Hypothalamic functions in patients with pituitary insufficiency
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Cranial radiotherapy is associated with decreased cardiac baroreflex sensitivity in patients with pituitary insufficiency

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Chapter 3

ABSTRACT

Objective: Cranial radiation therapy (CRT) has been linked to cardiovascular morbidity and mortality in patients with pituitary insufficiency. Baroreflex sensitivity (BRS) plays a major role in the development and progression of cardiovascular disorders. We investigated whether a history of CRT in patients with pituitary insufficiency affects BRS.

Design: Case-control study

Patients: In total 28 patients were studied: 13 hypopituitary patients with a history CRT [age 58 ± 15 yr; 7 men; BMI 23.1 ± 7.4 kg/m²] and 15 hypopituitary patients without CRT [age 51 ± 15 yr; 11 men; BMI 29.6 ± 5.6 kg/m²].

Measurements: The non-invasive xBRS method was used to determine BRS in supine position and during standing.

Results: In patients with CRT, BRS was lower in supine position [BRSsupine: 7.3 (interquartile range (IQR) 6.5 – 10.4) vs. 12.2 (IQR 6.8 – 23.8) ms/mmHg, \( p = 0.022 \)] and during standing [BRSstanding: 4.3 (IQR 3.2 – 5.3) vs. 8.2 (IQR 5.0 – 10.9), \( p = 0.005 \)] than in patients without CRT. Multivariate regression analysis with CRT, age, body mass index and systolic blood pressure confirmed that CRT is an independent determinant of BRSstanding (\( B = -0.283; \ SE = 0.094; p = 0.006 \)). Moreover, CRT was an important determinant in the final multivariate model of BRSsupine (\( B = -0.164; \ SE = 0.086; p = 0.068 \)).

Conclusions: A history of CRT is associated with a decreased BRS in patients with pituitary insufficiency. This finding suggests that BRS may be a link in explaining the increased cardiovascular morbidity and mortality in these patients.
INTRODUCTION

Cranial radiotherapy (CRT) is frequently used for the treatment of pituitary tumours. It is applied to treat hormone producing tumours (i.e. growth hormone- and adrenocorticotropic hormone secreting pituitary adenomas and prolactinomas), and to prevent tumour regrowth after surgery in patients with a non-functioning macroadenoma (1). However, CRT has been associated with a number of complications including hypothalamic-pituitary insufficiency (2), optic pathway injury (3;4), impaired neurocognitive functioning (5) and induction of de novo intracranial tumours (6). Of particular interest is the association between CRT and cardiovascular diseases. The risk of stroke is dose dependently associated with CRT (4;7-10). Moreover, premature mortality due to cardiovascular diseases has been reported in irradiated patients with pituitary insufficiency (10-13). The exact cause of increased cardiovascular risk in irradiated patients with pituitary insufficiency is unknown, but it is conceivable that CRT causes vascular injuries and hemodynamic changes (14). An indicator of cardiovascular health is baroreflex sensitivity (BRS), which is a measure of changes in heart rate in response to changes in blood pressure. When blood pressure rises, the carotid sinuses and aortic arch are stretched which in turn activate the baroreceptors. This baroreceptor signal is relayed via glossopharyngeal and vagal nerves and terminates within the nucleus tractus solitarius (NTS). Subsequently, the NTS neurons convey this signal via the ventrolateral medulla (VLM) and rostral VLM (RVLM) in the lower brainstem to the spinal cord, causing activation of the parasympathetic nervous system and inhibition of the sympathetic nervous system. The former reduces heart rate and the latter primarily reduces the systemic vascular resistance, together lowering blood pressure. Conversely, a decrease in arterial pressure reduces baroreceptor afferent discharge and triggers heart rate and systemic vascular resistance to increase (15). The BRS has been shown to predict mortality in patients with previous myocardial infarction (16-20) and it is associated with increased long-term mortality after acute ischemic stroke (21). As changes in the BRS reflect alterations in the autonomic control of the cardiovascular system and CRT is associated with increased cardiovascular diseases in patients with pituitary insufficiency, we investigated whether a history of CRT affects BRS in patients with pituitary insufficiency.

SUBJECTS AND METHODS

Subjects

Consecutive patients with pituitary insufficiency between 18 and 80 years old visiting our Endocrine Outpatient Clinic (Academic Medical Centre of the University of Amsterdam) were invited to participate in this cross-sectional study. Pituitary insufficiency was defined
as having at least one anterior pituitary hormone deficiency. Excessive production of
pituitary hormones had not been present for at least 5 years in subjects with a hormone
producing tumour. All patients were seen on a regular basis by an internist-endocrinologist
for clinical and biochemical evaluation. Conventional hormone replacement therapy was
given according to the standard clinical practice, consisting of L-thyroxine, hydrocortisone,
sex hormones, recombinant growth hormone (rhGH) and/or vasopressin analogues.
Exclusion criteria were a history of total body irradiation and the use of antihypertensive
medication, as these drugs affect autonomic control of the cardiovascular system.
The Medical Ethics Committee of the Academic Medical Centre approved the study
protocol which was conducted in accordance with the Declaration of Helsinki. All patients
provided written informed consent prior to participation in the study.

**Measurements**

After an overnight fast, examinations started at 8:30 AM in a quiet room, where ambient
temperature was controlled between 20 and 24 ºC. Patients were asked not to speak or
move during the measurements.

Office blood pressure was determined from the average of 5 consecutive automatic blood
pressure readings (Dinamap, Johnson & Johnson Medical Inc.) during 15 minutes of supine
rest. Pituitary hormone concentrations were measured in venous serum or plasma samples.
Beat-to-beat blood pressure was measured noninvasively using the Nexfin monitor (BMEYE
B.V. The Netherlands). This examination commenced with a 5 minute supine period to
bring physiologic functions to resting levels, followed by a baseline recording in supine
position during 20 minutes (BRSsupine). Subsequently, patients were asked to assume a
free standing position during 10 minutes to record postural stress (BRSstanding). Venous
blood samples were drawn 1 minute before and after 10 minutes of standing to determine
the concentrations of plasma epinephrine and norepinephrine.

Continuous non-invasive pressure measurement with The Nexfin monitor is based on the
volume clamp methodology (22) in combination with physiocal criteria (23). An inflatable
cuff with an optical blood volume measuring system is attached to the middle phalanx of
the left finger. By applying a cuff pressure equal to arterial pressure throughout the cardiac
cycle, blood volume is clamped to a certain level which is determined by the physiocal
criteria. In this way, calibrated recordings of finger arterial pressure are obtained. Brachial
arterial blood pressure is reconstructed from finger arterial pressure, by correcting for
differences in wave shape (24) and the decrease in mean arterial pressure (25). The cuffed
finger was held at mid-thorax level to avoid hydrostatics pressure differences.

For the quantification of the BRSsupine and BRSstanding, we used the xBRS method as
previously described (26). This method establishes the cross-correlation between systolic
blood pressure variations and subsequent variations in interbeat interval. The beat-to-beat
values of systolic blood pressure and interbeat interval were interpolated and resampled at
1 sec. Then, of 10 s windows the cross-correlation was calculated for delays of 0s to 5s and
the combination giving the highest correlation was accepted when \( P < 0.05 \). The slope of the regression line gave BRS, expressed in ms/mmHg. This process was repetitively repeated for a series of systolic blood pressure and interbeat interval samples 1 s later. Since the distributions of individual BRS values were best described as log-normal (26), geometric averages were used to obtain one value per subject. For each patient, we selected a period of eight minutes of uninterrupted measurements in the supine (BRSsupine) as well as the standing (BRSstanding) position to perform statistical analyses.

**Statistical analyses**

Data were analyzed with SPSS for Windows (version 19.0, SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate normal distribution of the parameters. BRSSupine and BRStanding were log-transformed to improve normality for statistical testing.

Normal distributed variables are presented as mean ± SD, non-normal distributed variables as median (25th-75th percentile) and categorical variables as counts. We used the Student’s t-test for normal distributed variables and the Mann-Whitney U test for non-normal distributed variables to evaluate group differences in numerical variables. The Chi-square test was used to analyze differences between categorical data in both groups. If the sample size was small or cells had an expected count less than 5, the Fisher exact test was used.

Multiple linear regression analysis was conducted to determine whether CRT influenced \( \log[\text{BRSSupine}] \) or \( \log[\text{BRStanding}] \) after adjusting for other possible confounding factors. We performed univariate regression analysis to assess the associations between \( \log[\text{BRS}] \) and respectively age, body mass index, systolic blood pressure, diastolic blood pressure, heart rate and CRT. Variables from these univariate analyses with \( p < 0.10 \) were included in the multivariable model and backward eliminated to a significance level of \( p < 0.10 \). For each regression model, we checked assumptions for linearity and constant variance. These were assessed by plotting residuals against predicted values, and investigate deviations for linearity and inconsistent variance. The statistical significance level for all analyses was set at \( p = 0.05 \) (two-sided) unless otherwise mentioned.

**RESULTS**

**Patient characteristics**

We included twenty-eight patients in the present study, of whom thirteen had been treated with CRT [age 58 ± 15 yr; 7 men; BMI 23.1 ± 7.4 kg/m²] and fifteen had not been treated with CRT [age 51 ± 15 yr; 11 men; BMI 29.6 ± 5.6 kg/m²]. One BRSSupine measurement in the CRT group was excluded because of insufficient technical quality of the recording.
Within the CRT group, eleven patients received post-operative CRT and two patients received CRT to prevent Nelson’s syndrome after bilateral adrenalectomy. The median interval between completion of radiotherapy and time of investigation was 21 yr (11-32

<table>
<thead>
<tr>
<th>TABLE 1. Clinical characteristics</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>History of Cranial Radiotherapy</strong></td>
</tr>
<tr>
<td>Age - yr</td>
</tr>
<tr>
<td>Male / Female - no.</td>
</tr>
<tr>
<td>Time between histological diagnosis and this study - yr</td>
</tr>
<tr>
<td>Body mass index - kg/(height)^2</td>
</tr>
<tr>
<td>Office systolic blood pressure - mmHg</td>
</tr>
<tr>
<td>Office diastolic blood pressure - mmHg</td>
</tr>
<tr>
<td>Office heart rate - min-1</td>
</tr>
<tr>
<td>Histology - no.</td>
</tr>
<tr>
<td>Macroadenoma - prolactinoma</td>
</tr>
<tr>
<td>Macroadenoma - GH producing</td>
</tr>
<tr>
<td>Macroadenoma - gonadotropinoma</td>
</tr>
<tr>
<td>Macroadenoma - non-functioning</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
</tr>
<tr>
<td>Microadenoma - ACTH producing</td>
</tr>
<tr>
<td>Pituitary hypophysitis</td>
</tr>
<tr>
<td>Pituitary apoplexia</td>
</tr>
<tr>
<td>Pituitary infarction</td>
</tr>
<tr>
<td>Pituitary insufficiency of unknown origin</td>
</tr>
<tr>
<td>Hypothalamic-pituitary hormone deficiency - no.</td>
</tr>
<tr>
<td>ACTH deficiency*</td>
</tr>
<tr>
<td>GH deficiency</td>
</tr>
<tr>
<td>TSH deficiency</td>
</tr>
<tr>
<td>LH/FSH deficiency</td>
</tr>
<tr>
<td>ADH deficiency</td>
</tr>
<tr>
<td>Biochemistry §</td>
</tr>
<tr>
<td>fT4 - pmol/L</td>
</tr>
<tr>
<td>T3 - nmol/L</td>
</tr>
<tr>
<td>Osmolality urine - mOsm/kg</td>
</tr>
<tr>
<td>Urine volume - mL/24h</td>
</tr>
<tr>
<td>Age adjusted IGF-1 - SD</td>
</tr>
</tbody>
</table>

§ Reference values: fT4 10.0 - 23.0; osmololality urine 300 - 900 mOsm/kg.
* Hydrocortisone tablets were used two or three times daily by all ACTH deficient patients and their total daily dosage did not differ between patients with and without CRT (20 (20-20) vs 20 (20-30); p-value = 0.198).
Baroreflex sensitivity in irradiated hypopituitary patients

Mean systolic office blood pressure was significantly higher in patients with CRT than without CRT. \([140 \pm 28 \text{ mmHg vs. } 121 \pm 14 \text{ mmHg}, p = 0.036]\). No differences were found between diastolic office blood pressure and office heart rate between the groups (\(p\) values 0.39 and 0.79).

All TSH-, ADH-, and ACTH deficient patients were on stable doses of L-thyroxine, desmopressin and hydrocortisone respectively. rhGH-therapy was given to 7 out of 11 CRT-patients with GH deficiency and 11 out of 12 non-CRT patients with GH-deficiency (\(p = 0.16\)).

Serum free T4 levels were in the normal range in all patients \((10.0 - 23.0 \text{ pmol/L})\) and there were no differences in serum free T4 \((p = 0.074)\), urine osmolality \((p = 0.48)\), urine volume \((p = 0.51)\) and IGF-1 SD scores \((p = 0.21, \text{ including GH deficient patients without rhGH})\)

\[\text{TABLE 2. Cardiovascular parameters}\]

<table>
<thead>
<tr>
<th>History of Cranial Radiotherapy</th>
<th>Yes (n=13)</th>
<th>No (n=15)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine position</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRSsupine</td>
<td>7.3 (6.5 - 10.4)</td>
<td>12.2 (6.8 - 23.8)</td>
<td></td>
</tr>
<tr>
<td>Log(BRSsupine) - ms/mmHg</td>
<td>0.89 ± 0.21</td>
<td>1.14 ± 0.32</td>
<td>0.022</td>
</tr>
<tr>
<td>SBP supine - mmHg</td>
<td>141 ± 19</td>
<td>129 ± 18</td>
<td>0.126</td>
</tr>
<tr>
<td>DBP supine - mmHg</td>
<td>78 ± 8</td>
<td>75 ± 10</td>
<td>0.423</td>
</tr>
<tr>
<td>HR supine - min(^{-1})</td>
<td>63 ± 8</td>
<td>61 ± 9</td>
<td>0.500</td>
</tr>
<tr>
<td>Epinephrine - nmol/L</td>
<td>0.05 (0.05 - 0.10)</td>
<td>0.05 (0.05 - 0.11)</td>
<td>0.413</td>
</tr>
<tr>
<td>Norepinephrine - nmol/L</td>
<td>1.26 (0.93 - 1.94)</td>
<td>1.04 (0.69 - 2.14)</td>
<td>0.964</td>
</tr>
<tr>
<td><strong>Free standing position</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRSstanding</td>
<td>4.3 (3.2 - 5.3)</td>
<td>8.2 (5.0 - 10.9)</td>
<td></td>
</tr>
<tr>
<td>Log(BRSstanding) - ms/mmHg</td>
<td>0.56 ± 0.24</td>
<td>0.88 ± 0.30</td>
<td>0.005</td>
</tr>
<tr>
<td>d(BRS) - ms/mmHg</td>
<td>-0.33 ± 0.16</td>
<td>-0.26 ± 0.23</td>
<td>0.378</td>
</tr>
<tr>
<td>dSBP standing - mmHg</td>
<td>5 ± 7</td>
<td>2 ± 14</td>
<td>0.170</td>
</tr>
<tr>
<td>dDBP standing - mmHg</td>
<td>8 ± 5</td>
<td>6 ± 8</td>
<td>0.571</td>
</tr>
<tr>
<td>dHR standing - min(^{-1})</td>
<td>13 ± 11</td>
<td>12 ± 5</td>
<td>0.893</td>
</tr>
<tr>
<td>Epinephrine after 10 min - nmol/L</td>
<td>0.11 (0.05 - 0.16)</td>
<td>0.06 (0.05 - 0.12)</td>
<td>0.456</td>
</tr>
<tr>
<td>Norepinephrine after 10 min - nmol/L</td>
<td>2.75 (1.61 - 5.05)</td>
<td>2.37 (1.36 - 3.01)</td>
<td>0.323</td>
</tr>
</tbody>
</table>

Data are presented as mean (sd) or median (interquartile range)

Differences between groups were tested with Student’s t-test or Mann Whitney U test where appropriate

Abbreviations: d(BRS): difference between \log(BRSsupine)\ and \log(BRSstanding); dSBP: difference between systolic blood pressure supine and systolic blood pressure standing; dDBP: difference between diastolic blood pressure supine and diastolic blood pressure standing; dHR: difference between heart rate supine and heart rate standing.
between the groups, neither was there a difference in total hydrocortisone dosage taken by ACTH deficient patients with and without CRT ($p = 0.20$) (table 1).

**Baroreflex sensitivity and (nor)epinephrine responses in supine position and after standing**

In supine position, log(BRS$supine$) was 22% lower in CRT patients than in non-CRT patients [$0.89 \pm 0.21$ ms/mmHg vs. $1.14 \pm 0.32$, $p = 0.022$]. In standing position, the log(BRS$standing$) was 36% lower in CRT-patients than in non-CRT patients [$0.56 \pm 0.24$ vs. $0.88 \pm 0.30$ ms/mmHg, $p = 0.005$].

After standing, a reflex decrease in BRS was seen in all CRT patients and 14 out of 15 non-CRT patients. The mean magnitude of BRS response to standing was not different between the groups.

At baseline, plasma epinephrine and norepinephrine levels were not different between the groups ($p = 0.41$ and $p = 0.96$), nor were levels after 10 minutes of standing ($p = 0.46$ and $p = 0.32$) (table 2).

**Determinants of baroreflex sensitivity**

Univariate linear regression analysis showed that age, heart rate and CRT were significantly associated with log(BRS$supine$) [$p = 0.029$, $r^2 = 14.5\%$; $p = 0.001$, $r^2 = 33.9\%$ and $p = 0.028$, $r^2 = 14.5\%$ respectively], and that heart rate and CRT were significantly associated with log(BRS$standing$) [$p = 0.005$, $r^2 = 24.3\%$ and $p = 0.005$, $r^2 = 23.8\%$ respectively] (tables 3 and 4). Additionally, systolic blood pressure met the criteria to be included in the multivariate model ($p = 0.082$, $r^2 = 8.1\%$).

Multivariate linear regression showed that CRT was not a significant determinant of log(BRS$supine$), although it was retained in the final model ($p = 0.068$) (table 5). In contrast, CRT was a significant determinant of log(BRS$standing$) and responsible for 18.6% of this models’ total goodness-of-fit ($r^2 = 42.9\%$) (table 6).

| TABLE 3. Univariate linear regression analysis of log(BRS$supine$) |
|---|---|---|---|---|
| Variable | R-square | Estimate | SE | $p$-value |
| Age [years] | 0.145 | -0.008 | 0.004 | 0.029 |
| Body Mass Index [kg/m$^2$] | -0.024 | -0.006 | 0.009 | 0.535 |
| Systolic Blood Pressure$supine$ [mmHg] | 0.059 | -0.005 | 0.003 | 0.117 |
| Diastolic Blood Pressure$supine$ [mmHg] | 0.042 | -0.009 | 0.006 | 0.155 |
| Heart Rate$supine$ [min$^{-1}$] | 0.339 | -0.021 | 0.006 | 0.001 |
| Cranial Radiotherapy (no Cranial Radiotherapy)* | 0.145 | -0.251 | 0.108 | 0.028 |

Values for log(BRS$supine$) are expressed in ms/mmHg
SE indicates standard error of estimate
*The reference group for categorical control variables is in parenthesis
DISCUSSION

In the present study we report that a history of CRT is associated with a decreased BRS in patients with pituitary insufficiency. Moreover, this association persists in BRSstanding after correction for other well-known factors affecting BRS, i.e. age, body mass index, heart rate and systolic blood pressure (27-29). CRT was also an important determinant in the final multivariate model of BRSsupine, although it did not reach significance.
The BRS represents an autonomic response of heart rate to a given change in systolic blood pressure. There are differences in time delay of the response mediated by parasympathetic and sympathetic efferents. Parasympathetic activation produces an immediate reaction within 200-600 milliseconds, whereas the reaction to sympathetic activation occurs with a delay of 2-3 seconds (30;31). This indicates that the ability of the BRS to control heart rate on a beat-by-beat basis is predominantly a vagal response. Consequently, our finding of a decreased BRS in CRT compared to non-CRT patients suggests a reduced capability to increase parasympathetic activity and/or to antagonize sympathetic activity in CRT patients with pituitary insufficiency (15). It is likely that the higher systolic blood pressure seen in our CRT patients can also be explained by the shift towards sympathetic dominance.

In both CRT and non-CRT patients we found that BRS was lower and heart rate, blood pressure and catecholamines were higher in standing position compared to supine position. Furthermore, the magnitude of change in BRS, heart rate, blood pressure and catecholamines from supine to standing position was comparable in CRT and non-CRT hypopituitary patients. These changes are normal hemodynamic responses, as active standing induces a sympathetic activation with an increase in heart rate, blood pressure, plasma catecholamines and a decrease in BRS (32;33). Apparently, the impaired reflex control of heart rate after CRT, indicated by the decreased BRS, is too mild to cause abnormal blood pressure adaptations to standing up. An explanation might be that particular components of the baroreflex arc are able to compensate the impaired response (34).

Although it is not possible to be conclusive on causality due to the cross-sectional nature of this study, there are pathophysiological mechanisms that could explain the decreased BRS seen in patients with CRT. Irradiation delivered to the pituitary is always accompanied by radiation doses to healthy surrounding tissue. Anatomically closely connected to the pituitary gland is the hypothalamus, which is thought to be more vulnerable to radiation injury than the pituitary (35). Pre-autonomic neurons in the dorsomedial nucleus, adjacent to the perifornical area and in the paraventricular nucleus of the hypothalamus are able to modulate the baroreflex function directly by influencing neurons located in the lower brainstem (i.e. NTS, RVLM) and spinal cord (36;37). Moreover, by releasing hormones such as vasopressin, oxytocin, corticotrophin releasing hormone, enkephalin and dynorphin are hypothalamic neurons able to influence the autonomic control of the cardiovascular system (38;39). Although speculative, it is conceivable that CRT injures hypothalamic pre-autonomic neurons or their projections to the baroreflex loop resulting in the decreased BRS seen in our patients. In addition, CRT may harm other forebrain regions or fibers of passage originating from these forebrain regions, as those are also able to modulate the key medullary nuclei subserving the baroreflex (40;41).

The proportion of patients with a history of a hormone producing tumour in the group with CRT is higher than in the group without, and it is speculated that patients exposed to a previous abundance of hormones may have been transitory hypertensive or underwent
arterial remodelling (42). Hypothetically, it is conceivable that these adaptations in turn reset the BRS. However, evidence in literature is scarce and excessive production of pituitary hormones had not been present for at least 5 years prior to this study.

An intriguing question remains whether the reduced BRS in irradiated patients with pituitary insufficiency plays a role in the development and progression of cardiovascular morbidity and mortality. Previous studies in various clinical populations, such as the ATRAMI study, report increased cardiovascular risk by BRS values below 3ms/mmHg (20). In our study, CRT patients had resting BRS values of approximately 7.8 ms/mmHg, and only 1 CRT patient had a BRS-value below 3ms/mmHg. However, comparison of our BRS-values with values from other studies must be made with care because different techniques of assessing BRS may provide different results (43). Therefore, it remains to be determined to what extent our observed reduction in BRS is a source of valuable information for the assessment of cardiovascular morbidity and mortality.

A limitation of this study is the relatively small sample size, which prevents further subanalyses according to additional cofactors. We have tried to minimize the possibility of confounding by including only patients with pituitary insufficiency, as endocrine deficiencies might influence the sympathovagal balance. For instance, the sympathetic tone is decreased in patients with hypothyroidism (44) or severe GHD (45) and glucocorticoids are important in maintaining hemodynamic responses to stress via the autonomic nervous system (46). As a consequence, pituitary hormone deficiencies might act as confounders of the relationship between CRT and BRS. However, the comparable proportion of various hormonal deficiencies and replacement therapies as well as the comparable serum hormone levels between groups argues against differences in hormonal substitution strategies as a causative factor for the decreased BRS observed in patients with CRT. Of course, future studies in other cohorts are needed to confirm our results.

To summarize, this is the first study to demonstrate a reduced BRS in CRT patients with pituitary insufficiency compared to non-CRT patients. Longitudinal investigations are necessary to determine whether cardiovascular morbidity and mortality can be attributed to a reduced BRS following CRT in patients with pituitary insufficiency.

ACKNOWLEDGEMENTS

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