

## The Kinetics of Metalloproteinase-9: The Significance of the Light-Dark Cycle in Metalloproteinase-9 in Acute Coronary Syndrome

### To the Editor:

We have read with great interest the recent article of Rodríguez et al,<sup>1</sup> in which the authors provide an excellent review of metalloproteinases (MMP) and atherothrombotic syndromes. However, we would like to make the following comments.

The inflammatory substrate implicated in acute coronary syndrome (ACS) is extremely complex and involves a number of factors related to both activation and modulation.<sup>2</sup> MMP-9, in addition to playing a relevant role in the pathophysiology of the atherothrombotic process, may be useful as a biomarker of atherosclerotic risk and a predictor of recurrent coronary artery disease.<sup>3</sup> Additionally, it has been observed that MMP-9 concentrations in patients with coronary artery disease are directly associated with inflammatory markers, such as C-reactive protein, interleukin 6, and fibrinogen.<sup>4</sup> However, it has also been shown that certain factors, such as age, sex, dyslipidemia, diabetes, hypertension, and smoking, can influence MMP-9 concentrations.<sup>5</sup>

The scientific literature has described circadian variations in the circulating concentrations of some cytokines and acute phase reactants among patients with ACS.<sup>5-7</sup> However, the existence of circadian variations in circulating MMP-9 concentrations has not been observed in healthy volunteers.<sup>8</sup> Recent work by our group has shown diurnal variations in MMP-9 serum concentrations among patients with ACS.<sup>9</sup> MMP-9 serum values were significantly higher during the light phase (at 9:00 AM) than the dark phase (at 2:00 PM), which indicates that the diurnal variability could, at least partly, have central neuroendocrine regulation, particularly with regard to melatonin, which is a circadian hormone.

MMP studies in patients with ACS offer considerable pathophysiological information regarding destabilization of the atherogenic process. Therefore, an extracellular matrix biomarker should be selected by standardizing the methods of measurement, establishing cutoff points to identify any values that clearly separate populations

with different risks, and establishing how often and at what time of the day the blood samples should be drawn.<sup>10</sup>

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## Response

### To the Editor:

We would like to thank Domínguez-Rodríguez et al for their interest in our article,<sup>1</sup> in which we point to metalloproteinases (MMP) 9 and 10 as promising biomarkers of cardiovascular risk. In their letter, these authors make an important observation by highlighting the relevance of circadian variations in circulating MMP-9 concentrations, based on their previous data showing diurnal variations in MMP-9 serum concentration in patients with acute coronary syndrome<sup>2</sup> not observed in healthy volunteers.<sup>3</sup> The information provided reinforces our opinion on the adequate validation of new candidates for biomarkers, and the need to demonstrate reliability, stability, low variability, and standardization of such markers in the methodology used to measure them.<sup>1,4</sup> Furthermore, the information provided by Domínguez-Rodríguez et al has led us to consider the possibility that circadian variations may affect circulating MMP-10 concentrations, a question we are currently investigating.

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