Conclusion Elevated Na leads to complex metabolic alterations preceding any energetic and functional impairment. Early prevention of Na overload and inhibition of Na/Ca(2+), could ameliorate metabolic dysregulation in hypotrophy and failure.

Methods and results The correlation between myocardial creatine and glucose (r2=0.67; p=0.002) is accompanied by increased Glucose transporter 4 (Glut4) (p<0.05) and sodium-glucose co-transporter SGLT1 gene expression. Thioredoxin interacting protein (Txnip), that inhibits glucose and creatine transport (via Glut4 and CrT, respectively) is elevated in CrT-OE (p<0.05), indicating activation of both metabolic pathways.

To test if modulating creatine in vivo alters glucose uptake, we measured 3H-2-deoxyglucose incorporation in isolated cardiomyocytes from CrT-OE and WT hearts. In WT, insulin caused a 2-fold increase (p<0.05) in glucose uptake, unaffected by exogenous creatine pre-exposure. CrT-OE cells showed blunted glucose uptake vs WT in response to insulin (p<0.05) and responded to creatine (p<0.01).

In a cohort of samples taken during coronary artery bypass surgery from diabetic and non-diabetic patients (n=8 each; blood glucose 90±7.1 and 138±16.5, respectively), there was a negative correlation between CrT and Glut4 transcript (r2=−0.5; p=0.028) further supporting the glucose-creatinine relationship in the clinical setting.

Conclusion Our observations suggest that changing myocardial creatine can regulate glucose uptake. Further studies will explore the potential use of creatine as a biochemical ‘switch’ to correct impaired glucose uptake and potentially insulin resistance.