**Supplementary Materials and Methods**

**Patients**

Inclusion criteria were: age over 18, arterial catheter *in situ*, urinary catheter *in situ*, anticipated stay >24 hours, and signed informed consent by patient or next-of-kin. Exclusion criteria were: chronic kidney disease stage IV/V (baseline eGFR <30ml/min/1.73m2), haemoglobin <7.5g/dL (≤9g/dL for patients with acute coronary syndrome), or do not resuscitate order. Patients could be enrolled at any point during their admission. Circulatory shock was defined as a requirement for vasopressors or inotropes to maintain end-organ perfusion despite adequate volume resuscitation (1, 2). AKI stage during ICU admission was defined per KDIGO guidelines (3) as follows: 0= no AKI; 1 = serum creatinine 1.5-1.9 times baseline or ≥0.3 mg/dL increase or urine output <0.5 ml/kg/h for 6-12 hours; 2 = serum creatinine 2.0-2.9 times baseline or urine output <0.5 ml/kg/h for ≥12 hours; 3 = serum creatinine ≥ 3.0 times baseline or increase in serum creatinine ≥4.0 mg/dL or CRRT or urine output <0.3 ml/kg/h for ≥24 hours or anuria for ≥12 hours. Chronic kidney disease stage was defined as per the KDIGO guidelines(4).

**Sample collection and measurements**

After colletion, blood was centrifuged at 3800rpm for 10 mins and plasma was removed. Cryoactivation of pro-renin to renin - which occurs optimally over 4 days in liquid plasma kept at -5°C (5) - was avoided by immediately processing and freezing plasma at -80°C.

Blood samples were drawn at morning 0600-0800, midday 1200-1400, evening 1800-2000 or night-time 0000-0200; a maximum of 8 samples were collected from each patient.

Physiological variables and medications of interest were recorded prospectively at the time of sample collection: minimum and maximum mean arterial pressure (MAP) during the preceding hour as measured by a radial or femoral arterial-catheter and recorded by the patient’s electronic monitor, urine output over the preceding hour as measured by an indwelling catheter, the dose of vasopressor and ionotropic support being delivered. Administration of drugs known to interfere with RAAS (β-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, spironolactone) within 72-hours, and furosemide within 6-hours, preceding blood collection was documented for each sample. In statistical analyses, “RAAS interfering drugs” was an interval variable with 3 possible values: none, drugs that may increase renin (ACEi/ARBs/spironolactone) and drugs that may decrease renin (beta-blockers). Furosemide dose was considered as a separate scale variable.

Spot urine concentrations of creatinine, sodium and chloride were measured daily as part of routine care. Creatinine-clearance was calculated using an average of the serum creatinine measured at the beginning and at the end of the 24 hour urine collection period (0800-0800) and the spot urine creatinine measurement at the end of the collection period ([Ucreat]xVurine/[Pcreat]).

**Calculation of Renin Removal by CRRT**

The following variables were recorded: patient weight, haematocrit, blood pump flow rate (Qb ml/min), the rate of ultrafiltration (Quf ml/min), effluent flow rate (Qeff ml/min), dialysate flow rate (Qd ml/min), pre-dilution injection rate (Qpre ml/min) and post-dilution injection rate (Qpost ml/min). The total mass transfer of renin (Mtr) was calculated as follows [27] where Mi is the inlet mass rate (U/min), Mo is the outlet mass rate (U/min), Ci is plasma renin concentration at the inlet port (U/mL), Co is plasma renin concentration at the outlet port (U/mL) and Ceff is renin concentration in the effluent (U/mL):

Qi= Qb x (1-hematocrit)

Qo= Qi –(QUF+Qpost)

Mi= Qi x Ci

Mo=Qo x Co

Mtr = Mi- Mo

The relative contributions of mass transfer by haemofiltration or haemodiafiltration (MHD/HDF) and membrane adsorption (Mad) were then calculated as follows: MHF/HDF = Qeff x Ceff

Mad = Mtr – MHF/HDF

**Statistical Analysis and Power Calculations**

The relationship between renin, physiological variables, medications and CRRT was part of a pre-specified analysis plan. Comparison of renin with lactate as a prognostic marker for ICU-mortality was also part of a pre-specified analysis plan; routine lactate measurements were used to avoid disruption of patient care. Analysis of relationships between lactate and medications was *post-hoc*. The effect size of diurnal variation on plasma renin activity as estimated from Gordon et al. (6) was large (f=0.7); a sample of 16 patients is required to have 90% power to detect f=0.5 for diurnal variation on plasma renin with alpha=0.05. An average of 5.45 renin measurements were available for each of 20 subjects giving 80% power to detect a correlation of r=0.3 or stronger between plasma renin and physiological parameters, with alpha=0.05 (7).

For the mixed effects model, an autoregressive (AR1) heterogeneous covariance structure gave the best model fit using the natural log of renin and lactate. Results shown here have been back-transformed from the natural log to represent percentage change, and are presented as the estimated fixed effect (EFE) and 95% confidence interval (95%CI), with the intra-class correlation coefficient (ICC) for each model.

Diurnal-variation was tested using the Friedman statistic. Receiver-operator curves and Fisher’s exact test were used to test mortality prediction.

**References:**

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