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.\(^3\) Other functions such as cortisol secretion,\(^4\) blood pressure variations,\(^5\) and vasoconstrictor tone\(^6\) also depend on these rhythms.

Our group has shown that interleukin 6 follows a light-dark cycle in patients with acute myocardial infarction.\(^7\) 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.\(^8\)

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 cyclical 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 pathophysiological 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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Prevention of Vascular Complications During Coronary Interventions: Choose a Different Access Route or Seal the Vessel?

To the Editor:

We read the article by Díaz de la Llera et al1 with interest and would like to offer some comments. Reducing the incidence of complications during primary angioplasty, now that adjuvant therapy is widespread, is important. Several studies have reported that radial arterial access (RAA) offers interesting advantages compared to the transfemoral technique and the authors contribute further evidence in this regard. The success and the safety of RAA in trained hands is beyond question, and the clearest advantage compared to the femoral approach appears to be related to the smaller number of vascular complications.

Patients treated with fibrinolytics and glycoprotein IIb/IIIa inhibitors have a greater risk of hemorrhagic complications, especially at the puncture site. In this context, an alternative suggestion is the use of vascular closing devices (VCD) to reduce the number of complications. Resnic et al8 compared manual compression (MC) versus VCD in 3027 patients treated with angioplasty and found a 45% reduction in vascular complications with VCD. In the subgroup of patients who received glycoprotein IIb/IIIa inhibitors, complications with VCD were reduced to 57%, (5.51% with MC vs 2.34% with VCD; P=0.02). Louvard et al9 also found a reduction in major hemorrhages at the puncture site from 7% to 2% with VCD. Appleget et al2 compared MC with the use of two different types of VCD in a series of 4525 patients who had undergone angioplasty and treatment with abiciximab. In the patients in whom the use of such devices was successful, the rate of minor, major, and combined complications was 1.8% versus 0.8%, 1.35% versus 0.9% and 2.5% versus 1.5%, respectively. In the RACE study, no femoral complications occurred in patients who underwent angioplasty and treatment with glycoprotein IIb/IIIa inhibitors using a new VCD versus 3.4% in the control group (P=0.03). Exaire et al10 found a low incidence of major hemorrhage and the need for transfusion (<1%) in patients from the TARGET study where either MC or various VCD were used. We emphasize that none of these studies was conducted exclusively in patients with primary angioplasty, although we consider that the main interest lies in facilitated and rescue angioplasty.

The learning curve for VCD is probably better than the one required for RAA, which means that its application can become widespread more easily. A trial comparing VCD with RAA would reveal the best strategy for patients with a high risk of presenting complications. Naturally, a cost-benefit analysis of the most suitable VCD and the impact of possible complications is essential.

Finally, dogmas in medicine are dangerous and, in a field where concepts and technology are in continuous development, as in intervention cardiology, we should be very receptive and have on hand—almost literally in the case of RAA—new and better approaches and treatments to provide our patients with the best possible care.

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Letters to the Editor


Response

To the Editor:

I would like to thank Barrera-Ramírez et al, for their interest in my article published in this Journal. I appreciate their interesting observations, although I differ from the partial view regarding the use of radial arterial access (RAA) in patients with acute myocardial infarction.

The number of local complications is extremely low (hematoma, need for transfusion and vascular repair surgery) when RAA is used in practically all the centers where percutaneous coronary intervention is carried out (PCI). Its convenience, the possibility of the patient immediately and safely walking out with no risk, and the cost-benefit ratio when using RAA compared to femoral arterial access (FAA) plus vascular closing devices (VCD) favors the use of RAA.

Patients treated with anticoagulants, a combination of antiplatelet drugs (aspirin and clopidogrel) plus glycoprotein IIb/IIIa inhibitors and fibronolytics are likely to present a greater number of local complications in the femoral arterial puncture site than those who do not receive such drugs. In a comparative study between RAA and FAA where both groups received glycoprotein IIb/IIIa inhibitors, Choussat et al analyzed the immediate outcome and local complications in both groups. In patients assigned to FAA, percutaneous closing with sutures was carried out (37%) and mechanical compression in the remaining patients. A significant reduction in local complications in the RAA group (0%) was found compared to the number of hemorrhagic complications in the FAA group (7.4%; P=.04).

I would like to fine-tune certain aspects relating to the articles mentioned by Barrera-Ramírez et al to avoid ambiguous interpretations. Louvard et al conducted a comparative prospective study of RAA and FAA in primary angioplasty with 1224 patients in two European hospitals. They reported a global rate of local complications in the RAA group of 0%, whereas the FAA group presented 2% major hemorrhagic complications in center A (using VCD) and 7% in center B (using manual compression). This difference was due to the low use of abciximab (5.8%) in center A and a more standardized use of it in center B (48.3%).

When the patients in the RAA groups from both centers were added (n=267) to the FAA group with CVD (Perclose) (n=889), the hemorrhagic complications were significantly higher in the Perclose group compared to the RAA group (2% vs 0%; P<0.05), despite the greater use of abciximab (30% vs 5.8%; P<0.01) and r-tPA (23.2 vs 14.2%; P<0.01) in the RAA group when compared to the FAA group (Perclose).

Applegate et al conducted an observational non-randomized study in patients treated with coronary angioplasty and abciximab where they compared manual compression (MC) with VCD (Angio-seal and Perclose). Peripheral retinopathy and old age are factors associated with an increased risk of local complications. Coincidently, this study showed that local complications were more frequent in the MC group than in the VCD group. Furthermore, it is noteworthy that the only independent predictive factor of complications was a failure in the application of VCD and that patients in whom the VCD failed were excluded from the figures for minor, major, and combined complications. Resnic et al retrospectively studied patients who had undergone coronary angioplasty and compared MC with VCD. They also stated that the patients assigned to MC were significantly older (P<0.001) than those in the VCD group, and that patients in whom VCD was applied successfully had to remain in bed with strict rest for 6 h. The overall number of local complications in the subgroup that did not receive glycoprotein IIb/IIIa inhibitors was not statistically significant, with a 29% reduction (P=.13; MC=3.62% and VCD=5.15%) in the risk of complications. The differences were significant in the subgroup who received glycoprotein IIb/IIIa inhibitors, with a 57% reduction in risk (P=.002; MC=2.34% and VCD=5.51%). The authors themselves conclude that these results should be confirmed with prospective and randomized studies.

The results of 2 meta-analyses recently published are required reading to correctly assess the use of various VCD. Koreny et al assessed 30 randomized studies that included 4000 patients and compared VCD with MC: they reported that the relative risk of hematoma was 1.14 (95% confidence interval [CI], 0.86-1.51; P=.35); bleeding 1.48 (95% CI, 0.88-2.48; P=1.4); developing an arteriovenous fistula 0.83 (95% CI, 0.23-2.94; P=.77) and developing pseudoaneurysm 1.19 (95% CI, 0.75-1.88; P=.46). They concluded that there is no evidence that VCDs are effective and that they could even increase the risk of hematoma and pseudoaneurysm. Nikolsky et al also assessed 30 studies that included 37066 patients and differentiated between diagnostic and PCI settings and several VCD (Angio-seal, Perclose and...
Epicardial Implantation of Biventricular Leads

To the Editor:

We would like to share in this letter our initial experience in implanting epicardial leads for left and biventricular pacing as well as congratulate the authors1 for the excellent results obtained. In our experience with our last four patients, it is possible to obtain a better view of the working area by making a higher incision, in the second or third intercostal space (in the left subclavicular region), to insert the video-assisted thoracoscopic device. In this way, instead of having the camera almost perpendicular (as shown in the photos from the cited article) and requiring different angles to see the different sectors, we can position the camera parallel to the long axis of the thorax leaving it effectively fixed there (with the help of a second operator who kept it fixed by simply placing the head of the device on the left shoulder of the patient) thereby considerably expanding the field of vision. Furthermore, as the incision is performed approximately in the same area where the generator will be implanted, the remaining scar is smaller, since once the endoscope is removed we only have to expand the incision and to make the pocket for the generator in the same place. The rest of our technique was effectively the same.

Theoretically, the epicardial approach allows us to choose at will the best possible place to implant the leads, although up to the present there is no clear evidence regarding how to choose the best implantation site (the basal postero- lateral region is large). Thanks to the input of Julio Spinelli (an engineer at Guidant, United States) we have also modified our technique (for both endocardial and epicardial implants) as follows: we connect the patient to the programmer (we use a Medtronic programmer) in order to have at least one surface lead in it. Once the best possible anatomical site is chosen, we connect the lead for setting thresholds and take note of whether the sensor of our left lead coincides with the end- half of the native QRS complex of the patient. In this way we at least confirm we are in an area of electrical delay. Otherwise, we will not be “resynchronizing” but possibly creating further asynchronism. Although the ultrasound scan tries to find out how to optimally guide the bi-ventricular pacing,2 the problem is that the settings are adjusted once the leads have been implanted in a given place. If the principle is to resynchronize areas with electromechanical delay

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by electric stimulation, it seems logical not to stimulate an area where there is no electric delay, even if this is a good anatomical site.

Once again, we would like to congratulate you for your excellent work.

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Response

To the Editor:

We congratulate Drs Ayala and Greentree for their experience and we totally agree that in order to obtain optimal ventricular systolic resynchronization the areas to be stimulated should be those with electromechanical delay in the left ventricle. In our work the posterolateral region was chosen based on the echocardiographic study and the pre-intervention left catheterization. With tissue Doppler echocardiography it is possible to identify with high accuracy the segments with greater electromechanical activation delay. Regarding catheterization, we carried out temporal endocardial pacing in different segments of the left ventricle in order to determine which anatomical site provides the best improvement in dP/dt.

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