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Endocrine stress reaction to surgery in brain-dead organ donors

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Abstract We studied the course of plasma levels of the stress markers adrenocorticotropic hormone (ACTH), cortisol, human growth hormone (h-GH), β-endorphin, and prolactin during retrieval surgery in eleven brain-dead organ donors scheduled for multiple organ explantation. Donors were divided into two groups according to hemodynamic stability. Hormones demonstrated a great variability in plasma levels and in the pattern of reaction, revealing a different degree of remaining pituitary function. β-Endorphin was the only stress hormone that showed a response to surgical stimuli in six patients. Only three of them developed a concomitant rise in ACTH. Cortisol, prolactin, and h-GH plasma levels did not change during the observation period. In the three cases with a slight elevation in ACTH, no subsequent change in cortisol was detectable. β-Endorphin showed greater variability and a tendency to higher levels in the group presenting with a higher arterial pressure, which resulted in a significant difference ($P < 0.005$) when distributions were compared using the Mann-Whitney U-test. No correlation was found between hypotensive episodes and deficiencies of other stress hormones. We conclude that pituitary function varies considerably in brain-dead organ donors without demonstrating a correlation to the onset of hypotension. Thus, we feel no need for a substitution treatment with any of the hormones investigated prior to organ explantation.

Key words Brain death, endocrine stress · Donor, endocrine stress · Stress hormones, brain death · Endocrine stress, brain death

Introduction

The occurrence of severe hypotension in brain-dead organ donors during organ retrieval surgery often requiring excessive volume substitution and catecholamine support is a problem well known to transplantation anesthesiologists [23]. However, both hypotension itself and its treatments may contribute to allograft damage [1, 6, 11, 13, 14, 22].

Dysfunction of endocrine systems (e.g., of T3, T4, insulin, and cortisol) has been said to be responsible for hypotension in brain-dead organ donors, and substitution has been reported to improve hemodynamic stability and allograft function after transplantation [16–20]. These results have, however, been questioned as low levels of the hormones discussed and the occurrence of hypotension failed to show a correlation [9, 10]. Yet, attention was mostly focused on hormonal activity in organ donors in the intensive care unit who were not undergoing somatosensoric stimulation.

In general, nociceptive surgical stimulation elicits an increased hypothalamic-pituitary-adrenal activity generally referred to as the stress response to injury [3, 29]. Although the importance of this stress response for maintenance of hemodynamic stability is still being discussed [2, 27], it is commonly known that failure of the

hypothalamic-pituitary-adrenal axis in particular can result in hypotension following surgical trauma [4, 28].

It is well accepted that, in spite of brain death, the function of the pituitary gland can remain active to a variable degree [9, 10, 16, 25]. However, as the transmission of stimuli arising from painful surgical manipulations from the spinal level to the hypothalamic-pituitary region is interrupted in brain death, a sufficient rise in stress hormones for the required adaptation to surgical stress is impeded. Thus, we hypothesized that hypotension in brain-dead organ donors during organ retrieval surgery might not be due to low residual hormone levels but to failure of the hypothalamic-pituitary system to respond to surgical stress. Therefore, our objective was to investigate the course of plasma levels of the stress markers adrenocorticotropic hormone (ACTH), cortisol, β-endorphin, prolactin, and human growth hormone (h-GH) during organ explantation and to correlate them to stressful surgical events and the occurrence of hypotension.

Patients and methods

Donors

The study protocol was approved by the ethics committee of the department. Eleven brain-dead organ donors scheduled for multiple organ explanation were included in the study. The median donor age was 41 years (range 25–61 years); there were two females and nine males. The causes of death included: subarachnoidal bleeding ($n = 6$), severe head injury ($n = 4$), and thrombosis of the basilar artery ($n = 1$). All donors fulfilled the Austrian legal criteria for brain death [21] that regulate the procedure (repetition of testing, status of the clinician concerned; exclusion of hypothermia, metabolic, and endocrine disturbances and drug action) that has to be followed until brain death may be declared. Clinical testing confirms absence of brain-stem and vestibulo-ocular reflexes and apnea after disconnection from the ventilator. Furthermore, Austrian law makes it mandatory to confirm brain death by nonfilling four-vessel angiography (two of our cases) or by a 6-h isoelectric EEG recording (nine of our patients) [21]. The mean time of artificial ventilation prior to explantation was 34.3 ± 13.2 h (SD). The time of explantation was between 3:00 and 7:00 a.m. in all donors.

The donors were divided into two groups, depending on the intraoperative hemodynamic course: group 1 without hypotension (mean arterial blood pressure > 60 mmHg; $n = 7$) and group 2 with hypotension (< 60 mmHg; $n = 4$).

Intraoperative management

The observation period started upon the arrival of the organ donor in the operating room and ended 45 min after sternotomy. To avoid confusing results due to differences in volume substitution and other therapeutic events (e.g., prostaglandin I2 application), later periods of the surgery were not included in our considerations. Artificial ventilation was maintained with an oxygen/air mixture with fractional inspiratory oxygen concentration (FIO_2 of 0.5. Hemodynamic stability could be achieved without the administration of catecholamines other than low-dose dopamine (maximum 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) prior and during surgery in seven cases. Central venous pressure was monitored continuously and was aimed at levels above 12 cm H_2O. Blood pressure was measured by means of a radial artery catheter. No analgesic or neuromuscular blocking agents were used during organ harvesting. Fluid substitution consisted only of crystalloids. Hemodynamic monitoring was performed continuously by means of a Siemens Sirecust 4000 computer-assisted documentation system.

Care was taken by the managing anesthesiologist to ensure that hemodynamic data at the points of measurement were not biased by mechanical compression of the large vessels or manipulation of the abdominal or thoracic organs. In cases of doubt, the surgeon was asked to interrupt manipulations for a short period to verify hemodynamic alterations.

Collection and processing of blood samples

Blood was collected at the following time points: before surgical manipulations started, after skin incision, after sternotomy, and at 15, 30, and 45 min thereafter. β-Endorphin was determined in ten donors, prolactin in five. Blood samples were collected in prechilled EDTA tubes, promptly centrifuged, separated, and stored at –20 °C until further processing.

For measurement of the pituitary hormones, commercially available kits were used. ACTH was determined by an immuno radiometric assay (IRMA; Eurodiagnostics, Apeldoorn, The Netherlands); its interassay variation is 3.7 % and intra-assay variation 3.4 %; normal values are 10–70 $pg \cdot ml^{-1}$. β-Endorphin was determined by a radio immuno assay (RIA; Incstar, Stillwater, Minn., USA); interassay variation is 10.7 % and intra-assay variation 5.0 %; normal values are 30–80 $pg \cdot ml^{-1}$. Cortisol was determined by a RIA (Incstar, Stillwater, Minn., USA); interassay variation is 3.7 % and intra-assay variation 1.5 %; normal values are 6–20 $\mu g \cdot dl^{-1}$. h-Gh was determined by an IRMA (Hybritech, Liege, Belgium); interassay variation is 12.7 % and intra-assay variation 8.7 %; normal values are 0–5 $ng \cdot ml^{-1}$. Finally, prolactin was determined by an enzyme-linked immunosorbent assay (ELISA; Serono, Coinsins, CH) interasssay variation is 5.5 % and intra-assay variation 2.8 %; normal values are 40 ng/ml.

Colloid osmotic pressure (COP), blood glucose, acid-base balance, blood gases, and electrolytes were sampled simultaneously. Blood lactate was analyzed at the beginning and at the end of the observation period.

Estimation of the endocrine × hemodynamic interaction

Hypotension was defined as a drop in the mean blood pressure below 60 mmHg, as this value is regarded as critical for kidney perfusion, and the data were grouped accordingly. Data collected in our study did not show a normal distribution. Correlations were calculated between endocrine and hemodynamic courses within the total collective and the two subgroups using Spearman's rank correlation test. The Mann-Whitney U-test was used to detect differences in hemodynamics and hormone levels between the two groups. An α-p-level of 0.05 was assumed to be significant.

Results

Organ harvesting was performed without complications in all of the brain-dead organ donors. No major bleeding or cardiac dysrhythmias occurred during the observation period. Fluid balance increased during the observa-

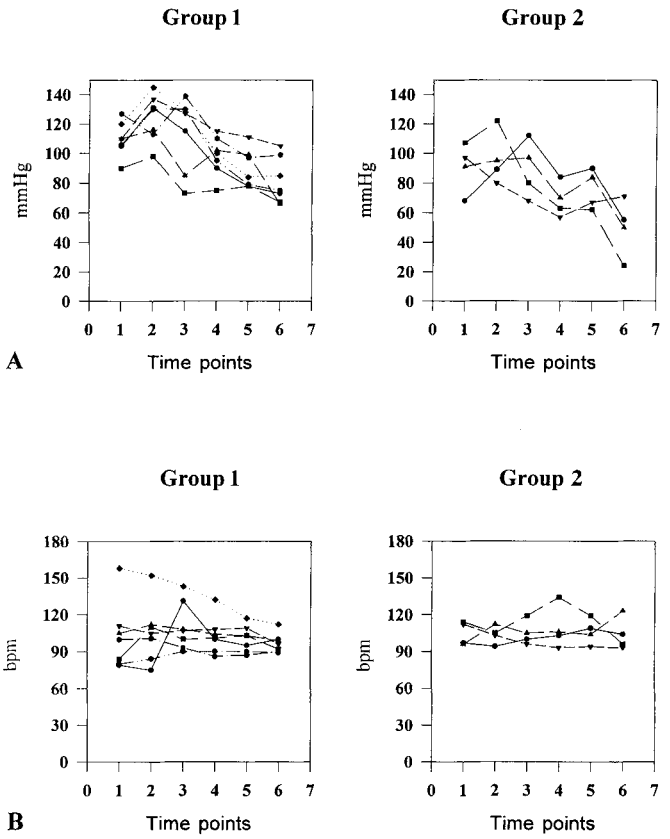

Fig. 1 **A** Mean arterial blood pressure and **B** heart rate during organ explantation in brain-dead organ donors. Group 1 was defined by a mean blood pressure above 60 mmHg and group 2 by one below 60 mmHg. Time points are baseline level (*1*), skin incision (*2*), sternotomy (*3*), 15 min (*4*), 30 min (*5*), and 45 min (*6*) thereafter

tion period by 1350 ± 250 ml (mean ± SD). Changes in blood pressure and heart rate are shown in Fig. 1 and Table 1. Blood pressure decreased as the operation went on. In four donors, mean arterial blood pressure dropped below 60 mmHg during surgery. Thus, seven donors were included in group 1 without hypotension and four in group 2 with hypotension. The difference in mean arterial blood pressure was significant ($P = 0.001$)

Blood gases were found to be in a supraoptimal range; base excess increased during the observation period from –2.6 ± 2.4 to –5.45 ± 2.5 mmol/l. No changes were found in blood lactate, serum sodium, or potassium levels. Blood glucose remained at an elevated level throughout the surgery (118 ± 25 mg/dl before surgery to 124 ± 38 mg/dl at the end of the observation period).

The courses of the stress hormones measured are given in Figs. 2 and 3 and in Table 2.

ACTH

Baseline levels were in the normal range. In two of the eleven donors, ACTH plasma levels were just above or below the detection limit of the test employed (one in group 1 and one in group 2). Neither of these two donors showed a reaction to nociceptive stimuli (Fig. 1). Nine donors displayed plasma levels in the normal range at each measurement. Three of them (one in group 1 two in group 2) displayed a major increase (33 %–60 %) at the time of skin incision and/or sternotomy and remained at levels above baseline in two cases (Fig. 2).

Cortisol

Ten donors showed baseline levels within the normal range; one displayed values below normal (4.8 μg · dl^{-1}). In all of the donors, plasma levels remained unchanged throughout the observation period and did not show any response to surgical stimuli, not even in those donors whose ACTH had increased during surgery.

β-Endorphin

β-Endorphin plasma levels were obtained in ten of the eleven patients. Three donors showed elevated baseline

Table 1 Mean arterial blood pressure, heart rate, and central venous pressure (CVP) changes during organ retrieval surgery. Values are given as mean ± SD. Difference between group 1 and group 2 in mean arterial blood pressure was significant ($P = 0.001$ by Mann-Whitney U-test)

		0	Skin incision	Sternotomy	+ 15 min	+ 30 min	+ 45 min
Mean arterial blood pressure (mm Hg)	Total	103 ± 16	114 ± 21	104 ± 25	87 ± 19	84 ± 14	68 ± 23
	Group 1	110 ± 12	124 ± 16	114 ± 25	98 ± 13	89 ± 13	81 ± 17
	Group 2	91 ± 17	97 ± 18	89 ± 19	68 ± 12	76 ± 13	50 ± 19
Heart rate (bpm)	Total	103 ± 22	105 ± 20	108 ± 16	105 ± 15	103 ± 10	94 ± 17
	Group 1	102 ± 28	106 ± 25	110 ± 20	103 ± 15	101 ± 11	94 ± 5
	Group 2	105 ± 10	104 ± 7	105 ± 10	109 ± 18	107 ± 10	94 ± 28
CVP (cmH_2O)	Total	13 ± 2.1	12.9 ± 1.8	12.8 ± 1.4	13.4 ± 1.6	12.8 ± 1.5	12.1 ± 1.5
	Group 1	13.2 ± 2.3	12.6 ± 2	12.9 ± 1.7	13.2 ± 1.6	12.8 ± 1.2	11.6 ± 1.6
	Group 2	12.5 ± 2.1	13.5 ± 1.3	12.75 ± 1	13.75 ± 1.7	12.75 ± 2.2	13 ± 0.8

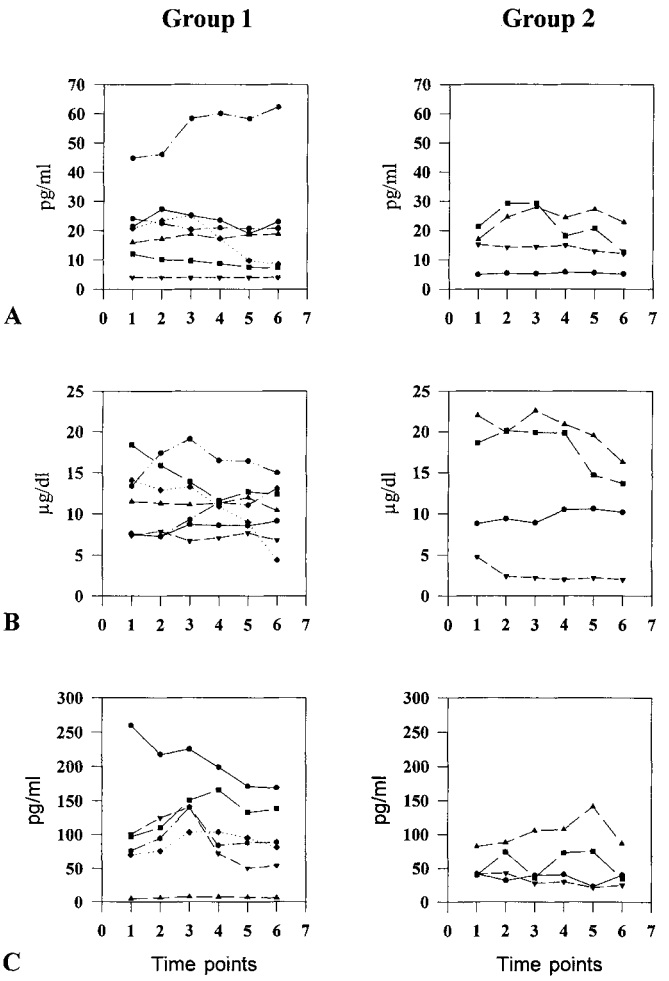

Fig. 2A–C Course of: **A** ACTH, **B** cortisol, and **C** β-endorphin during organ explantation surgery. Time points as in Fig. 1

levels (all in group 1). In one of these three, the plasma level decreased but still remained at supranormal values at the termination of the observation period; the other two donors demonstrated increasing plasma levels after skin incision and sternotomy, but these decreased thereafter. Normal baseline levels were found in six donors, (two in group 1 and four in group 2). Three of them developed a rise related to the surgical stimuli, one showed decreasing levels after sternotomy (group 2), and another one remained unchanged throughout the observation period (group 2). One of the donors (group 1) demonstrated a very low baseline level (4.8 pg · ml^{-1}) without remarkable changes in further measurements.

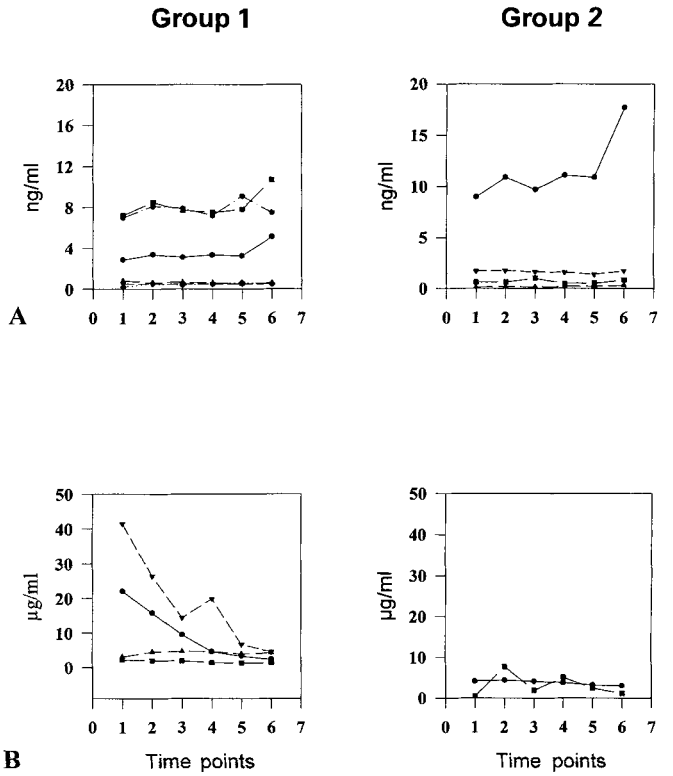

Fig. 3A,B Course of: **A** h-growth hormone and **B** prolactin during explantation surgery. Time points as in Fig. 1

Human growth hormone

With regard to h-Gh, two groups could be distinguished; baseline levels in the lower normal range were found in seven donors (four in group 1 and three in group 2) and in the upper normal range in four donors (three in group 1 and one in group 2). The first group showed no change in plasma levels, whereas an increase was found at 45 min after sternotomy in one donor in the second group. No other significant changes in plasma levels in connection with painful surgical stress were detected at any point of measurement.

Prolactin

Prolactin was determined in six patients (four in group 1 and two in group 2). Three donors were receiving low-dose dopamine (2 µg · kg^{-1} · min^{-1}), thus making interpretation difficult. Three donors (group 1) exhibited plasma values in the upper normal range and six in the lower normal range. Plasma levels were slightly elevated but well below the range that would be anticipated for a stress reaction.

Table 2 Hormonal changes during organ retrieval surgery. Values represent median (range)

		0	Skin incision	Sternotomy	+ 15 min	+ 30 min	+ 45 min
ACTH	Total	16.9 (4–44.9)	22.5 (4–46.2)	20.3 (4–58.4)	17.2 (4–60.1)	18.6 (4–58.3)	12.6 (4–62.3)
(pg · ml^{-1})	Group 1	20.8 (4–44.9)	22.5 (4–46.2)	20.3 (4–58.4)	17.2 (4–60.1)	18.6 (4–58.3)	18.7 (4–62.3)
	Group 2	16.5 (5–21.2)	19.4 (5.4–29.2)	21.2 (5.2–29.3)	16.5 (5.8–24.3)	16.8 (5.6–27.2)	12.4 (5.1–22.8)
Cortisol	Total	12.5 (7.4–22)	11.3 (2.4–20.1)	11.0 (2.2–22.6)	11.3 (2–20.9)	11.0 (2.2–19.5)	10.4 (2–16.3)
(μg · dl^{-1})	Group 1	11.5 (7.4–18.4)	11.3 (7.3–17.4)	11.1 (6.7–19.1)	11.3 (7.1–16.5)	11.1 (7.7–16.4)	10.4 (4.4–15)
	Group 2	18.6 (8.8–22)	14.7 (2.4–20.1)	14.4 (62.2–22.6)	15.2 (2–20.9)	12.7 (2.2–19.5)	11.95 (2–16.3)
β-Endorphin	Total	73 (4.8–260)	82 (6.3–217)	104 (7.6–225)	78.5 (7.2–199)	81.5 (7–171)	68 (6–169)
(pg · ml^{-1})	Group 1	86.5 (4.8–260)	102 (6.3–217)	140 (7.6–225)	93.7 (7.2–199)	91.4 (7–171)	85 (6–169)
	Group 2	41.9 (40–82.6)	58.5 (32.1–88)	37.8 (28–105)	56.9 (30–107)	49 (21.2–141)	37.2 (25.2–86.6)
h-GH (ng · ml^{-1})	Total	1.26 (0.14–9)	1.4 (0.2–10.9)	1.35 (0.15–9.7)	1.3 (0.2–11.1)	1.2 (0.22–10.9)	1.4 (0.3–17.7)
	Group 1	3.9 (0.2–7.2)	3 (0.5–8.5)	2.6 (0.4–7.9)	1.8 (0.5–7.5)	1.7 (0.5–9.1)	1.4 (0.5–10.7)
	Group 2	1.18 (0.14–9)	1.2 (0.2–10.9)	1.3 (0.15–9.7)	1 (0.2–11.1)	0.96 (0.22–10.9)	1.3 (0.3–17.7)
Prolactin	Total	3.65 (0.5–41.5)	6.1 (2–26.4)	4.4 (1.9–14.4)	4.6 (1.4–19.9)	3.25 (1.3–6.7)	4.5 (2.8–1.4)
(μg · ml^{-1})	Group 1	12.6 (2.2–41.5)	10.5 (2–26.4)	7.1 (1.9–14.4)	4.6 (1.4–19.9)	3.6 (1.3–6.7)	3.4 (1.4–4.5)
	Group 2	2.35 (0.5–4.2)	6.05 (4.4–7.7)	3 (1.9–4.1)	4.5 (3.8–5.1)	2.8 (2.4–3.2)	2.1 (1.1–3)

Interaction between stress hormones and hemodynamic changes

No correlation between mean arterial blood pressure and any of the endocrine parameters in the complete study group or in the separate groups could be detected with Spearman's rank correlation test.

Significant differences between groups 1 and 2 were found in mean arterial blood pressure ($P = 0.001$) as well as in β-endorphin plasma levels ($P = 0.003$). All other parameters displayed no significant differences between the two groups.

Discussion

To investigate a possible connection between hemodynamic deterioration and pituitary function in brain-dead organ donors, we studied the course of several hormones during organ retrieval surgery that were assumed to contribute to the trauma-related stress response. Our donors displayed different degrees of persisting pituitary function, as could be seen by the variability of baseline values and in responsiveness to surgical stress. Thus, the contribution of the hormones investigated to the maintenance of hemodynamic stability seems to be of minor importance and does not justify substitution during organ retrieval surgery.

Hormonal changes after brain death have been described by several authors [8–10, 20, 23–25], and hormonal insufficiency was postulated to be responsible for hemodynamic instability [16–20]. However, although substitution of triiodothyronine, insulin, and cortisol was shown to improve hemodynamic performance and allograft function [16–20, 26, 29, 31], other studies failed to demonstrate beneficial effects of hormone substitution [9, 10].

Several studies investigated the function of the anterior lobe of the pituitary gland under resting conditions prior to organ explantation and found sufficient serum levels of pituitary hormones in the majority of cases [8–10, 23–25]. Howlett et al. also investigated plasma levels of these hormones during organ harvesting but took one sample only throughout the surgery, thus possibly omitting adaptive endocrine reactions [9].

Thus, the question of endocrine insufficiency in brain death and hormonal substitution therapy was still not adequately answered, and the possibility remains that it is not reduced baseline levels of these hormones that are responsible for the occurrence of hypotension but rather the inability to adequately adapt to surgical stress during organ retrieval surgery. This mechanism is well known in patients with an insufficiency of the adrenal cortex, where a perioperative instability of circulation is common [4, 28], and it should be expected in brain-dead organ donors as the transmission of stimuli from the spinal level to the nonviable midbrain is impossible. Thus, in contrast to earlier investigations, we studied the reaction of hormones, expected to participate in this stress response, to painful surgical stimuli and we correlated plasma levels to blood pressure.

The variability in the values of plasma hormone baseline levels and in the pattern of reacting hormones seems to reflect a varying degree of damage endured by the pituitary gland at that point. In spite of the cessation of blood flow in brain death, the pituitary gland seems to possess a persisting blood supply from extradurally arising arteries [25]. We can only hypothesize whether the variability we found (1) is due to differences in the extent of this remaining blood supply, (2) depends predominantly on the length of time between the appearance of the noxious cause and surgery, or (3) might be due to the Etiology of brain death. Another explanation for the observed variability in baseline levels of hor-

mones would be changes due to a circadian rhythm. However, this cause seems rather unlikely as all surgeries were performed at the same time of day and as circadian rhythm is also said to vanish in brain death [8, 23].

A similar heterogeneity in intraoperative hemodynamics of brain-dead organ donors has been reported [5]. The variability in cardiovascular response to surgical stimulation could be due to different degrees of fluid substitution, myocardial depression following injury by excessive endogenous catecholamine release [6], loss of sympathetic tone [22], or endocrine disturbances. However, although the difference in mean blood pressure between our groups reached statistical significance, we could not attribute hemodynamic stability to the reactivity or level of one of the endocrine parameters tested. β-Endorphin was distinctly increased in one organ donor, so that the comparison between the high and low blood pressure group resulted in a significant difference. However, as our groups were small and not normally distributed, we had to use the Mann-Whitney U-test, which does not compare medians but distributions. Thus, when evaluating the raw data, it became apparent that normal and slightly elevated plasma endorphin levels did not exclude a drop in blood pressure (Fig. 2). We feel that these changes in β-endorphin levels might characterize a generally good condition of the organ donors and not a cause of hypotension.

The same applies to the differences in plasma levels in h-Gh. Two groups were distinguished, demonstrating plasma levels in either the upper normal range or the lower normal range. However, the distribution between the two hemodynamically different groups appeared to be even.

In contrast to other pituitary hormones, prolactin secretion is predominantly under the inhibitory influence of the brain. This inhibition is exerted by the release of a potent prolactin inhibitory factor, which was identified as dopamine, into the hypothalamopituitary portal system [12]. Thus, although a rise in plasma prolactin might be expected after disruption of this inhibitory regulation, no conclusion can be drawn from the results of the prolactin measurements as they were few in number and the effect of the low-dose dopamine infusion remains unclear in brain death.

Baseline levels measured in our study reconfirm findings reported by others that most brain-dead organ donors are still able to maintain sufficient anterior pituitary function for hours after the onset of brain death [8–10, 23–25]. However, some details of the courses of hormone levels were rather remarkable. Cortisol never reacted to surgical stress and did not even increase when its physiological regulator, ACTH, was increasing (Fig. 2). Thus, in our donors, the functional axis between pituitary and adrenal gland has deteriorated.

ACTH and β-endorphins seemed to be the only pituitary stress markers that reacted to surgical provocation in our study group. These hormones are synthesized from a common precursor [7] but seem to display an independent secretion pattern in brain death as only three of the six donors demonstrating a stress-related increase in β-endorphins showed a rise in ACTH.

We would like to emphasize that the diagnosis of pituitary insufficiency would need the support of provocation testing using releasing hormones. However, information concerning this subject is scarce. Only Schrader et al. [25] has performed provocation testing in two cases (of six studied) and received differing results. Moreover, histological and functional evaluations of the pituitary gland after brain death remain unclear.

In conclusion, we were unable to detect a correlation between the endocrine parameters tested and hemodynamic performance during organ retrieval surgery. Even the patient with the greatest deficiency in endocrine function demonstrated hemodynamic stability during explantation. We therefore feel no need to supplement any of the investigated hormones prior to or during organ explantation.

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