normal control subjects, both parameters are always within a very narrow range in all myocardial segments. Yet, despite this variation, UTC analysis could easily identify widespread changes of myocardial features in BMD patients compared with control subjects. In particular, cvIBS values in BMD patients were markedly different from the control group; no overlap was observed between cvIBS mean values in any of the sampled myocardial segments. Conversely, significant changes in cIBS were detected only in the inferior, posterolateral base and inferolateral mid-segments. These UTC findings in BMD patients as previously described in DMD patients (3) support the hypothesis that myocardial UTC analysis could reveal the early signs of a future evolution toward a segmental myocardial dysfunction.

Furthermore, we found that patients with a deletion encompassing exons 48 and/or 49 had lower values of cvIBS than patients with different or other deletions, possibly suggesting more subtle changes of myocardial physical properties in these patients, in agreement with a previous study suggesting a more frequent cardiac involvement in BMD patients carrying deletions involving exons 48 or 49 (2). Probably, cvIBS is able to detect a different “cellular milieu” and, finally, early changes of myocardial properties in BMD patients, even in the absence of functional myocardial dysfunction.

Our results show that a myocardial involvement is always present in BMD patients, independent of age, type of deletion, amount of dystrophin in muscle, and severity of skeletal muscle involvement, despite a normal left ventricular diastolic and systolic function.

This paper provides UTC values, in the widest number of myocardial segments ever sampled, in BMD patients with a functionally normal heart.

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Letters to the Editor

Link Between Arterial Inflammation and Circadian Rhythm: The Oversight Aspect in the Year 2004

We read with great interest the recent report by Moreno P et al. (1) concerning inflammation as one of the primary pathophysiological processes in cardiovascular disease. However, we would like to add two comments.

First, it has also been clearly documented that the occurrence of coronary syndromes during the day are not uniform; rather, they occur with rhythmic variation. The existence of a circadian rhythm in the acute coronary syndrome suggests that the problem might, in some way, be associated with, or started by, physiological rhythms, with peak activity at certain parts of the day or night. Numerous studies have tried to establish the cause for this circadian rhythm and its clinical and therapeutic implications (2). Experimental studies have shown that both immune cell number and immune functions may vary during the 24-h circadian period (3).

Second, the increase in mortality from cardiovascular events in winter might be due to alterations in the biological clocks located in the suprachiasmatic nuclei, whose rhythm is determined by day–night alternation, that is, by the light/darkness cycles. These cycles regulate functions such as the secretion of cortisol (4), blood pressure (5), vasomotor tone (6), tissue plasminogen activator (7), and pro-inflammatory cytokines (8,9).

Therefore, considering the potential association among inflammation and circadian rhythm, the presence of a variability during the 24 h of inflammatory and immunologic functions would permit, hypothetically, one to identify the light/dark times in which any peak of inflammatory activity could be associated with a greater incidence of cardiovascular events.

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REPLY

The specific commission of our review, titled “The Year in Atherothrombosis,” was to highlight clinically relevant studies in the field published within the last year (1). The letter from Dr. Domínguez-Rodríguez and colleagues highlights the importance of the circadian rhythm in the presentation of acute coronary events, a concept established several years ago. The last citation of their letter quotes a study published in 2004, evaluating the light/dark cycle of cytokines and melatonin plasma levels in patients with acute myocardial infarction (AMI) (2). This single, observational, case-control study suggested an association between the light/dark cycle of cytokines and melatonin and the risk of AMI. The investigators should be congratulated for their effort. However, the study is not mechanistic, and does not prove causality. Furthermore, the clinical significance of their findings still remains to be elucidated. As a result, in our judgment the study may not meet the criteria to be included as a clinically relevant publication in atherothrombosis in the year 2004.

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Viruses and Other Environmental Factors as Possible Sources of Phenotypic Heterogeneity in Familial Dilated Cardiomyopathy

In their interesting and recent state-of-the-art study, Burkett and Hershberger (1) stated that “familial dilated cardiomyopathy (DCM) demonstrates incomplete penetrance, variable expression, and significant locus and allelic heterogeneity, making clinical and genetic diagnosis complex.” The statement clearly describes a key problem encountered during the genetic dissection of human DCM. This problem reaches beyond the fact that multiple genes may cause the DCM phenotype in humans and that further loci shall be revealed in the future. Even within a single DCM family or within a group of unrelated DCM patients harboring defects in the same gene, there is often very large and currently unexplained phenotypic heterogeneity. There are at least two possible sources for this heterogeneity.

First, unless representative healthy control populations are screened for a given mutation one cannot be sure that this mutation is capable of causing the phenotype without additional cofactors (modifier genes or environmental agents) being present. In other genetic disorders the screening of large control populations has been the indispensable basis for the discovery of such cofactors. For example, smoking was identified as an essential environmental factor for the development of lung disease in genetic α1-antitrypsin deficiency, initially assumed to cause the disease per se on a pure genetic basis. For most mutations associated with DCM we do not yet have frequency data representative of the general healthy population that can be compared with the rather small DCM patient cohorts from which the disease association is usually derived. The relative pathogenic contribution of the gene defect per se as compared to hitherto unknown cofactors is therefore uncertain.

Second, data on possible environmental agents are sparse in molecular genetic studies of familial DCM. Regarding such cofactors, we have recently detected cardiac viral infections in 165 (67.4%) of 245 cases in a molecular virological survey based on myocardial biopsies from a series of DCM patients (2), with a broad spectrum of virus species being involved. Cardiotropic viruses thus emerged as prevalent environmental factors that may possibly cause or influence the course of DCM. The high frequency of cardiotropic viruses detected in that DCM series makes it highly likely that cardiac viruses are also encountered in familial DCM. They may explain part of the large phenotypic heterogeneity mentioned by Burkett and Hershberger (1), but will go unnoticed unless cardiac biopsies are specifically investigated using molecular virological methods. A synopsis of the current data suggests that a comprehensive picture of the pathogenesis of familial DCM can only be obtained if both genetic and environmental factors are analyzed. Studies of this type may lead to the