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## ORIGINAL INVESTIGATION

# Hemodynamic course during ablation and selective hepatic artery embolization for metastatic liver carcinoid: a retrospective observational study 

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## KEYWORDS

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Serotonin


#### Abstract

Background: Manipulation of carcinoid tumors during ablation or selective hepatic artery embolization (transarterial embolization, TAE) can release vasoactive mediators inducing hemodynamic instability. The main aim of our study was to review hemodynamics and complications related to minimally invasive treatments of liver carcinoids with TAE or ablation. Methods: Electronic medical records of all patients with metastatic liver carcinoid undergoing ablation or TAE from 2003 to 2019 were abstracted. Noted were severe hypotension (mean arterial pressure [MAP] $\leq 55 \mathrm{mmHg}$ ), severe hypertension (systolic blood pressure $\geq 180 \mathrm{mmHg}$ ), and perioperative complications. Associations of procedure type and pre-procedure octreotide use with intraprocedural hemodynamics were assessed using linear regression. A robust covariance approach using generalized estimating equation method was used to account for multiple observations. Results: A total of 161 patients underwent 98 ablations and 207 TAEs. Severe hypertension was observed in 24 ( $24.5 \%$ ) vs. 15 ( $7.3 \%$ ), severe hypotension in 56 ( $57.1 \%$ ) vs. 6 (2.9\%), and cutaneous flushing observed in $2(2.0 \%)$ vs. $48(23.2 \%)$ ablations and TAEs, respectively. After adjusting for preprocedural MAP, ablation was associated with lower intraprocedural MAP compared to TAE (estimate $-27 \mathrm{mmHg}, 95 \% \mathrm{Cl}-30$ to $-24 \mathrm{mmHg}, p<0.001$ ). Intraprocedural declines in MAP were not affected by preprocedural use of octreotide ( $p=0.7$ for TAE and $p=0.4$ for ablation).


[^0]Conclusions: Ablation of liver carcinoids was associated with substantial hemodynamic instability, especially hypotension. In contrast, a higher number of TAE patients had cutaneous flushing. Preprocedural use of octreotide was not associated with attenuation of intraprocedural hypotension.
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## Introduction

Carcinoids are neuroendocrine tumors that arise from enterochromaffin cells in the small bowel and are notable for the secretion of vasoactive amines (e.g., serotonin), prostaglandins, and vasoactive peptides. ${ }^{1,2}$ These substances are cleared in the hepatic circulation, but if the tumor metastasizes to the liver, they can enter the systemic circulation resulting in carcinoid syndrome with cutaneous flushing, diarrhea, bronchospasm, hypotension, hypertension, and right-sided heart failure. ${ }^{2,3}$ Chronic release of vasoactive amines can induce tricuspid and pulmonary valve thickening resulting in regurgitation or stenotic valve dysfunction.

Octreotide, a somatostatin analog, used for symptomatic treatment of carcinoid, ${ }^{2}$ has an anti-secretory effect on carcinoid tumor cells, and inhibits the release of serotonin and histamine. ${ }^{4}$ These mechanisms have been reported to reduce symptoms of flushing, diarrhea, and bronchospasm. ${ }^{2,5}$ However, chronic (home) use of octreotide is ineffective at preventing perioperative carcinoid crisis. ${ }^{6}$ Minimally invasive cytoreductive procedures (cryo-, radiofrequency, ethanol ablations, or selective hepatic artery embolization (transarterial embolization, TAE) are used to reduce tumor burden of carcinoid liver metastases. The indication for a specific procedure is based on tumor characteristics, notably size and multiplicity. Tumor manipulation during these procedures may incite the release of vasoactive substances triggering hemodynamic instability and carcinoid crisis. ${ }^{2,7}$ Intraprocedural hemodynamics has been infrequently described during minimally invasive treatment of metastatic carcinoid to the liver. ${ }^{6,8}$

The mechanism of cytoreductive tissue destruction differs between the ablation and TAE which may cause variable mediator release with differential symptomatology. We hypothesize that treatment of larger tumors, with TAE, will be associated with more hemodynamic volatility compared to ablation typically used for smaller hepatic carcinoid lesions. We also hypothesized that chronic octreotide use would not reduce the rate of intraprocedural hemodynamic volatility. The main aim of our study is to review hemodynamics and complications related to minimally invasive treatments of liver carcinoids.

## Methods

This study was approved by the Institutional Review Board and was conducted in compliance with the Health Insurance Portability and Accountability Act (IRB number 19-003192,
approved by Ellen R Olson, April 11, 2019). In compliance with State Statute 144.335, we included only patients who provided written authorization for research use of their medical records. The present study conforms to the requirements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

## Study design and patient selection

This was a single-center retrospective study of all consecutive patients treated from January 1, 2003, until April 11, 2019. The procedural logs of the Department of Radiology were interrogated to identify all cases of minimally invasive procedures used to treat metastatic carcinoid to the liver. All patients had a diagnosis of metastatic hepatic carcinoid by our hospital's oncologists. In our institution, percutaneous ablations are performed for more limited hepatic disease and tumors amenable to needle ablation; the number of lesions treated with this approach is based not only on size ( $<3-4 \mathrm{~cm}$ ) but also on location and underlying liver function. TAE is performed for large and innumerable metastases not amenable to ablation, and when anatomic location prohibits percutaneous ablation (adjacent to the gallbladder, central tumors, exophytic metastasis abutting an adjacent organ [colon, small bowel, kidney, etc.]) (Fig.1).

## Anesthetic and hemodynamic management

All ablation procedures are done under general anesthesia. The typical general anesthesia used in our radiology department is induction with propofol and succinylcholine followed by maintenance with inhalational agent (sevoflurane or desflurane). Hemodynamic instability, hypotension is usually treated with ephedrine (if the heart rate is low) or phenylephrine, and very infrequently vasopressin (1 unit. $\mathrm{mL}^{-1}$ ) which is reserved for the subset of hypotensive patients who are chronically treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Excessive hypertension is treated with deepening anesthetic levels, and adrenergic blockade, usually labetalol. Patients under monitored anesthesia care (universally used in present report for TAE) are sedated with propofol infusion, with or without midazolam and divided doses of fentanyl.

## Data ascertainment

Medical, radiological, and anesthesia records were manually abstracted to retrieve data on demographics, comorbid conditions and specifics regarding the carcinoid disease:


Figure 1 A, Digital subtraction angiographic image obtained prior to embolization shows bulky enhancing hepatic neuroendocrine metastases in the liver (arrows); B, Coronally-reformatted computer tomography image shows a subtle 1.8 cm neuroendocrine metastasis inferiorly in the right hepatic lobe (arrow) before microwave ablation and C) Hypoenhancing ablation defect following microwave ablation.
tumor characteristics and neuroendocrine activity (assessed from urinary 5 -hydroxyindoleacetic acid [5-HIAA], carcinoid symptoms/signs), chronic octreotide (use of octreotide at home before procedure due to symptomatic carcinoid disease), and carcinoid related medical conditions (carcinoid heart disease). The procedural course was abstracted for data regarding the hemodynamic course (preprocedural, highest and lowest intraprocedural blood pressures, and heart rate), cutaneous flushing, bronchospasms, and other complications. Severe hypotension was defined as mean arterial blood pressure (MAP) $\leq 55 \mathrm{mmHg}$, and severe hypertension as systolic blood pressure (SBP) $\geq 180 \mathrm{mmHg}$. These specific blood pressure values have associated with unfavorable outcomes in patients undergoing non-cardiac surgery. ${ }^{9,10}$ Recovery following procedure was reviewed for all complications, including episodes of severe hypertension and hypotension. Anesthesia records were reviewed for notes of cutaneous flushing, bronchospasm, or bronchodilators use. Hospital length of stay, intensive care unit admissions, 30-day hospital readmissions, and 30-day mortality were also noted.

## Statistical analyses

Categorical data are presented as number (percentage of patients), and continuous data as mean (standard deviation) or median (interquartile range). We used three regression analyses to describe three aims. First, we assess the association between procedure (ablation vs. TAE) and lowest intraprocedural MAP using a linear regression model adjusted for preprocedural MAP. As some subjects had multiple procedures in our data, a robust covariance approach using generalized estimating equation (GEE) method was used to account for the correlation of multiple observations within patients. Second, we assess the association between chronic octreotide and lowest intraprocedural MAP using linear regression with GEE. For this model, the explanatory variables were chronic octreotide and procedure type, and we also adjusted for preprocedural MAP. The procedure type by octreotide interaction effect was also included in the model to assess whether there is evidence of a differential relationship between octreotide and lowest MAP between procedure types. Finally, in our third model, we describe

Table 1 Characteristics at the time of first treatment with either ablation of TAE.

| Characteristic | Ablation $\mathrm{n}=77$ | TAE $\mathrm{n}=8$ |
| :--- | :--- | :--- |
| Age, years | $60.7(11.2)$ | $62.7(11.0)$ |
| Male sex | $39(50.6)$ | $44(52.4)$ |
| Body mass index, kg.m ${ }^{-2}$ | $28.5(6.0)$ | $27.4(7.1)$ |
| Comorbidities |  |  |
| Hypertension | $25(32.5)$ | $34(40.5)$ |
| Diabetes | $14(18.2)$ | $17(20.2)$ |
| Asthma | $4(5.2)$ | $6(7.1)$ |
| Preoperative blood pressure, mmHg |  |  |
| Systolic | $144(21)$ | $133(20)$ |
| Diastolic | $79(13)$ | $74(12)$ |
| Mean | $100(14)$ | $94(12)$ |
| Carcinoid features |  | $52(61.9)$ |
| Primary tumor | $58(75.3)$ | $10(11.9)$ |
| Small bowel | $10(13.0)$ | $8(9.5)$ |
| Lung | $3(3.9)$ | $2(2.4)$ |
| Pancreas | $4(5.2)$ | $1(1.2)$ |
| Rectum | $1(1.3)$ | $0(0.0)$ |
| Gastric | $1(1.3)$ | $1(1.2)$ |
| Renal | 0 | $10(11.9)$ |
| Ovary | 0 | $31(88.6)$ |
| Not reported | $25(51.0)$ | $5.8(4.3,8.9)$ |
| Urinary 5-HIAA > 10 mg/24 h | $2.1(1.5,3.2)$ | $7(8.3)$ |
| Largest tumor diameter, cm |  |  |
| Hypoalbuminemia | $3(3.9)$ | $9(10.7)$ |
| Heart involvement |  | $6(7.1)$ |
| Carcinoid heart disease | $2(2.6)$ | $4(4.8)$ |
| Tricuspid valve regurgitation | $1(1.3)$ | $6(7.1)$ |
| Pulmonary valve regurgitation | $1(1.3)$ | $7(8.3)$ |
| Right heart failure | $0(0.0)$ | $4(4.8)$ |
| Left ventricular dysfunction | $2(2.6)$ | $73(86.9)$ |
| Left-sided heart valve dysfunction |  |  |
| Preprocedure treatments-medical | $0(0.0)$ | $1(1.2)$ |
| Octreotide | $23(29.9)$ | $5(6.0)$ |
| Cyproheptadine | $0(0.0)$ | $128(61.8)$ |
| Chemotherapy | $0(0.0)$ | $17(8.2)$ |
| Prior surgeries/invasive treatments | $42(42.9)$ | $78(37.7)$ |
| Ablation or embolization | $14(14.3)$ |  |
| Lung resection | $66(67.4)$ |  |
| Small bowel resection |  |  |

5-HIAA, 5-hydroxyindoleacetic acid; TAE, transarterial embolization.
Data presented as mean (standard deviation), median (interquartile range), or number (percentage).
${ }^{\text {a }}$ This represents the measurement of the largest tumor in the liver (if multiple tumors the largest is reported).
${ }^{b}$ Includes moderate-severe aortic valve regurgitation with moderate mitral valve regurgitation ( $n=1$ ), moderate-severe mitral valve regurgitation $(n=2)$, severe mitral stenosis $(n=1)$.
the association between preprocedural and lowest intraprocedural MAP using linear regression with GEE. The model also included terms for procedure type and the procedure type by octreotide interaction effect. Results for all linear regression models are summarized using the linear estimate of the conditional mean difference (for example, in the first model, the estimated mean difference in lowest MAP for ablation patients vs. TAE patients, conditional on preprocedural MAP); 95\% confidence intervals and $p$-values. In all cases, a $p$-value of $<0.05$ was used to denote statistical sig-
nificance. Analyses were performed with SAS (SAS Institute, Cary, NC) and R statistical package (The R Foundation).

All available subjects were used for the analysis and a power calculation was not performed a priori. However, a sample size of 300 total independent observations, 100 ablation and 200 TAE, would provide $90 \%$ power to detect a difference of 4.8 mmHg in lowest intraprocedural MAP, based on a two-sided two-sample $t$-test with unequal variances and assuming a standard deviation of 12 mmHg in each group.


Figure 2 Clinical and hemodynamic characteristics in patients with metastatic liver carcinoid undergoing ablation or transarterial embolization. Symptomatic patients who were receiving chronic (home) octreotide, and patients who experienced severe intraprocedural hypotension, hypertension, and flushing. MAP, mean arterial pressure; SBP, systolic blood pressure.

## Results

During the study timeframe, 161 patients underwent ablation ( 77 patients $\mathrm{n}=98$ treatments) or TAE ( 84 patients $\mathrm{n}=207$ treatments) to treat metastatic liver carcinoid tumors. Three patients underwent both types of procedures, and ablation was the first procedure for all cases. Of the 77 patients undergoing ablation, 61 had one, 10 had two, and 6 patients had $\geq$ three ablation procedures, and the 84 patients undergoing TAE, 24 had one, 30 had two, and 30 had $\geq 3$ TAE procedures.

Table 1 summarizes patient and disease characteristics at the time of the first procedure. Ablations were performed in patients with multiple lesions (median [25th, 75th percentile] number of tumors was $3^{2,5}$ ), and TAE for more extensive lesions not amenable to ablation (Fig. 1, Table 1). In addition, patients undergoing TAE had a higher prevalence of carcinoid heart disease and were more likely on chronic octreotide.

Table 2 summarizes procedural characteristics for all performed procedures. Of the 98 ablation procedures, 67 (68.4\%), 23 ( $23.5 \%$ ), 4 ( $4.1 \%$ ), and 4 ( $4.1 \%$ ) were performed using radiofrequency, radiofrequency + ethanol, ethanol alone, and microwave ablations, respectively. Reflecting higher tumor burden, patients undergoing TAE were more often receiving chronic octreotide at the time of the procedure, ( $88.4 \%$ vs. $34.7 \%$ in TAE vs. ablation, respectively, Table 2, Figure 2. All ablations were performed under general anesthesia, while all (except one) TAEs were performed under moderate sedation. Flushing was observed, and intraoperative octreotide was administered more frequently during TAE procedures than ablations (Table 2, Fig. 2).

## Blood pressures during procedures

Hemodynamic instability (hypertension and hypotension) was more frequent during ablations than TAE (Fig. 3), also
evidenced by more frequent administration of vasoactive medications (phenylephrine and ephedrine) and greater administration of fluids (Table 2). Severe hypertension was recorded during 24 (24.5\%) and 15 (7.3\%), and severe hypotension in 56 ( $57.1 \%$ ) vs. 6 ( $2.9 \%$ ) ablation and TAE procedures, respectively (Fig. 2).

Lowest intraprocedural MAP among ablations was mean ( $\pm$ standard deviation) 54 (11) mmHg , and among TAE $78( \pm 12) \mathrm{mmHg}$. After adjusting for preprocedural MAP, ablation was associated with lower intraprocedural MAP compared to TAE (estimate $-27 \mathrm{mmHg}, 95 \% \mathrm{Cl}-30$ to $24 \mathrm{mmHg}, p<0.001$, Fig. 3). Chronic use of octreotide was not associated with lowest intraproceduralMAP for either procedure type (estimate $-1 \mathrm{mmHg}, 95 \% \mathrm{Cl}-5$ to +3 mmHg , $p=0.7$ for TAE, and $2 \mathrm{mmHg}, 95 \% \mathrm{Cl}-2$ to $+6 \mathrm{mmHg}, p=0.4$ for ablation). The estimated association between chronic octreotide and lowest MAP did not differ between procedure types (interaction $p=0.3$ ).

A secondary analysis was performed to examine the relationship between preprocedure and the lowest intraprocedural MAP. A higher preprocedure MAP was found to be associated with a larger intraprocedural MAP decline, and this association differed according to the procedure type (interaction $p<0.001$ ) in this analysis. Specifically, for each 10 mmHg increase in preprocedure MAP, the nadir intraprocedural MAP decreased by $4 \mathrm{mmHg}, 95 \% \mathrm{Cl} 3$ to 6 mmHg in TAE group, and $9 \mathrm{mmHg}, 95 \% \mathrm{Cl} 7$ to 10 mmHg in ablation group (both, $p<0.001$, Fig. 4).

## Other complications

The overall rate of postoperative complications rate was 9.5\% (29 out of 305 treatment sessions). In this cohort, only one bronchospasm was recorded ( $0.3 \%$ ). The most severe complication, bleeding, occurred in 7 patients (2.3\%). One patient developed a hepatic artery to common bile duct fistula with subsequent biliary hemorrhage requiring coil embolization. Another had intrahepatic hemorrhage requiring embolization. Three patients developed subcapsular hematomas, two of which required coil embolization for hemostasis. One patient developed a hematoma at the site of arterial puncture that resolved with manual pressure. One patient, a 73-year-old woman, developed severe retroperitoneal hemorrhage secondary to arterial puncture leading to hypovolemic shock and multi-organ failure, and eventual death. Another patient died, a 78 -year-old man, who was transferred to hospice care in the setting of advanced carcinoid disease.

## Discussion

We report the hemodynamic course of 161 patients with metastatic liver carcinoid undergoing 305 TAE or ablation procedures. The most important finding was that patients undergoing ablation compared to TAE had more hemodynamic volatility, especially hypotension. Also, the chronic use of octreotide was not associated with a reduction of hemodynamic volatility in either cytoreductive procedure type.

Indications for ablation vs. TAE for metastatic liver carcinoid depend on tumor characteristics: ablation is indicated

Table 2 Periprocedural course and complications for 305 minimally invasive cytoreductive procedures of metastatic liver carcinoid.

| Characteristics | Ablation $\mathrm{n}=98$ | TAE $\mathrm{n}=207$ |
| :---: | :---: | :---: |
| Preprocedural |  |  |
| Chronic octreotide treatment | 34 (34.7) | 183 (88.4) |
| Intraprocedural |  |  |
| Duration of surgery, minutes | 151 (112, 215) | 116 (92, 136) |
| Number of treated tumors | $3(2,5)$ | Extensive, single location |
| Type of anesthesia |  |  |
| General anesthesia | 98 (100.0) | 1 (0.5) |
| MAC + sedation | 0 | 206 (99.5) |
| Medications and fluids |  |  |
| Octreotide | 14 (14.3) | 72 (34.8) |
| Phenylephrine | 46 (46.9) | 4 (1.9) |
| Ephedrine | 44 (44.9) | 1 (0.5) |
| Crystalloid, Liters | 1.0 (0.6, 1.3) | $0.5(0,0.9)$ |
| Colloid | 4 (4.1) | 0 (0.0) |
| Events/complications |  |  |
| Cutaneous flushing ${ }^{\text {a }}$ | 2 (2.0) | 48 (23.2) |
| Bronchospasm | 0 (0.0) | 1 (0.5) |
| Hypertension, SBP $\geq 180 \mathrm{mmHg}$ | 24 (24.5) | 15 (7.3) |
| Hypotension, MAP $\leq 55 \mathrm{mmHg}$ | 56 (57.1) | 6 (2.9) |
| Bradycardia, HR $\leq 50 \mathrm{bpm}$ | 50 (51.0) | 37 (17.9) |
| Tachycardia, HR > 100 bpm | 33 (33.7) | 14 (6.8) |
| Postprocedural |  |  |
| Hospital length of stay, days | $1(1,1)$ | $1(1,2)$ |
| Any complications ${ }^{\text {b }}$ | 10 (10.2) | 19 (9.2) ${ }^{\text {b }}$ |
| Hypertension, SBP $\geq 180 \mathrm{mmHg}$ | 1 | 8 |
| Hypotension, MAP $\leq 55 \mathrm{mmHg}$ | 1 | 1 |
| Cutaneous flushing | 0 | 3 |
| Cardiac dysrrhytmia ${ }^{\text {c }}$ | 1 | 3 |
| Bleeding ${ }^{\text {d }}$ | 5 | 2 |
| Mental status changes | 0 | 2 |
| Pneumonia | 0 | 1 |
| Sepsis | 1 | 1 |
| Bowel obstruction | 1 | 1 |
| Intensive care unit admission | 2 (2.0) | 5 (2.4) |
| 30-day readmission | 3 (3.1) | 8 (3.9) |
| 30-day mortality | 0 | 2 (1.0) |

SBP, systolic blood pressure; MAP, mean arterial pressure; MAC, monitored anesthesia care; HR, heart rate; bpm, beats per minute. Data presented as number (percentage) and median (interquartile range).
${ }^{\text {a }}$ All 48 flushing episodes in TAE were in patients on chronic octreotide, 2 flushing episodes in ablation group were in patients who were not on home octreotide.
b 'Any complication' corresponds to the number (\%) of patients who had a complication, and in this category patients with multiple complications are counted once.
c Cardiac dysrhythmia included bradycardia ( $\mathrm{n}=2$ ) and tachyarrhythmia $(\mathrm{n}=2)$.
${ }^{d}$ In 5 patients bleeding episodes associated with ablation were hepatic ( $n=5$ ); two bleeding episodes associated with TAE was retroperitoneal and access site (groin).
for smaller tumors and TAE for larger and more extensive ones. Large carcinoids are more likely to be clinically symptomatic, as evidenced by more frequent use of chronic octreotide among TAE patients. All these elements can theoretically affect procedural hemodynamics. First, the mechanism of cytoreduction differs between procedures. TAE interrupts tumor blood supply causing ischemia with gradual cell disintegration; this results in slower release of vasoactive mediators. In contrast, ablation induces instant carcinoid cell lysis resulting in abrupt mediator release. ${ }^{11}$ Second, radiofrequency ablation can induce life-threatening
hypertensive crises during treatment of lesions other than neuroendocrine tumors. ${ }^{12}$ Third, all patients undergoing ablation require general anesthesia, while moderate sedation is often sufficient for TAE, and these differences in anesthetic management could independently contribute to hemodynamic outcomes.

In this cohort, ablation of liver carcinoids, compared to TAE, was more frequently associated with hemodynamic instability, especially hypotension. Hemodynamic volatility was 'procedure-specific,' i.e., severe hypotension was recorded in $57.1 \%$ vs. $2.9 \%$, and severe hypertension in $24.5 \%$
vs. $7.3 \%$, during ablation and TAE, respectively. The intraoperative decline in MAP was dependent on preprocedural MAP, and interestingly higher preprocedural MAPs resulted in more profound pressure declines (Fig. 4). Finally, although octreotide attenuates carcinoid symptoms, ${ }^{2}$ in this cohort, its chronic use was not associated with attenuation of procedural hypotension. Two previous retrospective studies have also suggested that octreotide may not be effective in preventing carcinoid crisis/symptoms; ${ }^{1,13}$ therefore, there is still a need for a randomized controlled trial to confirm or refute the role of chronic octreotide on procedural hemodynamics.

Kwon ${ }^{6}$ reviewed outcomes of 75 ablations, surgical resections with ablations, and TAE for liver carcinoid. Similar to our study, they reported that TAE patients had higher carcinoid burden compared to ablation patients, and fewer ablation patients received chronic octreotide ( $13 \%$ vs. $63 \%$, $p<0.05)$. Also, similarly to our observation, Kwon6 reported that over 30\% of patients experienced procedure-specific hemodynamic instability, i.e., they reported a trend for lower rates of hemodynamic instability during TAE (22\%) compared to surgical resection and/or ablation (42\%).

In the TAE group, chronic octreotide was used in 73 patients undergoing 183 procedures, and 48 procedures were complicated by cutaneous flushing (all affected patients were on chronic octreotide). In the ablation group, 23 patients who underwent 34 (88.4\%) treatments were medicated with chronic octreotide, but flushing was reported in only two patients, neither who were on chronic octreotide. There was no meaningful overlap between flushing and hypotension. Out of 50 patients who had flushing, only $4(8 \%)$ had severe hypotension. This suggests that different vasoactive mediators can be released during minimally invasive carcinoid cytoreduction, as well that they likely


Figure 3 Mean arterial pressures (MAP) before procedure and highest and lowest intraprocedural MAPs. Box indicates interquartile range; middle line, median; error bars, $1.5 \times$ interquartile. After adjusting for preprocedural MAP, ablation was associated with lower intraprocedural MAP compared to TAE (estimate $-27 \mathrm{mmHg}, 95 \% \mathrm{Cl}-30$ to $-24 \mathrm{mmHg}, p<0.001$ ).
act through separate vasomotor receptors resulting in either cardiovascular instability or flushing, and in our series simultaneous presence was rare.

## Procedural complications

The overall rate of perioperative complications was similar in patients undergoing ablation vs. TAE. After the procedure was completed, eight TAE patients developed severe hypertension; however, it remains unclear whether this could be attributed to delayed release of vasoactive mediators or pathophysiology of preexisting hypertension. In one


Figure 4 Association between preprocedural and lowest intraprocedural mean arterial pressure during ablation and transarterial embolization. For both procedures $p<0.001$ (linear regression model with general estimating equation analysis to account for repeated procedures).
case series, a number of patients after TAE experienced delayed fever, nausea, and abdominal pain, which lasted 48-72 hours. ${ }^{14}$ Furthermore, Fujie ${ }^{7}$ reported delayed carcinoid crisis 24 hours after TAE. These two reports suggest possible carcinoid symptomatology related to a delayed release of mediators following TAE. Bleeding due to subcapsular, retroperitoneal, or puncture site hematoma is a known risk following minimally invasive cytoreductive procedures. In our case series, the rate of bleeding was similar (2.3\%) to that reported after percutaneous hepatic radiofrequency ablations for any tumor type (2-6\%). ${ }^{15,16}$

Our study has several limitations. We report procedural hemodynamics for a large series of patients undergoing minimally invasive cytoreductive procedures for metastatic liver carcinoids. Extremes of blood pressure and heart rate were accurately retrieved from the electronic anesthesia records. This report has all limitations related to its retrospective design. We report a heterogeneous cohort that received different procedural and anesthetic management, which contributed to an inability to precisely separate the treatment modality (ablation vs. TAE) from anesthetic technique (general anesthesia vs. moderate sedation) effects. Furthermore, the reports of cutaneous flushing were reliant on provider documentation: patients are supine during TAE. Their face is easily observable for signs of flushing, while ablations are frequently performed in the lateral decubitus position, which could obscure observations and contribute to underreporting of this complication. Finally, only one patient had documentation of bronchospasm and received albuterol. Bronchospasm is a known part of carcinoid syndrome; thus, the low documentation frequency in this cohort raises concerns of under-reporting. However, documentation of medication use is reliable, and no other patient received bronchodilators, a surrogate indicator for bronchospasm. Therefore, we believe that the low bronchospasm rate in the present case series is accurate.

In conclusion, hemodynamics during cytoreductive procedures for hepatic carcinoid is dependent on the type of procedure, rather than tumor baseline neuroendocrine activity and associated clinical symptomatology: ablation was more frequently associated with hemodynamic volatility especially hypotension and TAE with flushing. The use of octreotide before the procedure, prescribed for symptomatic carcinoid, did not reduce intraprocedural hemodynamic volatility.

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## Conflicts of interest

Dr. Weingarten currently serves as a consultant to Medtronic in the role as chairman of the Clinical Endpoint Committee for the Prodigy Trial; has received research support from

Respiratory Motion, and unrestricted investigator-initiated grants from Merck. The other authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/ j.bjane.2021.03.015.

## References

1. Massimino K, Harrskog O, Pommier S, et al. Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. J Surg Oncol. 2013;107:842-6.
2. Mancuso K, Kaye AD, Boudreaux JP, et al. Carcinoid syndrome and perioperative anesthetic considerations. J Clin Anesth. 2011;23:329-41.
3. Kahil ME, Brown H, Fred HL. The Carcinoid Crisis. Arch Intern Med. 1964;114:26-8.
4. Chalabi M, Duluc C, Caron P, et al. Somatostatin analogs: does pharmacology impact antitumor efficacy? Trends Endocrinol Metab. 2014;25:115-27.
5. O'Toole D, Ducreux M, Bommelaer G, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. Cancer. 2000;88:770-6.
6. Kwon DH, Paciorek A, Mulvey CK, et al. Periprocedural Management of Patients Undergoing Liver Resection or Embolotherapy for Neuroendocrine Tumor Metastases. Pancreas. 2019;48:496-503.
7. Fujie S, Zhou W, Fann P, et al. Carcinoid crisis 24 hours after bland embolization: A case report. Biosci Trends. 2010;4:143-4.
8. Meij V, Zuetenhorst JM, van Hillegersberg R, et al. Local treatment in unresectable hepatic metastases of carcinoid tumors: Experiences with hepatic artery embolization and radiofrequency ablation. World J Surg Oncol. 2005;3:75.
9. Varon J, Marik PE. Perioperative hypertension management. Vasc Health Risk Manag. 2008;4:615-27.
10. Wesselink EM, Kappen TH, Torn HM, et al. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth. 2018;121:706-21.
11. Yamakado K, Takaki H, Uchida K, et al. Adrenal radiofrequency ablation in swine: change in blood pressure and histopathologic analysis. Cardiovasc Intervent Radiol. 2011;34:839-44.
12. Onik G, Onik C, Medary I, et al. Life-threatening hypertensive crises in two patients undergoing hepatic radiofrequency ablation. AJR Am J Roentgenol. 2003;181:495-7.
13. Condron ME, Pommier SJ, Pommier RF. Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. Surgery. 2016;159:358-65.
14. Gupta S, Yao JC, Ahrar K, et al. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J. 2003;9:261-7.
15. Nemcek AA. Complications of radiofrequency ablation of neoplasms. Semin Intervent Radiol. 2006;23:177-87.
16. Buscarini E, Buscarini L. Radiofrequency thermal ablation with expandable needle of focal liver malignancies: complication report. Eur Radiol. 2004;14:31-7.

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