

**The Impact of Early Compared to Late Morning Hours on Brachial Endothelial Function and Long-Term Cardiovascular Events in Healthy Subjects**

*Hirsch, L<sup>1</sup>; Feinberg, M<sup>1</sup>; Koren-Morag, N<sup>2</sup>; Shechter, M<sup>1</sup>*

*<sup>1</sup>Sheba Medical Center, Tel Hashomer, Israel; <sup>2</sup>The Sackler Faculty of Medicine, Tel Aviv, Israel*

Background: Cardiovascular events (CVE) tend to peak during early morning hours after waking.

Methods: To test whether acute early morning reduction in endothelial function may contribute to this circadian pattern, we prospectively assessed brachial artery endothelium-dependent flow-mediated dilation (FMD), using high resolution ultrasound, in 268 consecutive healthy subjects without any concomitant medications, 169 (63%) men and mean age 53±11 years. All subjects were followed for combined CVE which included mortality, myocardial infarction, hospitalization for heart failure or angina pectoris, stroke, coronary artery bypass grafting and percutaneous coronary interventions.

Results: The study cohort was divided to Group A [n=151 (56%) subjects] with FMD performed immediately after waking between 6:00 and 10:00 AM, and Group B [n=117 (46%) subjects] after 10:00 AM. The 2 groups were comparable regarding age, sex, height, weight, body mass index, resting heart rate, blood pressure, baseline brachial artery diameter and the prevalence of cardiovascular risk factors. FMD was significantly lower in Group A subjects compared to Group B (10.4±9.4% vs. 13.5±9.5%, p=0.007, respectively). Thereafter the study cohort was divided into 2 sub-groups < (n=128) and ≥ (n=140) the median FMD of 11.3%. These 2 groups were comparable regarding traditional cardiovascular risk factors, physical examination and laboratory results. In a mean follow-up of 45±21 months, the composite CVE were significantly more common in subjects with < vs. ≥ median FMD [18/128 (14.1%) vs. 1/140 (0.7%), p=0.007, respectively].

Conclusions: FMD is blunted in the early morning hours after waking in healthy subjects, suggesting a potential mechanism for higher CVE during early morning hours. Furthermore, median FMD independently predicts long-term adverse CVE in addition to the traditional risk factor assessment in healthy subjects with no apparent heart disease.