**Supplemental Digital Content 5. Heartrate Variability Measurement.**

Participants were asked to avoid caffeine for 8 hours beforehand, were sitting upright in a quiet environment, and were asked to keep talking or movement to a minimum during measurements. Due to constraints placed by the Course, it was necessary to measure HRV prior to blood sampling in study visits 1, 4 and 6. Beat-to-beat time series were produced using proprietary software (CheckMyHeart software version 2.2) and inspected manually to ensure appropriate identification of normal-normal intervals. R-R intervals were exported and analyzed using Kubios® HRV Premium version 3.2.0 (http://www.kubios.com). We examined mean heart rate, traditional markers of time domain (root mean square of successive differences (RMSSD), percentage of successive normal RR intervals greater than 50 ms, (pNN50)), and frequency domain (fast-Fourier transformed logarithms of low-frequency (0.04–0.15 Hz) and high frequency (0.15–0.40 Hz) power, LnLF and LnHF, respectively, and their ratio, LF:HF) (1). Sample entropy, a non-linear measure of chaos within the HRV signal, and indices of PNS and SNS activity were also assessed. The parasympathetic index represents a synthesis of mean heart rate, RMSSD and the standard deviation of short term HRV (SD1), while the parasympathetic index represents heart rate, stress index (as per Baevsky and Berseneva (2)) and mean standard deviation of long-term HRV (SD2), both reported to reflect the mean deviation from normal values (3). Parasympathetic and sympathetic index values of zero mean that the parameters are on average equal to their normal values, while positive and negative values reflect a relative increase or decrease, respectively.

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3. Nunan D, Sandercock GR, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing and clinical electrophysiology : PACE*. 2010;33(11):1407-17.