
**Increased Morning Cortisol Level**

**Effect of Sleep Fragmentation or Stress Response to the Last Annoying Stimulus?**

To the Editor:

Fragmented sleep has great effects on daily life, including sleepiness, impaired cognitive function, decreased mood, and elevated BP. In an excellent study in a recent issue of *CHEST* (January 2010), Stamatakis and Punjabi show that two nights of nonspecific sleep fragmentation in healthy volunteers led to decreased insulin sensitivity and glucose effectiveness despite normal sleep duration. This study helps to elucidate the influence of sleep fragmentation per se on glucose metabolism without the confounding effect of sleep duration or hypnotic insult, as seen in the case of obstructive sleep apnea. The authors concluded that increased sympathetic activity and adrenocortical activity likely mediate the adverse effects of poor sleep quality; based on the finding of increased morning cortisol levels and increased sympathetic activity.

They used auditory and mechanical stimuli to elicit EEG microarousals with a frequency of ≥ 30 events/h. If the stimuli failed, the subsequent stimulus got larger by increasing the tone volume of auditory stimuli or combining the two kinds of stimulus. In this study, most of the stimuli were effective, including the last one at the end of the sleep period, which was probably the largest stimulus in intensity. When a human is exposed to noxious or potentially noxious stimuli, there is an increased secretion of corticotropin and, consequently, a rise in the circulating cortisol. Approximately 90% to 95% of the cortisol in the plasma binds to plasma proteins, which slows the elimination of cortisol from the plasma. Therefore, cortisol has a relatively long half-life of 60 to 90 min and thus a lasting action. An increased morning cortisol level (measured at 8:00 AM in this study) may be the consequence of the last effective stimulus, elicited 1 or 2 h prior to measurement, rather than that of sleep fragmentation. As the authors stated, elevations of cortisol, even within the normal physiologic range, can decrease insulin sensitivity, enhance hepatic gluconeogenesis, and inhibit insulin secretion. To settle this dispute, one additional night of nonfragmented sleep following the two nights of fragmented sleep is needed as a sleep-recovery period, as stated in some sleep deprivation studies. In addition, one single stimulus is given near the end of the night, which is of the same intensity and timing as the last stimulus in the previous night of sleep fragmentation. If an elevated cortisol level is still observed in the coming morning (day 5), the disturbed glucose metabolism may not be attributed to the effect of sleep fragmentation.

Besides, evening cortisol concentration following sleep deprivation was raised in sleep deprivation studies, reflecting an impairment of negative feedback control of the hypothalamic-pituitary-adrenal axis. This finding was not observed in this study, suggestive of a different mechanism underlying sleep deprivation and sleep fragmentation, or just an unequal stress in intensity, which deserves further exploring.

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**Financial/nonfinancial disclosures:** The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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**DOI:** 10.1378/chest.10-0433

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**Quantifying Latent TB Infection**

**The Dilemma Continues**

To the Editor:

The study in the May 2010 issue of *CHEST* by Gallant et al, whereby they simultaneously compared the quantitative results of in vivo and in vitro assays for TB infection generates a lot of interest. There are a couple of issues that need to be addressed in this study:

The authors have used Bacillus Calmette-Guérin (BCG), purified protein derivative (PPD), and early-secreted antigenic target-6 (ESAT-6) as the triggers for the release of interferon (IFN)-γ in the in vitro assays. The authors have justified the use of PPD in both the in vitro and in vivo assays because it may avoid the antigen specificity as the confounding factor, but the use of BCG as an in vitro trigger remains questionable because the BCG status of the population in question is not known.
ESAT-6 and complement fixation protein-10 (CFP-10) have been suggested as standard triggers for IFN-γ release from lymphocytes, but the employment of BCG and PPD for this purpose warrants further research. The higher specificity of ESAT-6 and CFP-10 (ESAT-6 in this study) as compared with other triggers is reflected in the authors’ observation that among the 100 patients with tuberculin skin test induration of <5 mm, only 7% showed IFN-γ production in response to ESAT-6. On the other hand, 74% of the BCG subgroup and 65% of the PPD subgroup had positive IFN-γ production. This rather highlights the redundant nature of in vitro and in vivo assays, provided the antigens used are only ESAT-6 and CFP-10, although the higher specificity of these IFN-γ release assays is well proven.²

Latent TB infection has been a gray area for decades now because of the heterogeneous prevalence of the disease and infection around the globe. We need further studies to reach definite conclusions.

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Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Response

To the Editor:

Two interesting points are raised by Drs Khurana and Khurana about our study in CHEST (May 2010). As correctly pointed out, we did not attempt to verify the bacillus calmette-guerin (BCG) vaccination status of our study subjects. However, BCG vaccination at birth has been mandatory in the study area since 1975, and vaccine coverage in the Western Cape is very high at 90%. (95% CI, 90%-99.5%). Hence, we can safely assume that the majority of our study subjects were BCG vaccinated.

The other point concerns redundancy of in vivo and in vitro assays. Our study was not designed to evaluate the possible redundancy of cutoff points and positive vs negative responses. Rather, we focused on the correlation in the extent of responsiveness between assays and detected low correlation between assay readouts. From this, we inferred biologic nonredundancy of the different assays. We agree that further studies into the mycobacterial host responses, including the immune assays currently used for diagnosis of latent TB infection, are needed.

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Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.10-0473

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Is Pulmonary Arterial Hypertension Really a Late Complication of Systemic Sclerosis?

To the Editor:

We read with great interest the report by Hachulla et al in CHEST (May 2009) regarding the time of presentation of pulmonary arterial hypertension (PAH) during the course of scleroderma disease (SSc). In their cohort of 78 patients with SSc-associated PAH (PAH-SSc), the authors found the following: (1) 55% of the patients had early-onset PAH (ie, within the first 5 years of SSc-related non-Raynaud symptoms); (2) These patients were older at the time of SSc diagnosis and presented with more severe hemodynamics, although functional class (FC) and mortality outcomes were similar to those of patients with late-onset PAH; (3) Diffusing capacity of the lung for carbon monoxide (DLco) < 35% and FC class 4 were the only predictors for survival