Light/Dark Cycle Variations in Proinflammatory Cytokines in Acute Coronary Syndromes

To the Editor:

We have read with great interest the recent review by Angiolillo et al[1] that provided an excellent overview of inflammation in acute coronary syndromes, but we were surprised that the authors did not mention light-dark cycles of proinflammatory cytokines.

The implication or association of physiological rhythms with peak activity at a certain time of day or night might be suspected, given that the onset of cardiovascular accidents follows a circadian pattern.[2] Several studies suggest that increased cardiovascular mortality in winter might be related to alterations in the biological clock controlled by the suprachiasmatic nucleus. This is regulated by day-night alternations, that is, by light-dark cycles.[3,4] Other functions such as cortisol secretion,[5] blood pressure variations,[6] and vasomotor tone[9] also depend on these rhythms.

Our group has shown that interleukin 6 follows a light-dark cycle in patients with acute myocardial infarction.[8] These variations can be attributed to the centrally controlled release of this compound by the neuroendocrine system. Such control would be exercised through synthesis and release of melatonin by the pineal gland, which, in turn, is regulated by light-dark variations.[9]

Although the study of the light-dark variations in proinflammatory cytokines in itself lacks clinical relevance, these findings point the way to new lines of investigation in the field of biological rhythms in humans. More studies will be needed to help clarify the mechanisms that underlie the cyclic nature of the presentation of some acute coronary syndromes. Such knowledge will undoubtedly lead to therapeutic interventions that provide better protection at times of greatest risk.

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Response

To the Editor:

We appreciate the interest of Domínguez-Rodríguez et al in our manuscript, who express surprise that we have not considered light/dark patterns of pro-inflammatory cytokines in our review on the role of inflammation in acute coronary syndromes.[1] Circadian variations in cytokine secretion and activity is indeed a relevant topic. Particular interest has been devoted to this field since varying of inflammatory/immune functions during the 24-hour period may hypothetically allow identification moments of the day or of the night in which "inflammatory bursts" are most likely to occur and, accordingly, increase the incidence of cardiovascular events. Domínguez-Rodríguez et al should be commended for their pivotal work on describing light/dark secretion of interleukin-6 in patients with acute myocardial infarction.[2] Importantly, a circadian variation of proinflammatory cytokines has been suggested to be under neuroendocrine control, in particular by melatonin, attributing to this system anti-inflammatory properties.[3]

In our manuscript we reviewed pathophsyiological mechanisms involved in the development of acute coronary syndromes with emphasis on the inflammatory hypothesis. The inflammatory substrate involved in acute coronary syndromes is extremely complex with a large number of factors involved in both its enhancement and modulation, and its complete description goes beyond the possibilities of a review manuscript. Therefore, in our manuscript we focused on inflammatory mechanisms involved in acute coronary syndromes with a greater degree of scientific evidence, also based on our previous experience and line of research. Research on light/dark variations of pro-inflammatory cytokines is still in its preliminary phase. Furthermore, as Domínguez-Rodríguez et al also state in their letter, light/dark variations of proinflammatory cytokines still lack of clinical relevance. Indeed these studies are stimulating for future research and the development of novel therapeutic approaches based on

advances in this field are intriguing, but we strongly believe that the inflammatory process involved in the atherosclerotic process in general and in acute coronary syndromes in particular should be "tackled" in a different perspective. These should ideally target the triggers of inflammation. However, these triggers are still elusive and therefore modulation of the detrimental component of inflammatory responses which occur afterwards represent the next approach. In particular, the latter should have as a target cells, receptors or molecules which have a more direct relationship with the inflammatory process specifically involved. These may include drugs with specific anti-inflammatory properties, but most typically involve drugs which are not-specifically anti-inflammatory but have pleiotropic properties (including "anti-inflammatory") with functions that go beyond that of their primary reason for use. It is also important to remember that the contributing role of the inflammatory component on outcomes in acute coronary syndromes varies among individuals. Therefore, further research should be directed on the identification of patients which may truly benefit from these novel treatment strategies.

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