Relationship of a common polymorphism of the glucocorticoid receptor gene to traumatic memories and posttraumatic stress disorder in patients after intensive care therapy

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Objective: Glucocorticoids play a major role in the consolidation and retrieval of traumatic information. They act through the glucocorticoid receptor, for which, in humans, several polymorphisms have been described. In particular, the BclI single-nucleotide polymorphism is associated with hypersensitivity to glucocorticoids and with susceptibility to development of major depression. Furthermore, in patients with posttraumatic stress disorder carrying the BclI GG genotype, cortisol levels were lower and showed an inverse relationship to posttraumatic stress disorder symptom intensity. Here, we studied the association of the Bci polymorphism with plasma cortisol levels, traumatic memories, posttraumatic stress disorder symptoms, and health-related quality of life outcomes in 126 patients undergoing cardiac surgery and intensive care unit therapy.

Design: Prospective observational study.
Setting: Cardiovascular intensive care unit in a university hospital.
Patients: A total of 126 patients undergoing cardiac surgery and intensive care unit treatment.
Interventions: No interventions were performed.
Measurements and Main Results: Validated questionnaires were used to quantify end points. Measurements were taken 1 day before and 1 wk and 6 months after cardiac surgery. Homozygous carriers of the BclI G allele (n = 21) had significantly lower preoperative plasma cortisol levels and more long-term traumatic memories from intensive care unit therapy at 6 months after cardiac surgery than heterozygous carriers or noncarriers (1.9 ± 1.4 vs. 1.0 ± 1.2, p = .01). Anxiety was significantly more common as a long-term traumatic memory in homozygous BclI G allele carriers than in heterozygous carriers or noncarriers (57% vs. 35%, p = .03). Posttraumatic stress disorder symptom scores were significantly higher at discharge from the intensive care unit in homozygous BclI G allele carriers than in heterozygous carriers or noncarriers. Only heterozygous carriers or BclI G allele noncarriers had a significant gain in health-related quality of life physical function at 6 months after cardiac surgery (p < .01). Baseline values were not statistically different between carriers of the different BclI alleles.

Conclusion: Homozygous BclI G allele carriers are at risk for traumatic memories, posttraumatic stress disorder symptoms, and lower health-related quality of life after cardiac surgery and intensive care unit therapy. The BclI single-nucleotide polymorphism may help to identify individuals at need for tailored medical care.

Key Words: glucocorticoid receptor gene; genetic polymorphism; traumatic memories; stress; posttraumatic stress disorder; outcome

Animal and human studies have repeatedly shown that glucocorticoids influence memory in situations of acute and chronic stress (1–3). Glucocorticoids are known to enhance memory consolidation of emotionally arousing experiences (4, 5) but impair memory retrieval under stressful conditions (6, 7). Persistent traumatic memories of highly stressful experiences are a hallmark of stress-related disorders such as posttraumatic stress disorder (PTSD), and changes in glucocorticoid signaling have consistently been demonstrated in humans with PTSD (8–10) as well as in animal models of the disorder (11). In critically ill patients, traumatic memories from treatment in an intensive care unit (ICU) can be associated with PTSD stress symptoms and are influenced by the administered dosages of catecholamines and glucocorticoids in the ICU (12–14). Glucocorticoids influence cognitive and emotional processes through the glucocorticoid receptor (GR), and changes in GR sensitivity have been shown in patients with PTSD (10, 15) as well as other
stress-related disorders such as depression (16). In humans, several single-nucleotide polymorphisms (SNPs) of the GR gene have been described that influence GR sensitivity (17,18). Among these SNPs, the BclI polymorphism, which involves a restriction site in intron 2, 646 base pairs downstream from exon 2, of the GR gene and consists of a C-to-G nucleotide change (BclI *G), which has been associated with higher GR sensitivity to glucocorticoids. This hypersensitivity has been documented by an increased suppression of adrenocorticotropic and cortisol levels following a low-dose dexamethasone challenge (19,20) and a metabolic profile suggestive of GR hypersensitivity, including an increased risk for cardiovascular disorders (21).

We performed a hypothesis-driven study in patients with cardiovascular disease undergoing cardiac surgery (CS) to investigate whether patients homozygous for the BclI G allele (BclI *G), which has been associated with higher GR sensitivity, have more traumatic memories from ICU treatment and more marked PTSD stress symptoms than heterozygous carriers or noncarriers of this allele.

**PATIENTS AND METHODS**

**Patient Selection and Study Design**

Between June 7, 2004 and July 1, 2005, we prospectively screened all adult patients (>18 yrs) scheduled for heart surgery at the Department of Cardiac Surgery of the University of Munich for possible inclusion in our study. Inclusion criteria were planned coronary artery bypass grafting or cardiac valve replacement. Exclusion criteria were combined coronary artery and valve disease, emergency procedures, severe alcohol or drug abuse, major preexisting neurologic disease or psychiatric illness (e.g., major depressive or bipolar disorder, PTSD, somatiform disorder), current use of steroids and severe comorbidities, such as chronic organ dysfunction (renal, liver, or pulmonary), or cancer. Patients not qualified for study inclusion fulfilling the above-mentioned exclusion criteria were identified by chart review, patient interview, and direct communication with the attending cardiac surgeons or the private physicians of the patients.

Eligible patients were evaluated for standardized traumatic memories and PTSD symptom scores at study inclusion and then followed prospectively. Plasma cortisol levels were measured pre- and postoperatively. Reevaluation for traumatic memories from ICU treatment and the development of PTSD stress symptoms was performed 1 wk after discharge from the ICU and at 6 months thereafter. Plasma cortisol concentrations, traumatic memories, and PTSD stress symptom intensities were then compared between homozygous carriers and heterozygous carriers/noncarriers of BclI *G.

The study was approved by the Institutional Review Board of the Ludwig-Maximilians University of Munich (protocol 198/89 and 140/99), and data protection met the standard set by German law. Written informed consent was obtained from all subjects (including an additional consent for the genetic study).

**Instruments and Key Measures**

**Patient and Treatment Data.** General patient assessment consisted of demographics, a detailed evaluation of the type and severity of cardiac disease, intraoperative data (e.g., duration of surgery and cardiopulmonary bypass), and the prospective recording of predefined ICU treatment variables, including the use and dosages of epinephrine, β-adrenergic antagonists, glucocorticoids, and the sedative drugs midazolam and propofol. These drugs were selected for documentation and analyses because possible effects of these substances on traumatic memory and PTSD symptoms after ICU treatment have previously been described (12).

**Preoperative Assessment.** One day before their scheduled operations, the patients were approached by trained research assistants and received a detailed explanation of the purpose of the study. The patients were informed that we were interested in their present and postoperative state of physical and mental health, without any direct referral to traumatic memories or PTSD symptoms. After informed consent, the patients completed validated questionnaires evaluating standardized traumatic memories and chronic stress symptoms including those of PTSD.

**Follow-Up.** One week after discharge from the ICU, while in the normal cardiovascular ward, the patients were approached again and asked to complete the same instruments on traumatic memories from the ICU and PTSD-related symptoms as they did preoperatively. Six months after CS, the patients were contacted by telephone and, after repeated oral consent, received the same set of questionnaires.

**Quantification of Traumatic Memories and PTSD Symptoms.** All patients completed a standardized and validated questionnaire evaluating different categories of traumatic memory and PTSD symptoms from ICU treatment (22). The questionnaire consists of two parts: part A evaluates four standardized categories of traumatic memory from the ICU, and part B quantifies the presence and intensities of 10 PTSD-related symptoms. This questionnaire has been validated in patients after ICU therapy (22) and used in several other studies in patients after ICU therapy or CS (14, 23–26).

**Traumatic Memories.** A category of traumatic memory as measured by part A of the questionnaire was defined as the patient's subjective recollection of 1) nightmares, 2) respiratory distress/dyspnea, 3) feelings of anxiety/panic, or 4) pain at any time between 1 wk before CS and 1 wk after discharge from the ICU. When completing the questionnaire, the patients were asked to answer each of these four items "yes" or "no," independent of the number of occasions the adverse experience occurred (only frequencies were scored). The number with which these four items is answered "yes" by a subject is termed the number of categories of traumatic memory. The intensity of traumatic memories was not specifically evaluated.

**PTSD-Related Chronic Stress Symptoms.** The severity and presence of PTSD symptoms was quantified by part B of the questionnaire. This part of the questionnaire resulted from a modification of the Post-Traumatic Stress Symptom 10-Questions instrument (27) and evaluates the presence and intensity of 10 PTSD-related stress symptoms: 1) sleep disturbance, 2) nightmares, 3) depression, 4) hyperalertness, 5) withdrawal (emotional numbness and inability to care for others), 6) generalized irritability, 7) frequent changes in mood, 8) guilt, 9) fear and avoidance reactions with regard to the ICU, and 10) increased muscle tension. When evaluating these symptoms, the patients were asked to think back to the last few days ("presently—that means in the past few days—I suffer from ..."), and then they were asked if they had symptoms expressed by statements such as "Jumpy, I am easily frightened by sudden sounds or sudden movements" (to evaluate hyperalertness), "fear of places and situations which remind me of the intensive care unit" (to evaluate avoidance reactions), or "a bad conscience, have guilt feelings" (to evaluate guilt). Patients rated their symptoms using a scale from 1 (never) to 7 (always). A summary score could then be calculated that ranges from 10 to 70 points, with increasing scores indicating a higher prevalence and intensity of PTSD symptoms. The questionnaire has been specifically validated in patients after ICU therapy using a double-blind interview performed by psychiatrists. The interviews were performed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria to diagnose PTSD. This validation process demonstrated a high internal consistency (Cronbach’s α = 0.93) and a high test–retest reliability (intraclass correlation coefficient r = 0.89) of the instrument. The specificity and sensitivity for diagnosis of PTSD after ICU treatment at a cutoff value of 35 points of the questionnaire were 97.5% and 77%, respectively (22).

**Health-Related Quality of Life and Chronic Pain.** Health-related quality of life (HRQOL) was measured using the German version of the self-administered Medical Outcomes Study Short Form Survey that consists
of 36 questions (28). Pain intensities were determined by using a visual analog scale ranging from 0 to 10, where 0 indicated no pain and 10 the worst imaginable pain (visual analog scale pain scores). Pain and HRQL measurements were performed at the preoperative visit and 6 months after surgery.

DNA Preparation and Genotyping

After enrollment in the study, 10 mL of blood was collected in EDTA-coated tubes from each patient. Blood samples were kept frozen at −20°C. Genotyping was performed in those patients who had a complete set of questionnaires across all three time points of measurements at conclusion of the study.

Genomic DNA was extracted using the QIAamp DNA blood maxi kit (Qiagen, Hilden, Germany). Information on the BclI polymorphic site of the GR was derived from the database of SNPs established by the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP/index.html). Genotyping was done by pyrosequencing on a PyroMark ID system (Biotage, Uppsala, Sweden). Primers for the BclI polymorphism were 5′-CTT GCA GAA GAG GAT TCA CAT CT-3′ (forward), 5′-GTG TGT CTG CCT GAA ATG-3′ (reverse), and 5′-GTG TAT CTC AGA AAA GAC CT-3′ (sequencing). Primers for rs3781230 were 5′-AGG TCT TGC TCA CAG GGT TCT-3′ (forward), 5′-TTT TGC ACC ATG TTG ACA CCA-3′ (reverse, 5′-biotinylated), and 5′-ACA AGT TAT GTC TGA T-3′ (sequencing primer). Genotype distributions were in Hardy-Weinberg equilibrium.

Measurement of Plasma Cortisol Levels

Blood sampling for cortisol measurements was performed between 7 and 8 AM at the preoperative time point and in the morning of the first postoperative day. Plasma cortisol levels were measured by isotope dilution liquid chromatography–tandem mass spectrometry as previously described by our group (29).

Twenty-nine patients from the study sample received hydrocortisone after the preoperative time point at induction of anesthesia. The use of hydrocortisone was not randomized but left to the discretion of the attending anesthesiologists. Hydrocortisone was administered starting with a loading dose (100 mg over 10 mins), followed by a continuous infusion of 10 mg/hr for 24 hrs (postoperative day 1), which was reduced to 5 mg/hr on postoperative day 2, and then tapered to 3 × 20 mg intravenously on postoperative day 3, and 3 × 10 mg intravenously on postoperative day 4. Stress doses of hydrocortisone given during the first 24 hrs were calculated to be approximately equivalent to the endocrine secretion rate of the adrenal glands under maximal stimulation (30).

Statistical Analyses

All variables were tested for normal distribution using the Kolmogorov-Smirnov test. For the initial statistical analyses and to increase statistical power, heterozygous carriers and noncarriers of the BclI *G SNP were combined into one group and compared to the second group of homozygous BclI *G carriers. Normally distributed continuous variables between homozygous carriers and heterozygous carriers/BclI *G noncarriers were compared by t tests. Nonparametric data were compared by the Mann-Whitney U test. To delineate possible gene–dose effects, additional comparisons between noncarriers and heterozygous and homozygous subgroups were performed when the differences between combined and homozygous groups were significant. For these comparisons, analysis of variance in normally distributed data and Kruskal-Wallis One Way Analysis of Variance on Ranks in nonparametric data with Fischer’s least significant difference post hoc test was used. Cortisol measurements were transformed to log10 values before comparison because untransformed values were skewed. The log cortisol was normally distributed. Discrete variables were analyzed with the chi-square test or Fisher’s exact test, when appropriate. All statistical calculations were performed using the SPSS 17.0 statistical package (SPSS Inc., Chicago, IL). Results are expressed as mean ± SD. In graphs, mean ± SEM is shown to improve clarity. A p value of <.05 was considered as statistically significant for all comparisons.

RESULTS

Patient Selection

A total of 150 patients were initially included in the study. Of these patients, 13 (8.7%) had died during postoperative ICU treatment, and 137 individuals had complete questionnaires 1 wk after discharge from the ICU. A further 11 (8.0%) patients died during the follow-up period, and 126 patients returned complete questionnaires 6 months after CS. These 126 individuals represent the final study population and were subjected to genotyping.

Results of Genotyping

A total of 51 patients (40.5%) were noncarriers of BclI *G, 54 (42.9%) were heterozygous BclI *G carriers, and 21 (16.6%) were homozygous carriers. Heterozygous carriers and noncarriers were combined into one group (n = 105) and compared to the homozygous group (n = 21). Baseline and treatment variables did not differ significantly between both groups and are shown in detail in Tables 1 and 2.

Differences Between Homozygous Carriers and Heterozygous Carriers/Noncarriers of BclI *G

Homozygous BclI *G carriers had lower basal plasma concentrations and showed no increase in plasma cortisol when receiving stress doses of hydrocortisone. At the preoperative time point, homozygous carriers of the BclI *G had significantly lower log10-transformed plasma cortisol levels than heterozygous carriers/noncarriers with no significant postoperative differences in plasma cortisol concentrations (Fig. 1). A subgroup analysis with regard to the BclI *G alleles using analysis of variance with Fischer’s least significant difference post hoc test revealed no significant difference in preoperative log10-transformed plasma cortisol levels between heterozygous carriers and noncarriers (mean difference of −0.05 ± 0.09, p = .64) but a significant difference between homozygous BclI *G carriers and heterozygous individuals (mean difference of −0.25 ± 0.12, p = .03) and a strong trend toward higher cortisol levels in noncarriers compared to homozygous patients (mean difference of −0.21 ± 0.12, p = .07). A total of 23 of the 105 heterozygous carriers/noncarriers of the BclI *G SNP had received stress doses of hydrocortisone after the preoperative time point vs. 6 of the 21 homozygous carriers. Heterozygous carriers/noncarriers who had received hydrocortisone had significantly higher log10-transformed plasma cortisol levels than heterozygous carriers/noncarriers who were not treated with glucocorticoids (1.3 ± 0.4 vs. 1.0 ± 0.4 μg/dL, p = .02). In homozygous individuals, the use of hydrocortisone did not result in increased plasma cortisol levels, and log10 cortisol plasma concentrations in homozygous individuals with and without the administration of hydrocortisone were nearly identical (1.0 ± 0.6 vs. 1.0 ± 0.5 μg/dL, p = .99).

Homozygous BclI *G Carriers Had More Traumatic Memories from ICU Therapy. The number of recollected traumatic memories from ICU therapy dif-
Table 1. Comparison of patient and treatment variables and disease severity at study inclusion between homozygous BclI G allele carriers and heterozygous carriers or noncarriers of the allele

<table>
<thead>
<tr>
<th>Patient and Treatment Variables</th>
<th>BclI GG Carriers (n = 21)</th>
<th>Heterozygotes and Noncarriers of the BclI G Allele (n = 105)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)*</td>
<td>67.1 ± 10.8</td>
<td>65.8 ± 9.3</td>
<td>.60</td>
</tr>
<tr>
<td>Body weight (kg)*</td>
<td>78.9 ± 11.9</td>
<td>78.0 ± 16.3</td>
<td>.74</td>
</tr>
<tr>
<td>Height (cm)*</td>
<td>173.1 ± 8.4</td>
<td>170.3 ± 8.4</td>
<td>.80</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>15/6</td>
<td>81/24</td>
<td>.58</td>
</tr>
<tr>
<td>Preoperative β-blocker use (%)</td>
<td>33</td>
<td>35.2</td>
<td>.87</td>
</tr>
<tr>
<td>American Society of Anesthesiologists score*</td>
<td>3.1 ± 0.9</td>
<td>3.0 ± 0.9</td>
<td>.50</td>
</tr>
<tr>
<td>New York Heart Association score*</td>
<td>2.2 ± 0.8</td>
<td>2.4 ± 1.6</td>
<td>.74</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society score*</td>
<td>1.3 ± 2.3</td>
<td>1.7 ± 1.3</td>
<td>.68</td>
</tr>
<tr>
<td>Acute Physiology and Chronic Health Evaluation II score*</td>
<td>9.7 ± 3.8</td>
<td>8.0 ± 3.2</td>
<td>.18</td>
</tr>
<tr>
<td>Perioperative ejection fraction (%)</td>
<td>57 ± 18</td>
<td>58 ± 14</td>
<td>.66</td>
</tr>
<tr>
<td>Duration of extracorporeal circulation (mins)</td>
<td>136 ± 59</td>
<td>120 ± 45</td>
<td>.18</td>
</tr>
<tr>
<td>Duration of aortic cross-clamping (%)</td>
<td>95 ± 60</td>
<td>78 ± 31</td>
<td>.54</td>
</tr>
</tbody>
</table>

*Values are the mean ± SD; *American Society of Anesthesiologists classification of perioperative risk; *New York Heart Association classification of heart failure; *Canadian Cardiovascular Society classification of angina pectoris.

Table 2. Treatment variables and incidence of postoperative organ failures in the homozygote carrier and heterozygote carrier/noncarrier group of the BclI G allele

<table>
<thead>
<tr>
<th>Treatment Variables</th>
<th>BclI GG Carriers (n = 21)</th>
<th>Heterozygotes and Noncarriers of the BclI *G Allele (n = 105)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of postoperative stay in the intensive care unit (days)*</td>
<td>5.5 ± 7.2</td>
<td>5.3 ± 1.2</td>
<td>.95</td>
</tr>
<tr>
<td>Duration of postoperative mechanical ventilation (hrs)*</td>
<td>25 ± 23</td>
<td>24 ± 19</td>
<td>.86</td>
</tr>
<tr>
<td>Duration of epinephrine therapy (days)*</td>
<td>2.1 ± 1.8</td>
<td>1.5 ± 1.6</td>
<td>.20</td>
</tr>
<tr>
<td>Duration of sedation (days)*</td>
<td>0.3 ± 0.5</td>
<td>0.4 ± 0.5</td>
<td>.39</td>
</tr>
<tr>
<td>Postoperative use of β-adrenergic antagonists (% of patients)</td>
<td>52.4</td>
<td>54.3</td>
<td>.87</td>
</tr>
<tr>
<td>Perioperative use of hydrocortisone % of patients</td>
<td>28.6</td>
<td>21.9</td>
<td>.78</td>
</tr>
<tr>
<td>Acute heart failure (% of patients)</td>
<td>9.5</td>
<td>8.6</td>
<td>.67</td>
</tr>
<tr>
<td>Acute renal failure (% of patients)</td>
<td>14.3</td>
<td>11.4</td>
<td>.38</td>
</tr>
<tr>
<td>Acute lung injury (% of patients)</td>
<td>9.5</td>
<td>5.7</td>
<td>.67</td>
</tr>
</tbody>
</table>

*Values are the mean ± SD; *postoperative sedation was performed in the intensive care unit with either midazolam or propofol; *acute heart failure was defined by a significantly reduced cardiac function necessitating the application of positive inotropics (the drug of first choice was epinephrine in all patients); *acute renal failure was defined by a doubling of the preoperative plasma creatinine level or oliguria; *acute lung injury was defined as a PaO2/FIO2 ratio of less than 300 during postoperative mechanical ventilation; *there were no significant differences in the demographic or short- or long-term outcome variables described in the table when homozygous BclI GG carriers who had received hydrocortisone (n = 6) were compared to homozygous individuals who did not (n = 15). Likewise, no differences were found between the demographic and treatment and outcome variables when heterozygous carriers/noncarriers with (n = 23) and without (n = 82) hydrocortisone use were compared (data not shown).

Homozygous BclI *G Carriers Had Higher PTSD Symptom Scores After ICU Therapy. At the preoperative time point, there were no significant differences in PTSD symptom scores between groups. PTSD symptom scores were higher 1 wk after discharge from the ICU in homozygous BclI *G carriers than in heterozygous carriers or noncarriers (25 ± 11 vs. 19 ± 9, p = .02). Subgroup analyses according to the BclI *G carrier state revealed comparable PTSD symptom scores between noncarriers and heterozygotes (mean difference of −1.0 ± 0.2, p = .64) and significantly higher stress symptom scores in homozygotes as compared to heterozygotes (mean difference of −5.4 ± 2.6, p = .04) and noncarriers (mean difference of −6.3 ± 2.7, p = .02). PTSD stress symptom scores in the BclI *G homozygotes were still higher 6 months after surgery, but due to an increase in scores in the heterozygous carrier/noncarrier group during the follow-up period, this difference was no longer statistically significant (p = .37, Fig. 4). A total of 4 of 21 patients (19%) from the homozygous BclI *G group were above the 35 point cutoff value for diagnosis of PTSD vs. 11 of 105 individuals (10%) in the heterozygous carrier/noncarrier group (p = .44).

Homozygous BclI *G Carriers Had Lower HRQL Outcomes. The 36-question Medical Outcomes Study Short Form Survey HRQL physical function summary scores 6 months after surgery were significantly lower in homozygotes as compared to heterozygous carriers or BclI *G noncarriers (38.0 ± 11.6 in homozygotes vs. 45.6 ± 10.4 in heterozygous carriers or noncarriers, p = .02). Subgroup analyses according to the BclI *G carrier state demonstrated a gene–dose effect. Ho-
mozygotes reported significantly lower physical function summary scores than heterozygous individuals (mean difference of 7.36/11002 7.36/11006 3.6, p = 0.04) and noncarriers (mean difference of 7.89/11002 7.89/11006 3.4, p = 0.02). There were no other significant differences in HRQL outcomes between groups. Homozygous individuals showed a trend toward higher visual analog scale chronic pain scores 6 months after surgery when compared to the heterozygous carrier or noncarrier group (3.1/11006 4.1 vs. 1.4/11006 2.4, p = 0.08). There were no significant preoperative differences in HRQL or visual analog scale pain scores between carriers of the different BclI alleles.

DISCUSSION

The main finding of this study is that homozygous BclI *G carriers are at an increased risk for adverse outcomes of CS and ICU therapy when compared to heterozygous carriers or noncarriers of the BclI *G allele. This unfavorable outcome included not only the presence of more traumatic memories from the ICU and an associated increase in PTSD stress symptoms but also impairment in physical function and a trend toward a higher incidence of chronic pain. As this increased susceptibility of BclI GG carriers for the development of traumatic memories and PTSD-related stress symptoms became evident only after exposure to the stressful events of CS and ICU therapy, this effect may represent a gene–environment interaction.

Homozygous BclI *G Carriers Had Lower Plasma Cortisol Levels. During the moderately stressful preoperative period, homozygous BclI *G carriers showed significantly lower cortisol plasma levels. This finding is corroborated by another study that investigated healthy volunteers exposed to a standardized psychological laboratory stressor (the Trier Social Stress Test). Homozygous BclI *G carriers in this study showed a significantly lower cortisol response (31) that was more pronounced when the stress exposure was repeated (32). Interestingly, when BcI GG homozygotes in our study received stress doses of hydrocortisone, plasma cortisol levels did not increase, whereas heterozygotes/noncarriers showed a significant augmentation of cortisol concentrations. The lower cortisol levels in homozygous carriers of the BclI *G genotype could be due to an enhanced adrenal negative feedback action on the hypothalamus–pituitary–adrenal axis (19), an increase in cortisol metabolism, or a combination of these and possibly other, unknown factors.

In a well-characterized sample of Vietnam veterans with PTSD, the presence of the G allele in the BclI gene was associated with lower basal cortisol levels and higher scores on the Clinician-Administered PTSD Scale in a gene–dose-dependent fashion. Furthermore, Clinician-Administered PTSD Scale scores and basal cortisol levels were negatively correlated (33). Other recently described SNPs of the GR gene that enhance receptor responsiveness to cortisol (in particular the FKBP5 gene) resulted in a comparable phenotype in individuals with traumatic memories after exposure to a massive stressor (childhood maltreatment or the World Trade Center attack) with low basal cortisol levels (34) and an increased risk for PTSD (10).
Study Limitations

Although we found evidence of lower plasma cortisol concentrations during preoperative stress and after the administration of hydrocortisone in the homozygous BclI *G carriers which could be due to enhanced hypothalamus–pituitary–adrenal axis feedback as a result of increased GR responsiveness (19), we did not specifically test our patients for the presence of GR hypersensitivity but drew further evidence from several other, carefully performed studies. Increased glucocorticoid sensitivity with the GG phenotype is suggested by hyperinsulinemia, increased abdominal visceral fat, lower lean body mass (42–44), and the above-mentioned increased negative feedback sensitivity of the hypothalamus–pituitary–adrenal axis (19). The increased risk for stress-related disorders after trauma exposure in the presence of a genetically determined GR hyperresponsiveness has been confirmed by other studies in different patient populations and with different GR SNPs (34, 45). Furthermore, the BclI polymorphism has highly tissue-specific effects, and this, as mentioned above, could result in both increased and decreased GR sensitivity in different tissues and different neuronal networks within the brain (31, 46), which makes it difficult to directly relate glucocorticoid signaling in different brain areas to specific neuropsychological findings. Furthermore, the BclI polymorphism is intronic, and its effect on the GR gene may be indirect, serving only as a marker of other mutations affecting re-

**Homozygous BclI *G Carriers Had More Traumatic Memories and Higher PTSD Stress Symptom Scores.** Glucocorticoids play an important role in the regulation of emotional memory. Enhanced glucocorticoid signaling during stress has repeatedly been shown to strengthen the consolidation of emotionally arousing experiences (35) but to impair emotional memory retrieval (6, 36, 37). Furthermore, glucocorticoids are known to have long-term facilitating effects on the extinction of traumatic memories (3). Homozygous BclI *G allele carriers show enhanced GR sensitivity (19) but lower basal cortisol concentrations. At the moment, it is not entirely understood how this genotype resulted in an increased number of traumatic memories and higher PTSD stress symptom scores. It is possible that the increased GR sensitivity of homozygous BclI *G carriers resulted in an enhanced consolidation of the traumatic experiences. On the other hand, it is also possible that the lower plasma cortisol levels found in homozygous BclI *G carriers facilitated the retrieval of traumatic memories accompanied by a failure to extinguish traumatic information (3). Both effects—and their interaction—could help to explain our findings. These assumptions are corroborated by a number of recent findings. One study indicated that long-term survivors of severe acute respiratory distress syndrome with septic shock and multiple traumatic memories from ICU therapy had significantly lower plasma cortisol levels and significantly higher PTSD symptom scores (38). On the other hand, increas-

**Figure 3.** Number of traumatic memories from intensive care unit treatment at six months after cardiac surgery in relationship to the BclI *G polymorphism of the glucocorticoid receptor gene. *p < .01 when homozygotes were compared to noncarriers of the G allele. #p < .05 for the difference in traumatic memories between heterozygotes and homozygotes. Data are mean ± SEM.

**Figure 4.** Comparison of changes in posttraumatic stress disorder (PTSD) stress symptom scores following intensive care unit (ICU) treatment in cardiac surgical patients across three time points of measurements between heterozygous carriers or noncarriers of the BclI *G allele and homozygous BclI *G allele carriers (*p = .02). Data are mean ± SEM.
ceptor function. There is, however, evidence that intronic polymorphisms are involved in the splicing process by, among other effects, changing the sequence of so-called intronic splicing silencers and enhancers and through other effects that are important for gene expression (47). Finally, despite the fact that our study was hypothesis driven, had a good rationale for the association under study, and investigated a relatively large and homogeneous cohort of patients exposed to a standardized stressor, the power of our study to exclude possible false-positive associations is still relatively low. Our findings therefore need replication in a larger study cohort.

Regardless of these limitations, our findings support the notion that variants of the GR gene might influence traumatic memories, PTSD symptoms, and HRQOL after ICU therapy and that some of these effects may be due to changes in corticoid signaling. Preoperative genotyping of the GR may help to identify individuals at need for tailored medical care.

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