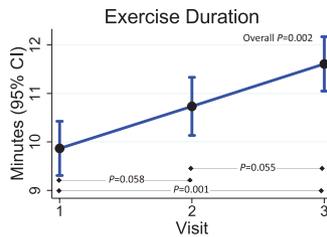


**Recycling of Lipoprotein(a)
(p 1091)**

Sharma et al examine how Lipoprotein(a) enters cells and what happens to it once inside.

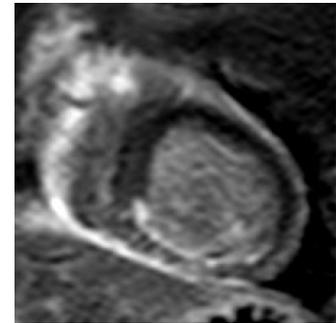
Elevated plasma levels of lipoprotein(a) (Lp(a)) are associated with an increased risk of cardiovascular disease and coronary heart disease. The generation of Lp(a), following synthesis of its precursor apoprotein(a) in the liver, is well understood. But how Lp(a) subsequently exits the plasma and what becomes of it within cells is largely unknown. A number of receptors have been suggested to be responsible for Lp(a) uptake, but the findings have been inconclusive. To unravel the mystery, Sharma and colleagues investigated 3 candidate receptors within the same cell type. Lp(a) from healthy individuals was added to cultured human liver cells, while each of the 3 receptors were inactivated in turn. Uptake of Lp(a) was unchanged for 2 of the inactivated receptors, but blocking the third—plasminogen receptor (PlgRKT)—reduced Lp(a) uptake dramatically. Further genetic deletion and overexpression experiments confirmed the role of PlgRKT in Lp(a) uptake. The team also examined the intracellular fate of Lp(a), discovering that, after endocytosis, the lipoprotein was separated into its LDL and apoprotein(a) components. The LDL was ultimately degraded in lysosomes, while the apoprotein(a) was recycled. These findings should aid in the development of therapies aimed at lowering plasma Lp(a), say the authors.



**Inorganic Nitrate in HFpEF
(p 1151)**

Inorganic Nitrate provides fitness benefits for patients with heart failure, report Zamani et al.

Evidence indicates that patients suffering from heart failure with preserved ejection fraction (HFpEF) have impaired signaling of the powerful vasodilator nitric oxide (NO). Beetroot juice contains large amounts of inorganic nitrate, which can be converted within the body to NO. And recent studies have found that drinking beetroot juice can improve vasodilation and peak oxygen uptake in heart failure patients. It can also improve patients' stamina during exercise. Whether pharmacological preparations of inorganic nitrate can produce similar results, however, has not been examined. Zamani and colleagues gave 12 patients with HFpEF daily oral doses of inorganic nitrate—specifically potassium nitrate (KNO₃)—for 2 weeks. At the end of each week, the patients performed cycling exercises. Three patients were given potassium chloride as a placebo to rule out any potential effects of potassium. The team found that while peak oxygen uptake was unchanged in the KNO₃ recipients, exercise duration increased significantly and quality-of-life measures improved compared with controls. In general, the KNO₃ was well tolerated by the subjects. The results of this analysis, while encouraging, are based on a relatively small sample size, the authors noted. They, therefore, suggest that larger randomized trials are now warranted.



Cell Therapy for Single Ventricle Physiology (p 1162)

Children with a particular congenital heart defect respond well to cell therapy, report Ishigami et al.

Children born with single ventricle physiology, such as left ventricle hypoplasia, have just 1 functional ventricle and thus suffer the effects of insufficient tissue oxygenation. Patients require regular, life-long monitoring even after palliative surgery and have a high risk of heart failure and premature death. Cardiosphere-derived cells (CDCs), which are isolated from heart tissue after surgery, possess regenerative potential and have thus been considered a candidate cell type for repairing damaged hearts. Indeed, a phase I trial of CDC infusions for the treatment of children with single ventricle physiology indicated that the procedure was safe, feasible, and associated with some improvement in ventricle function. Ishigami and colleagues now report the results of a follow-up phase II randomized trial in which children who had received palliative surgery were given coronary infusions of autologous CDCs. After 3 months, the cell recipients showed significantly improved ventricle function compared with controls and, for some, reduced cardiac fibrosis. After a year, the patients showed improvements in clinical heart failure status and quality of life (compared with their before-treatment assessments). The results of this trial provide encouragement that a currently underway phase III trial might yield similarly positive outcomes.

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