CLINICAL IMPLICATIONS

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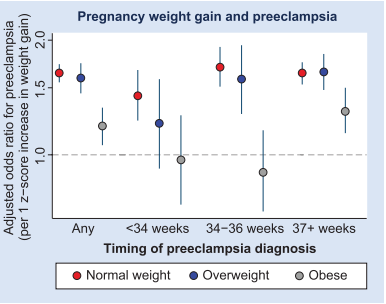
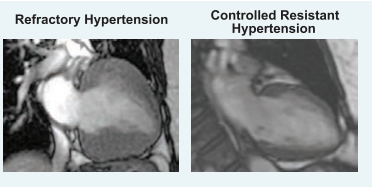
Pregnancy Weight Gain and Preeclampsia (p 433)



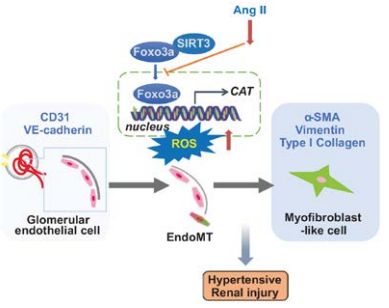
Obesity is known to increase a woman's risk of developing preeclampsia during pregnancy. However, the role of excess pregnancy weight gain in the development of preeclampsia remains unclear. In this study, we examined this association using a unique cohort derived from population-based antenatal electronic medical records linked with hospital outpatient and admissions data from 62 705 nulliparous pregnant women in the Swedish counties of Stockholm and Gotland, 2008 to 2013. The cohort enabled us to determine the gestational age of preeclampsia diagnosis and identify serial weight gain measurement up to (but not including) the time of diagnosis. We found that higher pregnancy weight gain was an independent predictor of developing preeclampsia. For example, at 37 weeks' gestation, every 4.6 kg (10 lbs or 1 z score) of extra weight gain was linked with a 64% increased risk of developing preeclampsia in normal-weight women. The risks associated with higher pregnancy weight gain were more pronounced in leaner women than in obese women and were stronger predictors of term onset rather than early preterm onset preeclampsia. Weight gain patterns in women who subsequently developed preeclampsia began to diverge by 25 weeks, establishing the importance of weight gain in the second half of pregnancy. These findings emphasize the importance of monitoring pregnancy weight gain in clinical practice as a predictor for subsequent preeclampsia. Monitoring is particularly important among leaner women.

Intracardiac Volumes in Refractory Hypertension (p 343)



Refractory hypertension (RfHTN) is an extreme phenotype of antihypertensive treatment failure defined as uncontrolled blood pressure despite the use of ≥5 different antihypertensive agents, including chlorthalidone and spironolactone. In the current study, we used cardiac magnetic resonance imaging and biochemical markers to compare the intravascular volume status between patients with RfHTN and controlled resistant hypertension defined as blood pressure controlled on ≥4 antihypertensive agents. The findings demonstrate that patients with RfHTN have no evidence of increased intravascular fluid retention compared with patients with controlled resistant hypertension based on atrial and ventricular volumes or B-type natriuretic peptide. There was evidence of a more pronounced cardiac remodeling in patients with RfHTN, as demonstrated by increased left ventricular wall thickness and a delayed left ventricular filling pattern. These findings, along with prior studies from our group suggesting that RfHTN is characterized by heightened sympathetic activity, provide important insight into the cause of antihypertensive treatment failure. The findings, if confirmed, would have important clinical implications in suggesting that RfHTN might best benefit from successful modulation of sympathetic tone as opposed to further intensification of diuretic therapy. Furthermore, the severe adverse cardiovascular remodeling present in patients with RfHTN highlights their high risk of cardiovascular complications absent better blood pressure control.

SIRT3 Inhibits EndoMT in Hypertensive Renal Injury (p 350)



Endothelial to mesenchymal transition (EndoMT) has emerged as an important contributor to renal fibrosis and mediator of chronic kidney disease. In contrast with our understanding of epithelial to mesenchymal transition, the mechanisms regulating EndoMT in renal disease are poorly understood. SIRT (sirtuin) 3 is a mitochondrial deacetylase that protects the endothelium and kidney via antioxidant and anti-inflammatory effects. In this study, we demonstrate evidence for EndoMT and a concomitant decrease in SIRT3 expression in the kidneys of mice made hypertensive by infusion of Ang II (angiotensin II). In SIRT3 knockout mice, we observed a marked increase in EndoMT, reactive oxygen species production, and renal injury. In contrast, in mice with overexpression of endothelial SIRT3, we observed a decrease in EndoMT, reduced oxidative stress, and preserved renal function. We showed that SIRT3 interacts with the transcription factor Foxo3a (forkhead box O3a) and improves its nuclear translocation and activity. We further showed that SIRT3 increases Foxo3a-dependent catalase expression and attenuates oxidative stress, which in turn suppresses EndoMT. Collectively, we have discovered a previously unknown role of the SIRT3 regulation of EndoMT in hypertensive renal injury and have defined a pathway involving SIRT3, Foxo3a, and catalase as a potential therapeutic target to prevent renal fibrosis and disease.

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