Plasma Catecholamines in Patients with Serious Postoperative Infection

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PREVIOUS REPORTS indicate that urinary catecholamine excretion is not significantly increased in patients after major operation, but is elevated following severe trauma or during a complicated postoperative course. Measuring urinary catecholamines after major surgical procedures, Franksson, Gemzell and Euler[10] found that epinephrine was not elevated in patients who made an uneventful recovery. Although urinary excretion of norepinephrine was increased occasionally, it was normal in the majority of these patients. Patients with major trauma or postoperative complications had consistently increased urinary norepinephrine. In patients with burns Goodall, Stone and Haynes[12] found increased urinary excretion of catecholamines. The rise of norepinephrine was usually greater than epinephrine and was approximately proportional to the severity of the burns. Goodall[13] also observed histological depletion of catecholamine granules in the adrenal medulla of patients who died following severe burns. Urinary catecholamines do not reflect the intermittent circulating plasma concentrations, and in septic patients with or without hypotension, oliguria or anuria may preclude measurement of urinary catecholamines.

Using the ethylenediamine method, Hammond, Aronow and Moore[16] measured plasma catecholamines in a group of surgical patients. They found that plasma norepinephrine and epinephrine were normal in most patients following major surgical procedures, but were increased in patients with postoperative complications. The ethylenediamine method for the determination of plasma catecholamines has been criticized for its inability to distinguish accurately between norepinephrine and epinephrine;[21] hence a batch method using the more discriminating trihydroxyindole method to measure plasma norepinephrine and epinephrine has been developed in this laboratory.[14]

It has not been demonstrated previously that patients with sepsis following operation have plasma catecholamine concentrations greater than those seen in non-septic postoperative patients. This study reports the concentration of plasma norepinephrine and epinephrine measured in patients with severe septic complications following operation and a group of postoperative patients without infection.

Materials and Methods

Ten patients in an intensive care unit with life threatening forms of sepsis such as septicemia, gas gangrene and poorly controlled intra-abdominal abscesses formed the study group. Blood pressure, pulse, temperature, central venous pressure and urine output were recorded. Simultaneously, arterial blood was drawn for measurement of pH, P_{O_2} and P_{CO_2} on a Radiometer Model 27 blood gas analyzer, and venous blood was obtained for determination of plasma catecholamines.[14] Similar studies were made from a control group of ten non-septic patients on the first and second days after operation.

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TABLE 1. *Postoperative Patients with Sepsis*

Patient	Day Observed	NE ng./ml.	E ng./ml.	Pulse	B. P. mm. Hg	CVP cm. H_2O	Urine ml./hr.	Temp. °C	pH	pCO_2 mm.Hg	Diagnosis
1	1	2.47	0.02	110	100/60	10	50	37.4	7.29	46	*Cl. welchii* cellulitis (R)
54 years	3	0.48	0.02	108	95/50	4	200	37.0	7.50	32	flank,disseminated intra-
	4	0.35	0.12	104	85/55	7	45	37.3	7.43	32	vascular coagulation
	5	0.35	0.05	100	100/65	6	65	37.0	7.42	29	
2	1	2.33	0.25	160	110/70	7	200	38.0	7.51	32	*E.coli* abdominal abscesses
31 years	2	2.19	0.25	160	110/70	0	30	38.4	7.48	27	post appendectomy
	3	1.05	0.14	135	120/70	0	50	38.7			
	6	0.84	0.23	132	130/95	3	75	37.5	7.41	42	
	7	1.12	0.39	140	125/80	3	40	37.8			
3	1	4.10	1.53	150	80/40	4	0	40.8	7.21	28	Esophagectomy for Ca
53 years	1	3.91	1.03	144	70/30	6	0	41.0	7.19	24	esophagus, *Proteus morganii*
	1	3.80	0.94	130	80/50	7	15	40.0	7.20	23	septicemia
	1	2.87	1.12	140	70/40	7	24	40.0	7.23	27	
4	1	1.65	0.23	170	140/80		30	39.0			*Cl. welchii* cellulitis (R) flank
62 years	2	1.08	0.28	124	160/80	16	45	38.8	7.35	38	
	4	0.43	0.08	100	160/80	9	100	38.8	7.45	43	
5	1	1.49	0.40	150	60/30	13	0	41.0	7.22	43	Anterior resection, Cl.
59 years											welchii cellulitis and
											myositis abdominal wall,
											renal failure
6	1	2.26	0.33	120	150/80		0	36.7	7.29	47	*A. aerogenes* infection in
27 years	2	1.98	0.17	120	130/80	6	0	37.0	7.26	52	compound fracture (R) leg,
	3	1.77	0.32	135	140/80	1	0	38.6	7.38	42	renal failure
	4	1.56	0.05	135	130/80	3	10	38.0			
	32	0.40	0.01	100	140/90		125	37.4			
7	1	3.16	0.48	130	100/60	8	15	39.0	7.28	23	Prostatectomy, *E. coli*
83 years	1	2.49	0.39	124	95/50	9	25	39.2	7.29	31	septicemia
	1	2.36	0.51	128	90/50	7	65	41.0	7.30	27	
	1	1.65	0.36	110	100/60	6	70	38.0	7.31	36	
	2	1.42	0.32	104	110/60	7	110	38.2	7.38	29	
	2	0.75	0.14	96	110/60	7	250	37.0	7.39	34	
8	1	1.55	0.30	115	100/70	9	35	39.8	7.57	15	Post-op Longmire procedure,
72 years	3	0.29	0.03	70	90/55	5	80	37.0	7.49	28	*Pseudomonas aeruginosa*
	4	0.64	0.02	76	100/60	7	50	36.3	7.46	33	septicemia
	5	0.42	0.15	80	90/60	4	45	36.5			
9	1	0.92	0.09	88	80/40	11	25	41.0	7.37	29	(R) Hemicolectomy, *E. coli*
47 years	1	0.51	0.03	74	100/70	12	120	39.0	7.43	28	septicemia
	1	0.49	0.06	76	110/70	10	200	37.0	7.36	34	
	1	0.39	0.08	78	110/70	10	100	37.0	7.39	37	
10	1	1.81	0.13	110	140/70	6	90	39.0	7.45	30	Leaking duodenal stump
32 years	2	0.44	0.10	80	125/70	8	100	37.5	7.49	25	post gastrectomy,
	3	0.51	0.08	72	110/70	6	60	38.0			peritonitis, *Klebsiella*
	4	0.39	0.12	80	125/55	8	60	38.0			*pneumoniae, Proteus*
	5	0.84	0.20	120	125/65	7	55	39.7	7.48	25	*morganii, Strep. fecalis*
	6	0.41	0.08	72	140/75	7	105	37.7			

Normal NE .25 ± .10 ng./ml
Normal E .04 ± .04 ng./ml

Results

Postoperative Patients with Sepsis (10), Table 1: When the seriously ill patients were first seen, mean plasma norepinephrine was 2.17 ng./ml. (± 0.92) and mean plasma epinephrine was 0.38 ng./ml. (± 0.43). Using the student *t* test on these data and the data obtained on the first postoperative day from the group without infection, it was found that plasma norepinephrine ($p < 0.001$) and plasma epinephrine ($p < 0.05$) were significantly greater in the septic patients. It was not possible to compare the second norepinephrine and epinephrine concentrations between the septic and non-septic patients since the intervals between collection of blood varied considerably in the septic group.

In every patient with sepsis, plasma norepinephrine was higher than plasma epinephrine. An analysis of co-

TABLE 2. *Postoperative Patients Without Sepsis*

Patient	Day post-op.	NE ng./ml.	E ng./ml	Pulse min.	B. P. mm. Hg	Urine ml./hr.	Temp. °C	Operation
1	First	0.54	0.32	100	190/75	75	36.9	Aorto-femoral bypass
	Second	0.57	0.46	110	190/75	125	37.5	
2	First	0.60	0.13	72	150/80	80	37.0	Splenectomy for idiopathic
	Second	0.28	0.06	88	120/65	70	38.0	thrombocytopenic purpura
3	First	0.30	0.06	84	165/80	75	37.2	Cholecystectomy and operative
	Second	0.17	0.05	80	180/90	50	37.0	cholangiogram
4	First	0.15	0.02	78	150/85	60	37.0	Cholecystectomy, common bile
	Second	0.15	0.04	84	145/80	50	37.4	duct exploration, sphincter-otomy
5	First	0.38	0.01	120	110/70	55	36.4	Cholecystectomy
	Second	0.47	0.01	120	110/75	60	37.0	
6	First	0.29	0.24	94	150/80	50	37.0	Inguinal hernia repair
	Second	0.43	0.38	82	145/75	70	37.6	
7	First	0.18	0.04	68	130/90	45	36.8	Bilateral inguinal hernia
	Second	0.19	0.07	68	120/80	55	36.8	repair
8	First	0.44	0.05	104	140/80	80	37.6	Bilateral varicose vein,
	Second	0.27	0.08	100	140/80	50	37.8	stripping and ligation
9	First	0.15	0.02	68	150/60	60	36.8	Femoral popliteal bypass
	Second	0.18	0.07	80	150/80	40	37.3	
10	First	0.40	0.14	94	130/70	75	37.4	Femoral popliteal bypass
	Second	0.52	0.14	92	125/75	80	37.4	

Normal NE .25 ± .10 ng./ml.
Normal E .04 ± .04 ng./ml.

variance to compare the changes in both catecholamines showed a rise of norepinephrine correlated with a rise of epinephrine ($r = 0.77$, $p < 0.01$ at 95% confidence limits). Plasma catecholamines were elevated when either urinary output or central venous pressure indicated that volume replacement was not necessary. Seven of the ten patients with sepsis were not hypotensive when plasma norepinephrine and epinephrine were elevated, and although arterial P_{CO_2} was slightly increased on occasion, it was usually normal or low when the catecholamines were high. Six patients in this group died from the complications of sepsis.

Postoperative Patients without Sepsis (10), Table 2: Twenty-four hours after surgery, mean plasma norepinephrine was 0.34 ng./ml. (±0.16) and mean plasma epinephrine was 0.10 ng./ml. (±0.10). On the second postoperative day, mean plasma norepinephrine was 0.32 ng./ml. (±0.16) and mean plasma epinephrine was 0.14 ng./ml. (±0.15). The paired comparison *t* test did not show a significant change in mean plasma norepinephrine or epinephrine from the first to the second day. In some patients in this group, both catecholamines exceeded the normal range but mean plasma norepinephrine and epinephrine were within or near the upper limit of normal observed previously in healthy adults. Plasma norepinephrine always exceeded plasma epinephrine, but analysis of covariance at 95% confidence limits indicated that there was no correlation between these catecholamines. All patients in this group had an unremarkable postoperative course and none died.

Relationship of Plasma Catecholamines to Systolic Blood Pressure and Pulse: Fisher's 'Z' transformation technic was used to examine the relationship of plasma norepinephrine and epinephrine to systolic blood pressure and pulse in septic and nonseptic patients. In postoperative patients without infection, increased systolic blood pressure correlated with increased plasma epinephrine ($r = 0.65$, $p < 0.02$) but in the postoperative patients with serious septic complications, systolic blood pressure fell as plasma epinephrine increased ($r = -.47$, $p < 0.02$). There was no correlation of plasma norepinephrine with systolic blood pressure and pulse or plasma epinephrine with pulse in either group.

Case Reports

Case 1. This 54-year-old lady was admitted with central abdominal pain and a diagnosis of small bowel obstruction. Laparotomy was performed and small bowel adhesions lysed. During

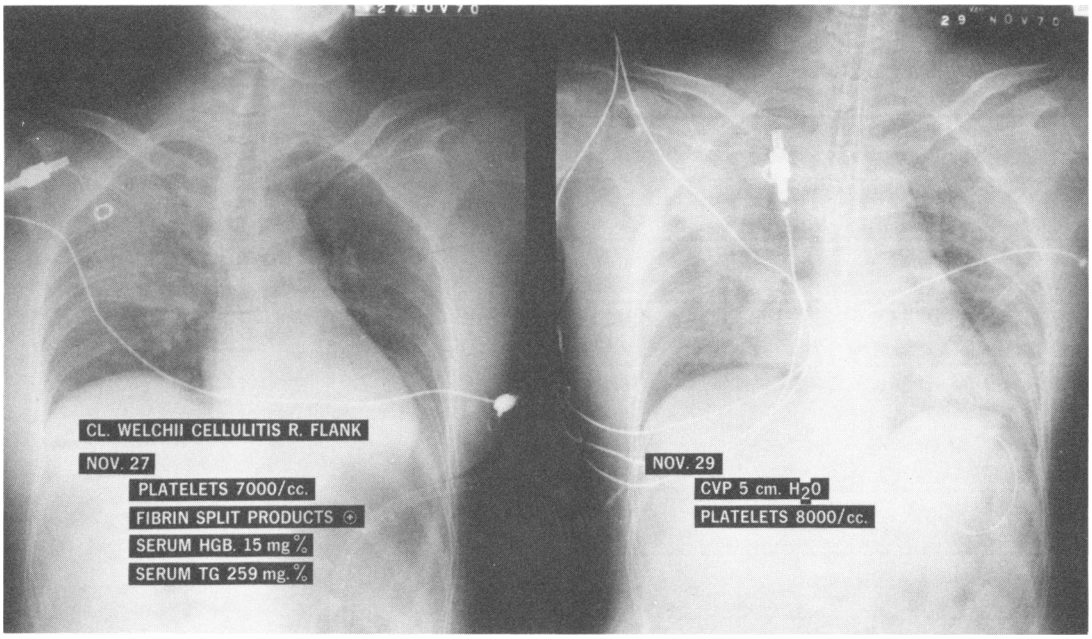

FIG. 1. This patient with *clostridium welchii* cellulitis of the right flank and disseminated intravascular coagulation had radiological evidence of pulmonary edema, but central venous pressure was normal.

operation the small bowel was inadvertently entered but closed without difficulty. Twenty-four hours following operation she became confused, her pulse was 140 per minute, temperature, 40°C, respiratory rate, 28 per minute and urine output, 10 ml. per hour. Crepitation originating in the abdominal wound and extending into the right flank was palpated and gram positive bacilli were identified on a gram stain of the wound exudate.

She was given massive doses of penicillin and taken to the hyperbaric chamber where debridement was performed during a 2-hour treatment with 100% oxygen at 3 ATA. The same evening she was given a second 2-hour hyperbaric oxygen treatment and her general condition improved. The next morning it was noted that the serum hemoglobin was 15 mg./100 ml., platelets, 7000/cc. and fibrin split products were present in the plasma. Plasma norepinephrine was 2.47 ng./ml., plasma epinephrine, 0.02 ng./ml., and serum triglyceride, 259 mg./100 ml. At this time blood pressure was 100/60, pulse, 110, central venous pressure, 10 cm. H_2O, urine output, 50 ml./hr. and P_{CO_2}, 46 mm.Hg. Two days later it was noted that she had lung lesions which occur in association with severe sepsis, that is, radiologic changes consistent with the diagnosis of pulmonary edema in association with a normal central venous pressure (Fig. 1). On the fifth day after the onset of the illness plasma norepinephrine and serum triglyceride had returned to normal, and 10 weeks later, after secondary wound closure and skin grafting, she was discharged from hospital.

Case 2. Six weeks previously, this 31-year-old patient had a ruptured appendix followed by three surgical procedures for drainage of abdominal and pelvic abscesses and a Bacteriodes organism was cultured from the purulent exudate. Despite this aggressive surgical treatment she continued to complain of severe abdominal pain, but on physical examination there was no localized abdominal tenderness. Six days later her condition had deteriorated considerably and there was generalized abdominal tenderness on palpation. Her pulse was 160 per minute, respiratory rate, 32 per minute, temperature, 38°C., central venous pressure, 7 cm. H_2O, urine output, 200 ml./hr., P_{O_2}, 86 mm.Hg, P_{CO_2}, 32 mm.Hg and pH, 7.51. She was confused and there was marked peripheral cyanosis. Plasma norepinephrine was 2.33 ng./ml. and plasma epinephrine, 0.25 ng./ml. The following day laparotomy was performed and three separate abdominal abscesses were drained. *Escherichia coli* bacteria were cultured from pus obtained at operation.

Immediately following operation her clinical condition was unchanged; plasma norepinephrine was 2.19 ng./ml. and plasma epinephrine, 0.25 ng./ml. On the second postoperative day her pulse had decreased to 135 per minute, there was no peripheral cyanosis and plasma norepinephrine and epinephrine had decreased to 1.05 ng./ml. and 0.14 ng./ml. respectively. By the fourth postoperative day she had improved further, and her plasma norepinephrine was 0.84 ng./ml. and plasma epinephrine, 0.23 ng./ml. She continued to improve and subsequently was discharged from the hospital.

Discussion

The data in this study show that plasma norepinephrine and epinephrine were slightly increased in some patients following uneventful major surgical procedures, but mean plasma norepinephrine and epinephrine were near the upper limit of normal observed in healthy adults. However, both norepinephrine and epinephrine were significantly higher in postoperative patients with severe septic complications than in postoperative patients without sepsis. While it is recognized that urinary catecholamine excretion is difficult to relate to plasma concentrations, these data are consistent with the observations of Franksson, Gemzell and Euler.[10] Increased systolic blood pressure was correlated with increased plasma epinephrine in postoperative patients without infection, but systolic blood pressure fell as plasma epinephrine increased in patients with serious septic complications. The physiological explanation for these results is unclear. Plasma norepinephrine always exceeded plasma epinephrine and occasionally remained elevated when epinephrine had returned to normal.

The cause of increased plasma catecholamines in patients with serious postoperative infection is not clear. Altered release, catabolism or excretion would affect plasma catecholamine concentrations, but the effect of sepsis on these parameters is unknown.

Long *et al.*[19] showed that in sepsis, glucose oxidation increased more than twice, whereas the metabolic rate increased only slightly. Muller, Faloona and Unger[24] have demonstrated that the plasma concentration of the gluconeogenic hormone, glucagon, increases when there is increased requirement for endogenous glucose. Since glucagon causes increased catecholamine release,[28] it is possible that additional glucose requirements in sepsis may raise plasma catecholamine concentrations indirectly. Duner's[8] studies indicate that a fall of blood glucose concentration initiates the release of catecholamines, particularly epinephrine, from the adrenal medulla via nervous pathways from the hypothalamus.[7] Direct stimulation of catecholamine release via the hypothalamus would be expected in dogs with hypoglycemia resulting from the intravenous injection of *E. coli* endotoxin,[2] and on occasion may occur clinically because hypoglycemia has been reported in patients with severe sepsis.[23]

Either metabolic or respiratory acidosis will raise plasma catecholamine concentrations.[20] Some of the patients in this study had metabolic acidosis which may have caused increased plasma catecholamines but none had significant respiratory acidosis. Hypotension will cause adrenal medullary catecholamine release via the baroreceptor reflex.[18] Although some patients in this study had low blood pressures, most were normotensive and none were hypovolemic when plasma catecholamines were elevated. These observations suggest that factors other than the baroreceptor reflex are more important causes of increased plasma catecholamines in postoperative patients with serious septic complications.

Gallin and associates[11] observed marked hyperlipidemia in association with lipid present in the prebeta fraction on lipoprotein electrophoresis of patients with serious gram-negative infection. In Case 1, transient hypertriglyceridemia associated with high plasma norepinephrine was observed. Fatty change also has been noted at postmortem in the liver of patients who died following gram-negative sepsis[25] and experimental infusion of norepinephrine into healthy dogs causes hypertriglyceridemia, increased very low density lipoprotein in the plasma[4] and acute fatty liver.[9] Recent studies in this laboratory showing a rise in serum triglyceride correlated with a rise in plasma norepinephrine but not epinephrine 12 hours after the injection of live *E. coli* bacteria into dogs suggest that the hypertriglyceridemia associated with gram-negative sepsis is related to endogenous norepinephrine release induced by gram-negative bacteremia.[15]

Both norepinephrine and epinephrine inhibit the insulin response to glucose.[26,27] Cerasi and colleagues[5] have shown by glucose and epinephrine infusion studies that inhibition of insulin release is dependent on the rate of infusion of epinephrine. However, at all rates of infusion which were studied, epinephrine reduced insulin secretion.[5] In patients with severe burns the negative nitrogen balance can be reduced greatly by infusions of glucose and insulin.[17] Since insulin is an anabolic hormone, the significance of impaired insulin release secondary to raised plasma catecholamines as a cause of the high catabolic rate in patients with serious postoperative infection requires further study.

Disseminated intravascular coagulation is a frequent complication of septicemia.[1] McKay[22] found hematological changes consistent with disseminated intravascular coagulation as well as electron microscopic evidence of fibrin in the microcirculation of rabbits and monkeys following continuous epinephrine infusion. Whitaker, McKay and Csavossy[29] also noted the severity of hemolysis and red cell fragmentation following epinephrine infusion was related to the amount of intravascular clotting. Both disseminated intravascular coagulation and hemolysis were completely prevented by prior alpha adrenergic blockade with dibenzyline but only partially prevented by heparin.

Berk[3] has suggested that increased beta rather than increased alpha adrenergic stimulation causes many of the pathophysiological changes in septic shock, and has reported encouraging results in the treatment of septic shock with the use of the beta adrenergic antagonist, propranolol. However, Carlson[4] noted a high mortality following a continuous 8-hour infusion of the alpha adrenergic drug, norepinephrine, into healthy dogs at the rate of 1 μg./Kg./min. A high mortality also has been reported in patients with severe sepsis, particularly if associated with hypotension,[6] and in this study in which norepinephrine concentration exceeded epinephrine concentration, there were six deaths in the group of ten patients with serious postoperative infection.

It is well recognized that norepinephrine or epinephrine are contraindicated in the treatment of patients with severe sepsis. It remains to be shown whether the increased plasma catecholamines noted in the postoperative septic patients are beneficial or detrimental. Experimental evidence suggests that sustained high concentrations of circulating catecholamines produce diverse deleterious effects; hence, further studies are needed to compare plasma catecholamine concentrations in animals subjected to continuous catecholamine in-

fusion with those measured in patients with severe sepsis.

Summary

Plasma norepinephrine and epinephrine were slightly increased in some patients following uneventful major surgical procedures, but mean plasma norepinephrine and epinephrine were within or near the upper limit of normal observed in healthy adults. Both mean plasma norepinephrine and epinephrine were significantly higher in postoperative patients with severe septic complications than in postoperative patients without sepsis. Plasma norepinephrine always exceeded plasma epinephrine and occasionally remained elevated when epinephrine had returned to normal.

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