Overture for growth hormone: Requiem for interleukin-6?*

Claudius Conrad, MD, PhD; Hanno Niess; Karl-Walter Jauch, MD; Christiane J. Bruns, MD, PhD; Wolfgang H. Hartl, MD; Lorenz Welker, MD

Background: **Music has been used for therapeutic purposes since the beginning of cultural history. However, despite numerous descriptions of beneficial effects, the precise mechanisms by which music may improve human well-being remain unclear.**

Methods: **We conducted a randomized study in ten critically ill patients to identify mechanisms of music-induced relaxation using a special selection of slow movements of Mozart's piano sonatas. These sonatas were analyzed for compositional elements of relaxation. We measured circulatory variables, brain electrical activity, serum levels of stress hormones and cytokines, requirements for sedative drugs, and level of sedation before and at the end of a 1-hr therapeutic session.**

Results: **Compared with controls, we found that music application significantly reduced the amount of sedative drugs needed to achieve a comparable degree of sedation. Simultaneously, among those receiving the music intervention, plasma concentrations of growth hormone increased, whereas those of interleukin-6 and epinephrine decreased. The reduction in systemic stress hormone levels was associated with a significantly lower blood pressure and heart rate.**

Conclusion: **Based on the effects of slow movements of Mozart's piano sonatas, we propose a neurohumoral pathway by which music might exert its sedative action. This model includes an interaction of the hypothalamic–pituitary axis with the adrenal medulla via mediators of the unspecific immune system. (Crit Care Med 2007; 35:2709–2713)**

KEY WORDS: Mozart; Mozart effect; relaxation; interleukin-6; growth hormone; intensive care unit

Music has been an essential part of healing since the beginning of cultural history. The earliest known evidence for this phenomenon comes from descriptions of therapeutic musical interventions in cuneiform writings in Mesopotamia from 4000 BC (1). Another early example is described in the Bible's Old Testament, in which David, playing the kinnor, treated the depressed king Saul with his music, dated 1000 BC (2).

Today, music is used frequently in the context of modern medical therapy. Psychiatry, psychology, obstetrics, and pediatrics are fields in which music has proven therapeutic benefit (3–8). This benefit has also been extended to perioperative settings, ranging from premedication areas, to operating rooms, to intensive care units, where it has documented utility as an adjuvant therapeutic measure (9–16). In 1914, Kane (16) used music to relieve the patient's "horror of surgery." Allen and Blascovich (17) demonstrate that surgeons perform mental subtraction tasks faster when simultaneously exposed to self-chosen music (18).

Intensive care units represent a particular environment where patients are exposed to a high degree of stress due to their disease severity, circadian rhythms, and high noise level. It has been demonstrated that music application is an effective way of reducing stress in that environment, and there have been protocols established on how music should be administered to critically ill patients (16, 17). However, the precise physiologic mechanisms by which music might achieve this reduced stress response have not been elucidated.

Recent studies clearly indicate a close, bidirectional communication between the neuroendocrine and immune systems. Hypothalamic hormones, apart from their neuroendocrine role, have been shown to influence immune function (19–22). Growth hormone-releasing hormone, for example, is not only produced by neurosecretory cells of hypothalamic nuclei, but also synthesized by immunocompetent cells (23, 24). Interleukin-6 (IL-6) and other cytokines play a central role in immune modulation and also have demonstrable effects on the neuroendocrine system (25–28). It has been shown that music can influence the IL-6 level in healthy volunteers (29).

Numerous studies have focused on adrenocorticotropic hormone (ACTH) and cortisol to investigate the effects of music on the neurohormonal pathway (30, 31). Escher et al. (31) showed that in a patient receiving a gastroscopy, ACTH level could be beneficially influenced by music. Gerra et al. (29) were interested in the neurophysiologic response of healthy volunteers to techno music. They thus compared the influence of techno music with classical music on plasma norepinephrine, epinephrine, growth hormone, prolactin, ACTH, cortisol, and β-endorphin. Other studies have examined how these "classic" hormones of the human stress response are affected by music. A well-conducted study demonstrated anxiolytic effects of music mediated through ovarian steroid in female mice (32).

We designed the present study to learn whether a well-defined selection of Mozart music can alleviate stress in critically ill patients and how this effect is mediated physiologically. The chosen set

***See also p. 2858.**

From the Department of Surgery, Massachusetts General Hospital, Boston, MA (CC); Department of Surgery, University of Munich-Grosshadern, Munich, Germany (HN, KWJ, CJB, WHH); and the Department of Fine Arts, Institute of Music Science, University of Munich, Munich, Germany (LW).

The authors have not disclosed any potential conflicts of interest.

Drs. Hartl and Welker contributed equally to this article.

For information regarding this article, E-mail: cconrad1@partners.org

DOI: 10.1097/01.CCM.0000291648.99043.B9

of outcome variables is based on the current literature on the human neurohormonal stress response (32).

METHODS

Patients. The study included ten critically ill patients with an Acute Physiology and Chronic Health Evaluation II score of >16. (33). They were selected randomly in the early postoperative period (day 1 after surgery). Inclusion criteria were as follows: patients had to be intubated for mechanical ventilation and had to be sedated with the short-acting narcotic agent propofol at comparable doses. Patients were then randomized to music and no-music groups. The two groups were comparable with respect to operative procedures performed, duration of operation, age, and sex. There was one female patient in the music group. In previous studies looking at healthy volunteers, sex has not been shown to affect the hormones and cytokines influenced by music.

Music. For music therapy, we used slow movements from the Mozart piano sonatas; these were selected based on analyses for the compositional elements of relaxation. These elements included duration, dynamic, tempo, or the repetition of a theme with slight variations. A detailed description of these elements is beyond the scope of this article. The slow movements were played in chronological order of composition: KV283, "Andante" (1775); KV311, "Andantino con espressione" (1777); KV330, "Andante cantabile" (1783); KV332, "Adagio" (early 1780s); KV333, "Andante cantabile" (1783); KV545, "Andante" (1788); KV570, "Adagio" (1789); and KV576, "Adagio" (1789).

Protocol. The patients were randomized into two groups: one group received music, whereas the other group did not receive music, but still had headphones applied. At 9 am of the first postoperative day, propofol sedation was terminated in all patients. At 15 mins after discontinuation of the propofol drip, the patient's Ramsay sedation scale score was judged by the nursing staff (34). Music was then administered via headphones for a period of 1 hr, after which routine sedation was reinitiated.

During the entire study, we recorded heart rate, blood pressure, and brain electrical activity. At the end of the music session, the nursing staff again scored the patient with respect to his or her degree of sedation using the standardized Ramsay sedation scale. The nurses were blinded as to whether the patient received music via the headphones. If propofol sedation had to be resumed during the study, the amount of propofol necessary for sufficient sedation in the two groups was recorded. Before and after the music intervention, blood samples were obtained and shipped on ice for immediate analysis via an intrahospital tubing system. Blood samples were drawn from previously existing arterial catheters, which had been placed either before the operation or at arrival to the intensive care unit. Concentrations of the following substances were measured: dehydroepiandrosterone, growth hormone, epinephrine, norepinephrine, ACTH, cortisol, IL-6, prolactin, and prolactin monomere. The following assays were used, which are among those routinely used in the core chemistry laboratory: cortisol, dehydroepiandrosterone, and prolactin—automated immunoassays (Elecsys, Roche Diagnostics, Basel, Switzerland); prolactin monomere—analysis with the same assay (Elecsys, Roche Diagnostics) after precipitation with polyethylene glucol; human growth hormone and ACTH—automated immunoassays (Advantage, Nichols Institute Diagnostics, San Clement, CA); IL-6 and epinephrine (IL-6-EASIA-CB, Firma Biosource, Solingen, Germany); norepinephrine—high-power liquid chromatography with electrochemical detection kit (Chromsystems, Munich, Germany).

We also evaluated differences in brain electrical activity using an electroencephalogram with the standard leads in the occipital, temporal, and frontal region. Criteria for study discontinuation were predefined and included mean arterial pressure of >100 mm Hg, heart rate of >150 beats/min, diaphoresis, coughing, or a pressure alarm by the ventilator due to an inadequate patient–machine coordination. The study was approved by the institutional review board.

Statistics. Data were analyzed using SPSS Version 14.0.1 (SPSS, Chicago, IL). Within the same group, comparisons were made by the paired Student's *t*-test. We used this test to compare the respective variables before and after the music intervention in each group. Between-group comparisons were evaluated with the unpaired Student's *t*-test, comparing the group that received music with the group that did not receive music. To achieve this, we transformed the data by dividing the final value by the initial value, allowing us to compare changes from baseline. To analyze data of the Ramsay sedation scale, we used the chi-square test because the Ramsay sedation scale values are independent variables. Differences with a resultant p value of $<.05$ were considered significant. Raw data are given as mean rank ± SEM.

Table 1. Baseline characteristics of examined patients

	Age	Gender	Propofol Before Intervention, mg	Diagnosis	Surgery
Music group					
1	61	F	15	Pancreatic cancer, intrahepatic hemorrhage	Percutaneous drainage
2	55	M	15	Large-bowel perforation	Left-sided hemicolectomy
3	55	M	12	Small-bowel fistula	Fistula closure
4	77	M	25	Cancer of the cardia	Esophagogastric resection
5	47	M	15	Lung cancer	Left-sided pneumonectomy
Control					
6	71	M	24	Abdominal aortic aneurysm	Aortic replacement by synthetic graft
7	45	M	6	Pulmonary metastasis	Wedge resection of right lower lobe
8	71	M	24	Abdominal bleeding	Vascular suture at the celiac trunk
9	46	M	24	Polytrauma	External fixation at both lower limbs
10	71	M	24	Esophageal carcinoma	Esophagectomy, gastric pull-through

F, female; M, male.

RESULTS

Characteristics of both patient groups are given in Table 1. The heart rate in the control group increased (120 ± 9 beats/min before therapy, 125 ± 7 beats/min after therapy; $p < .05$), whereas it remained the same in the music group. However, there was no significant difference among between-group comparisons. Arterial blood pressure increased in the control group (95 ± 6 mm Hg before therapy, 106 ± 6 mm Hg after therapy; $p < .05$) and decreased in the music group (Fig. 1). Patients in the music group did not require any additional sedation by propofol, whereas among patients in the control group, propofol was occasionally necessary to allow sufficient patient–ventilator coordination. All patients in the music group were designated a grade 2 in the Ramsey scale, whereas the patients in the nonmusic group mainly received a score of 1, suggesting an inadequate degree of sedation (chi-square test, $p < .05$). The effect of music intervention seemed to last beyond the period during which Mozart's music

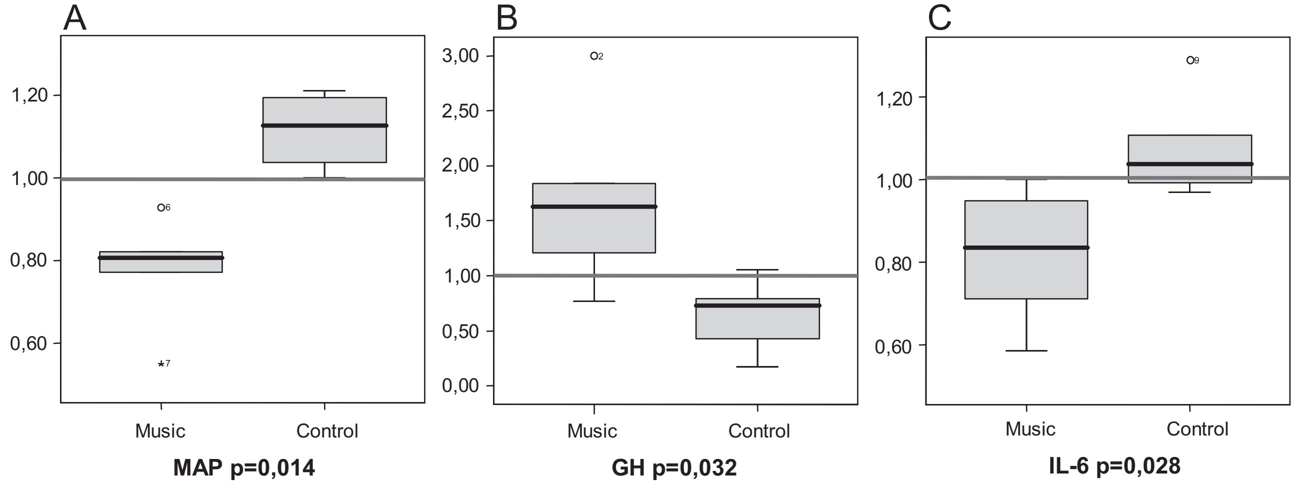

Figure 1. Central variables of the stress response as influenced by music: Mean arterial pressure (*MAP*) [*A*] and serum concentrations of growth hormone (*GH*) [*B*] and interleukin-6 (*IL-6*) [*C*]. Data represent relative changes from baseline after a music therapy session or a control session.

was played. The patients in both groups were left without sedation for 30 mins after the music had stopped and the patients in the music group seemed calmer and more relaxed than the patients in the control group. However, no objective measurement was performed beyond the immediate postintervention period.

Significant differences were found between the music and control groups with regard to levels of dehydroepiandrosterone, growth hormone, IL-6, and epinephrine. Serum levels of dehydroepiandrosterone rose significantly in controls (1.040 ± 0.416 μg/mL before therapy, 1.120 ± 0.423 μg/mL after therapy, $p < .05$) but remained unchanged during music therapy. Between-group comparisons were significant ($p < .05$) (Fig. 2). Serum levels of growth hormone remained unchanged in controls (5.98 ± 1.74 ng/mL before therapy, 4.36 ± 1.57 ng/mL after therapy, $p = .05$) but rose significantly after music therapy by 60% ($p < .05$). Between-group comparisons were significant ($p < .05$) (Fig. 1). Serum levels of IL-6 remained unchanged in controls (1657 ± 1251 ng/mL before placebo, 1616 ± 1210 ng/mL after placebo, $p = .388$) but decreased significantly after music therapy by 83% ($p < .05$). Between-group comparisons were significant ($p < .05$) (Fig. 1). Simultaneously, serum concentrations of epinephrine remained unchanged in controls (154 ± 47 pg/mL before placebo, 189 ± 43 pg/mL after placebo, $p = .436$) but fell significantly after music therapy by an average of 55% ($p < .05$). Between-group comparisons were significant ($p = .05$) (Fig. 2).

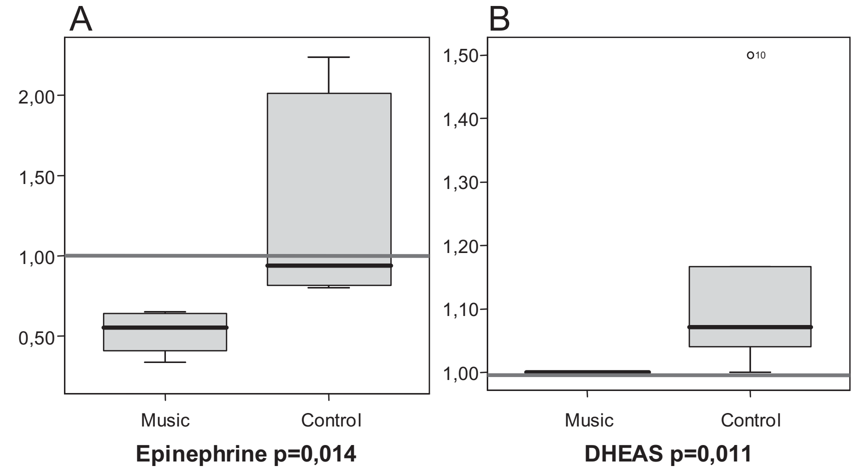

Figure 2. Serum concentrations of epinephrine and dehydroepiandrosterone (*DHEAS*). Data represent relative changes from baseline after a music therapy session or a control session.

With respect to prolactin ($p = .27$), prolactin monomer ($p = .08$), norepinephrine ($p = .22$), ACTH ($p = .36$), or cortisol ($p = .92$) concentrations, we did not find significant differences. Using electroencephalogram technology, we did not find significant differences in brain electrical activity between the music and the control groups.

DISCUSSION

The present work confirms that the application of a certain type of music in critically ill, intubated patients leads to measurable anxiolytic reactions (35–39). In addition, the results of this study may serve as a scientific basis for understanding some of the beneficial music effects that have been observed in intensive care units. That the need for narcotic agents is reduced when music is applied has been previously demonstrated for patients in the intraoperative phase (12, 40–42). Our study extends this observation to the intensive care unit setting, where we have shown that among severely ill patients, music application beneficially alters cardiovascular variables.

We found a significant decrease in dehydroepiandrosterone, epinephrine, and IL-6 concentrations in the music group, as has been previously described in healthy volunteers (29, 43). In addition, we found that growth hormone plasma concentrations increased significantly and IL-6 decreased when critically ill patients were exposed to Mozart's music. This finding may help to define the mechanism by which music exerts its beneficial effects on a cellular level (Fig. 3). One

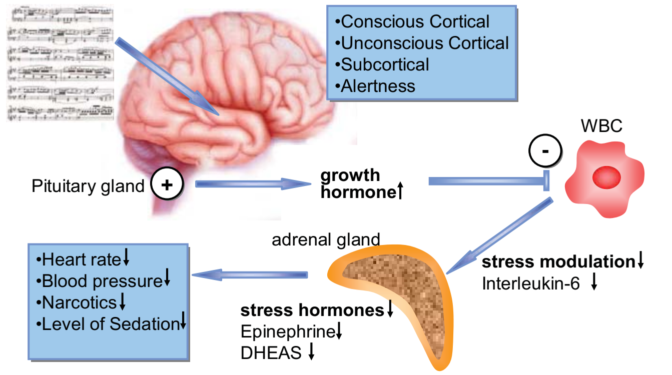

Figure 3. Hypothetical neurohumoral pathway of music action during the human stress response. *WBC*, white blood cell; *DHEAS*, dehydroepiandrosterone.

explanation for the increased growth hormone release while listening to music may stem from the *transfer effect*. It has been reported previously that listening to Mozart's music can lead to an increased activation of brain regions that are not directly involved in the process of listening (44). This controversially discussed mechanism uses the trion model of brain organization and would be compatible with our findings that music application did not measurably affect electroencephalographic signals.

Striking alterations in the hypothalamic–anterior, pituitary–peripheral hormone axes are the hallmark of critical illness, the degree of alteration being associated with high risk for morbidity and mortality. Early endocrine intervention strategies aimed to correct the hormone balance have been shown ineffective, or even harmful, because of an inadequate understanding of the detailed pathophysiology underlying these changes. Extensive research, however, has provided crucial insights, with the demonstration of the biphasic response of the anterior pituitary to the severe stress of critical illness (45).

The effect of music on pituitary growth hormone release may be central to the secondary sedative actions of music. These actions may result from an indirect effect on the sympathetic nervous system via attenuation of nonspecific inflammatory reactions. Pituitary growth hormone release is stimulated on exposure to hypothalamic growth hormone–releasing factor. However, growth hormone–releasing hormone is synthesized by the hypothalamus but is present also in the immune cells. Some recent data also suggest an immunomodulatory role of the neuropeptide. Studies have demonstrated that there is an inverse correlation between growth hormone-releasing factor availability and IL-6 release from peripheral blood mononuclear cells (46). These observations may help explain why music application reduced IL-6 concentrations in our study. The modulatory effect of music application on IL-6 availability may then be the central pathway of stress reduction, as IL-6 is a potent activator of the adrenocortical and sympathoadrenal axes (4). Other mechanisms by which music-induced growth hormone secretion might foster the immune response is via inhibition of Fas-induced apoptosis in activated T and B lymphocytes (47). According to our results, effects of music application on the sympathoadrenal axis seem to be dominant, as we did not observe significant alterations of ACTH and cortisol concentrations during music therapy, whereas adrenaline concentrations did indeed decline.

Furthermore, the acute hypertensive response to psychosocial stress depends significantly on a direct, presumably peripheral IL-6 effect. This effect seems to be specific to blood pressure control rather than related to a global upregulation of the stress response and may further elucidate the marked decrease of blood pressure observed during music-induced IL-6 attenuation (47–49). Lee et al. demonstrated that IL-6 contributes to the hypertensive response to acute psychosocial stress caused by switching male mice to a cage previously occupied by a different male mouse. Male C57BL6 (wild type) and IL-6 knockout mice were implanted with biotelemetry devices to monitor mean arterial pressure, heart rate, and motor activity in the unrestrained state. Baseline mean arterial pressure was blunted significantly in knockout mice, whereas several other hormones involved in blood pressure regulation were similar in both groups. Thus, the acute hypertensive response to psychosocial stress depends significantly on IL-6 and could be the most important mechanism by which music might exert its calming effect (48). It should be noted that, in contrast to our findings, music application attenuated the activity of the adrenocortical axis significantly in studies performed by other groups. This discrepancy is probably related to the fact that our patients were in a much more severe state of critical illness. In such conditions, adrenocortical insufficiency has been described, and the stress response may be predominantly maintained by the sympathoadrenal axis (45).

Although this study begins to elucidate some of the physiologic mechanisms dictating music's therapeutic benefit, it also raises new questions that warrant further investigation. We do not know, for instance, whether the observed effect is specific to Mozart's music or perhaps related to the underlying severity of the clinical situation studied. It is also unknown how other types of music would possibly affect the human stress response and whether those responses are related to previously known musical preferences. Future studies are necessary to investigate how this beneficial effect of music can be further integrated clinically, as there is potential not only for musical interventions to reduce our dependence on sedative drugs, but also to ultimately improve outcomes of morbidity and mortality in the critical care setting.

REFERENCES

1. Spintge D: "Musik-Medizin-Physiologische Grundlagen und praktische Anwendungen". Stuttgart, Germany, Gustav Fischer, 1992
2. 1 Samuel 16:32
3. Shapiro RA, Berland T: Noise in the operating room. *N Engl J Med* 1972; 287:1236–1238
4. Mullooly VM, Levin RF, Feldman HR: Music for postoperative pain and anxiety. *J N Y State Nurses Assoc* 1988; 19:4–7
5. Wigram T, Lawrence M: Music therapy as a tool for assessing hand use and communicativeness in children with Rett syndrome. *Brain Dev* 2005; 27(Suppl 1):S95–S96
6. Gold C, Heldal TO, Dahle T, et al: Music therapy for schizophrenia or schizophrenia-like illnesses. *Cochrane Database Syst Rev* 2005; 2:CD004025

7. Haus R, Hennecke KH: Music therapy for prematures. *Z Geburtshilfe Neonatol* 2003; 207:255–257
8. Loewy J, Hallan C, Friedman E, et al: Sleep/sedation in children undergoing EEG testing: A comparison of choral hydrate and music therapy. *J Perianesth Nurs* 2005; 20: 323–332
9. Cowan DS: Music therapy in the surgical arena. *Music Ther Perspect* 1991; 9:42–45
10. Cork RC, Guillory EA, Viswanathan S, et al: The effect of patient controlled sedation on recovery from ambulatory monitored anesthesia care. *Am J Anesth* 1995; 94–110
11. Heiser RM, Chiles K, Fudge M, et al: The use of music during the immediate postoperative recovery period. *AORN J* 1997; 65:777–778, 781–785
12. Koch ME, Kain ZN, Ayoub C, et al: The sedative and analgesic sparing effect of music. *Anesthesiology* 1998; 89:300–306
13. Wang SM, Kulkarni L, Dolev J, et al: Music and preoperative anxiety: a randomized, controlled study. *Anesth Analg* 2002; 94: 1489–1494
14. Chlan L, Tracy MF, Nelson B, et al: Feasibility of a music intervention protocol for patients receiving mechanical ventilatory support. *Altern Ther Health Med* 2001; 7:80–83
15. Chlan L, Tracy MF: Music therapy in critical care: Indications and guidelines for intervention. *Crit Care Nurse* 1999; 19:35–41
16. Kane E: The phonograph in the operating room. *JAMA* 1914; 62:1829–1830
17. Allen K, Blascovich J: Effects of music on cardiovascular reactivity among surgeons. *JAMA* 1994; 272:882–884
18. Fontaine CW, Schwalm ND: Effects of familiarity of music on vigilant performance. *Percept Mot Skills* 1979; 49:71–74
19. Blalock JE, Smith EM: Conceptual development of the immune system as a sixth sense. *Brain Behav Immun* 2007; 21:23–33
20. Pawlikowski M, Stepien H, Komorowski J: Hypothalamic-pituitary-thyroid axis and the immune system. *Neuroimmunomodulation* 1994; 1:149–152
21. Spangelo BL, Gorospe WC: Role of the cytokines in the neuroendocrine-immune system axis. *Front Neuroendocrinol* 1995; 16:1–22
22. Weigent DA, Blalock JE: Associations between the neuroendocrine and immune systems. *J Leukoc Biol* 1995; 58:137–150
23. Khorram O, Garthwaite M, Golos T: The influence of aging and sex hormones on expression of growth hormone-releasing hormone in the human immune system. *J Clin Endocrinol Metab* 2001; 86:3157–3161
24. Stephanou A, Knight RA, Lightman SL: Production of a growth hormone-releasing hormone-like peptide and its mRNA by human lymphocytes. *Neuroendocrinology* 1991; 53: 628–633
25. Spangelo BL, Judd AM, Call GB, et al: Role of the cytokines in the hypothalamic-pituitary-adrenal and gonadal axes. *Neuroimmunomodulation* 1995; 2:299–312
26. Arzt E, Paez Pereda M, Costas M, et al: Cytokine expression and molecular mechanisms of their auto/paracrine regulation of anterior pituitary function and growth. *Ann N Y Acad Sci* 1998; 840:525–531
27. Gloddek J, Lohrer P, Stalla J, et al: The intrapituitary stimulatory effect of lipopolysaccharide on ACTH secretion is mediated by paracrine-acting IL-6. *Exp Clin Endocrinol Diabetes* 2001; 109:410–415
28. Thiele JO, Lohrer P, Schaaf L, et al: Functional in vitro studies on the role and regulation of interleukin-6 in human somatotroph pituitary adenomas. *Eur J Endocrinol* 2003; 149: 455–461
29. Gerra G, Zaimovic A, Franchini D, et al: Neuroendocrine responses of healthy volunteers to 'techno-music': Relationships with personality traits and emotional state. *Int J Psychophysiol* 1998; 28:99–111
30. Migneault B, Girard F, Albert C, et al: The effect of music on the neurohormonal stress response to surgery under general anesthesia. *Anesth Analg* 2004; 98:527–532
31. Escher J, Hohmann U, Anthenien L, et al: Music during gastroscopy (German). *Schweiz Med Wochenschr* 1993; 123:1354–1358
32. Chikahisa S, Sano A, Kitaoka K, et al: Anxiolytic effect of music depends on ovarian steroid in female mice. *Behav Brain Res* 2007; 179:50–59
33. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
34. Carrasco G: Instruments for monitoring intensive care unit sedation. *Crit Care* 2000; 4:217–225
35. Formisano R, Vinicola V, Penta F, et al: Active music therapy in the rehabilitation of severe brain injured patients during coma recovery. *Ann Ist Super Sanita* 2001; 37: 627–630
36. Almerud S, Petersson K: Music therapy: A complementary treatment for mechanically ventilated intensive care patients. *Intensive Crit Care Nurs* 2003; 19:21–30
37. Harikumar R, Raj M, Paul A, et al: Listening to music decreases need for sedative medication during colonoscopy: A randomized, controlled trial. *Indian J Gastroenterol* 2006; 25:3–5
38. Chlan L: Effectiveness of a music therapy intervention on relaxation and anxiety for patients receiving ventilatory assistance. *Heart Lung* 1998; 27:169–176
39. Updike P: Music therapy results for ICU patients. *Dimens Crit Care Nurs* 1990; 9:39–45
40. Lepage C, Drolet P, Girard et al: Music decreases sedative requirements during spinal anesthesia. *Anesth Analg* 2001; 93:912–916
41. Hodge B, Thompson JF: Noise pollution in the operating theater. *Lancet* 1990; 335: 891–894
42. Cruise CJ, Chung F, Yogendran S, et al: Music increases satisfaction in elderly outpatients undergoing cataract surgery. *Can J Anaesth* 1997; 44:43–48
43. Stefano GB, Zu W, Cadet P, et al: Music alters constitutively expressed opiate and cytokine processes in listeners. *Med Sci Monit* 2004; 10:MS18–MS27
44. Rauscher FH, Shaw GL, Ky KN: Music and spatial task performance. *Nature* 1993; 365:611
45. Chrousos GP: The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; 332:1351–1362
46. Siejka A, Stepien T, Lawnicka H, et al: Effect of the growth hormone-releasing hormone [GHRH(1–44)NH2] in IL-6 and IL-8 secretion from human peripheral blood mononuclear cells in vitro. *Endocr Regul* 2005; 39: 7–11
47. Mitsunaka H, Dobashi H, Sato M, et al: Growth hormone prevents Fas-induced apoptosis in lymphocytes through modulation of Bcl-2 and caspase-3. *Neuroimmunomodulation* 2001; 9:256–262
48. Lee DL, Leite R, Fleming C, et al: Hypertensive response to acute stress is attenuated in interleukin-6 knockout mice. *Hypertension* 2004; 44:259–263
49. Vanhorebeek I, Van den Berghe G: The neuroendocrine response to critical illness is a dynamic process. *Crit Care Clin* 2006; 22: 1–15