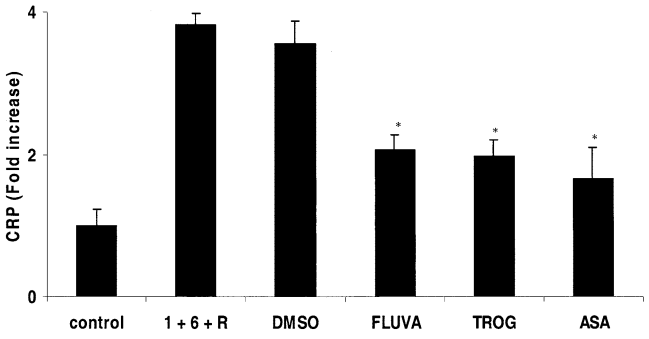

Figure 2. Modulation of C-reactive protein (CRP) synthesis in human adipocytes treated with dimethylsulfoxide (DMSO) (control), fluvastatin (FLUVA), troglitazone (TROG), or aspirin (ASA). Values are expressed as the "-fold" increase in the level compared with the level in untreated cells, and each **bar** represents the mean ± SD of duplicate determinations. *$p < 0.05$ vs. combination of cytokines. 1 + 6 + R = interleukin-1 + interleukin-6 + resistin.

resistin. Interestingly, treatment of adipocytes with two other adipocytokines, adiponectin and leptin, did not lead to CRP production. Furthermore, treatment with several anti-inflammatory drugs shown to be effective in reducing serum CRP levels, such as aspirin, troglitazone, and fluvastatin (10,11), leads to reduction, but not complete inhibition, of CRP release from adipocytes. This might explain in part the beneficial cardiovascular effects of these drugs.

In conclusion, our study demonstrates that human adipocytes can produce CRP under the stimulation of several proinflammatory cytokines; moreover, CRP production may be modulated by selected pharmacologic intervention. The mechanism(s) underlying these findings are not fully defined, and further studies are needed in this area.

Paolo Calabro, MD
David W. Chang, MD
James T. Willerson, MD
***Edward T. H. Yeh, MD**

*The University of Texas–Houston Health Science Center
1515 Holcombe Boulevard, Box 449
Houston, TX 77030-4009
E-mail: etyeh@mdanderson.org

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Letters to the Editor

Physiological Mechanisms of Atrially Induced Heart Rate Turbulence

We read with interest the study by Vikman et al. (1) and are pleased that this respectable group shares our interest in atrially induced heart rate turbulence. Although we understand the reasoning behind the suggestion that "vagal inhibition in response to premature atrial excitation is absent, or even that transient enhancement of vagal outflow occurs before atrial fibrillation," we would like to offer the investigators an alternative explanation for their findings.

We all would surely agree that less effective ventricular contraction and compensatory pause after premature beats is responsible for transient hemodynamic deficit, missed baroreflex afferent input, and early vagal inhibition. This mechanism is applicable for both ventricular and atrial premature complexes (APCs). Autonomic modulation of sinus nodal discharge after APCs may explain values of turbulence onset (TO) ≤ 0. When TO >0 is found, the underlying mechanism has to be different. The mechanism suggested by Vikman et al., namely the temporary direct suppression of sinus node automaticity, is certainly plausible. This phenomenon, which may mask (or overwhelm) the autonomic component of early acceleration, has been previously demonstrated (2).

Because of a missing relationship between TO and APC prematurity, Vikman et al. rejected the hypothesis that sinus resetting is the predominant factor influencing the temporal changes of TO. However, this lack of correlation seems to us compatible rather than incompatible with sinus nodal resetting. Autonomically mediated TO should be positively related to the APC coupling interval, whereas TO mediated by direct suppression of sinus node automaticity should be negatively related to the APC coupling interval. Thus, coexistence of both mechanisms may effectively offset the relationship between TO and APC prematurity.

Although TO and turbulence slope after ventricular premature complexes and turbulence slope after APCs reflect heart rate vagal modulation, this is not the case for TO after APCs (3). We have not found any significant relationship between atrial TO and other previously established surrogates of heart rate vagal modulation in large Holter databases (Wichterle et al., unpublished data, 2005).

We thus wonder whether Vikman et al. (1) would agree that their finding might be interpreted as either 1) temporal decrease of vagal modulation, or 2) temporal change of APC prematurity (which cannot be exactly assessed from Holter recording) and/or site of origin of APCs—all factors potentially facilitating sinus node resetting. We believe that the latter possibility might be more probable because none of the other investigated indices of autonomic modulation (including

spectral measures of heart rate variability and turbulence slope after APCs) revealed any significant change before the onset of spontaneous atrial fibrillation episode.

Dan Wichterle, MD*
Marek Malik, PHD, MD

*2nd Department of Internal Medicine
1st Medical School
Charles University
U Nemocnice 2
Prague, 128 08
Czech Republic
E-mail: wichterle@hotmail.com

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REPLY

We are very pleased to get an intellectual input from Wichterle and Malik related to the mechanisms of heart rate (HR) turbulence after atrial premature beats (APBs). The major observation of our study (1) was that "paradoxical" increase of R-R intervals after APBs, resulting in a positive turbulence onset (TO), precedes the spontaneous onset of atrial fibrillation (AF) episodes. Our interpretation was that enhanced vagal responses to APBs might be the major factor behind this phenomenon.

Wichterle and Malik propose another potential mechanism, discussed also in our report, that resetting of sinus node activity after APBs might be the possible mechanism behind the paradoxical TO. The resetting phenomenon might then reflect the change in the origin or prematurity of APBs in the vicinity of AF episodes. For example, the APBs originating from the pulmonary veins might result in a different resetting of the sinus node.

As commented on by Wichterle and Malik, the TO after APBs has actually no relationship with other markers of autonomic tone measured from 24-h electrocardiograph recordings. This observation is consistent with our previous study (2). However, it should be noted that tonic autonomic regulation may be completely different from reflex regulation in response to acute hemodynamic fluctuation. Therefore, the lack of this correlation does not exclude the potential contribution of vagal reflexes in response to APBs, and it is evident that we do not seem to have enough data at the moment to precisely define the mechanisms of HR behavior after APBs. New study designs are needed to clarify this issue—for example, studies where APBs are delivered from various sites of atria, including pulmonary veins, with and without autonomic blockade.

Saila Vikman, MD
***Heikki Huikuri, MD, FACC**

*Division of Cardiology
Department of Medicine
Oulu University Hospital
Kajaanintie 50
90220 Oulu
Finland
E-mail: heikki.huikuri@ppshp.fi

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Genetic Testing in Clinics for Congenital Heart Disease in Adults

We read with interest the report by Beauchesne et al. (1) regarding 22q11.2 microdeletion in adults with selected conotruncal abnormalities. We have pursued a policy of screening for 22q11.2 microdeletion in such patients who are seen in a dedicated clinic for congenital heart disease in adults. This, however, is not a tertiary center, but a large district United Kingdom general hospital. As such, the numbers are smaller and have been performed as the patients come through clinic. To date, 8 of 16 patients with pulmonary atresia ventricular septal defect have been tested and 3 patients have 22q11.2 microdeletion (37.5%). One of these is of Chinese ethnic origin but probably has dysmorphic features. He had a sister who died with truncus arteriosus. The second patient has clear dysmorphic features with mental retardation. The third does not have dysmorphic features but is mentally retarded. Thirty-two of 55 patients with tetralogy of Fallot have been screened. None have 22q11.2 microdeletion, but one with very dysmorphic features has deletion of the long arm of C11 and is thought to have Jacobsen syndrome, which has been associated with endocardial cushion defects and coarctation of the aorta (2); we have not found this or 22q11.2 microdeletion in 4 of 33 patients with endocardial cushion defects or 20 of 88 coarctation patients tested so far. We agree with the investigators that screening of such high-risk patients is mandatory—especially given the implications for 50% transmission. As the genetic basis for congenital heart disease becomes clearer, more assiduous attention is likely to be needed, especially for those involved in maternal medicine.

***Leisa J. Freeman, MB, ChB, FRCP, ILTM**
Antonia Hardiman, BSc, SRN
Sheila Wood

*Department of Cardiology
Norfolk and Norwich University NHS Hospital
Colney Lane
Norwich
NR4 7UZ
United Kingdom
E-mail: leisa.freeman@nnuh.nhs.uk

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