IN BRIEF

CARDIOMYOPATHIES

Ketogenesis in arrhythmogenic cardiomyopathy

Sudden cardiac death is often the first manifestation of arrhythmogenic cardiomyopathy (AC), given the lack of markers to predict disease progression. A study in *Science Translational Medicine* reports that the myocardial levels of enzymes involved in ketone metabolism are increased in patients with AC, in agreement with the hypothesis that metabolic markers of increased fatty acid oxidation (FAO), such as those involved in ketone production and utilization, might provide clues for the diagnosis of AC. Specifically, the plasma levels of the ketone body β-hydroxybutyrate (β-OHB) were higher among probands than in healthy volunteers and correlated with the occurrence of major adverse cardiac events. Furthermore, plasma β-OHB concentration increased progressively with disease severity, supporting its use as a clinical marker of adverse disease progression in both patients with AC and their asymptomatic relatives.

ORIGINAL ARTICLE Song, J.-P. et al. Elevated plasma β-hydroxybutyrate predicts adverse outcomes and disease progression in patients with arrhythmogenic cardiomyopathy. *Sci. Transl Med.* **12**, eaay8329 (2020)

INTERVENTIONAL CARDIOLOGY

LVAD versus balloon pump in patients with AMI

In patients undergoing percutaneous coronary intervention for acute myocardial infarction (AMI) complicated by cardiogenic shock, use of an intravascular microaxial left ventricular assist device (LVAD) is associated with worse clinical outcomes than use of an intra-aortic balloon pump (IABP). This finding comes from a propensity-matched, registry-based, retrospective cohort study that assessed 28,304 patients, 6.2% of whom received haemodynamic support with an LVAD and 29.9% with an IABP. In the propensity-matched cohort ($n = 3,360$), LVAD use was associated with a greater risk of in-hospital death (45.0% versus 34.1%) and major bleeding (31.3% versus 16.0%) than IABP use. Importantly, these associations were consistent regardless of the timing of device placement. Additional research is required to understand the optimal device choice for these patients.

ORIGINAL ARTICLE Dhruva, S. S. et al. Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* https://doi.org/10.1001/jama.2020.0254 (2020)

VASCULAR DISEASE

Cocoa might improve walking performance in PAD

Cocoa consumption improves some metrics of walking performance among old patients with peripheral artery disease (PAD), according to a new study in *Circulation Research*. Investigators of the phase II, double-blind COCOA-PAD trial randomly assigned 44 patients with PAD (mean age 72.3 years) to consume a flavanol-rich cocoa beverage or an identically appearing placebo beverage thrice daily. At the 6-month follow-up, cocoa consumption improved the 6-min walking distance measured 2.5 h after drinking the study beverage by 42.6 m compared with placebo, but did not improve the 6-min walking distance measured 24 h after study beverage intake. Furthermore, cocoa consumption did not alter maximal and pain-free treadmill walking distance or brachial artery flow-mediated dilatation but improved calf muscle perfusion and capillary density compared with placebo.

ORIGINAL ARTICLE McDermott, M. M. et al. Cocoa to improve walking performance in older people with peripheral artery disease: the Cocoa-Pad pilot randomized clinical trial. *Circ. Res.* https://doi.org/10.1161/CIRCRESAHA.119.315600 (2020)

ACUTE CORONARY SYNDROMES

Previous MI attenuates emergency haematopoiesis and inflammation

A novel mouse model of recurrent myocardial infarction (MI) reveals that a first MI can diminish the expression of haematopoietic maintenance factor in bone marrow macrophages, which leads to reduced emergency haematopoiesis and inflammatory responses to a subsequent MI. These findings, published in the *Journal of the American College of Cardiology*, indicate that haematopoietic and innate immune responses are influenced by a preceding MI.

Recurrent MI is associated with poor outcomes and high morbidity and mortality. After an MI event, neutrophils and monocytes from haematopoietic organs are recruited to the heart, in a process termed emergency haematopoiesis, to promote myocardial healing. "Because many of these immune cells have life spans that are shorter than a day, we believe that investigating bone marrow production of immune cells is important," explains Matthias Nahrendorf, the lead author of the study. The investigators developed a surgical mouse model of recurrent MI by ligating the left circumflex artery and then, 10 days later, ligating the left anterior descending coronary artery, inducing two sequential MIs in the same mouse. The numbers of myeloid cells in the blood and leukocytes in the infarct zone were lower after a recurrent MI than after a first MI.

Next, the investigators used mice joined in parabiosis, with a shared circulation, to establish that a circulating factor released after the first MI caused the diminished emergency haematopoiesis in response to a subsequent MI. This bone marrow tolerance was potentially mediated by reduced expression of haematopoietic maintenance factor in bone marrow macrophages. Finally, using

METABOLISM

Inhibiting fatty acid oxidation promotes cardiomyocyte proliferation

Mammalian hearts lose the capacity to regenerate within the first week after birth, which coincides with a metabolic shift from anaerobic glycolysis in utero to fatty acid β-oxidation postnatally. A new study published in *Nature Metabolism* shows that inhibition of fatty acid metabolism to promote oxidation of glycolysis-derived pyruvate promotes cardiomyocyte proliferation and improves left ventricular function after myocardial infarction.

"Since fatty acid utilization is known to be more pro-oxidant than glucose-derived pyruvate metabolism, we wanted to see whether forcing myocytes to use glucose-derived pyruvate would decrease oxidative stress, particularly in the form of oxidative DNA damage," says Hesham Sadek, the lead author of the study. The investigators fed neonatal mice with fatty-acid-deficient milk, which prolonged the postnatal period during which cardiomyocytes retained their proliferative capacity. However, the cells eventually entered cell cycle arrest.

Next, the researchers used a tamoxifen-inducible, cardiomyocyte-specific *Pdk4*-knockout mouse. *Pdk4* encodes pyruvate dehydrogenase kinase 4 (PDK4), and deletion of this gene selectively increases oxidation of pyruvate derived from glycolysis rather than fatty acid β-oxidation. *Pdk4* deletion resulted in reduced DNA damage and expression of DNA-damage response markers, decreased cardiomyocyte size and increased cardiomyocyte proliferation. Tamoxifen-induced deletion of *Pdk4* at 1 week after induction of myocardial infarction was associated with reductions in cardiac fibrosis, left ventricular dilatation and myocardial