Measurement of endothelial dysfunction markers. Briefly, to 100µL of serum 50µL of internal standard containing solution (50µM d7-ADMA, d4-cystine, d8-homocystine, and d3-methionine; all in HPLC-grade water) and 40µL of 500mM DTT solution were added. For protein precipitation, 400µL of 0.05% trifluoric acid plus 0.1% formic acid containing acetonitrile solution were added to the sample. This solution also contained 500nM d3-SAM and d5-SAH as internal standards for adenosine, SAM and SAH analysis. The sample was finally vortexed for 5 minutes, centrifuged for 10 minutes at 13,000g and transferred into a HPLC vial.

20µL of the supernatant were injected onto a 4.6x12.5 mm guard/extraction column (Eclipse XDB-C8, 5µm, Agilent Technologies, Palo Alto, CA) inline with a 3.0x150 mm analytical column (RP-Amide, 3.5µm, Supelco, St. Louis, MI). For adenosine, SAM and SAH analysis, the starting mobile phase concentrations consisted of 5% acetonitrile and 95% 10 mM ammonium formate buffer (pH 3.4) with a flow of 0.6mL/min for the first minute. After one minute, the flow rate was increased to 0.8mL/min and a gradient from 5% to 95% acetonitrile within 2.5 min was run. Acetonitrile was then held at 95% for 0.5 minutes. The column was re-equilibrated for 1 min to starting conditions.

For all other compounds, the gradient started at 3% methanol and 97% 10mM ammonium formate buffer and was maintained at a flow of 0.8mL/min throughout the assay. At minute 4.5, the solvent gradient reached 25% methanol; after this the methanol content was raised to 98% and held for additional 1.5min. Hereafter the columns were re-equilibrated to the starting conditions for the remaining 2 minutes of the assay.

Prostaglandins (P) were extracted from 200 µL plasma following protein precipitation with 300 µL methanol/ 0.2M $ZnSO_4$ (70/30 v/v). Automated inline extraction was used for sample analysis. 425 µL of the extracted sample were injected onto a 4.6x12.5 mm Zorbax XDB-C8 guard/ extraction column (Agilent Technologies). The flow rate during the injection was 500µL/min and was increased to 3000 µL/min within one minute. The composition of solvents was 80% of aqueous 0.1% formic acid and 20% of methanol. After sample cleanup for one minute, the switching valve was activated and the analytes were back-flushed onto the 3x150mm 3.5 micron Zorbax XBD-C8 analytical column (Agilent Technologies). A solvent gradient of methanol and 0.1% aqueous formic acid was used for the chromatographic separation of study compounds within the next 11 minutes.

Bioactive lipid mediators. Briefly, to 200 µL of serum, 800 µL methanol/ $ZnSO_4$ (70:30, v/v)

protein precipitation solution containing the internal standards (2 ng/mL mixture of internal standards, see below) were added. Samples were vortexed for 10 minutes, centrifuged for 10 minutes at 13,000g and transferred into HPLC vials. Fifty µL of the supernatants were injected onto a 4.6x12.5 mm guard column (Eclipse XDB-C18, 5µm, Agilent Technologies) and then back-flushed with 100% acetonitrile onto a 1.0x250 mm analytical column (Luna C18(2), 3µm, 100A, Phenomenex, Torrance, CA). For HPLC separation, the starting mobile phase consisted of 65% acetonitrile/0.1% formic acid (9:91 v/v) and 35% acetonitrile with a flow of 0.2 mL/min for the first minute. After 2 minutes, the gradient consisted of 82% acetonitrile and was increased to 95% acetonitrile within 8 minutes. Acetonitrile was then held at 95% for 2 minutes. The column was re-equilibrated for 2 min to starting conditions.

Krebs cycle intermediates and purine metabolites. Analytes were separated using a 150 x 3 mm Luna HILIC, 3 µm column (Phenomenex) at an HPLC solvent flow rate of 450 µL/min. The solvents were 0.1% aqueous formic acid (mobile phase A) and acetonitrile (mobile phase B). The gradient was: 0-1 min 5% acetonitrile, 1.0-3.5 min 5% acetonitrile to 15% acetonitrile, 3.5-4.5 100% acetonitrile. The column was then re-equilibrated to starting conditions (5% acetonitrile) between 4.6 and 5.5 min. The mass spectrometry parameters were identical for both positive (0 - 1.79 min) and negative (1.8 - 5.5 min) periods and were as follows; ion source gas one: 40, ion source gas two 45, source temperature 500ºC , collision gas 10, curtain gas 20, and ion source voltage 4500V.