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HIGHLIGHTS OF BASIC AND TRANSLATIONAL RESEARCH IN HEART FAILURE

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At this year’s Heart Failure Congress in Paris, France, the basic and translational research track was further expanded compared with the previous years based on the growing interest, also from clinicians, for mechanistic insights into the pathophysiology and treatments of HF. This year’s focus was on (among other topics) cardiomyopathies, metabolic aspects of HF, two HF comorbidities (ie, diabetes and cancer), iron metabolism, and arrhythmias. The track was rounded up by a session in which the results of the past three workshops held by the Committee of Translational Research of the HFA were presented, and this session was introduced by a special lecture given by the famous cardiologist Eugene Braunwald.

CARDIOMYOPATHIES

Two sessions were dedicated to the pathophysiology and treatment of cardiomyopathies. Denise Hilfiker-Kleiner (DE) reported on recent developments in peripartum cardiomyopathy (PPCM). In her previous seminal work, she had discovered that, in patients with PPCM, an aberrant cleavage of the nursing hormone prolactin into a 16 kDa peptide induces maladaptive cardiac remodeling and HF. Formation of this 16 kDa prolactin is prevented by inhibiting the production of the full-length prolactin using bromocriptine. Several smaller clinical studies revealed that bromocriptine improves LVEF and the outcome of patients with PPCM. Data from more recent mechanistic studies revealed that, in addition to the 16 kDa peptide, the PAI-1/UPAR signaling pathway contributes to microvascular dysfunction in patients with PPCM, a key driver of the cardiomyopathy phenotype. She presented data from a randomized multicenter trial on 57 patients with PPCM, revealing that both prolonged (8 weeks) and short-term (1 week) treatment with bromocriptine improved LVEF by 21% and 24%, respectively. After the 8-week treatment, more patients displayed full recovery of LVEF than after a 1-week treatment. Overall, the results further support a potential benefit of bromocriptine in addition to standard guideline-recommended HF therapy in patients with PPCM, suggesting that, overall, 1 week of bromocriptine treatment is sufficient to promote healing in patients with PPCM, although critically ill patients with an LVEF <30% may benefit from prolonged treatment.

In recent years, the Takotsubo syndrome has moved to the focus of extensive clinical and preclinical research. Elmir Omerovic (SE) reported on the progress in both fields. Although it is widely accepted that a catecholamine surge may play an important pathophysiological role, the exact downstream signaling pathways (ie, which adrenergic receptors and associated signaling cascades and consequences are involved) are still incompletely understood. The development of animal models of Takotsubo syndrome, which recapitulate the phenotype, will presumably shed important new insights into the underlying mechanisms in the coming years.

Hypertrophic cardiomyopathy (HCM) is the most common monogenetic cardiac disorder that is frequently caused by mutations in genes that encode sarcomeric proteins. A common mutual mechanism of various mutations is that the affinity of the myofilaments to calcium is increased, which implies that, at any given cytosolic calcium concentration, more myofilaments are activated in HCM than in normal hearts. Based on the results from two different animal models of HCM, Christoph Maack (DE) reported a novel concept that, through this increase in myofilament calcium sensitivity, a mismatch in the mitochondrial redox state occurs, which leads to oxidative stress that underlies the commonly observed arrhythmias in HCM and potentially the induction of left ventricular hypertrophy. Consequently, targeting this energy mismatch and/or mitochondrial ROS production reduced arrhythmias, which could resemble a novel therapeutic strategy for patients with HCM.

METABOLIC ASPECTS OF HEART FAILURE

Several lines of evidence have shown that metabolism is substantially affected in patients with HFREF and HFPEF. Reduced cardiac phosphocreatine predicts an adverse outcome in patients with HFREF, coining the idea of the failing heart as an “engine out of fuel.” In the past 20 years, tremendous effort has been devoted to finding the underlying mechanisms and determining how to treat this energy deficit; one important aspect of this is substrate metabolism. The normal heart is an omnivore that can use fatty acids or glucose as substrates, where glucose is more efficient than fatty acids in generating ATP. Gary Lopaschuk (CA) explained how, in HF and diabetes, cardiac substrate metabolism is altered. In diabetes, metabolism is shifted from glucose to fatty acid utilization, which reduces the metabolic flexibility of the heart, and, by activating uncoupling proteins, metabolic efficacy is decreased, while the formation of ROS is increased. In HF, cardiac uptake of fatty acids and glucose into the cytosol are increased, while their oxidation in the mitochondria is impaired. This provokes accumulation of metabolic intermediates in the cytosol that can induce (partly mal-
adaptive) signaling in their own right. Drugs that inhibit fatty acid oxidation, such as perhexiline or trimetazidine, can increase glucose oxidation and, thereby, presumably shift metabolism toward glucose utilization. Although smaller trials suggested benefits, the evidence that such drugs improve the outcome of patients with HF is still lacking.

A recent observation is that, in this situation of reduced fatty acid and glucose oxidation, the failing heart relies more on alternative fuels, such as ketone bodies. Kieran Clarke (UK) gave a deeper insight into ketone body metabolism. She and her colleagues have developed a highly energetic ketone body diet called ΔG⁰, which increases maximal endurance in top athletes. However, whether this is related to improving the endurance capacity of the heart or skeletal muscles or both and whether such a diet would be beneficial in patients with HF is currently unresolved. Recently, emagliflozin, an inhibitor of the renal sodium-glucose transporter that lowers blood glucose levels, has reduced the risk of hospitalization and death due to HF. While one likely underlying mechanism is the drug’s diuretic and blood pressure-lowering effect, it has alternatively been suggested that, by elevating ketone bodies, emagliflozin provides a “super fuel” for the heart (the so-called “thrifty substrate hypothesis”). This hypothesis, however, has been questioned by Clarke since the elevations of ketone bodies in these patients, which resemble elevations occurring in normal humans after 12 to 24 hours of fasting, may not be sufficient to account for a relevant improvement in cardiac function. Similar concerns have been raised previously by Lopaschuk and Verma.

Johannes Backs (DE) reported on the connection between epigenetics and metabolism. He and his colleagues found that the consequence of diabetes on the heart depends on preexisting epigenetic alterations secondary to other cardiovascular risk factors (unpublished data). In other words, if preexisting neuroendocrine activation has altered epigenetic regulation through histone deacetylase 4, diabetes may aggravate the cardiac phenotype, while, in otherwise healthy subjects with normal nuclear histone deacetylase 4 localization, diabetes may even exert cardioprotective effects.

To summarize, metabolic alterations in HF are likely contributing to maladaptive cardiac remodeling and the energetic deficit of the failing heart. The advent of metabolomic profiling (and other techniques) has deepened our understanding of substrate utilization in recent years; however, further research will be necessary to design the right interventions to improve metabolic defects in patients with HREF and HFPEF.

**CANCER AND THE HEART**

Alexander Lyon (UK) gave a brilliant introduction to the topic. Over the past decades, the median survival from any cancer has increased, which is why we are now seeing more patients with chemotherapy-induced cardiac dysfunction or HF. When treating cancer, signaling pathways that induce cell survival (of the cancer cell) are often targeted, which means that the survival of cardiac and noncardiac myocytes are also negatively affected by chemotherapies. Lyon reported data from various studies addressing cardiovascular outcomes in response to cancer treatments, with a special focus on trastuzumab-induced cardiotoxicity. He highlighted the importance of a dose dependency of such effects and the potential use of biomarkers to identify patients at risk for cardiotoxicity.

Heinrich Taegtmeyer (US) highlighted similarities between heart and cancer cells regarding metabolism. The “Warburg effect” of cancer cells is characterized by a shift of isoforms of PKM from an adult (PKM1) to a fetal isoform (PKM2). In failing human hearts, such a shift can be observed, which may highlight the similarities in metabolism in failing heart cells and cancer cells. Furthermore, during cancer, so-called oncometabolites accumulate due to changes in cancer cell metabolism. One of these oncometabolites, D-2-hydroxyglutarate, impairs the functioning of the Krebs cycle, which may induce contractile dysfunction, resembling a metabolic cause of HF development during cancer (independent of chemotherapy).

Catherine Vergely (FR) and her team recently discovered from epidemiological studies that obesity is a risk factor for anthracycline and trastuzumab cardiotoxicity in patients with breast cancer. She also discussed the results of preclinical studies and the potential mechanisms that underlie the obesity-induced sensitivity of patients toward chemotherapies. Some of these factors involved elevated levels of leptin and cytokines, such as IL6, TNF-α, or PAI-1, and decreased levels of adiponectin and omentin, which may converge onto decreased pro-survival signaling within cardiac myocytes and impaired metabolism and oxidative stress in the mitochondria.

Kari Alitalo (FI) rounded up this interesting session by suggesting that gene therapy with VEGF-B could protect hearts from doxorubicin-induced cardiotoxicity. Based on a preclinical mouse model, he revealed that such an intervention reduces doxorubicin-induced cardiac atrophy, protected endothelial cells from apoptosis, and preserved the myocardial capillary network. Furthermore, the doxorubicin-induced whole body wasting (cachexia), which impairs the quality of life and increases the drug toxicity in patients to decrease their survival, was inhibited by VEGF-B treatment in doxorubicin-treated mice. For the potential continued development of VEGF-B gene therapy, further preclinical and clinical research is required.

**IRON METABOLISM**

In patients with HF, iron deficiency is associated with adverse outcomes, and restoring iron levels in these patients with intravenous infusions of iron improves morbidity and symptoms, but not survival. Ewa Jankowska (PL) introduced these clinical aspects, highlighted the evidence from randomized clinical trials, and discussed diagnostic dilemmas and future therapeutic perspectives of iron deficiency and treatment. Tibor Kempf (DE) presented preclinical data that, in myocardial infarction, genetically-induced iron deficiency impairs mortality and cardiac function and that intravenous iron supplementation could rescue these deficits. In their model, iron deficiency was associated with decreased activity of respiratory chain complex I and subsequently respiration. These results suggest that
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iron supplementation restores cardiac energy reserve and function in iron-deficient hearts.

Hossein Ardehali (US) delivered some counterpoints to this line of evidence. He highlighted that iron overload, which occurs in various diseases, such as hemochromatosis, thalassemia, sickle cell disease, or Friedreich’s ataxia, causes mitochondrial damage by excessive formation of ROS, which is fostered by the Fenton or Haber-Weiss reactions in which iron catalyzes the formation of the highly toxic hydroxyl radical. He also presented preclinical evidence that, in myocardial ischemia/reperfusion injury and doxorubicin-induced cardiotoxicity, mitochondrial iron depletion is protective, whereas iron overload is harmful. He concluded that, for the long-term treatment of patients with HF without iron deficiency, iron chelation might be beneficial, whereas, in patients with HF and iron deficiency, iron supplementation would be useful.

ARRHYTHMIAS

Up to 50% of patients with HF die by sudden cardiac death, and arrhythmias are mostly related to scar formation and/or disturbed calcium handling in cardiac myocytes. A second problem in HF is that, by structural and electrical cardiac remodeling, asynchronous contraction of the left ventricle reduces the efficacy of cardiac ejection of blood. This session focused on the implications of the cardiac myocytes’ transversal (t) tubular system for calcium handling and, consequently, for contractility and the risk for arrhythmias.

William Louch (NO) presented interesting data on how an increase in transmural wall stress (as occurs in HF) disturbs the t-tubular system in cardiac myocytes, which disturbs calcium handling. Such disturbances were also associated with a reduced expression of junctophilin-2, an important protein that guides the well-coordinated calcium-induced calcium release from the sarcoplasmic reticulum. Overall, the structural remodeling of cardiac myocytes by itself can induce contractile deficit and possibly arrhythmias.

Jean-Pierre Benitah (FR) explained how hyperaldosteronism, a common feature in patients with hypertension and/or HF, could disturb excitation-contraction coupling and induce hypertrophy that involves transient receptor potential channels. These mechanisms may underlie the beneficial effects of aldosterone antagonism in the treatment of patients with HF. Julia Gorelik (UK) presented data provided by cutting-edge microscopy in which they identified differences in receptor and calcium signaling in the t-tubuli and the crests (i.e., the areas between the t-tubuli on the surface of the cell). They observed that, during HF, t-tubular remodeling disturbs calcium and CaM handling in cardiac myocytes, which may all predispose a patient to contractile dysfunction and arrhythmias. Finally, Frank B. Sachse (US) presented insights from studies on models and patients with dysynchronous HF; he also discussed how cardiac dysynchronicity induces t-tubular remodeling and defects in calcium handling, while CRT can reverse some of these maladaptive changes. These data provide insight on how CRT in patients with HF improves cardiac function acutely, induces reverse cardiac remodeling, and lowers the risk of (sudden cardiac) death.

CONCLUSIONS

Together, the basic and translational science program once again highlighted how important it is to understand the underlying mechanisms of HF and its comorbidities to design rationale therapies directed against the progression of the syndrome.

REFERENCES