

Circadian Relationship of Serum Uric Acid and Nitric Oxide

To the Editor: Nitric oxide–mediated damage has been implicated in a number of neurological diseases including stroke^{1,2} and multiple sclerosis (MS).³ For instance, monocytes expressing high levels of nitric oxide synthetase have been found in plaques from the brains of patients with MS.⁴ The proximal agent of neuronal cell damage may be peroxynitrite, which is formed in vivo from the synthesis of nitric oxide and superoxide.

Uric acid is a known peroxynitrite scavenger, and several lines of evidence suggest that high serum levels of uric acid may offer protection against development of MS. For instance, a survey of 20 million patient records revealed that MS and gout were mutually exclusive diagnoses.⁴ In a murine model of MS, administration of uric acid was found to have a linear dose-response protective effect, and patients with MS have lower levels of uric acid than controls.^{4,5} To further assess this possible inverse relationship between nitric oxide and uric acid, we performed a circadian analysis of these 2 substances in a series of subjects without a history of either MS or gout.

Methods

In 1979, 11 healthy male volunteers, then aged 32 to 57 years, were selected from a military reserve unit on the basis of good venous access. In 1979, and again in 1988, 1993, and 1998, blood was obtained at 3-hour intervals over a 24-hour period, and the uric acid concentration of each sample was measured. Nitric oxide levels were also measured in the 1998 samples. Five of the subjects developed type 2 diabetes during the study period, but no other chronic diseases were reported. Data were analyzed for circadian characteristics by population multicomponent analysis.⁶

Results

The mean uric acid levels at the 4 successive measurement years were 0.40 mmol/L (95% confidence interval [CI], 0.33-0.46 mmol/L), 0.40 mmol/L (95% CI, 0.36-0.43 mmol/L), 0.39 mmol/L (95% CI, 0.33-0.45 mmol/L), and 0.38 mmol/L (95% CI, 0.35-0.42 mmol/L), respectively. This stability of uric acid over time allowed us to pool the values for the analysis. A significant circadian rhythm was obtained for a harmonic model with 2 components (with periods of 24 hours and 8 hours) for both uric acid ($P<.001$) and nitric oxide ($P=.004$). The timing of uric acid peak and nitric oxide trough concentrations is virtually cosynchronous, at 5:08 and 5:32, respectively ([Figure 1](#)).

Comment

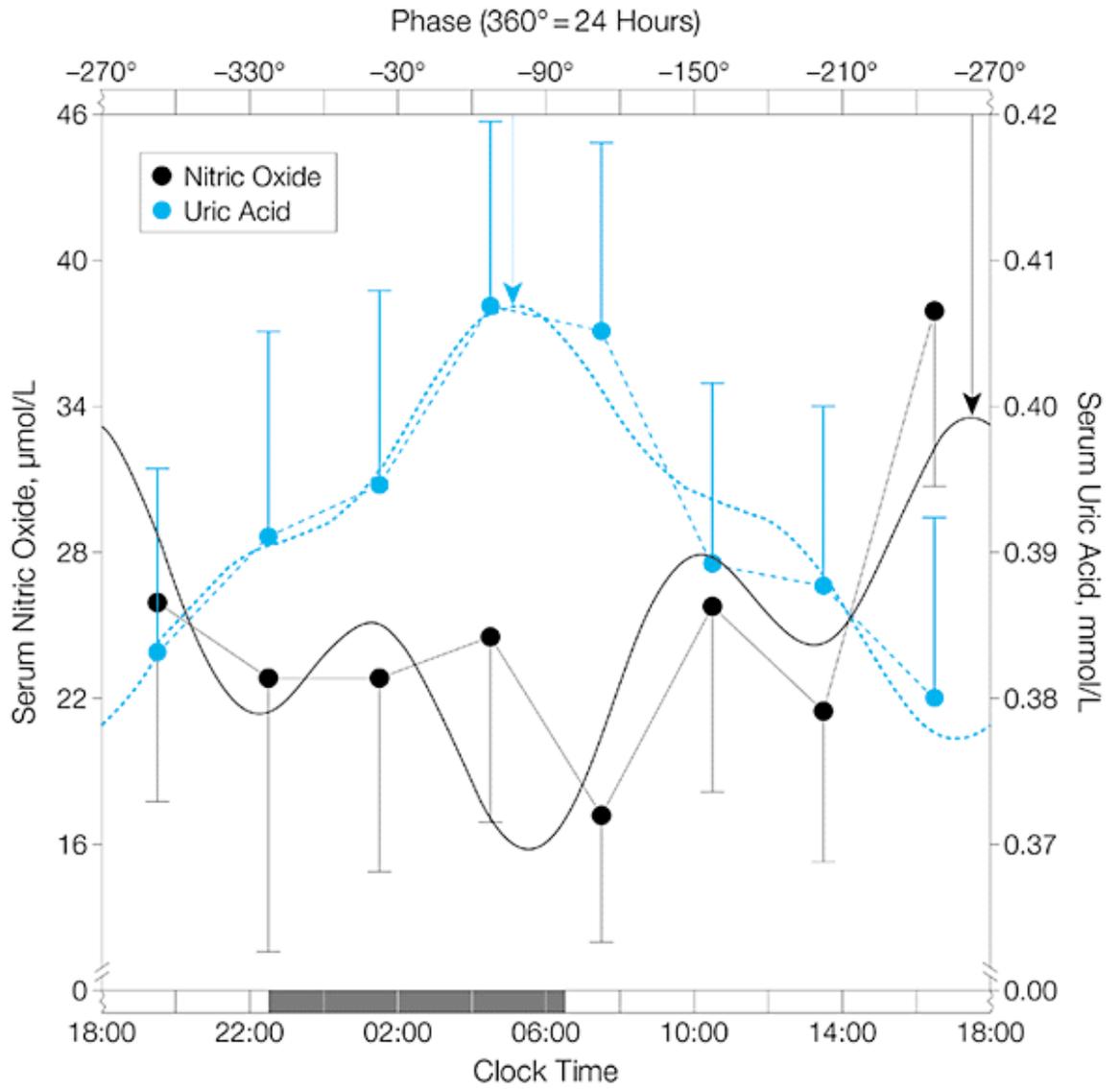
The temporally reciprocal relationship between uric acid and nitric oxide in these men suggests that their concentrations are physiologically related. This observation supports previous results of the protective effects of uric acid in nitric oxide–mediated diseases, such as MS.

References

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	No.	<i>P</i>	MESOR (95% CI)	Amplitude	Orthophase	Bathypase
Nitric Oxide	11	.004	24.58 (11.3-37.9)	8.91	17:32	05:32
Uric Acid	46	<.001	0.39 (0.37-0.41)	0.01	05:08	17:00