Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

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Chapter 3

INCREASED PERIOPERATIVE CATECHOLAMINE EXCRETION IN PATIENTS WITH DISSEMINATED CARCINOID.

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Submitted

Abstract

Carcinoid tumors can produce several other biogenic amines apart from serotonin. Catecholamines such as norepinephrine, epinephrine and dopamine may contribute to carcinoid crises especially during anesthesia and surgery.

Aim of this study was to analyze the catecholamine production peri-operatively in patients with a metastatic midgut carcinoid.

Methods Sixteen metastatic carcinoid patients and seven patients undergoing pancreatic surgery were studied. All patients received octreotide before, during and after surgery. Perioperative blood samples and urine were collected. Plasma and urinary serotonin, (nor)epinephrine, dopamine and metabolites were measured. During surgery hemodynamic parameters were monitored.

Results One patient was excluded because of early post-operative norepinephrine infusion for a carcinoid crisis. Eleven patients were especially monitored before during and after manipulation of the tumor. Five of these 11 carcinoid patients experienced a 25% drop in mean arterial pressure; the other six patients were stable. Besides serotonin no elevated plasma levels of other amines were found in carcinoid patients before, during and after surgery. However the mean urinary excretion of epinephrine, dopamine and serotonin were all markedly increased in carcinoid patients compared to the control group (respectively 20 times: $p<0.007$; 15 times: $p<0.001$; 80 times: $p<0.001$).

Conclusion In patients with metastatic carcinoid disease peri-operative urine levels of catecholamine and its metabolites are markedly elevated compared to controls, suggesting high levels of plasma catecholamines. However, in the presence of octreotide this did not threaten hemodynamic stability.

Introduction

Carcinoid tumors are endocrine neoplasms derived from the enterochromaffin cells. They are usually classified according to their site of origin into carcinoids of the foregut (respiratory tract, stomach, duodenum and pancreas), midgut (small bowel, cecum and appendix) and hindgut (colon and rectum).[1,2] Because of their presumed embryological origin from neuronal entoderm and their ability to take up and decarboxylate amine precursors, carcinoids are referred to as "gut APUDomas". The APUD (amine precursor uptake and decarboxylation) concept points out the ability of cells to synthesize and store biogenic amines and polypeptides. Tumors arising from the APUD system resemble histologically and functionally (endocrine properties) the cells from which they arose[3]. Catecholamines production by carcinoids has been studied rather limited. Goedert et al demonstrated substantial amounts of both dopamine and norepinephrine in addition to serotonin in a mesenteric metastasis of an ileal carcinoid tumor and the presence of the norepinephrine- synthesizing enzymes in the tumor.[4] Moreover, Feldman found in 35% and Kema et al in 38% of serotonin producing carcinoid patients increased plasma levels of dopamine, norepinephrine, epinephrine and their principle urinary metabolites.[5-8] There are however no data available concerning the extent of this production and the effects on the clinical situation during stressful situations such as surgery. A carcinoid crisis is a much feared peri-operative complication.

Aim of this study was to analyze the catecholamine production peri-operatively in patients with a metastatic midgut carcinoid.

Methods

Eligible were all patients with a histologically proven, disseminated midgut carcinoid, undergoing laparotomy because of carcinoid related problems from September 1998 till January 2000 in the University Medical Center in Groningen. The research protocol did not interfere with the scheduled treatment. The control group consisted of non-carcinoid patients who were scheduled for pancreatic surgery. The study was approved by the medical ethical committee of the University Medical Center Groningen. All patients gave informed consent.

All patients (controls included) received octreotide 100 μg 3 times a day subcutaneously starting three days before, till at least four days after surgery. The patients got an intravenous line the evening prior to surgery for overnight infusion with glucose/saline (individualized volumes) to compensate for fasting.

Anesthesia was performed according to routine procedures. There were no imperative guidelines regarding the use of epidural techniques or management

of circulatory instability. Besides a trial dose to assess the proper position of the catheter, patients did not receive epidural local anesthetics during surgery. The hemodynamic parameters were monitored using the arterial pressure before, during and after the operation in order to reveal the occurrence of hemodynamic instability, as one of the features of carcinoid crisis. Respiratory data (O_2 saturation, respiratory pressure) were monitored for signs of bronchoconstriction.

Patients received no dietary restriction other than those required before and after surgery. Twenty-four-hour urine was collected in polypropylene bottles during 5 days, starting one day before until 3 days after surgery. After volume measurement, samples were obtained to which $Na_2S_2O_5$ and EDTA were added. Samples were acidified with acetic acid and then frozen at –20°C. Starting of the urine collection was scheduled 24 hr prior to the time of surgery. Analyzed were: 5-hydroxyindolacetic-acid (5-HIAA), serotonin, total (free and conjugated) catecholamines (epinephrine, norepinephrine, dopamine) and free (unconjugated) catecholamine metabolites (metanephrine, normetanephrine, 3-methoxy tyramine vanillylmandelic acid (VMA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)).

Blood samples were collected every morning during 4 days, using EDTA Vacutainers tubes (6 and 10 ml) starting the day before surgery via a venous line introduced in the forearm at least 10 min before sampling or, during surgery, via an arterial line introduced in the forearm prior to surgery while the patient was anesthetized. Blood samples during surgery were collected with 30 min intervals starting from skin incision until 2 hr after detubation or arrival at the IC-ward. Furthermore, additional samples were collected after palpation (traction) of the mesentery and palpation of the liver (metastases). Plasma samples were put on ice without delay and processed within 2 hr after sampling. The tubes were centrifuged for 30 min at 120 g and 4 °C. Platelet counts were measured with a Coulter Counter Model S plus 4. Analyzed were serotonin, norepinephrine, epinephrine and dopamine. An extensive description of the analytical chromatographic methods used for measurement of the blood and urinary biogenic amine (metabolites) was published previously by Kema et al.[6]

Statistical analysis of the data of the two groups was performed using the Mann-Whitney U test (non parametric test for two independent samples) and correlations by a Spearman Rank test. Only p-values < 0.05 were considered significant.

Results

Sixteen consecutive carcinoid patients were entered in the study. Table 1 shows the patient and surgical characteristics. One patient was excluded from analysis because of peri-operative carcinoid crisis requiring norepinephrine to maintain adequate blood pressure. The control group consisted of seven patients. The median operating time of the control group was twice the operating time in the carcinoid group.

	carcinoid patients	control patients
Number	15	7
Median age in years (range)	55 (52-80)	62 (25-72)
Sex: male / female	7 / 8	4 / 3
Operation (number)	15	7
small bowel resection	13	
hemihepatectomy	1	
retroperitoneal mass resection	1	
pancreatic tail resection		1
lateral pancreaticojejunostomy (Puestow)		1
pylorus preserving pancreaticoduodenectomy		5
Operating time in min (range)	120(60-300)	250(180-390)

Table 1: Patients characteristics

None of the other patients experienced a carcinoid crisis peri-operatively; there were no complications during surgery.

Plasma epinephrine levels (figure 1A) before surgery were similar in both groups. During surgery there were no significant alterations in epinephrine levels at sample points. Noteworthy were the elevated levels of epinephrine during the stay at the recovery room. The days after surgery epinephrine levels were normal in both groups.

Plasma norepinephrine levels (figure 1B) before and during surgery were similar in both groups. Only at 30 min after recovery the epinephrine levels in the carcinoid patients were lower than in controls. During the two days after surgery, norepinephrine levels were similar in both groups but still elevated.

Plasma dopamine was below the detection limit in all patients.

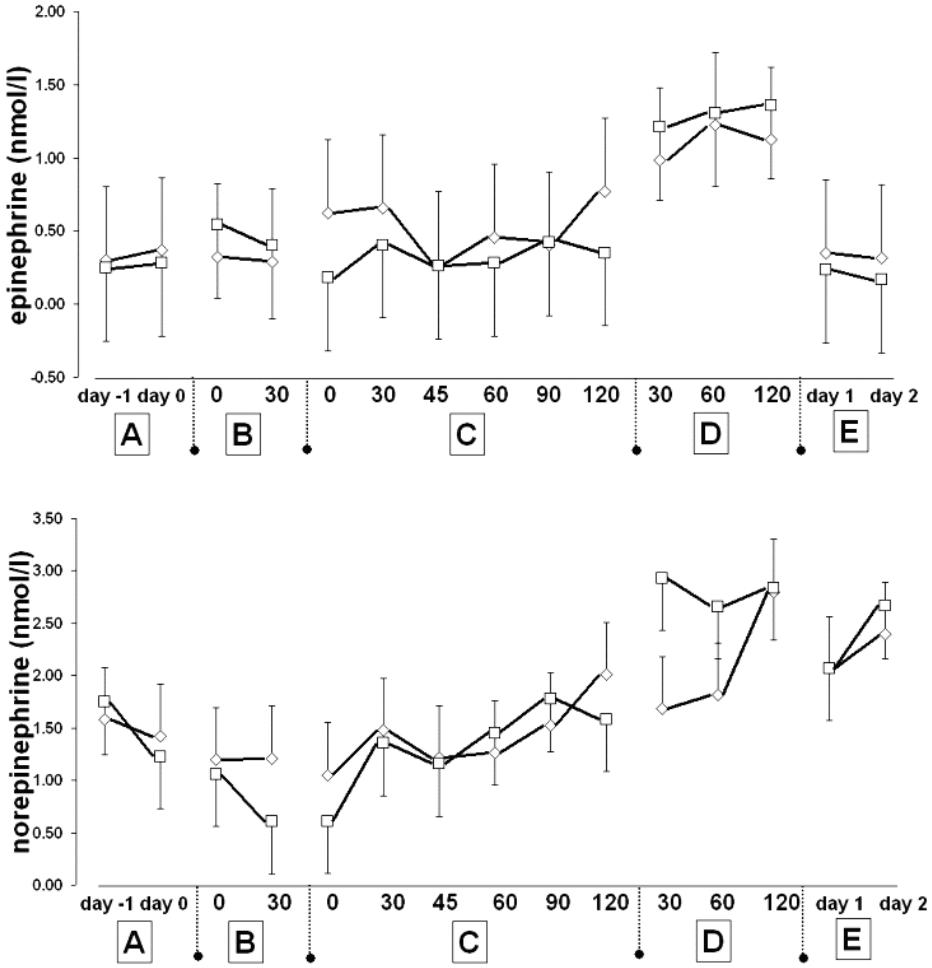

Figure 1a-b: Peri-operative catecholamine concentration in serum (mean ± SD); 1a: epinephrine, 1b: norepinephrine. A: before surgery, B: anesthesia, C: surgery, D: at recovery, E: days after surgery
◊ = carcinoid patients, □ = control patients

Sampling during tumor manipulation by the surgeon ("event") resulted in 5 of 11 patients in a median drop of mean arterial pressure (MAP) of 24% (SD: 13–30) combined with a 40% drop of plasma epinephrine at 15 min (p = 0.03, SD: 17%–82%, figure 2a). The plasma norepinephrine response at the moment of the "event" was varying, half of them increasing the other half decreasing (p = ns). In 6 of the 11 patients there was no significant change in MAP, and no significant alterations in plasma catecholamine concentration (figure 2b).

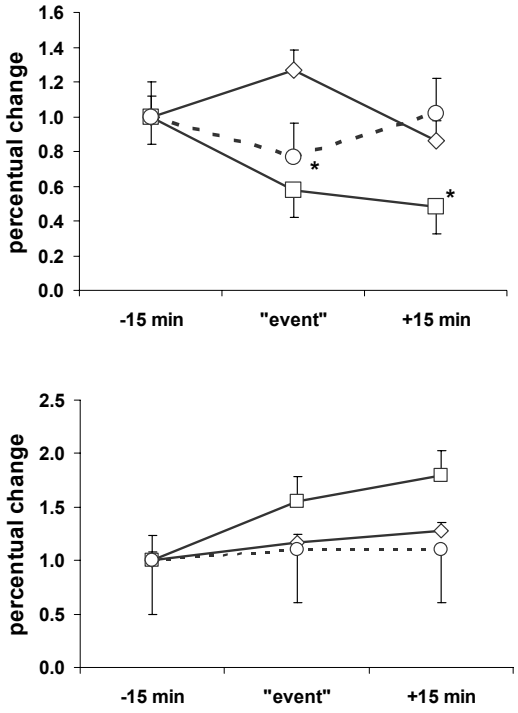

Figure 2a-b: Percentual changes in mean arterial pressure (MAP) and (nor)epinephrine concentrations before, during and after provocation ("event" e.g. tumor manipulation, mesenteric traction). 2a: patients responding with a fall in MAP following the event, 2b: patients responding without fall in MAP. X-axis: 15 min before and after the "event".
○ = MAP, Δ= norepinephrine, □ = epinephrine

Before during and after surgery there was no difference in plasma catecholamine concentration between carcinoid patients and controls. Figure 3 displays the urinary excretion of norepinephrine, epinephrine, dopamine, serotonin and 5-HIAA.

Urine excretion from carcinoid patients and controls showed markedly higher excretion of 5-HIAA ($p < 0.005$), norepinephrine ($p < 0.005$) and dopamine ($p < 0.01$) during all 5 days. In carcinoid patients epinephrine ($p < 0.05$), HVA ($p < 0.05$) and VMA ($p < 0.05$) were raised only during the first two days. Urine DOPAC ($p < 0.05$), normetanephrine ($p < 0.05$) and finally metanephrine ($p < 0.001$) were raised in carcinoid patients compared to controls on the 3 days after operation

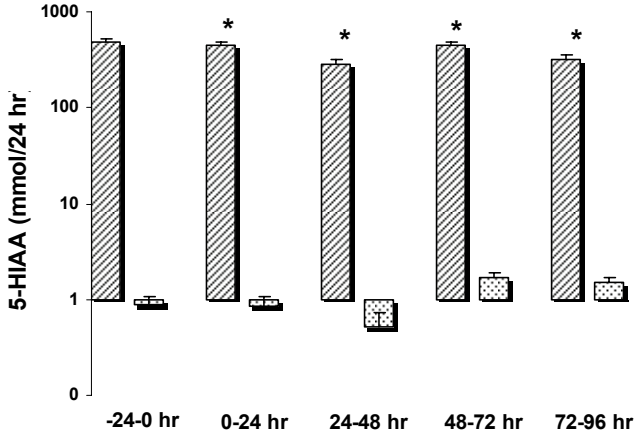

Fig 3a

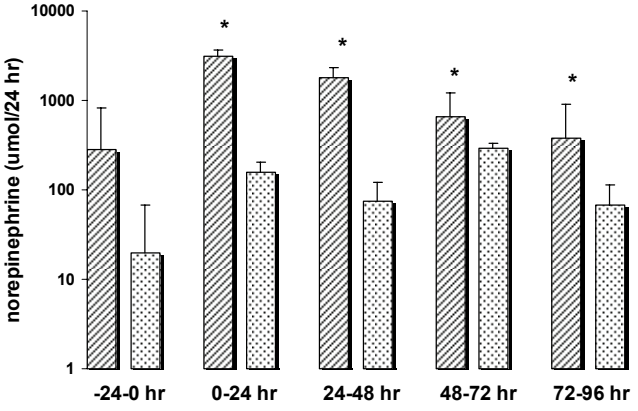

Fig 3b

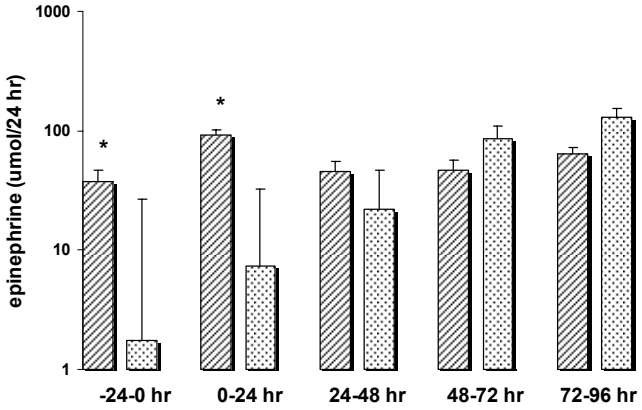

Fig 3c

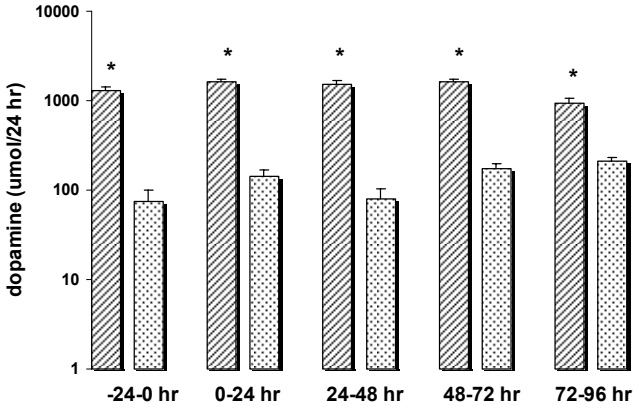

Fig 3d

Figure 3a-d: Peri-operative 24 hr urine excretion (* indicates $p<0.05$, mean ± SD) of 5-HIAA (mmol/24 hr) and norepinephrine, epinephrine and dopamine (µmol/24 hr)

(▨ = carcinoids, ⬚ = controls)

Discussion

To our knowledge this is the first article to describe to this extent the peri-operative amine output in plasma and urine. In carcinoid patients the peri-operatively collected urine showed highly elevated levels of catecholamine (metabolites) compared to controls. We were however not able to detect elevated levels of plasma catecholamines. In our series of carcinoid patients undergoing surgery no carcinoid crisis occurred except in one patient. This patient had to be excluded for biochemical analysis because of peri-operative infusion of inotropic medication. There are only few data with respect to the incidence of the carcinoid crisis. The estimated incidence is considered to be around 10% in patients not receiving octreotide.[9] The advent of octreotide strongly reduced the peri-operative carcinoid crisis.[10,11] In the present study there was no difference in baseline plasma catecholamines between carcinoid patients and controls. Analyzing the collected urine samples however, clearly demonstrated raised catecholamine (metabolite) excretion in the carcinoid group. One of the explanations of the absence of elevated plasma levels might be the site of venous sampling which was behind the two major metabolizing organs (liver and lung). Sampling in the portal vein and inferior caval vein might have been more effective. Another explanation might be an enhanced metabolizing capacity in carcinoid patients, due to persisting catecholamine production. There was a tenfold increase of 24 hr norepinephrine excretion in carcinoid patients on the day of operation compared to before operation. The percentage epinephrine excretion rose equally in both groups but in absolute terms much higher in the carcinoid group (2900 μmol/24 hr versus 150 μmol/24 hr).

The operating time was longer in the control group. Therefore bias with respect to the interpretation of the figures is unlikely, because the longer operating time in the control group might actually have led to a higher instead of a lower excretion of catecholamine (metabolites). The epinephrine excretion increased in both groups, but remarkable is the marked epinephrine increase 48-96 hr after operation in the control group. In both patient groups the same post-operative mobilizing regimen was applied. The increased epinephrine excretion is most likely caused by postoperative pain. The urinary dopamine excretion in the carcinoid patients was fairly stable. In the control patients it doubled on the day of operation and rose further the second and third day after operation.

One can easily understand the danger of imbalance during stress response with these large amounts of catecholamines stored in the tumor. Although octreotide is supposed to stabilize the plasma membrane of the carcinoid cells resulting in decreased excretion of hormones[12], our data suggest some effect in

stabilizing the end organ. One could hypothesize down regulation of catecholamine receptors or of the gene expression in downstream signaling pathways.

We conclude that high postoperative urinary excretion of catecholamine (metabolites) suggests increased levels of circulating catecholamines in carcinoid patients which appear not to pose a major threat to the homeostasis during operation induced stress in the presence of an umbrella of octreotide. However adequate reduction of stress especially pain after surgery should be taken care of.

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