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Hypotension following patent ductus arteriosus ligation: the role of adrenal hormones

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Abstract

Objective—To test the hypothesis that an impaired adrenal response to stress might play a role in the hypotension that follows patent ductus arteriosus (PDA) ligation.

Study design—We performed a multicenter study of infants born at <32 weeks gestation who were about to undergo PDA ligation. Serum adrenal steroids were measured three times: before and after a cosyntropin (1.0 microgram/kg) stimulation test (performed prior to the ligation), and at 10–12 hours after the ligation. A standardized approach for diagnosis and treatment of postoperative hypotension was followed at each site. A modified Inotrope Score (1 x dopamine (μg/kg/min) + 1 x dobutamine) was used to monitor the catecholamine support an infant received. Infants were considered to have catecholamine-resistant hypotension if their highest Inotrope Score was >15.

Results—Of 95 infants enrolled, 43 (45%) developed hypotension and 14 (15%) developed catecholamine-resistant hypotension. Low post-operative cortisol levels were not associated with the overall incidence of hypotension following ligation. However, low cortisol levels were associated with the refractoriness of the hypotension to catecholamine treatment. In a multivariate analysis: the odds ratio for developing catecholamine-resistant hypotension was OR=36.6, CI=2.8–476, p=0.006. Low cortisol levels (in infants with catecholamine-resistant hypotension) were not due to adrenal immaturity or impairment; their cortisol precursor concentrations were either low or unchanged and their response to cosyntropin was similar to infants without catecholamine-resistant hypotension.

Conclusion—Infants with low cortisol concentrations following PDA ligation are likely to develop postoperative catecholamine-resistant hypotension. We speculate that decreased adrenal stimulation, rather than an impaired adrenal response to stimulation, may account for the decreased production.

Keywords

cortisol; hydrocortisone; surgery; dopamine; newborn

Between 25-to-35% of preterm infants having surgical ligation of the patent ductus arteriosus (PDA) develop systemic hypotension and hemodynamic deterioration approximately 8-to-14 hours after the surgical procedure (1–3). The factors responsible for postoperative hypotension are unclear. Retrospective studies have not identified differences in the surgical, anesthetic, or intraoperative fluid management among the infants who develop postoperative hypotension (1, 4). Indices of impaired myocardial performance are often observed prior to the development of hypotension (5–8), and prophylactic administration of milrinone, begun shortly after the surgery, appears to reduce the incidence of postoperative cardiorespiratory instability. However, some infants continue to develop post-ligation hypotension despite early treatment of low ventricular output with milrinone (7, 8).

Treatment with volume expanders and catecholamine infusions can usually correct the post-ligation hypotension. However, approximately 15% of infants develop catecholamine-resistant hypotension. In these infants, a “low stress-dose” of hydrocortisone can normalize

their blood pressure (3, 5, 6). Currently, there is no information about the ability of the premature infant to increase cortisol production after surgery.

Preterm infants are known to have an altered adrenal response to hypotension and postnatal stress during the first week of life: in 30% the cortisol levels are increased with postnatal stress (9, 10) but in 70% the levels are either similar to or lower than those of healthy infants (11–15). The low cortisol concentrations do not appear to be due to low corticosteroid binding globulins (16), Nor are they explained by a diminished pituitary response to stress in hypotensive preterm infants because corticotropin releasing hormone causes a robust increase in ACTH, but only a blunted cortisol response in the same infants (14, 17–19).

These findings suggest that the premature adrenal gland might not respond appropriately to elevated ACTH levels (15, 20, 21). Sick preterm infants have high circulating concentrations of 17-hydroxyprogesterone, 11-deoxycortisol, and cortisone. This pattern suggests that the activity of the enzymes that convert cortisol precursors to cortisol or from cortisol to cortisone may be altered (22–25). Although adrenal function usually returns to normal by 14 days after birth (17, 18), several reports suggest that the abnormal accumulation of cortisol precursors and impaired production of cortisol may persist for several weeks in preterm infants (15, 20).

Two reports suggest that infants at risk for developing peri-operative hypotension may have depressed cortisol responses to cosyntropin ($ACTH^{1–24}$) stimulation (8, 26). Therefore, we designed a prospective study to test the following hypotheses: 1) infants who develop hypotension after PDA ligation have a diminished post-operative cortisol response compared with infants who are normotensive; 2) infants who develop catecholamine-resistant hypotension have the most diminished cortisol response and have a limited ability to convert cortisol precursors to cortisol (or a more rapid conversion of cortisol to cortisone); and, 3) preoperative measurements of cortisol precursors or metabolites (before and after cosyntropin stimulation) will be able to predict which infants are likely to develop post-ligation cardiopulmonary deterioration.

Methods

Between May 2009, and February 2012, 95 infants were enrolled at 12 sites with Institutional Review Board approval and parental consent. Infants were eligible for the study if they were: (1) delivered between $23^{1/7}$ – $31\ ^{6/7}$ weeks gestation; and (2) scheduled for PDA ligation. The criteria to determine the need for ligation were not standardized between the centers. The decision to perform the ligation was made by the clinical care teams. Infants were excluded from the trial if they had: (1) major or lethal congenital or chromosomal abnormalities; (2) congenital heart defects (excluding patent ductus arteriosus and small atrial or ventricular septal defects); or (3) had received hydrocortisone or dexamethasone within 5 days of the planned surgery.

The PDA left-to-right shunt was scored (moderate or large) with an echocardiogram prior to ligation as previously described (27). The following clinical measures of cardiorespiratory status were recorded prospectively (starting 24 hour prior to surgery, until 96 hours after

surgery): arterial blood gases, blood pressures, heart rates, hematocrits, number of fluid boluses, and the amount, duration and type of vasopressor support, and the anesthetics, analgesics and sedatives the infants received.

Steroid Measurements

Three serum samples (0.7 ml blood/sample) were collected for steroid metabolite measurements. Two samples were obtained no more than 48 hours before the surgery as part of a cosyntropin ($ACTH^{1-24}$) stimulation test: 1) a *baseline* value, and 2) a value obtained 60 minutes after intravenous cosyntropin (1.0 microgram/kg). Previous studies found that 90% of healthy preterm infants have normal stimulated cortisol responses 60 minutes after this dose of cosyntropin whereas sick, ventilated infants have significantly lower cortisol responses (13, 15, 28).

A third serum sample for steroid metabolites was obtained between 10–12 hours after the surgery. This time-point was chosen because post-ligation hypotension usually is present by 8-to-14 hours after the ligation (1–3). (Note: the third sample was collected before the first hydrocortisone dose, if hydrocortisone was started before the 10–12 hour sample time point.

Steroid assays were performed by ultra-performance liquid chromatography tandem mass spectrometry as previously described (29). Cortisol, cortisone, 17-hydroxyprogesterone, 11-deoxycortisol, 21-deoxycortisol, deoxycorticosterone, corticosterone, progesterone, and androstenedione were assayed simultaneously in a single run. Values measured by this technique have correlation coefficients between 0.8 and 0.99 when compared with those obtained by radioimmunoassy (30).

Serum cortisol concentrations had a skewed distribution in our population. Therefore, we expressed the cortisol values as both absolute and log (base 10) transformed values. Because the adequacy of an infant's cortisol response for maintaining blood pressure depends on both the circulating cortisol level and the stress experienced by the infant, we defined a "decreased cortisol response" after ligation as one in which the cortisol level was in the lower-third (tertile) of the postoperative cortisol concentrations found in the study population. In our study, all infants underwent the same operation. Therefore, by using this definition we could match the appropriateness of the cortisol response to the level of stress that the infant was experiencing.

Surgical and Postoperative Management

All infants received a muscle relaxant (pancuronium, rocuronium, vecuronium or cisatracurium) and fentanyl anesthesia (8 infants also received ciboflurane, propofol, or ketamine). Left mid-axillary thoracotomies were performed through the fourth intercostal space and the ductus were ligated using metal clips. Morphine or fentanyl infusions were begun after the ligation and tapered over 6 to 24 hours depending on an infant pain profile score. At one study site (7 infants), a milrinone infusion was started shortly after the ligation as part of an institutional protocol designed to prevent postoperative hypotension (7, 8).

Management of Hypotension in Study Infants

Because vasopressor management of hypotension was the primary outcome, the hypotension treatment regimen needed to be directive rather than at the discretion of the clinicians. A standardized approach that determined when volume expanders and vasopressors would be initiated, and the rate at which they would be increased, was agreed upon by all participating centers. Blood pressure (BP) was measured directly with an arterial line and transducer, or noninvasively using the oscillometric method. An arterial line and transducer were used to measure blood pressure continuously in all infants receiving catecholamine infusions or hydrocortisone for blood pressure support.

Hypotension was defined as "mean BP less than the 3rd percentile for postmenstrual age (31, 32) that lasted more than 15 minutes". Operationally this meant that infants were considered to be hypotensive, and require treatment for their hypotension, if their mean blood pressure was less than [(postmenstrual age in mm Hg) − (3 to 4 mm Hg)].

When infants failed to maintain an adequate BP (defined as "BP greater than the hypotensive range"), no more than 3 fluid boluses (isotonic saline 10 mL/kg per dose) could be given initially to correct presumed hypovolemia. If the fluid boluses were unsuccessful in maintaining an adequate BP, catecholamine support could be added. The choice of dopamine or dobutamine was left to the clinical neonatologist. Infusion of dopamine or dobutamine was started at a rate of 5 μg/kg/min. The dose could be increased by 2.5 μg/kg/min every 15 minutes until an adequate BP was achieved. Combinations of dopamine and dobutamine could also be used.

We used a modified Inotrope Score (33) to measure the amount of catecholamine support that an infant received to maintain an adequate BP. The modified Inotrope Score was calculated as the sum of all catecholamines corrected for potency: (1 x dopamine (μg/kg/min) + 1 x dobutamine + 100 x epinephrine).

If a combination of dopamine and/or dobutamine (with an Inotrope Score >15) failed to maintain an adequate BP, epinephrine and/or a "low stress dose" of hydrocortisone could be added. The "low stress dose" of intravenous hydrocortisone could not be used unless the catecholamine infusion rates had an Inotrope Score >15. Hydrocortisone was started at 1 mg/kg/day and could be increased up to 3 mg/kg/day to maintain an adequate BP. The results of the steroid measurements were not available during the study and were not used in the decision to start hydrocortisone treatment.

The severity of the hypotension was defined by the maximum support needed to maintain an infant's BP above the hypotensive range: *minimal* = volume boluses alone; *mild* = maximum Inotrope Score less than 10; *moderate* = maximum Inotrope Score 10-to-15; and *severe (or catecholamine-resistant) hypotension* = maximum Inotrope Score greater than 15. *Catecholamine resistant hypotension* was classified as an Inotrope Score >15 based on the study centers' experience prior to the study (namely, that infants who failed to maintain an *adequate* BP with dopamine infusions ≤15 μg/kg/min usually required dopamine infusions > 20 μg/kg/min). As a result, most infants who failed to maintain an *adequate* BP with

dopamine infusions ≤15 μg/kg/min were started on hydrocortisone for additional treatment rather than increase the amount or number of catecholamine infusions.

Statistical Analyses

The χ^2 test was used to compare categorical risk factors and outcomes, and the Student t-test or Mann-Whitney test was used to compare the means or medians of continuous variables.

An adjusted multivariable logistic regression model was used to determine the effects of specific predictive variables on the outcome of interest. We first identified the perinatal and neonatal risk factors that were most associated with hypotension using bivariate analyses (Table I). A model was built for hypotension through forward selection. Variables were added to the model in order of increasing statistical significance. Variables were dropped from the model if their p-value rose to ≥ 0.1 after the addition of other variables.

After the models were built, the steroid predictive variables were individually forced into the models to evaluate their effect when adjusted by the other predictors. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using the multivariable model. A p-value of <0.05 for the predictive variables was considered significant. All analyses were performed using STATA 12 (College Station, TX) statistical software.

Results

Ninety-five infants were enrolled in the study prior to PDA ligation; 52 infants were normotensive throughout the post-operative period, and 43 infants developed hypotension: 14 infants had *minimal* hypotension (i.e., were treated with volume boluses alone (18±6 ml/kg)); 29 also received catecholamines (dopamine-alone, 72%; dobutamine-alone, 7%; dopamine and dobutamine, 21%). Six infants had mild, 9 moderate, and 14 severe/catecholamine-resistant hypotension. Twelve of the14 infants with catecholamine-resistant hypotension were treated with hydrocortisone. Peak Inotrope Scores occurred during the first 6 hours after surgery in 6 infants (21%), between 6–12 hours in 10 (34%), between 12–24 hours in 9 (31%), and between 24–48 hours in 4 (14%).

Infants who developed hypotension were more likely to be younger, weigh less, and be receiving dopamine at the time of ligation. They were also more likely to have received prolonged resuscitation at birth (10 min Apgar ≤5) (Table I).

There was a significant increase in cortisol concentrations following the ligation among infants who remained normotensive during the post-operative period (median cortisol pre-ligation (interquartile range) = 10.2 (6.2–16.6) ng/ml; post-ligation = 14.5 (10.4–42.7) ng/ml, $p<0.05$). This was also true for the study population as a whole (median cortisol pre-ligation (interquartile range) = 10.8 (6.9–27.7) ng/ml; post-ligation = 20.8 (9.3–47) ng/ml, $p<0.05$).

We hypothesized that hypotensive infants would have lower post-operative cortisol concentrations than normotensive infants. However, we found no significant difference in postoperative cortisol concentrations between the two groups (Table II). In fact, infants who

developed minimal/mild or moderate hypotension had significantly higher post-operative cortisol concentrations than normotensive infants (Table II).

Although low post-operative cortisol concentrations were not associated with the overall incidence of hypotension, they were associated with its severity and resistance to catecholamine treatment. Infants who developed catecholamine-resistant hypotension had significantly lower cortisol concentrations than normotensive infants or infants with milder degrees of hypotension (Table II). In our multivariable analysis (that included the previously defined nonsteroidal risk factors; Table I), low cortisol concentrations at 10–12 hour after ligation was a significant and independent risk factor for developing catecholamine-resistant hypotension ($OR_{\text{cortisol lower tertile}}$ =36.6, CI=2.8–476, p=0.006). Similarly, the risk for developing catecholamine-resistant hypotension decreased significantly with increasing postoperative cortisol concentration ($OR_{\text{cortisol (log10)}}$ =0.06, CI=0.01–0.50, p=0.009).

We hypothesized that infants with catecholamine-resistant hypotension would have increased concentrations of cortisol precursors and metabolites during the postoperative period. However, we found just the opposite: post-ligation precursor and metabolite levels were either unchanged or significantly decreased (11-deoxycortisol, 21-deoxycortisol, cortisone) in infants who developed catecholamine-resistant hypotension (Table III).

Neither the cortisol nor other steroid measurements, performed prior to ligation (at baseline or after the cosyntropin stimulation test), were predictive of which infants would be at risk for developing post-ligation catecholamine-resistant hypotension (Table III).

Discussion

We hypothesized that an immature or impaired adrenal response to stress (with low levels of cortisol and high levels of cortisol precursors) might be responsible for the post-operative hypotension that often follows PDA ligation. Our findings do not support this hypothesis. In fact cortisol concentrations in infants who developed post-operative hypotension (responsive to catecholamine or volume resuscitation) were significantly higher than cortisol concentrations measured in normotensive infants (Table II). Although low cortisol levels do not appear to be associated with the overall incidence of hypotension, they do appear to be related to the refractoriness of the hypotension to catecholamine treatment. Infants who developed hypotension that was resistant to catecholamine treatment had significantly lower cortisol concentrations than normotensive infants or infants with milder degrees of hypotension (that responded to catecholamine and volume resuscitation) (Table II).

Our findings also do not support the hypothesis that impaired adrenal production might be responsible for low cortisol values in infants who develop catecholamine-resistant hypotension. Cortisol precursors and metabolites were significantly decreased, rather than increased, in infants who developed catecholamine-resistant hypotension (Table III). In addition, infants who developed catecholamine-resistant hypotension had the same increase in cortisol and cortisol-precursors after cosyntropin (exogenous $ACTH^{1–24}$) as infants who never developed catecholamine-resistant hypotension (Table III). In hindsight, these findings should not be so surprising because the blunted, immature adrenal response to

cosyntropin, seen shortly after birth in preterm infants, usually normalizes by the end of the second week (17, 18). In our study, the average age at ligation was 4 weeks (70% of the infants who developed post-ligation catecholamine-resistant hypotension were more than 2 weeks old when they were ligated). We suggest that decreased adrenal stimulation (perhaps secondary to poor integration of cerebral signals or decreased hypothalamic or pituitary output) is a better explanation for the low postoperative cortisol concentrations observed in infants with catecholamine-resistant hypotension.

Because we found that postoperative catecholamine-resistant hypotension was not caused by adrenal impairment, it should come as no surprise that the tests performed prior to the ligation (e.g., cosyntropin stimulation and cortisol precursor measurements), which were designed to identify infants with adrenal impairment, did not identify infants at risk for developing postoperative catecholamine-resistant hypotension.

Our study has certain limitations. The size of the PDA was not a criterion for study entry, and pre-ligation echocardiograms were not interpreted by the same sonographer. This design might have altered our ability to detect a relationship between PDA size and postoperative hypotension (if one existed). However, previous single center retrospective studies have not detected a relationship between these two variables. Because we investigated a single surgical procedure and a specific anesthesia regimen, our findings may not be applicable to other surgeries in the newborn period.

Our study was not a controlled treatment trial, and therefore our data cannot tell us whether low cortisol values play a role in the development of catecholamine-resistant hypotension or simply are predictive of its occurrence. We speculate that when post-operative hypotension occurs, low cortisol concentrations contribute to its refractory nature and lead to the development of catecholamine-resistant hypotension: 12 of the 14 infants with Inotrope Scores greater than 15 were treated with hydrocortisone (1.5±1.0 mg/kg/d); the Inotrope Scores in these infants dropped by 16±10 points (from 21±8 to 5±6) during the next 6 hours. In contrast, 2 other infants with Scores greater than 15, and 8 infants with Scores between 10–15, were not treated with hydrocortisone at the same time after ligation; their Inotrope Scores either did not change or increased during the next 12 to 24 hours (from 14±4 to 15±10) ($p<0.01$). Only a future, prospective controlled trial will elucidate the contribution of low cortisol production to the severity of postoperative hypotension.

In conclusion, we found that low postoperative cortisol concentrations were not associated with the incidence of postoperative hypotension following PDA ligation. They were, however, associated with the severity of hypotension when it occurred, and its resistance to catecholamine treatment. We speculate that decreased adrenal stimulation, rather than adrenal immaturity or impairment, may be responsible for the decreased cortisol concentrations in these hypotensive infants.

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Abbreviations

PDA	Patent ductus arteriosus
RSS	Respiratory severity score
BP	Blood pressure
ACTH	Adrenocorticotropic hormone

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Appendix

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Table 1

Patient demographics and risk factors associated with Postoperative hypotension

	Hypotension		
	None (n=52)	**Minimal/mild/moderate/severe (n=43)**	**p-value***
Gestation –wks	26.1 ± 2.1	25.6 ± 2.2	-
Gestation ≤25 wks (%)	50	72	0.029
Birth weight -gm	880 ± 295	791 ± 316	-
Sex – male (%)	60	56	-
Preterm labor (%)	73	79	-
PROM >18 hr (%)	20	28	-
Betamethasone > 24 hr (%)	42	37	-
Preeclampsia (%)	12	16	-
Chorioamnionitis (%)	21	21	-
Diabetes (%)	4	9	-
Race -caucasian (%)	25	33	-
Caesarean section (%)	65	72	-
Apgar Score (5 min) ≤3 (%)	24	26	-
Apgar Score (10 min) ≤5 (%)	4	21	0.011**
RDS (%)	98	98	-
Surfactant (%)	94	98	-
Pulmonary hemorrhage (%)	6	16	0.097
Dopamine during 1st 24 hr after birth (%)	23	45	0.023
Sepsis (onset ≤3 d) (%)	2	7	-
Sepsis (onset >4 d) (%)	20	14	-
Hydrocortisone treatment prior to study (%)	13	9	-
Indomethacin or Ibuprofen prior to study (%)	75	81	-
IVH ≥ grade 3 prior to study (%)	23	26	-
NEC/perforation prior to study (%)	19	14	-
ACTH stimulation test-time before surgery - hr	21 ± 22	25 ± 56	-
Postnatal age at ligation - wks	4.6 ± 2.7	2.8 ± 2.5	0.002
Postmenstrual age at ligation (wks)	30.6 ± 3.5	28.4 ± 3.3	0.002
Weight at ligation - gm	1330 ± 541	1026 ± 502	0.006**
PDA size (large) prior to ligation (%)	59	67	-
RSS prior to ligation	3.5 ± 2.4	2.8 ± 1.6	-
Inotrope Score preligation	0.3 ± 1.2	2.7 ± 6.2	0.008**
Fentanyl dose during ligation – μg/kg	15 ± 13	15 ± 13	-
Ligation duration - min	39 ± 21	33 ± 14	-

Values represent mean ± standard deviation or percent (%).

* p-values ≥0.1 are not shown.

** Variables used in the final multivariable model for catecholamine-resistant hypotension.

Note: other variables were dropped from the model if their p-value rose to ≥ 0.1 during forward selection.

Table 2

Postoperative Cortisol concentrations: Comparisons between different groups of Normotensive and Hypotensive infants

Patient Groups	Postoperative Cortisol concentrations			
	Cortisol–ng/ml (interquartile range)	**Cortisol-log(10) (±sd)**	**Cortisol concentrations in lower tertile**	**Cortisol concentrations in upper tertile**
Normotension compared with Hypotension *(minimal/mild/mod & catechol-resistant)*				
Normotension (n=52)	14.9 (10–42)	1.31 (±0.55)	32%	28%
Hypotension *(minimal/mild/mod & catechol-resistant)* (n=43)	28 (8.6–55)	1.38 (±0.62)	36%	38%
Hypotension *(minimal/mild/mod)* **compared with Normotension**				
Hypotension *(minimal/mild/mod)* (n=29)	40.8 * (12–69)	1.56 * (±0.58)	18%	57% *
Normotension (n=52)	14.9* (10–42)	1.31 * (±0.55)	32%	28% *
Hypotension *(catechol-resistant)* **compared with Normotension**				
Hypotension *(catechol-resistant)* (n=14)	8.9 * (5.1–12)	1.03 * (±0.57)	71% *	0%
Normotension (n=52)	14.9* (10–42)	1.31 * (±0.55)	32% *	28%
Hypotension *(catechol-resistant)* **compared with Hypotension** *(minimal/mild/mod)*				
Hypotension *(catechol-resistant)* (n=14)	8.9 * (5.1–12)	1.03 * (±0.57)	71% *	0% *
Hypotension *(minimal/mild/mod)* (n=29)	40.8* (12–69)	1.56 * (±0.58)	18% *	57% *
Hypotension *(catechol-resistant)* **compared with Normotension or Hypotension** *(minimal/mild/mod)*				
Hypotension *(catechol-resistant)* (n=14)	8.9 * (5.1–12)	1.03 * (±0.57)	71% *	0% *
Normotension or Hypotension *(minimal/mild/mod)* (n=81)	29.2 * (11–54)	1.40 * (±0.57)	27% *	38% *

Values represent median (interquartile range) of absolute cortisol values, mean (± standard deviation) of the log (base 10) transformed cortisol values, or percent (%) of infants with cortisol values in the lower or upper third of the distribution of postoperative cortisol concentrations.

* p-values <0.05 when comparing the two patient groups.

Hypotension severity is defined by the maximum support needed to maintain BP above the hypotensive range (see Methods): *minimal* = volume boluses alone; *mild* = maximum Inotrope Score < 10; *moderate* = maximum Inotrope Score 10-to-15; and *catecholamine-resistant hypotension* = maximum Inotrope Score > 15.

Table 3

Serum steroid concentrations associated with Catecholamine-Resistant Hypotension

	Hypotension				
	None, minimal, mild, or moderate (n=81)		Catecholamine-resistant (n=14)		
	median (ng/ml)	interquartile range (ng/ml)	median (ng/ml)	interquartile range (ng/ml)	p-value*
Cortisol-pre	11.4	7.8–31	12.3	6.9–33	-
Cortisol-ACTH	87.7	62–137	80.1	43–178	-
Cortisol-postop	29.2	11–54	8.9	5.1–12	0.007
17OHP-pre	1.6	0.6–4.2	2.4	2.0–3.1	0.072
17OHP-ACTH	2.6	1.1–5.7	3.8	2.7–6.1	-
17OHP-postop	1.0	0.5–3.0	1.1	0.7–1.6	-
Cortisone-pre	16	12–24	15	10–20	-
Cortisone-ACTH	17	14–24	16	10–21	-
Cortisone-postop	16	13–26	12	7.0–20	0.035
11-deoxycortisol-pre	2.5	1.4–4.0	1.3	1.3–4.1	-
11-deoxycortisol-ACTH	5.4	3.1–8.3	4.2	3.1–9.1	-
11-deoxycortisol-postop	2.5	1.4–4.4	1.1	0.7–2.0	0.009
21-deoxycortisol-pre	2.1	1.0–4.0	1.3	1.1–4.1	-
21-deoxycortisol-ACTH	5.4	3.1–8.3	4.2	3.1–9.2	-
21-deoxycortisol-postop	2.5	1.1–4.3	1.1	0.3–2.0	0.027
Progesterone-pre	0.5	0.2–1.0	0.5	0.5–0.7	-
Progesterone -ACTH	0.8	0.3–1.5	0.8	0.7–1.6	-
Progesterone-postop	0.4	0.1–0.9	0.3	0.1–0.9	-
11-DOC-pre	0.09	0.0–0.3	0.15	0.0–0.8	-
11-DOC-ACTH	0.42	0.2–0.8	0.45	0.1–2.5	-
11-DOC-postop	0.13	0.0–0.6	0.02	0.0–0.6	-
Corticosterone-pre	1.4	0.6–3.1	0.9	0.4–5.9	-
Corticosterone-ACTH	16.1	8.6–29	9.6	6.2–31	-
Corticosterone-postop	1.7	0.8–5.6	0.9	0.4–1.5	0.057

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	Hypotension				
	None, minimal, mild, or moderate (n=81)		Catecholamine-resistant (n=14)		
	median (ng/ml)	interquartile range (ng/ml)	median (ng/ml)	interquartile range (ng/ml)	p-value*
Androstenedione-pre	0.5	0.2–0.8	0.4	0.3–0.6	-
Androstenedione-ACTH	1.0	0.4–1.5	0.9	0.3–1.7	-
Androstenedione-postop	0.3	0.1–0.6	0.2	0.1–0.3	0.045
DHEAS-pre	963	525–2141	2317	819–4073	-
DHEAS-ACTH	1639	847–3044	2131	469–4102	-
DHEAS-postop	751	283–1793	535	370–1533	-

* Mann-Whitney test was used to compare the variables. p-values ≥0.1 are not shown.

Definitions: pre, values obtained prior to ACTH stimulation test (prior to ligation); ACTH, values obtained 60 min after ACTH stimulation (prior to ligation); postop, values obtained between 10–12 hr after ligation.