# The Influence of Concentration/Meditation on Autonomic Nervous System Activity and the Innate Immune Response: A Case Study

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**Objective:** In this case study, we describe the effects of a particular individual's concentration/meditation technique on autonomic nervous system activity and the innate immune response. The study participant holds several world records with regard to tolerating extreme cold and claims that he can influence his autonomic nervous system and thereby his innate immune response. **Methods:** The individual's ex vivo cytokine response (stimulation of peripheral blood mononuclear cells with lipopolysaccharide [LPS]) was determined before and after an 80-minute full-body ice immersion during which the individual practiced his concentration/meditation technique. Furthermore, the individual's in vivo innate immune response was studied while practicing his concentration/mediation technique during human endotoxemia (intravenous administration of 2 ng/kg LPS). The results from the endotoxemia experiment were compared with a historical cohort of 112 individuals who participated in endotoxemia experiments in our institution. **Results:** The ex vivo proinflammatory and anti-inflammatory cytokine response was greatly attenuated by concentration/meditation during ice immersion, accompanied by high levels of cortisol. In the endotoxemia experiment, concentration/meditation resulted in increased circulating concentrations of catecholamines, and plasma cortisol concentrations were higher than in any of the previously studied participants. The individual's in vivo cytokine response and clinical symptoms after LPS administration were remarkably low compared with previously studied participants. **Conclusions:** The concentration/meditation technique used by this particular individual seems to evoke a controlled stress response. This response is characterized by sympathetic nervous system activation and subsequent catecholamine/cortisol release, which seems to attenuate the innate immune response. **Key words:** concentration, meditation, innate immune response, cytokines, autonomic nervous system, cortisol.

**ANS** = autonomic nervous system; **HRV** = heart rate variability; **LPS** = lipopolysaccharide; **EEG** = electroencephalography; **MSNA** = muscle sympathetic nerve activity; **PBMC** = peripheral blood mononuclear cell.

## INTRODUCTION

Although the innate immune system is crucial to our survival, an excessive inflammatory response can result in tissue damage and organ injury (1). Therefore, limiting the innate immune response could reduce disease burden and improve outcome. It has long been known that the sympathetic nervous system can attenuate systemic inflammation directly via activation of β2-adrenoceptors by catecholamines (2). In addition, as part of a stress response, increased levels of catecholamines are often accompanied by elevations in cortisol, a well-known immunodepressant (3). More recently, the parasympathetic nervous system has been shown to modulate innate immunity because electrical stimulation of the efferent vagus nerve greatly attenuates the inflammatory response in animal models (4). The autonomic nervous system (ANS) is generally regarded as a system that cannot be willingly influenced. However, several recent investigations suggest that, through certain concentration/meditation techniques, it is possible to modulate autonomic activity (5–8). In light of the effects of the ANS on the innate immune system, concentration/meditation techniques may influence inflammatory parameters. Although limited ex vivo data support this hypothesis (9,10), in vivo evidence has yet to be obtained.

A Dutch man, aged 51 years, holds several world records with regard to withstanding extreme cold, including the fastest half marathon barefoot on ice/snow and standing fully immersed in ice for 1 hour 50 minutes. This person claims to achieve these remarkable feats through a special concentration/meditation technique. He claims that he can influence his ANS and also his immune response. Herein, we describe a set of three distinct experiments in this individual, focusing on the effects of his concentration/meditation technique on ANS parameters and the innate immune response, both ex vivo and in vivo. A schematic overview of the experimental protocols is depicted in Figure 1. In the next sections, we summarize the main findings; detailed descriptions of the methods and results of the three experiments are presented in an online document (Supplemental Digital Content, http://links.lww.com/PSYMED/A43).

## EXPERIMENT 1: CONCENTRATION/MEDITATION DURING ICE IMMERSION

In the first experiment, we determined the effects of concentration/meditation during ice immersion on plasma cortisol levels and cytokine production of ex vivo stimulated peripheral blood mononuclear cells (PBMCs) and macrophages. Thirty

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The research participant described in this study provided written consent to the publication of details of these experiments and information that may serve to identify him.

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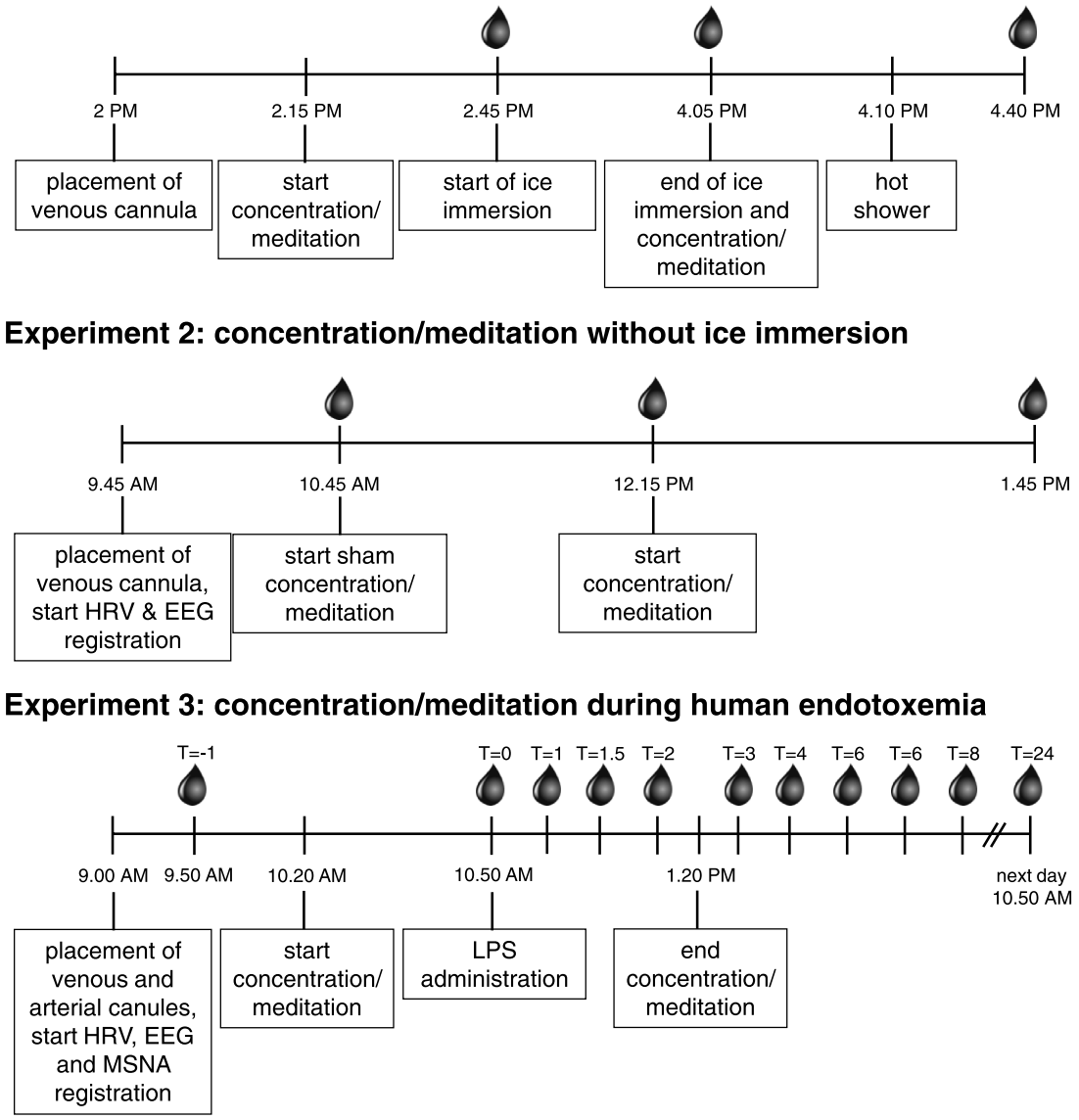


Figure 1. Schematic representation of the three experiments performed in the subject. Drops indicate blood withdrawal. HRV = heart rate variability; EEG = electroencephalography; MSNA = muscle sympathetic nerve activity; LPS = lipopolysaccharide.

minutes after the start of concentration/meditation (just before ice immersion), cortisol levels were already relatively high and rose to slightly higher levels immediately after the end of the ice immersion period, after which they decreased (Fig. 2A). Lipopolysaccharide (LPS)-induced production of both proinflammatory and anti-inflammatory cytokines by ex vivo stimulated PBMCs obtained after ice immersion was greatly attenuated compared with PBMCs obtained before (Fig. 3A). This effect was not only observed after stimulation with LPS but also when PBMCs were stimulated with other (components of) heat-killed pathogens such as *Candida albicans* and *Staphylococcus aureus* (data not shown). Strikingly, in monocyte-derived macrophage cultures stimulated with LPS 6 days after the ice immersion, a similar pattern was observed (Fig. 3B).

### EXPERIMENT 2: CONCENTRATION/MEDITATION WITHOUT ICE IMMERSION

In the second experiment, we determined the effects of concentration/mediation without ice immersion on plasma cortisol and catecholamine levels, heart rate variability (HRV) and electroencephalography (EEG) parameters, and ex vivo stimulated PBMC and macrophage cytokine production. Cortisol and norepinephrine levels were not increased by concentration/meditation (sham versus concentration/meditation: cortisol, 0.39 and 0.36 μmol/L; norepinephrine, 2.12 and 2.25 nmol/L). In contrast, plasma epinephrine concentration increased from 0.23 to 0.36 nmol/L. HRV analysis revealed that concentration/meditation resulted in an increase in total spectral power; however, no effects on autonomic balance were observed. Stimulation of

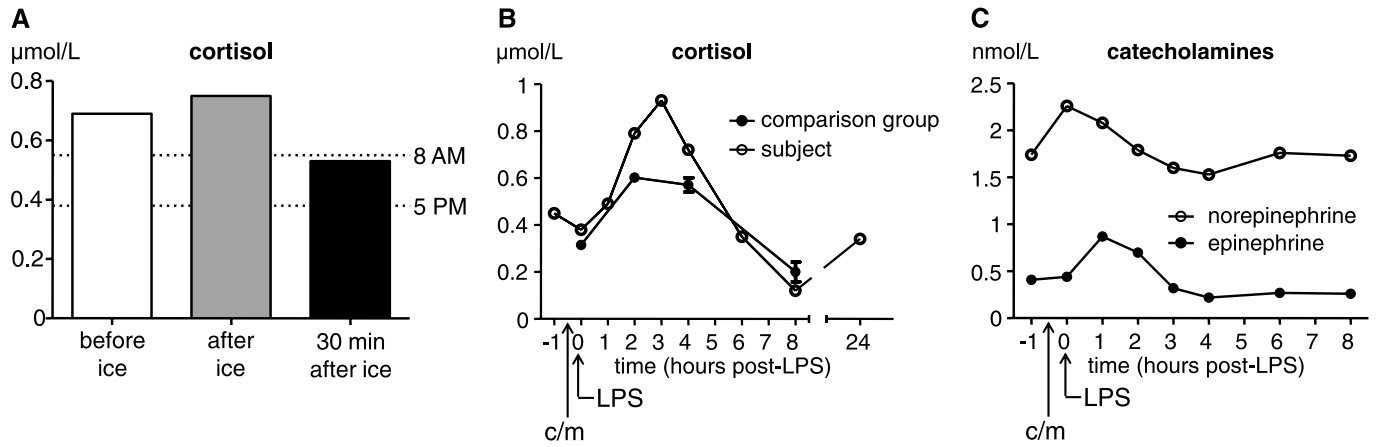


Figure 2. Plasma levels of cortisol before and after ice immersion (A). Plasma levels of cortisol (B) and catecholamines (C) during experimental human endotoxemia. In panel A, dotted lines indicate the reference values for cortisol in our center at 8 AM and 5 PM (circadian variation). In panel B, cortisol data of the study participant and a subset of the comparison group (mean ± standard error of the mean, $n = 15$) are shown. The area under the curve of the individual's cortisol time course (only using time points also measured in the comparison group: $T = 0$, $T = 2$, $T = 4$, and $T = 8$) was outside the reference range (mean ± 1.96* SD) of the comparison group.

PBMCs or macrophages revealed no effects of concentration/meditation on cytokine production ex vivo (data not shown).

## EXPERIMENT 3: CONCENTRATION/MEDITATION DURING HUMAN ENDOTOXEMIA

In the third experiment, we determined the effects of concentration/meditation on measures of autonomic activity (plasma cortisol and catecholamine levels, HRV, and muscle sympathetic nerve activity [MSNA]), as well as EEG and the innate immune response in vivo during experimental human endotoxemia (LPS administration). The cytokine, hemodynamic, temperature, and illness score results from the endotoxemia experiment in this person (Clinical Trial Registry number NCT01352871) were compared with a historical cohort of 112 healthy male volunteers who participated in human endotoxemia trials in our institution and therefore underwent the same protocol (comparison group; NCT00246714, NCT00513110, NCT00783068, NCT00785018,

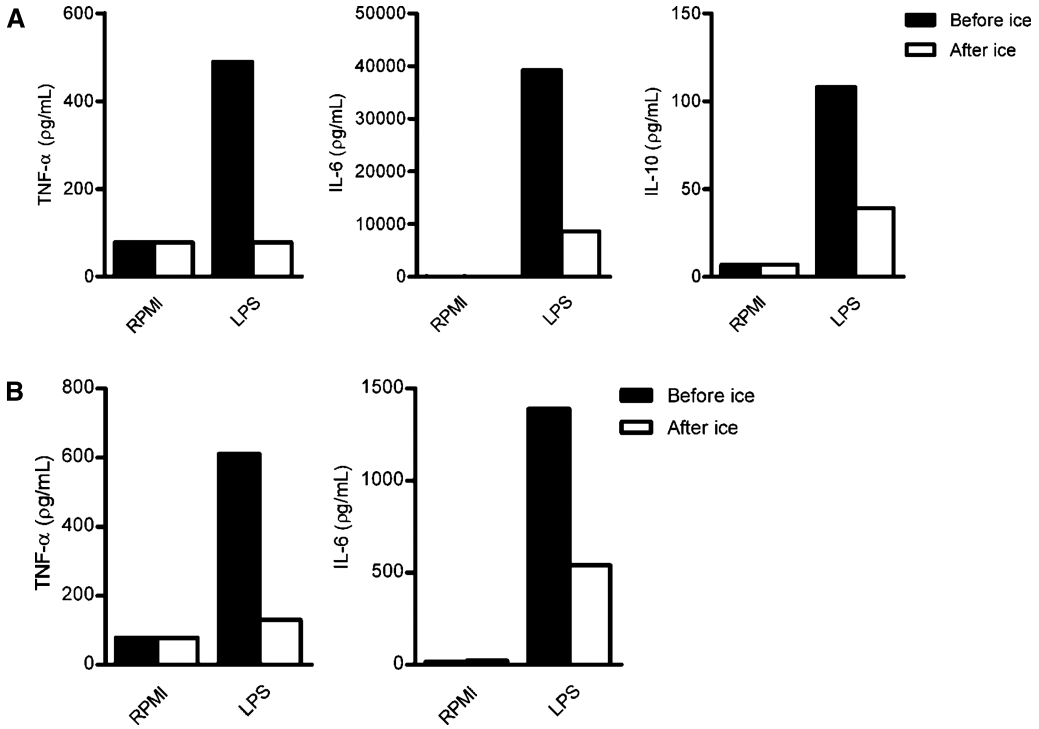


Figure 3. Production of proinflammatory (tumor necrosis factor α [TNF-α] and interleukin 6 [IL-6]) and anti-inflammatory (IL-10) cytokines in peripheral blood mononuclear cells (A) and monocyte-derived macrophages (B) obtained before and after ice immersion, which were ex vivo stimulated with Rosswell Park Memorial Institute (RPMI) (control) or lipopolysaccharide (LPS) (10 ng/mL) for 24 hours (TNF-α and IL-6) or 60 hours (IL-10). Macrophages were obtained by culturing monocytes for 6 days in the presence of 10% pooled human serum.

NCT00916448, NCT01349699, and NCT01091571). LPS administration in the subject resulted in remarkably few symptoms: he only reported a mild headache for 10 minutes at $T = 1.5$ (the time point at which the illness score normally peaks), yielding a symptom score of 1 compared with a symptom (mean [standard deviation {SD}]) score of 6.6 (2.8) ($n = 112$) at $T = 1.5$ in the comparison group. Of note, only 1 of the 112 individuals of the comparison group exhibited an equally low symptom score. Plasma cortisol levels at the time of LPS administration were similar to those of a subset of the comparison group in which cortisol was determined (Fig. 2B). However, the increase in cortisol after LPS administration was much more pronounced in the study participant compared with this comparison group. Both plasma norepinephrine and epinephrine levels peaked after concentration/meditation and gradually returned to baseline levels (Fig. 2C). Besides an initial increase in total spectral power and SD of all normal R-R intervals (which is the time domain correlate of total spectral power), no clear-cut effect of concentration/meditation on HRV indices was observed. Furthermore, the common decrease in HRV indices after LPS administration was also present in the individual and to a similar extent as in a subset of the comparison group in which HRV was determined. The individual exhibited quite vigorous movement during the concentration/meditation period, which led to dislocation of the MSNA electrodes. Therefore, only a reliable (mean [SD]) baseline recording (before the start of the concentration/meditation period) was obtained as follows: total MSNA, 28.3 (2.1) bursts per minute and frequency-corrected MSNA, 47.5 (5.5) bursts per 100 beats, which is comparable with what was previously reported in individuals under resting conditions (11). LPS-induced plasma levels of inflammatory cytokines were remarkably low in the individual (Fig. 4). The areas under the curve of the comparison group individuals' cytokine responses were ranked, and the subject's area under the curve cytokine response lied within the 18th percentile for tumor necrosis factor α, 5th percentile for interleukin 6, and 13th percentile for interleukin 10.

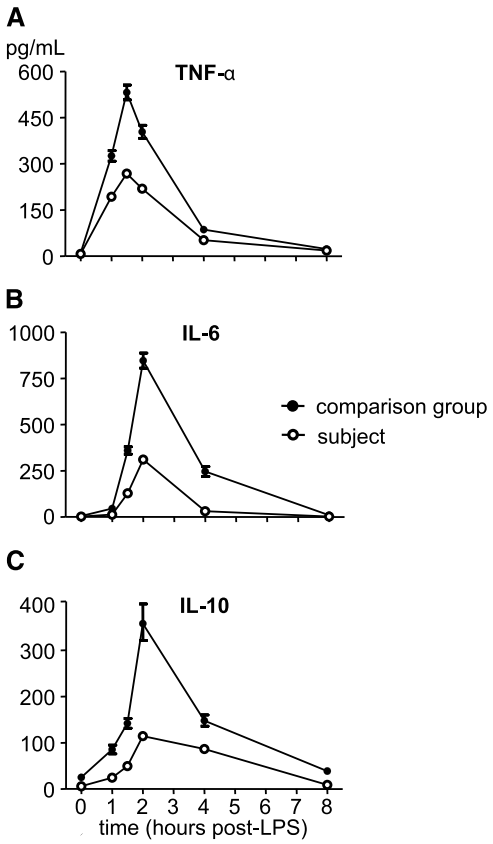


Figure 4. Plasma levels of proinflammatory, such as tumor necrosis factor α (TNF-α) (A) and interleukin 6 (IL-6) (B), and anti-inflammatory (IL-10) (C) cytokines during experimental human endotoxemia. Data of the study participant and the comparison group (mean ± standard error of the mean, $n = 112$) are shown.

## DISCUSSION

In summary, concentration/meditation during ice immersion resulted in high cortisol levels and suppressed cytokine production ex vivo. In addition, we demonstrate that concentration/meditation during experimental endotoxemia resulted in elevated levels of (nor)epinephrine and cortisol, associated with a remarkably mild innate immune response in vivo. The relatively minor effects of concentration/meditation in the absence of an external stimulus (Experiment 2) suggest that the individual needs and external stimulus (e.g., ice immersion or LPS infusion) to optimally concentrate/meditate. These data suggest that this particular concentration/meditation technique evokes a stress response characterized by activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. Both catecholamines and cortisol are well-known immunosuppressants (2,3). Furthermore, in patients with heart failure, plasma cortisol levels correlated negatively with ex vivo cytokine production (12). Therefore, this concentration/meditation-induced stress response might explain the observed immunosuppression.

Increased cortisol levels after LPS administration have been reported before (13). However, whereas baseline cortisol levels in the endotoxemia experiment were comparable with those of the healthy volunteers who were previously studied, the LPS-induced increase was more pronounced than in any of the individuals who we have previously studied. The remarkable differences in the ex vivo cytokine responses between the leukocytes stimulated before and up to 6 days after ice immersion may be explained by the fact that the leukocytes obtained after ice immersion had been subjected to high cortisol and/or catecholamine levels for a prolonged period (>2 hours) compared with the cells obtained before. In accordance with a previous study, this indicates that immune cells can be deactivated for a prolonged period after short-term exposure to corticosteroids (14).

We did find an increase in HRV total spectral power during concentration/meditation, which was not surprising in light of the large fluctuations in heart rate during this period. However, we did not find evidence for increased sympathetic activity using HRV analysis. It has been reported that, although certain HRV indices (particularly high-frequency power) correlate well with parasympathetic modulation (15), sympathetic correlates of HRV are still disputed (16). For that reason, HRV analysis might not be an appropriate tool to investigate sympathetic activity. Furthermore, HRV is known to be affected by breathing patterns/

frequency (17); therefore, the individual's extremely irregular breathing may have influenced the measurements.

The individual reported exceptionally few symptoms during endotoxemia. However, the "illness score" is a highly subjective parameter, and the individual may be used to extreme circumstances. Meditation is generally associated with reduction of stress and catecholamine/cortisol levels (10,18). These discrepant results compared with our study might be explained by the fact that the other studies, in contrast to ours, have evaluated effects of meditation in the long term. Furthermore, the concentration/meditation technique practiced by this individual is very different to those used in other studies. This particular technique is not targeted at relaxation of the body but rather seems to activate it. This is supported by data from a previous report showing that the individual's oxygen consumption doubled during ice immersion (19), indicating that practicing this technique results in increased metabolism.

With respect to the individual's particular concentration/meditation technique, our findings might better be compared with studies investigating the effects of acute stress on the inflammatory response. Individual exposed to a standardized laboratory stressor or acute psychological stress displayed elevated levels of cortisol and norepinephrine, accompanied by decreased tumor necrosis factor α expression (20–22). In accordance, a very recent and remarkable study demonstrated a profound rise in catecholamine and cortisol levels during bungee jumping, which was associated with significantly reduced cytokine production in ex vivo LPS-stimulated whole blood (23). Furthermore, hyperventilation (followed by breath holding) is an obvious element of the individual's concentration/meditation technique and might have direct effects on sympathetic nervous system activity and/or stress hormones. Hyperventilation seems to increase (nor)epinephrine, whereas effects on cortisol release are conflicting (24,25).

Our study has several limitations. First and foremost, we describe a set of studies on a single individual, making it impossible to determine a cause-effect relationship between concentration/meditation and the ANS and/or the innate immune response. Nevertheless, case reports with remarkable findings can yield valuable information (26) and are important in hypothesis generation for further research. This study is further limited by the absence of an additional endotoxemia experiment in which the individual did not practice his concentration/meditation technique. This is rather a limitation of the human endotoxemia model; our group has demonstrated that repeated LPS administrations result in the development of endotoxin tolerance (27). Finally, the individual is considerably older than the 112 healthy volunteers used for comparison. Because older age is associated with a more pronounced cytokine response during endotoxemia (28), age seems not to explain the low cytokine levels observed in the individual.

In conclusion, this particular individual's concentration/meditation technique seems to result in a consciously controlled stress response, characterized by sympathetic nervous system activation and subsequent catecholamine/cortisol release. This response seems to attenuate the innate immune response. The individual claims that he can teach others this technique. Therefore, further investigations should establish whether the results obtained can be reproduced in larger groups of individuals.

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