Plasma Catecholamines in Pheochromocytoma: Effect of Urographic Contrast Media

J. Raisanen[1]
B. Shapiro[1]
G. M. Glazer[2]
S. Desai[1]
J. C. Sisson[1]

Hypertensive crises have been provoked in pheochromocytoma patients by the injection of contrast media during angiography and venography. Fear of similar reactions to intravenous urographic contrast medium injection during computed tomography has led to studies without contrast enhancement when pheochromocytoma is suspected. With extraadrenal pheochromocytomas, intravenous contrast enhancement may be essential for tumor location by computed tomography. The catecholamine responses to injection of urographic contrast medium were examined in eight patients with pheochromocytoma and in 12 undergoing computed tomography for other reasons. Plasma norepinephrine concentrations fell in nonpheochromocytoma patients ($p < 0.005$), while in pheochromocytoma patients the response was unpredictable, rising in six individuals, although the mean response was not significant ($p > 0.35$). In five patients the magnitude of the increase in norepinephrine concentrations was large enough to have led to a pressor effect had alpha adrenergic blockade not been used. It was concluded that intravenous urographic contrast medium may elevate plasma catecholamines in a significant proportion of patients with pheochromocytoma, but that with adequate alpha adrenergic blockade this should pose no threat.

The diagnosis of pheochromocytoma is suspected in patients with hypertension and episodes of headache, sweating, and palpitations [1, 2], and it is confirmed by elevated concentrations of catecholamines or their metabolites in plasma or urine [3–5]. Although most pheochromocytomas arise in the adrenal medulla, they may be found at sites of chromaffin tissue anywhere from the pelvic floor to the base of the skull [1, 2, 6]. Accurate localization of these lesions is a prerequisite for successful surgical management and remains a major radiologic challenge [7]. To this end, a number of radiologic techniques including excretory urography with nephrotomography [8, 9], angiography [10,11], venography [12, 13] with sampling of catecholamine concentrations, and computed tomography (CT) [14–17] have been used. Although intravenous administration of iodinated contrast media for urography has proved to be relatively safe [8, 9], both angiography and venography are reported to carry the risk of fatal hypertensive crises [18–20]. CT has become the radiologic technique of choice for pheochromocytoma detection and is less invasive than arteriography or venography. Although adrenal pheochromocytomas can be evaluated by CT without administration of urographic contrast material, we have shown that accurate identification of extraadrenal pheochromocytoma, particularly in the thorax, requires bolus injection of contrast medium [21]. There has been at least one report in the literature of a hypertensive crisis that was probably precipitated by contrast-enhanced CT [22]. Such crises are believed to result from provoked release of catecholamines from the pheochromocytoma [1]. We examined the effect of bolus intravenous injection of urographic contrast medium during CT on plasma catecholamines in eight patients with pheochromocytoma and in 12 control patients undergoing body CT for other reasons.

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[1]Department of Internal Medicine, Division of Nuclear Medicine, University of Michigan Medical Center, Ann Arbor, MI 48109. Address reprint requests to B. Shapiro.

[2]Department of Radiology, University of Michigan Medical Center, Ann Arbor, MI 48109.

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TABLE 1: **Clinical and Biochemical Features of Pheochromocytoma Patients**

Case No., Site of Lesion	Dose of Phenoxybenzamine (mg/day)	Urinary Excretion Rates (μg/24 hr)				
		Norepinephrine	Normetanephrine	Epinephrine	Metanephrine	VMA
1, Adrenal	10	41	690	387	747	30,800
2, Metastatic malignant	20	367	67	20	28	26,000
3, Paracardiac (arch of aorta)	30	267	132	10	21	19,000
4, Adrenal	10	439	2673	5	252	30,700
5, Metastatic malignant	160	1383	2212	53	96	96,800
6, Metastatic malignant	40	533	2914	28	20	37,200
7, Adrenal	20	748	687	53	42	52,000
8, Paracardiac (left atrium)	10	195	75	30	15	3,700

Note.—VMA = vanillymandelic acid. Normal urinary excretion rates: norepinephrine, <120 μg/24 hr; normetanephrine, <165 μg/24 hr; epinephrine, <30 μg/24 hr; metanephrine, <85 μg/24 hr; and VMA, <7000 μg/24 hr.

Subjects and Methods

Eight patients with clinical, biochemical, and scintigraphic [23] evidence of pheochromocytoma were studied (table 1); all patients had histologic confirmation of pheochromocytoma. Each patient was receiving phenoxybenzamine in sufficient dosage to cause alpha blockade at the time of CT (normotensive with asymptomatic postural hypotension and nasal congestion). An intravenous catheter was inserted into the antecubital fossa, wrist, or ankle for contrast injection. This catheter was also used to obtain a 3 ml blood sample before contrast injection. After a scouting scan, 100 ml of iothalamate meglumine 60% (600 mg/ml, Conray 60, Mallinckrodt) was delivered by hand-injection in two 50-ml boluses followed by Conray 30 (300 mg/ml) drip infusion. CT images of the region of interest were obtained immediately after the bolus injection. Ten min after the initial injection (or about the time that 150 ml of contrast solution had been infused) a second 3-ml blood sample was drawn. Two pheochromocytoma patients received two contrast infusions (bolus plus drip) on the same occasion, for a total of 10 studies. The identical procedure was used for 12 control patients undergoing CT scanning for reasons other than pheochromocytoma.

The blood samples were collected in chilled tubes, kept on ice, and centrifuged at 4°C, after which the plasma was separated and stored at −20°C until assay. Catecholamine concentrations were measured using the radioenzymatic method of Peuler and Johnson [24] (Upjohn, CAT-A-KIT).

To test the reliability of this assay in the presence of iothalamate meglumine, catecholamines were measured in samples of normal plasma containing concentrations of contrast medium within the ranges encountered during an actual scan (2.40–40.08 mg Conray 60 per ml plasma). The blood was drawn and centrifuged as described above, and varying amounts of contrast were added to the plasma, which was then stored for assay at −20°C. Plasma catecholamine concentrations before and after contrast medium injection were compared using the Student *t* test for paired variables.

TABLE 2: **Plasma Catecholamines before and after Contrast Injection in Patients with Pheochromocytoma**

Case No.	Norepinephrine (pg/ml)			Epinephrine (pg/ml)		
	Before	After	% Change	Before	After	% Change
1	5124	5988	+16.9	1552	2081	+34.1
2	555	644	+16.0	74	80	+8.1
	676	633	−21.2	44	33	−25.0
3	1975	1369	−30.7	96	65	−32.3
4	2733	3899	+42.6	677	392	−42.1
5	7911	5751	−27.3	400	341	−14.8
6	3909	5104	+30.6	401	378	−5.7
	3087	4347	+40.8	250	322	+28.8
7	4567	5439	+19.1	47	73	+55.3
8	1596	1614	+1.1	22	39	+77.3

TABLE 3: **Plasma Catecholamines before and after Contrast Injection in Control Subjects**

Case No.	Norepinephrine (pg/ml)			Epinephrine (pg/ml)		
	Before	After	% Change	Before	After	% Change
1	559	529	−5.4	39	31	−20.5
2	257	324	+26.1	48	135	+181.3
3	603	504	−16.4	35	35	0
4	678	669	−1.3	22	27	+22.7
5	178	76	−57.3	25	12	−52.0
6	1035	879	−15.1	55	57	+3.6
7	379	225	−40.6	44	19	−56.8
8	318	221	−30.5	24	28	+16.7
9	525	230	−56.2	24	11	−54.2
10	375	316	−15.7	8	11	+37.5
11	685	496	−27.6	45	48	+6.7
12	220	186	−15.5	39	10	−74.4

Results

The catecholamine concentrations in normal plasma did not differ significantly from those in normal plasma containing varying concentrations of contrast material (2.4, 5.0, 10.02, 20.04, 40.08 mg/ml plasma), indicating the validity of the assay in the presence of urographic contrast material.

Plasma catecholamines before and after intravenous injection of urographic contrast medium during CT are shown in tables 2 and 3 for eight patients with pheochromocytoma (10 trials) and 12 control patients. The percentage change from precontrast levels is also shown.

In seven trials in patients with pheochromocytoma, norepinephrine increased after contrast injection; the average increase was 23.9%. On three occasions norepinephrine fell an average of 26.4%. Overall, in 10 trials, plasma norepinephrine concentrations increased by an average of 8.8% after infusion of intravenous contrast medium. These differences in pre-

and postcontrast norepinephrine values are not significant overall ($p > 0.25$); however, it should be noted that in several patients with pheochromocytoma, large absolute increases in norepinephrine concentration occurred after contrast injection. In no instances did symptoms, other than those that normally follow contrast administration, occur. Pulse and blood pressure were unchanged when measured after completion of the CT study. The norepinephrine concentrations in 12 control patients decreased by an average of 21.3% (falling in all but one instance); this decrease was predictable and significant ($p < 0.005$).

There was an average rise of plasma epinephrine of 8.4% in patients with pheochromocytoma (five trials showing a fall averaging 24.0% and five showing a rise averaging 40.7%); the mean postcontrast change was not significant. There was an increase in plasma epineprhine concentration after contrast injection in the 12 control patients averaging 0.88% (six patients showing an increase that averaged 44.8%, five a decrease averaging 51.6%, and one no change); this change likewise is not significant. The catecholamine concentration never exceeded the normal range in these control patients.

Discussion

Many patients referred to our hospital for evaluation of suspected pheochromocytoma have undergone CT without intravenous urographic contrast medium because of fear of provoking hypertensive crises. These nonenhanced scans limit the accuracy of CT in detection of extraadrenal pheochromocytoma [21]. Contrast-provoked crisis is believed to be from stimulation of catecholamine release [1]. Silverberg et al. [25] investigated the acute pressor effect of norepinephrine in normal subjects and showed that the threshold concentration for increasing blood pressure was 1800 pg/ml. An increase in 350 pg/ml of norepinephrine to about 2150 pg/ml increased the mean systolic pressure by 24 mm Hg and mean diastolic pressure by 19 mm Hg. In six of eight patients with pheochromocytoma in our series, baseline norepinephrine values were above this threshold range. As noted, the catecholamine response to contrast medium was unpredictable in patients with pheochromocytoma, and mean catecholamine response to contrast medium was not significantly different pre- and postinjection. Despite this lack of significant change in mean norepinephrine values, in five patients with pheochromocytoma the plasma norepinephrine increased by over 860 pg/ml after contrast injection; this magnitude of increase would be expected to result in a pressor effect in normals according to the data of Silverberg et al. [25].

In conclusion, we have shown that patients with pheochromocytoma behaved differently than patients without pheochromocytoma in their catecholamine response to the bolus injection of urographic contrast medium used during CT scanning. In the control group, plasma norepinephrine values significantly decreased after contast injection. In patients with pheochromocytoma there was an unpredictable plasma norepinephrine response to urographic contrast medium. Since our data indicate that some patients with pheochromocytoma will have a large rise of plasma norepinephrine after contrast administration, we recommend that they be alpha-blocked before definitive CT evaluation.

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