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Pressure overload-induced functional and metabolic impairments in type 2 diabetic hearts are ameliorated by inhibition of xanthine oxidase.

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Background: We have recently demonstrated that AMP deaminase (AMPD) is upregulated in OLETF, obese type 2 diabetic (T2DM) rats, and that the upregulated AMPD contributes to depletion of myocardial ATP at the time of pressure overload, leading to diastolic dysfunction. On the other hand, AMPD promotes the formation of IMP from AMP, and IMP is in turn further converted to hypoxanthine and xanthine, substrates of xanthine oxidase (XO), which produces uric acid with ROS as a byproduct. Based on these findings, we tested the hypothesis that inhibition of XO ameliorates the pressure overload-induced diastolic dysfunction in T2DM rats.

Methods and results: Metabolomic analyses of the left ventricular myocardium revealed that levels of myocardial hypoxanthine and xanthine were significantly higher by 30% and 28%, respectively, in OLETF than in LETO, non-diabetic control rats, under the condition of pressure overloading (200-230 mmHg) induced by phenylephrine infusion. Myocardial XO activity in OLETF was 57.9% higher than that in LETO, and the activity was significantly attenuated by oral administration of topiroxostat, an XO inhibitor, at 0.1-0.5 mg/kg/day for 14 days in a dose-dependent manner. Pressure volume loop analyses showed that the pressure overloading induced by phenylephrine infusion resulted in significantly higher LVEDP in OLETF than in LETO (18.3±1.5 vs. 12.2±1.3 mmHg, p<0.05, n=7), though LVEDPs at baseline were comparable in OLETF and LETO (5.6±0.4 vs. 4.7±0.7 mmHg). Treatment with topiroxostat significantly suppressed the pressure overload-induced elevation of LVEDP in OLETF (18.3±1.5 vs. 11.3±1.1 mmHg, p<0.05) but not in LETO. Tau, the time constant of LV pressure decay, was significantly prolonged to 14.7±0.7 ms (p<0.05) by pressure overloading in OLETF but not in LETO, though baseline Tau values were similar in LETO and OLETF (6.1±0.2 vs. 8.0±0.4 ms). The prolongation of Tau by pressure overloading in OLETF was significantly attenuated by treatment with topiroxostat. Ea/Ees, an index for ventricular-arterial coupling, was higher in OLETF than in LETO (2.3±0.3 vs. 1.6±0.3, p<0.05) under the condition of pressure overloading, and it was also improved by topiroxostat in OLETF (1.2±0.2, p<0.05). Myocardial ATP content was lower in OLETF than in LETO under the condition of pressure overloading (2966±400 vs. 1818±171 nmol/g wet tissue, p<0.05), but treatment with topiroxostat significantly restored the ATP level (2629±307 nmol/g wet tissue). Conclusion: In T2DM hearts, not only XO activity but also XO substrates are upregulated and upregulated AMPD may be involved in the upregulation. Inhibition of XO ameliorates pressure overload-induced diastolic dysfunction and improves ventricular-arterial coupling most likely through augmented ATP preservation.