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Abstract 17500: A Crisis of the Heart

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A Crisis of the Heart

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A 59 year old female with a notable past medical history of metastatic neuroendocrine tumor (G2) was admitted for elective transarterial catheter embolization (TACE) of her liver lesions to reduce tumor bulk. Her primary malignancy was suspected of small bowel origin previously treated with resection. She did not have any signs of cardiac involvement on prior transthoracic echocardiograms. She was receiving outpatient octreotide treatments for management of carcinoid syndrome. Her symptoms included nausea, flushing, diarrhea and severe weight loss. She also was noted to have worsening fatigue and weakness per family.

During the TACE procedure, she developed hypertension up to 204/102 mmHg treated with labetalol initially, then continuous esmolol infusion with the initiation of continuous octreotide due to concern for possible carcinoid reaction. Esmolol was weaned off soon thereafter. She subsequently developed acute hypoxia with chest x-ray demonstrating new pulmonary edema compared to prior imaging (**Figure 1**). Early the following morning she had acute hypotension with systolic pressures in 50s mmHg with sinus tachycardia in 120s BPM and she was transferred to the intensive care unit for close monitoring. On exam, she was a thin woman, diaphoretic and delirious. Her cardiovascular exam demonstrated regular and tachycardic heart rate with normal cardiac sounds, no elevated jugular venous distension and no lower extremity edema. She has bilateral crackles on lung auscultation. Her exam was otherwise non-focal. Her electrocardiogram demonstrated sub-millimeter ST-segment elevations in the anterolateral leads with nonspecific T-wave changes in the lateral leads (**Figure 2**) and her troponin I level had up-trended from 2ng/dL up to 14 ng/dL. There were no dynamic changes on serial electrocardiograms. A bedside point-of-care cardiac ultrasound demonstrated severely impaired left ventricular systolic function without regional wall motion abnormalities (**Video 1**). Her blood pressures fluctuated between hypotension and hypertension requiring intermittent low dose vasopressor support with norepinephrine (up to 0.05 mcg/kg/min). With the clinical picture concerning for carcinoid crisis, the octreotide dosing was up-titrated up to 500 mcg/hr. In the setting of worsening hemodynamic changes, signs of myocardial injury, and ultrasound findings, suspicion for stress cardiomyopathy was high but the patient was taken to the catheterization lab to rule out coronary artery obstruction or dissection. Coronary angiogram findings are demonstrated in **Figure 3** showing diffuse vasospasm without a clear culprit lesion. Her left ventricular end-diastolic pressure (LVEDP) was elevated at 40 mmHg, Pulmonary arterial oxygen saturation was 25%, and her cardiac index was severely decreased at 1.42 L/min/m consistent with cardiogenic shock. Her complete right heart catheterization pressures are shown in **Table 1**. Her LVEDP improved to 15 mmHg with the initiation of afterload reduction with nitroprusside. For left

ventricular venting, a left axillary Impella device was placed. A discussion was had with endocrinology, oncology, anesthesia, cardiology, and the intensive care unit regarding medical management of carcinoid crisis and appropriate inotropic and vasopressor support considering the complex hormonal balance. She was started on stress dose steroids with hydrocortisone, famotidine and diphenhydramine for antihistamine effects, cyproheptadine for 5HIAA blockade and continued on nitroprusside for afterload reduction.

The differential diagnosis for the etiology of her cardiogenic shock included octreotide causing coronary vasospasm, endogenous catecholamine fluctuation triggering a stress cardiomyopathy, and exogenous catecholamine administration causing diffuse vasospasm. We believe this was a rare case of octreotide mediated coronary vasospasm resulting in global LV dysfunction and cardiogenic shock. Octreotide was believed the most likely culprit due to timing and up-titration correlating with worsening cardiac function (**Figure 4**). Exogenous catecholamine administration (including norepinephrine and epinephrine) can cause diffuse vasoconstriction due to alpha adrenergic activation[1]. However, this is commonly seen in cases with high dose vasopressor use, in contrast to our patient's clinical situation. Similar effects are rarely seen with dobutamine administration, although also at much higher bolus dosing[2]. Her catecholamine levels were mildly elevated, but our endocrinology colleagues were reassured that this was common with carcinoid crisis and not elevated to levels concerning for pheochromocytoma, or an endogenous catecholamine etiology. Unfortunately, octreotide was the only mainstay treatment for her carcinoid crisis, and data regarding the best approach for medically supporting her hemodynamic instability with vasopressors and inotropic agents was limited and further urged the utility of this case report.

Carcinoid syndrome is a constellation of systemic effects related to excessive hormone release by metastatic neuroendocrine tumors (NETs). The majority of NETs arise from the gastrointestinal tract with fewer originating in the pancreas[3]. They become clinically significant with liver and lung metastasis because the hormones released are not metabolized and inactivated by these involved organs. Vasoactive products associated with carcinoid syndrome include serotonin, histamine, tachykinins, kallikrein, and prostaglandins secreted by gastroenteropancreatic NETs[4]. Serotonin promotes intestinal secretion and motility and stimulates fibroblast growth which may contribute to valvular fibrosis seen in carcinoid heart disease. Histamine, kallikreins, prostaglandins and tachykinins cause a variety of vasodilatory symptoms including flushing, increased gut motility, and increased vascular permeability. Carcinoid crisis is the result of massive release of bioactive products causing hemodynamic compromise and persistent severe vasoactive symptoms. It is often precipitated by certain procedures such as hepatic biopsy, resection, and artery embolization.

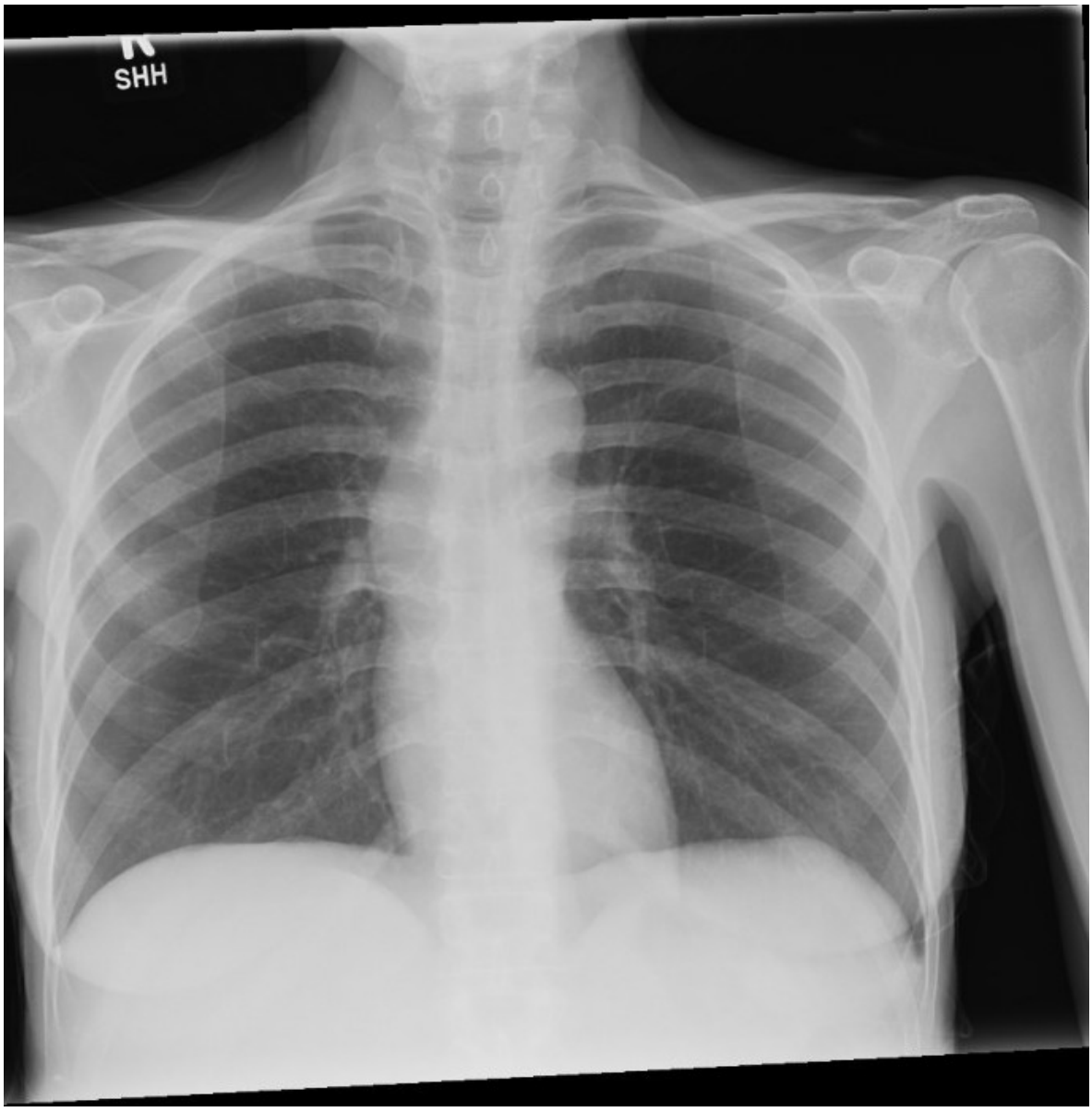
Intraoperative carcinoid crisis is thought to be catecholamine-mediated causing life-threatening hemodynamic instability, most commonly hypotensive crisis [5]. Hypertensive crisis, as seen in our patient, is rare and only seen in about 7% of cases with an unclear pathophysiology. The mainstay medical treatment of carcinoid crisis is administration of somatostatin analogues such as octreotide titrated to symptom control[6]. Somatostatin inhibits the secretion of a number of hormones and can be used in addition to histamine blockers and steroids for supportive management. Some studies have demonstrated a prophylactic utility of octreotide administration pre-op to prevent carcinoid crisis, which is now becoming common practice with the goal to minimize tumor activity prior to exposure to noxious stimuli (resulting in sympathetic activation) and traumatic hormone release during surgery[7].

Octreotide is generally very well tolerated with minimal complications unless the patient has sensitivity to octreotide or any of its components[8]. It is not associated with peripheral vasoconstriction but is commonly used in cirrhotic patients for its local splanchnic vasoconstrictive properties in the management of bleeding esophageal varices[9]. However, in the case of our patient, with the findings on coronary angiogram and fluctuating peripheral blood pressures, there was a high suspicion that preoperative and continued octreotide infusion resulted in significant coronary vasospasm. Her vasopressor support at time of coronary angiogram was minimal and unlikely to contribute, with the only relevant factor being up-trending octreotide dosing. At this point in the decision-making process, the team focused on balancing risks and benefits and attempted decreasing her octreotide dosing as tolerated (based on carcinoid symptoms) with close monitoring in the intensive care unit.

An additional point of discourse focused on appropriate vasopressor and inotropic support options. In vasoactive crisis resulting in refractory and critical hypotension, vasopressin is the preferred agent for pressor support[10]. Epinephrine carries a concern for triggering serotonin hormonal release and stimulation of the autonomic nervous system. Dobutamine and dopamine are contraindicated because of their beta agonist properties theoretically causing further sympathetic activation and propagating serotonergic activity. Norepinephrine has the capability of activating kallikrein and signaling the synthesis of bradykinin resulting in paradoxical vasodilation and resultant hypotension. Phenylephrine at low doses has minimal effect on sympathetic activation and can be attempted if needed. Inotropic and vasopressor agents, their mechanism of action, and suspected effects in carcinoid crisis are summarized in **Table 2**. Typically, volume resuscitation is another mainstay in management of carcinoid crisis, which was an additional point of concern in our patient with cardiogenic shock.

The complicated hormonal regulation and subsequent effects on peripheral vasculature in this patient highlights the importance of understanding not only the pathophysiology of the disease state and pharmacokinetics of medications involved, but also balancing theoretical concerns with available data in decision making. Oftentimes when the data is not present or strong, the most important thing that can be done is monitoring the patient closely with each titration and medication change. Our patient was supported with the help of multiple specialists who continued to have regular multidisciplinary discussions resulting in changes in her inotropic and vasopressor support (switching from dobutamine to milrinone, and titrating vasopressin). Eventually her carcinoid symptoms improved (nausea, diarrhea and flushing) and octreotide was discontinued. Her cardiogenic shock was managed with continued light diuresis and afterload reduction and eventually we were able to wean off Impella support and then off milrinone. She continued to struggle with delirium and occasional supraventricular tachycardias (likely atrial tachycardia) managed on beta blocker therapy. Her cardiac function was improved on repeat echocardiogram one month later (**Video 2**).

Figure 1: Chest X-ray on admission (a) vs. onset of hypoxia (b)

a) 

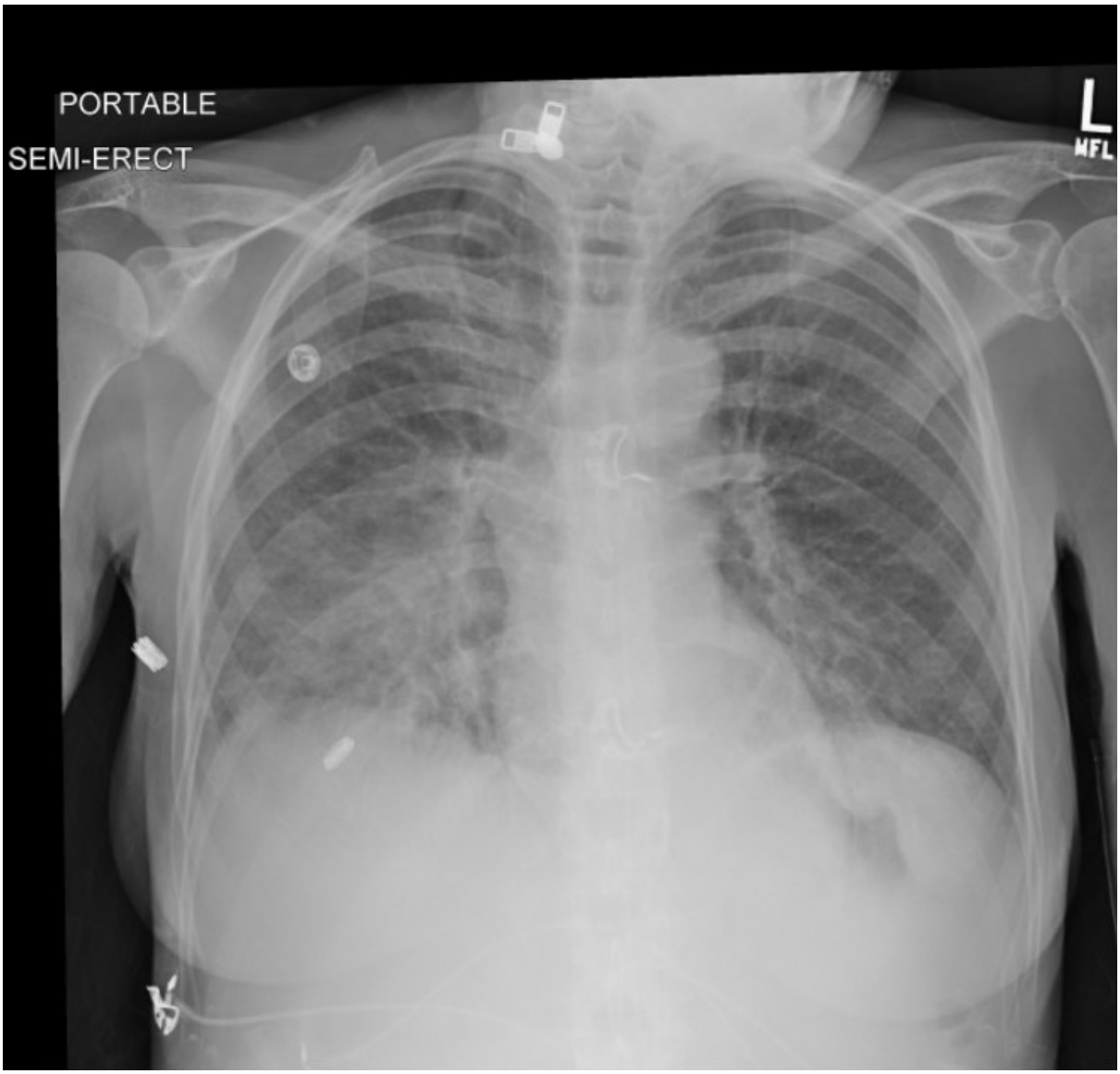
b) 

Figure 2: Electrocardiogram

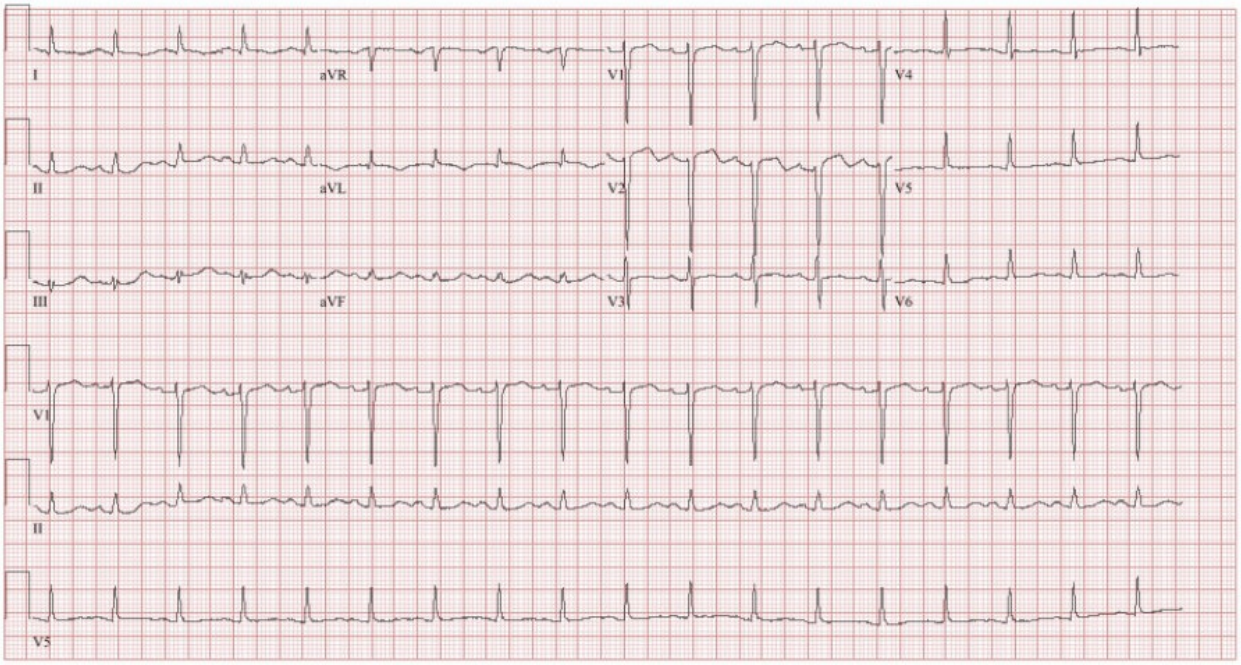


Figure 3: Right and left coronary angiogram demonstrating diffuse coronary vasospasm

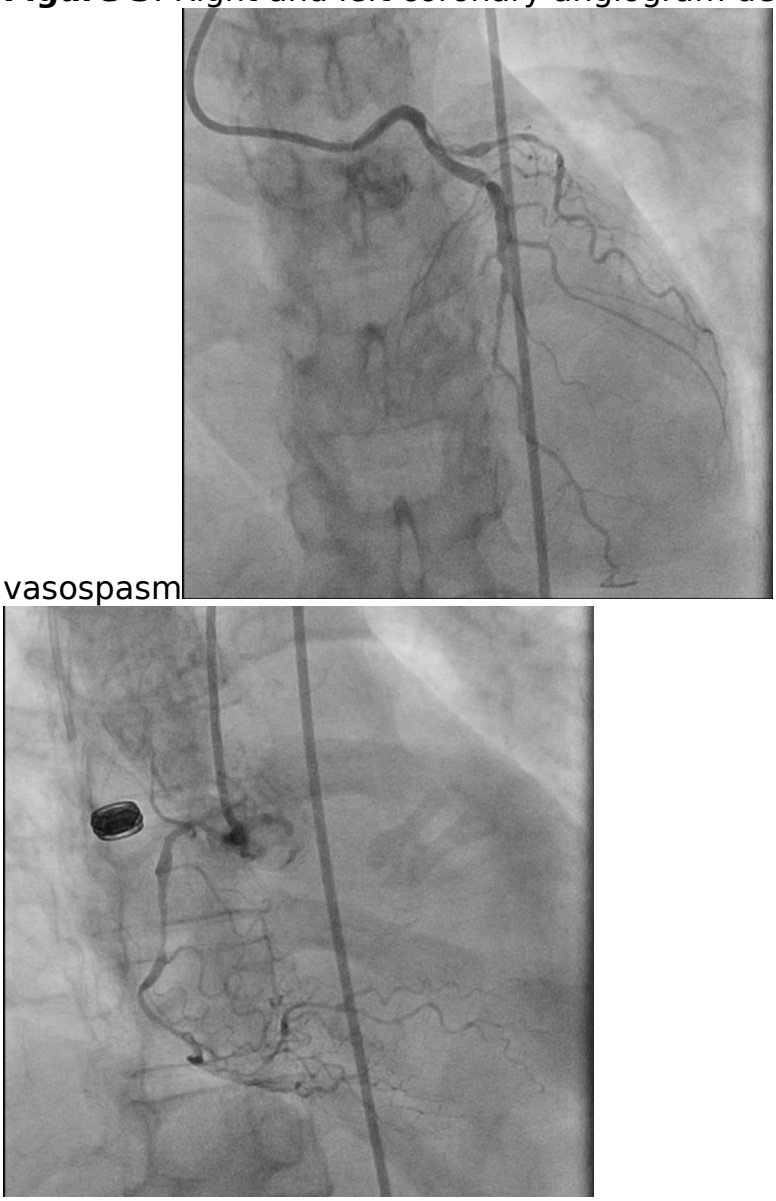


Figure 4: Timeline of infusions and hemodynamic changes

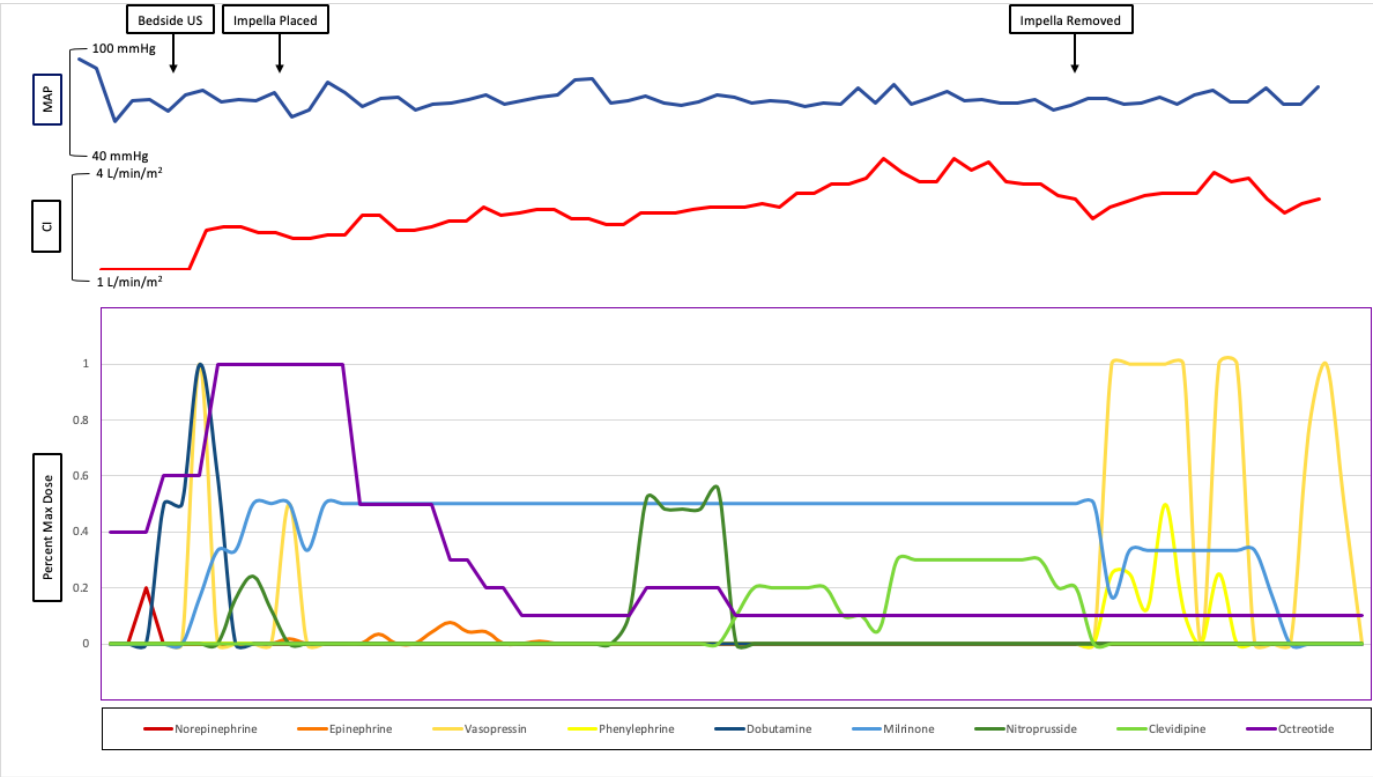


Table 1: Right Heart Catheterization Measured Pressures

Location	Pressure (Mean) mmHg	Oximetry
Arterial	91/66 (78)	100%
RA	8/7 (7)	
RV	28/9 (10)	
PA	29/19 (23)	25%
PCWP	21/21 (21)	
LV	79/6 (15)	
CO (TD)	2.1 L/min	

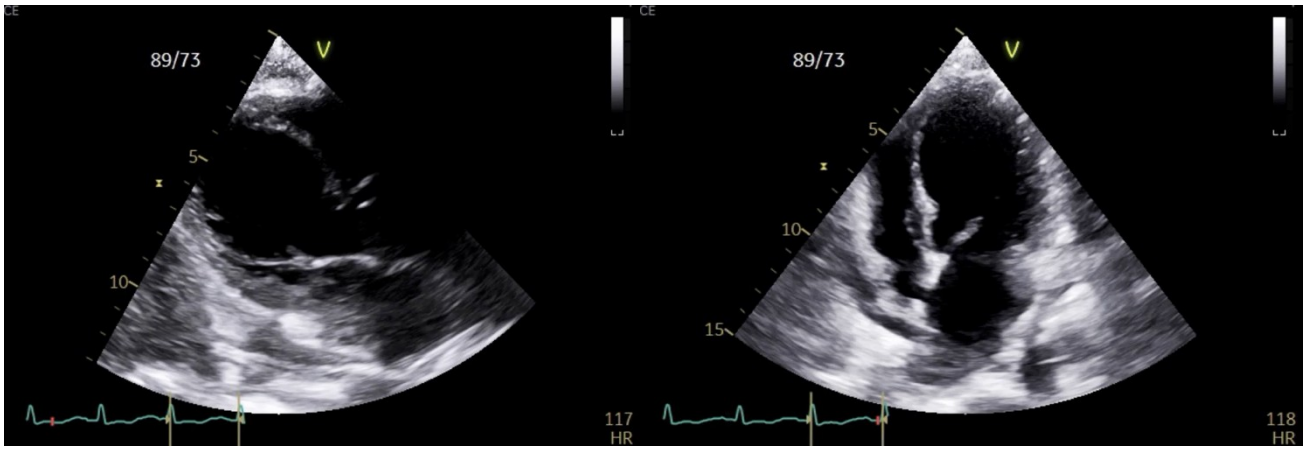
CI (TD)	1.42 L/min/m	
PVR	1.04 WU	
SVR	29.64 WU	

Table 2: Vasopressor and Inotropic Agents in Carcinoid Crisis

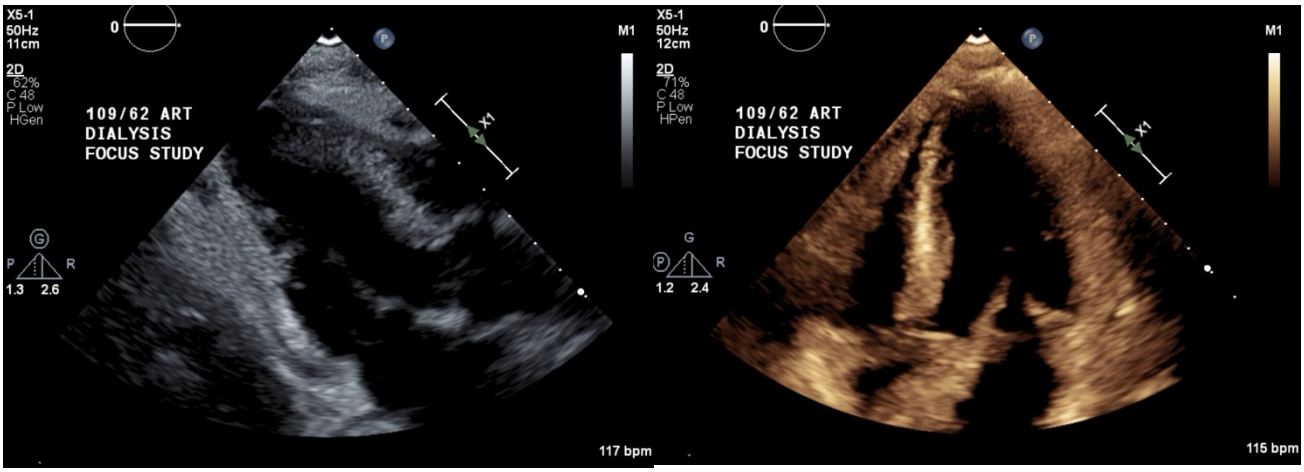
Vasopressor Support	Mechanism of Action	Effect during Carcinoid Crisis
Norepinephrine	Beta and Alpha agonist	Peripheral vasoconstriction Activate kallikrein→ vasoactive crisis
Epinephrine	Alpha and Beta agonist B1>B2	Peripheral vasoconstriction Stimulating serotonin release Stimulation of ANS
Vasopressin	Vasopressin smooth muscle receptors	Preferred agent for blood pressure support in Carcinoid Crisis
Phenylephrine	Pure Alpha-1 agonist	Increased vagal tone may oppose sympathetic activity Increases catecholamine activity
Inotropic Support		
Dobutamine	Beta agonist, B1>B2	Vasoconstriction (high doses) Direct sympathetic activation
Dopamine	Dopaminergic receptors (type 1 and 2)	Vasoconstriction (high doses) Direct sympathetic activation
Milrinone	Phosphodiesterase III inhibitor→ increased intracellular calcium→ increased myocardial contraction	Has net vasodilatory effect may precipitated vasoactive crisis
Isoproterenol	Beta agonist (nonselective)	Systemic vasodilatory effects may precipitate vasoactive crisis

Levosimendan	Calcium sensitizer to increase inotropy	Venous and arteriolar vasodilation may precipitate vasoactive crisis

Video 1: Transthoracic echocardiography demonstrating severe global LV dysfunction (parasternal long axis and four chamber views)



Video 2: Repeat transthoracic echocardiography demonstrating improved LV function (parasternal long axis and four chamber views)



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