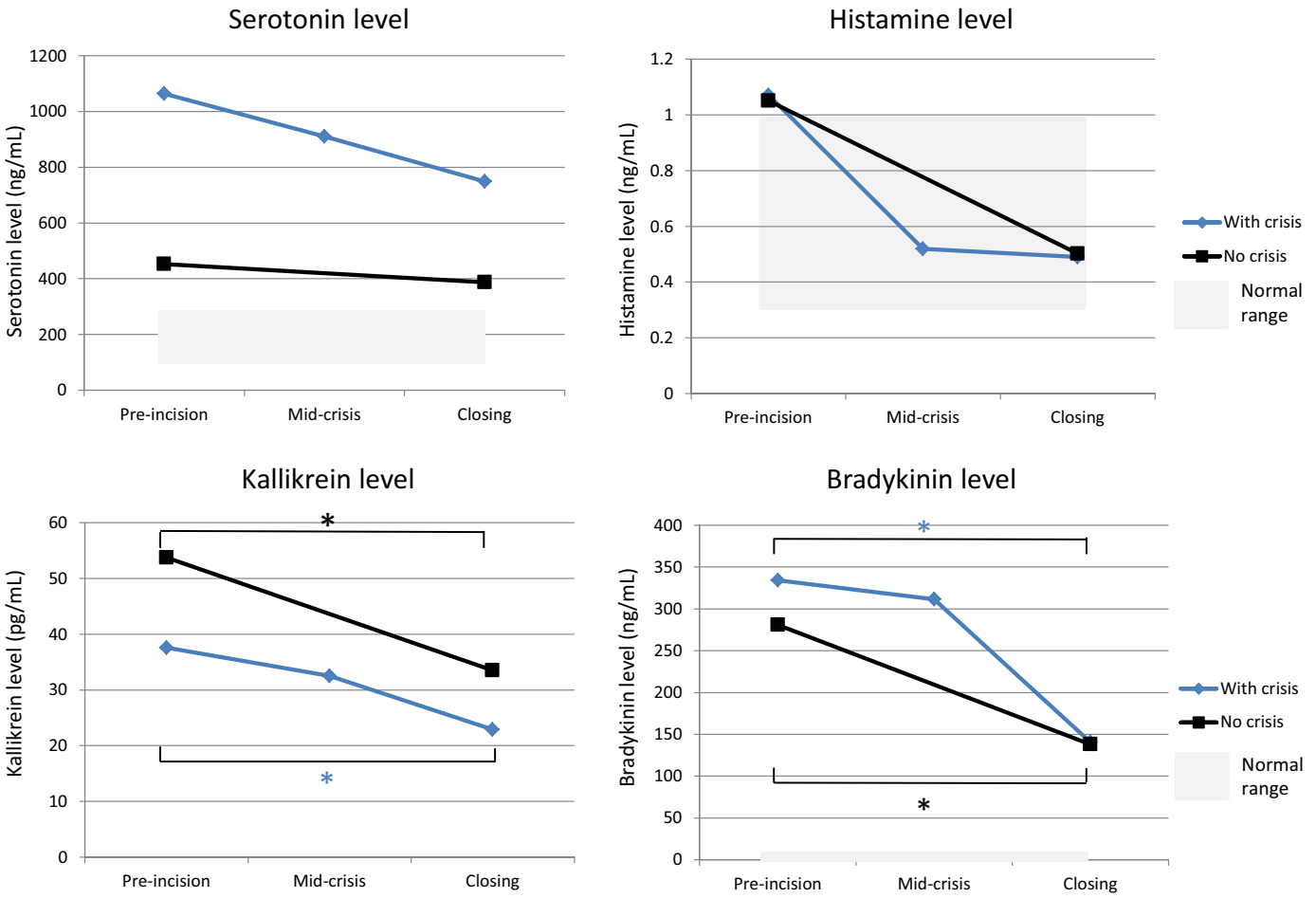

Fig. 1. Levels of serotonin, histamine, kallikrein, and bradykinin at preincision, mid-crisis, and closing time points in patients with and without intraoperative carcinoid crisis. *Note:* Normal range for whole-blood serotonin is 101–283 ng/mL, plasma histamine 0.3–1.0 ng/mL, and plasma bradykinin 3.0–4.8 ng/mL.[25] A normal range is not available for plasma kallikrein. *$P \leq .05$

Table 5
Adjusted odds ratios and 95% confidence intervals for the risk of intraoperative carcinoid crisis from parsimonious multivariate logistic regression model

Factor (per unit increase)	Adjusted OR	95% CI		*P* value
		lower	upper	
Age at operation (5 year)	1.04	0.70	1.56	.8467
Anesthesia time (10 min)	1.11	0.96	1.27	.1328
EBL (50 mL)	0.97	0.90	1.05	.4178
Preincision serotonin (100 ng/mL)	1.10	1.01	1.19	.0151
Preincision histamine (0.1 ng/mL)	1.00	0.96	1.03	.7853
Preincision kallikrein (10 pg/mL)	0.92	0.75	1.13	.4144
Preincision bradykinin (50 ng/mL)	1.04	0.96	1.11	.3670

Note: N = 46. Model c-statistic (AUC) = 0.75. $P \leq .05$ considered statistically significant.
AUC, area under the curve; *CI*, confidence interval; *EBL*, estimated blood loss. *OR*, odds ratio.

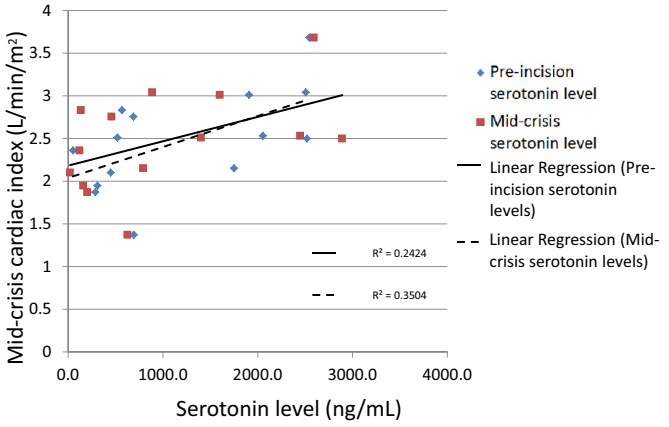

Fig. 2. Linear regression of preincision and mid-crisis serotonin levels and mid-crisis cardiac index in patients with intraoperative carcinoid crisis.

negative relationship between mid-crisis serotonin levels and the mid-crisis systemic vascular resistance (r = –0.54, $P = .039$) (Fig. 4). In addition, mid-crisis serotonin levels positively correlated with the mid-crisis cardiac index ($r = .56$, $P = .030$) and cardiac output ($r = 0.53$, $P = .043$) using the Pearson correlation. There were no correlations using the Pearson correlation between any of the other hormone levels at either the preincision or mid-crisis time points with pulmonary artery pressure, heart rate, mean arterial pressure, or systolic blood pressure.

Patients with intraoperative carcinoid crisis who required at least 1 vasopressor bolus for treatment of their hypotension had greater levels of preincision serotonin (1,413 ng/mL vs 294 ng/mL, $P = .004$), mid-crisis serotonin (1,223 ng/mL vs 221 ng/mL, $P = .010$), and closing serotonin (1,022 ng/mL vs 145 ng/mL, $P = .022$) than those who did not require vasopressor support. There were no differences in histamine, kallikrein, or bradykinin

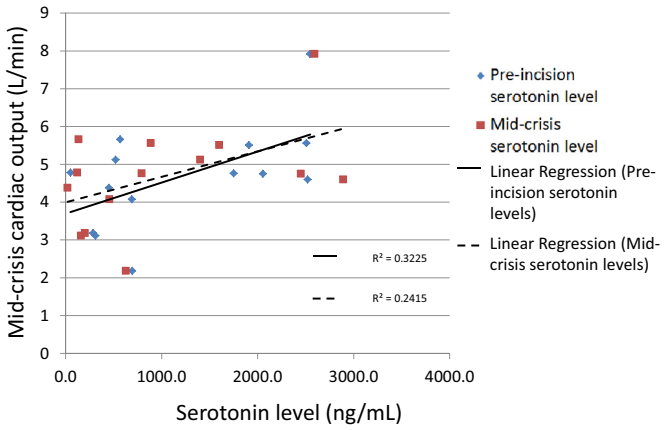

Fig. 3. Linear regression of preincision and mid-crisis serotonin levels and mid-crisis cardiac output in patients with intraoperative carcinoid crisis.

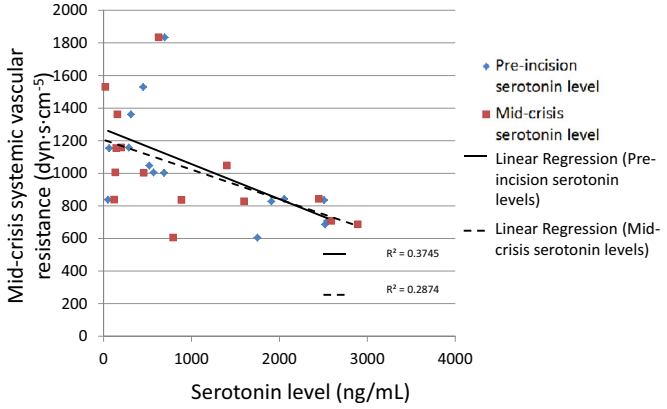

Fig. 4. Linear regression of preincision and mid-crisis serotonin levels and mid-crisis systemic vascular resistance in patients with intraoperative carcinoid crisis.

levels between these groups at any of the measured time points.

Discussion

This prospective study of the pathophysiology of intraoperative carcinoid crisis has revealed multiple unexpected differences from the hypothetic model of carcinoid crisis being caused by sudden, massive release of hormones associated with carcinoid syndrome. Many studies, most of which were performed in the 1960s, have suggested prominent roles for serotonin, histamine, and bradykinin in the manifestations of carcinoid syndrome, namely the diarrhea and flushing.[10–12,20] Although previous work has indicated that carcinoid syndrome is a risk factor for intraoperative carcinoid crisis,[14] data directly supporting the connection between these hormones and carcinoid crisis are lacking. Thus, direct study of these hormones, using modern biochemical assays, was performed to determine their relative roles and to possibly identify pharmacologic targets for intervention. These hormonal investigations were coupled with invasive monitoring of cardiac and hemodynamic parameters to elucidate the pathophysiology of intraoperative crisis and potentially guide treatment.

The predominant finding of this study was that there was no massive release or even a change of serotonin, histamine, kallikrein, or bradykinin levels during the hypotensive carcinoid crisis. Therefore, none of these vasoactive hormones can be directly implicated as being responsible for triggering a crisis. These observations suggest that an intraoperative carcinoid crisis may be an entirely separate pathophysiologic entity from that of carcinoid syndrome, rather than the extreme end of a spectrum of symptoms, and that the assumptions regarding its mechanism based on studies of carcinoid syndrome may be incorrect. Furthermore, there is no physiologic basis for targeting any of these hormones pharmacologically for either prophylaxis against or treatment of a crisis.

Another unexpected finding was that there was no “typical” hormone profile for carcinoid patients with liver metastases. The preincision serotonin, histamine, kallikrein, and bradykinin serum profiles in the patients in this study varied widely, although mean values of serotonin and bradykinin did exceed the upper limits of normal. Within this wide variability, we found that patients who had an intraoperative crisis had greater preincision serotonin levels than patients who did not have a crisis. Thus, increased serotonin levels appear to be a marker of risk for intraoperative carcinoid crisis, even though serotonin does not appear to be the causative hormone. This finding is in agreement with our previous observation that carcinoid syndrome is also a marker of risk.[14] Because serotonin is known to be a potent vasoconstrictor,[16] it would not be expected to cause hypotension unless it caused vasoconstriction in the cardiac vasculature, leading to cardiac pump failure, or in the pulmonary vasculature, impeding delivery of blood to the left heart. TEE, however, found that all cardiac functions were normal and unchanged compared with the baseline during a crisis, ruling out cardiac pump failure as a mechanism. Pulmonary artery catheterization also showed that mean pulmonary arterial pressures decreased significantly during a crisis, ruling out pulmonary vasoconstriction. Instead, TEE consistently showed intracardiac hypovolemia during the crisis. The observed combination of intracardiac hypovolemia, decreased systemic blood pressure, and no change in central venous pressure or compensatory increase in systemic vascular resistance indicates that the pathophysiology of intraoperative carcinoid crisis is most consistent with distributive shock. The underlying mechanism is thus most likely to be vasodilation decreasing return of venous blood to the heart, resulting in hypotension.

Further supporting distributive shock as a mechanism was the observation of decreased systemic vascular resistance during the crisis, although it is difficult to determine definitively whether this represented peripheral vasodilation secondary to the crisis itself or a background effect of general anesthetic.[21] A strong case for the latter could be made, based on the lack of change in systemic vascular resistance between the mid-crisis and closing time points. Highly significant negative correlations between both preincision and mid-crisis serotonin levels and systemic vascular resistance during a crisis were, however, detected. Furthermore, patients with high preincision serotonin levels were more likely to require vasopressor treatment for hypotension during a crisis. These findings indicate that increased serotonin levels are not only a marker of risk for a crisis but also for the severity of the crisis.

Historically, physicians have used octreotide for both prophylaxis and treatment of carcinoid crisis.[8,9,22–24] This choice was logical under the assumption that a carcinoid crisis is caused by the same hormones as carcinoid syndrome. We have systematically studied the use of outpatient octreotide LAR, preoperative and intraoperative boluses of octreotide, and continuous infusion of octreotide and found them all to be ineffective at preventing an intraoperative hypotensive carcinoid crisis.[13,14] Regardless of these findings, we continued to administer octreotide LAR, a loading dose of intravenous octreotide, and a continuous infusion of intravenous octreotide to all patients in this study to avoid introducing additional variables that might confound comparisons with other work. Despite the use of octreotide, a high rate (35 %) of otherwise inexplicable hypotensive events occurred during this study, providing additional data that prophylactic octreotide is ineffective. Failure to find data supporting the theory that a carcinoid crisis is

caused by massive release of the hormones octreotide is known to suppress further weakens its potential role as a prophylactic agent. Continued reliance on octreotide for prevention may result in potentially dangerous complacence among providers.

Rather, providers should recognize that intraoperative crisis occurs in a substantial percentage of carcinoid patients, particularly those with liver metastases and carcinoid syndrome, and be prepared to treat it promptly and aggressively. The most appropriate treatment for hypotension consistent with distributive shock would be the administration of intravenous fluids and vasopressors. Future work should focus on the relative efficacies of various vasopressors for quickly restoring hemodynamic parameters to normal and evaluating whether beta-adrenergic agonists, which traditionally have been avoided in carcinoid patients for fear of provoking a secondary crisis, actually provoke a secondary crisis or are effective treatment options.

References

1. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9:61–72.
2. Mancuso K, Kaye AD, Boudreaux JP, Fox CJ, Lang P, Kalarickal PL, et al. Carcinoid syndrome and perioperative anesthetic considerations. *J Clin Anesth*. 2011;23:329–341.
3. Kahil ME, Brown H, Fred HL. The carcinoid crisis. *Arch Intern Med*. 1964;114:26–28.
4. Lips CJ, Lentjes EG, Hoppener JW. The spectrum of carcinoid tumours and carcinoid syndromes. *Ann Clin Biochem*. 2003;40:612–627.
5. Vaughan DJ, Brunner MD. Anesthesia for patients with carcinoid syndrome. *Int Anesthesiol Clin*. 1997;35:129–142.
6. Magabe PC, Bloom AL. Sudden death from carcinoid crisis during image-guided biopsy of a lung mass. *J Vasc Interv Radiol*. 2014;25:484–487.
7. Morrisroe K, Sim IW, McLachlan K, Inder WJ. Carcinoid crisis induced by repeated abdominal examination. *Intern Med J*. 2012;42:342–344.
8. Woltering EA, Wright AE, Stevens MA, Wang YZ, Boudreaux JP, Mamikunian G, et al. Development of effective prophylaxis against intraoperative carcinoid crisis. *J Clin Anesth*. 2016;32:189–193.
9. Kvols LK. Therapeutic considerations for the malignant carcinoid syndrome. *Acta Oncol*. 1989;28:433–438.
10. Oates JA, Pettinger WA, Doctor RB. Evidence for the release of bradykinin in carcinoid syndrome. *J Clin Invest*. 1966;45:173–178.
11. Gustafsen J, Boesby S, Man WK. Histamine in carcinoid syndrome. *Agents Actions*. 1988;25:1–3.
12. Pharmacology of the carcinoid syndrome. *Lancet*. 1968;1:404–405.
13. Massimino K, Harrskog O, Pommier S, Pommier R. Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. *J Surg Oncol*. 2013;107:842–846.
14. Condron ME, Pommier SJ, Pommier RF. Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. *Surgery*. 2016;159:358–365.
15. Breil I, Koch T, Belz M, Van Ackern K, Neuhof H. Effects of bradykinin, histamine and serotonin on pulmonary vascular resistance and permeability. *Acta Physiol Scand*. 1997;159:189–198.
16. MacLean MR, Dempsie Y. Serotonin and pulmonary hypertension—From bench to bedside? *Curr Opin Pharmacol*. 2009;9:281–286.
17. Mason DT, Melmon KL. Abnormal forearm vascular responses in the carcinoid syndrome: The role of kinisns and kinin-generating system. *J Clin Invest*. 1966;45:1685–1699.
18. Majeed F, Porter TR, Tarantolo S, Duhachek-Stapelman A, Xie F, Elhendy A. Carcinoid crisis and reversible right ventricular dysfunction after embolization in untreated carcinoid syndrome. *Eur J Echocardiogr*. 2007;8:386–389.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
20. Mason DT, Melmon KL. New understanding of the mechanism of the carcinoid flush. *Ann Intern Med*. 1966;65:1334–1339.
21. de Wit F, van Vliet AL, de Wilde RB, Jansen JR, Vuyk J, Aarts LP, et al. The effect of propofol on haemodynamics: Cardiac output, venous return, mean systemic filling pressure, and vascular resistances. *Br J Anaesth*. 2016;116:784–789.
22. Kinney MA, Warner ME, Nagorney DM, Rubin J, Schroeder DR, Maxson PM, et al. Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *Br J Anaesth*. 2001;87:447–452.
23. Kvols LK, Martin JK, Marsh HM, Moertel CG. Rapid reversal of carcinoid crisis with a somatostatin analogue. *N Engl J Med*. 1985;313:1229–1230.
24. Marsh HM, Martin Jr JK, Kvols LK, Gracey DR, Warner MA, Warner ME, et al. Carcinoid crisis during anesthesia: Successful treatment with a somatostatin analogue. *Anesthesiology*. 1987;66:89–91.
25. Mersey JH, Williams GH, Emanuel R, Dluhy RG, Wong PY, Moore TJ. Plasma bradykinin levels and urinary kallikrein excretion in normal renin essential hypertension. *J Clin Endocrinol Metab*. 1979;48:642–647.

Discussion

Dr James Howe (Iowa City, IA): It's a great body of work that Dr. Pommier's group is doing to examine a really important clinical problem that we don't all understand.

What I am trying to take away from your talk is whether we should be giving patients octreotide during these cases, or do we just give it to people with preoperative elevated serotonin levels? When they have these crises, what do we do? Do we give them volume, phenylephrine, vasopressin? Do you avoid epinephrine like it has been recommended because this may cause increased release of vasoactive amines? How should what you have learned help us move forward?

Dr Kristen E. Limbach: Thank you for that excellent question. Based on prior studies that have looked at both bolus octreotide and continuous infusion of octreotide for the duration of the operation, none of those have shown any difference in terms of rate of crisis. Our data continue to support that. Anecdotally, our institution has stopped using prophylactic octreotide and has found no increased rate of carcinoid crisis after that change. We have done about a hundred cases without prophylactic octreotide at this point.

In terms of what we should be doing to treat carcinoid crisis, given the mechanism of distributive shock that our study suggested, the way we treat distributive shock would be fluids and pressors. If you think of sepsis guidelines, et cetera, those really emphasize early fluids and early pressors.

Dr Subash Patel (Chicago, IL): You have described a physiologic model that looks like a sepsis model. When you look at distributive shock, the prime mediator for distributive shock, in hyperdynamic circulation like this, is nitric oxide. Did you look at NO as a marker for this phenomenon that you are observing?

Dr Kristen E. Limbach: Unfortunately, were not able to measure nitric oxide in this study. However, many of the downstream effects of some of the hormones studied include increased NO. Because we did not see a massive increase at the time of crisis, one could potentially extrapolate that NO may or may not be a potential mediator here. It's really difficult to tell with what we have, and it might be something we could look at in the future.

Dr Steven Libutti (Bronx, NY): Do you still have the samples that you used to look at the cytokines?

Dr Kristen E. Limbach: Yes, sir, we do.

Dr Steven Libutti (Bronx, NY): I would suggest looking at IL-6, because serotonin is a known inducer of IL-6 expression. IL-6 is a major vasodilator working at the endothelial level. It has a longer half-life than nitric oxide, and I think it would be more likely to be the effector cytokine for what you are seeing. And, if you see elevated IL-6 levels, then you would have a potential therapeutic strategy around preventing the vasodilatation, whether it be anti-

body therapy, or what have you. So, I would strongly encourage you to look at IL-6.

You should look at IL-6, IL-8, and tumor necrosis factor (TNF) because those are the likely cytokines. I would be willing to bet it's going to be one or all of those three that are elevated as a result of the serotonin.

Dr Kristen E. Limbach: Thank you so much. I appreciate that.

Dr Janic Pasieka (Calgary, AB): Would you define what mid-crisis is? Because this is dynamic. The patient starts to go into crisis. And then there are interventions being done, and then you are drawing the blood at mid-crisis. What can you say to reassure me that mid-crisis for each of these diverse patients was essentially around the same time?

Dr Kristen E. Limbach: Thank you for that excellent question. So, as you all saw on the video that was demonstrated, crisis can be a very dramatic time in the operating room—the patient having a profound episode of hypotension. A lot of things need to happen in a very short period for the care of that patient.

Typically, our samples were drawn as soon as a crisis had been declared. As the patient went into a hypotensive episode, the decision had to be made rather quickly: Was this a crisis or not? The surgeon and anesthesiologist made that decision together, and then the samples were drawn. In terms of our hemodynamic data, all of the data were reported at the nadir of that crisis.

Dr Xavier Keutgen (Chicago, IL): I just wanted to ask you a few questions about the types of surgery that you were doing.

Was there a difference in the operations you did and whether you observed a crisis or not?

The second question is whether there is a threshold for serotonin levels. Do you say that everybody with a high serotonin level preoperatively, even if it was just 10% above normal, is at risk for this?

My third point comes back to the samples, which are probably very precious. I have a theory that at this point we cannot measure things that these tumors are secreting. So, there are newer ways, like metabolomics, et cetera, that I would really look into to figure out if maybe it's IL-6, maybe it's another cytokine, or maybe it's something else that these tumors are secreting that we are just not aware of. Because I personally know of many patients that have a "carcinoid crisis" with a completely normal hormonal profile.

Dr Kristen E. Limbach: To address your first question, there was no difference between operation types in terms of rate of crisis or of any of the hormones that we measured. The predominant operative procedures that were done for these patients was hepatic debulking, resection of a mesenteric nodal mass, resection of the primary tumor, and prophylactic cholecystectomy. Those were the most frequently performed operative procedures and, as I said, there were no differences between crisis and non-crisis and no differences in their hormone profiles.

In terms of a serotonin threshold, I would be very cautious in interpreting the pre-incision serotonin as being associated with risk of crisis and therefore as an indicator that we should base our operative anesthesia protocols on that serotonin level. The adjusted odds ratio in that model was 1.1, so extremely weak. And some of our patients with the highest serotonin levels did not have a crisis, and vice versa.

So I would still be very vigilant with all carcinoid patients in terms of their operative care.

And regarding your last comment, yes, we will certainly hold onto those samples.

Dr Herb Chen (Birmingham, AL): You mentioned you are not using octreotide anymore. Correct? Are you repeating the studies with the sampling for the patients that are not on octreotide?

Dr Kristen E. Limbach: We have not begun that process, although I think there are a lot of things we would like to understand now in terms of what the role of octreotide may be in the octreotide-naive patient.

There are, of course, many reports out there of octreotide saving the day, being given in a bolus fashion after a profound carcinoid crisis. Anecdotally, we have seen increased return of blood flow to the right heart with administration of octreotide in an octreotide-naive patient. So, I think there are several studies on the horizon in terms of what we should be looking at now that we have stopped using prophylactic octreotide.

Dr John Chabot (New York City, NY): You have a unique opportunity in this experimental setup to look at mixed venous blood and arterial samples simultaneously. Did you do that? And did you see what contributions the lungs may have to clearing these agents?

Dr Kristen E. Limbach: We actually did draw both peripheral and central samples. However, many of the findings that we had with the peripheral samples were repeated with central samples, and it was very difficult to interpret the pre-incision hormone profiles (which were only peripheral) in the context of a centrally drawn mid-crisis and closing serotonin level, and, of course, repeat that with the other hormones. So, we had a lot of difficulty interpreting the exact role of the central venous level and these were all peripheral values that were reported.

Dr Mira Milas (Phoenix, AZ): Recently in the anesthesia literature, it has come to light that lisinopril and ACE inhibitors can cause a profound hypotensive episode in combination with some anesthetics, so that those medications are now being scrutinized to a high degree in order to prevent patient complications.

So, as you try to understand the mechanism of this, did you look at anesthetic combinations? Did you look at preoperative patient medications, or anything else that would be coexistent with these biomarkers and their patterns that could be contributing?

Dr Kristen E. Limbach: Thank you, Dr Milas, for that excellent question. We did look at anesthetic types and found no differences. Most of our patients had propofol. Very few had an inhaled anesthetics or anything like that, so we really did not find anything in particular in terms of differences between the groups there.

We did not analyze the baseline medication profiles. In prior studies, we had not seen any difference there, so we did not make that a priority. It's something that would be interesting to look at for the future.