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Lüscher, Thomas F

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An update on heart failure: from experimental findings to clinical trials

Thomas F. Lüscher, MD, FESC

Editor-in-Chief, Zurich Heart House, Careum Campus, Moussonstrasse 4, 8091 Zurich, Switzerland

Heart failure increasingly not only accounts for a significant part of cardiovascular morbidity and mortality, but is also responsible for many hospitalizations as outlined again in the most recent ESC Guidelines.[1] Millions of patients worldwide are admitted for acute heart failure each year, and physicians are confronted with the challenge of reducing symptoms while preventing end-organ dysfunction without causing additional harm, and the intermediate-term challenges of improving clinical outcomes such as hospital readmission and survival. Acute heart failure therefore is an important new frontier for research and clinical emergency management. A novel development are vasodilator drugs, as discussed in detail in a clinical review '**Agents with vasodilator properties in acute heart failure**' by John R. Teerlink and colleagues from the University of California San Francisco in California, USA.[2] Unfortunately, there are limited data supporting the efficacy of currently available therapies. After diuretics, vasodilators are the most common intravenous therapy, but neither nitrates, nitroprusside, nor nesiritide has evidence supporting their ability to provide meaningful effects on clinical outcomes, except early symptom improvement. Recently, numerous novel agents with vasodilating properties have been developed, such as serelaxin,[3] natriuretic peptides such as ularitide[4] and cenderitide, beta-arrestin-based angiotensin II type 1 receptor ligands (TRV120027), nitroxyl donors (CXL-1020 abd CXL-1427), soluble guanylate cyclase modulators such as cinaciguat[5] and vericiguat, short-acting calcium channel blockers such as clevidipine, and the potassium channel activator nicorandil. These development programmes range from the stage of early dose-finding studies to large, multicentre mortality trials. There is an urgent need for agents with vasodilating properties that will improve both in-hospital and post-discharge clinical outcomes, and these novel approaches may provide opportunities to address this need.

Triggers of acute heart failure are dietary mistakes, arrhythmias, especially atrial fibrillation,[6] drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs),[7,8] and infections. Thus, vaccination in patients with chronic heart failure might be a promising strategy to avoid unnecessary hospitalizations. In a FAST TRACK entitled '**Influenza vaccination and risk of hospitalization in patients with heart failure: a self-controlled case series study**',[9] Kazem Rahimi and colleagues from the University of Oxford in the UK investigated the impact of influenza vaccination on the risk of hospitalization in heart failure. To this end, they used linked primary and secondary health records in England between 1990 and 2013. Using a self-controlled case series design with conditional Poisson regression, they estimated the incidence rate ratio of the number of hospitalizations in a year following vaccination with an adjacent vaccination-free year in the same individuals. They found the uptake of vaccination to be varied and generally low; only 49% in 2013. Among 59 202 heart failure patients, influenza vaccination was associated with a lower risk of hospitalization due to cardiovascular disease, with an odds ratio of 0.70, with more modest effects for hospitalization due to respiratory infections, with an odds ratio of 0.84, and all-cause hospitalizations, with an odds ratio of 0.96. The relative effects were greatest in younger patients below the age of 66, with no difference between men and women. In validation analyses, effects were not significant for consecutive years without vaccination. This strongly suggests that in heart failure, influenza vaccination is associated with reduced risk of hospitalizations, especially for cardiovascular disease. Improved efforts for a greater uptake of vaccination among heart failure patients are thus needed. These clinically important findings are further discussed in an **Editorial** by Scott Solomon from the Brigham and Women's Hospital in Boston.[10]

Guidelines for the management of chronic heart failure use randomized controlled trials to support treatment as the basis of their recommendations. In a subsequent clinical manuscript '**How robust are clinical trials in heart failure?**', John J.J.V. McMurray and colleagues from the Western Infirmary in Glasgow, UK[11] remind us that the significance of an observed treatment effect relies on the use of a boundary *P*-value, most commonly $P < 0.05$. However, whether we should rely on arbitrary threshold *P*-values to report results as 'statistically significant' has been repeatedly questioned. Thus, the 'fragility index' has been proposed as an additional measure of the robustness of trial findings. The fragility index is the minimum number of events needing to change from a non-event to an event to render a significant result non-significant. Hence, the authors calculated the fragility index to examine the robustness of statistically significant randomized controlled trials in chronic heart failure. Two reviewers extracted data from randomized controlled trials supporting

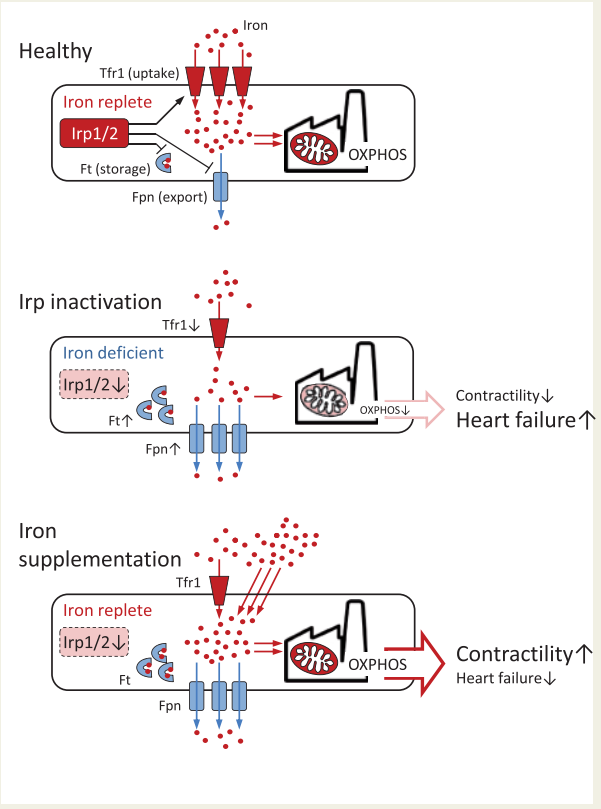

Figure 1 *Summary of key findings.* Iron-regulatory proteins (Irp1/2) secure iron availability in cardiac myocytes by enhancing iron uptake (via the transferrin receptor, Tfr1) and reducing iron export (via ferroportin, Fpn) and storage (bound to ferritin, Ft). Under iron replete conditions, enough iron is available to feed iron-sulphur cluster-containing proteins required for mitochondrial oxidative phosphorylation (OXPHOS). Reflecting net changes in iron uptake, export, and storage, cardiomyocyte-selective Irp inactivation leads to intracellular iron deficiency. Similarly, IRP activity is reduced in the failing human heart. Iron deficiency in cardiomyocytes impairs oxidative phosphorylation and adaptation to acute and chronic increases in workload. Iron supplementation restores intracellular iron availability by increasing Tfr1- and non-Tfr1-mediated iron uptake, thereby enhancing oxidative phosphorylation and resistance to stress (from Haddad S, Wang Y, Galy B, Korf-Klingebiel M, Hirsch V, Baru AM, Rostami F, Reboll MR, Heineke J, Flögel U, Groos S, Renner A, Toischer K, Zimmermann F, Engeli S, Jordan J, Bauersachs J, Hentze MW, Wollert KC, Kempf T. Iron-regulatory proteins secure iron availability in cardiomyocytes to prevent heart failure. See pages 362–372.)

treatment recommendations in chronic heart failure guidelines. Twent-five eligible trials were identified, with a median sample size of 2331 patients and a median number of 689 primary endpoints. For the primary endpoint, the median fragility index was 26 with a range from 0 to 118. The fragility index was ≤10 in a third of these 20 trials. Of note, in one-fifth, the number of patients lost to follow-up in the treatment group exceeded the fragility index. Thus, the results of large randomized controlled trials in chronic heart failure hinge on a small number of events. The fragility index offers an additional, easy to understand metric, which augments the standard reporting of boundary *P*-values for statistical significance. The fragility index helps in the interpretation of the robustness of the results of randomized controlled trials. The manuscript is accompanied by an interesting **Editorial** by Rickey Edward Carter from the Mayo Clinic in Rochester, Minnesota, the chief statistical editor of the *European Heart Journal*.[12]

A less common form of heart failure is peripartum cardiomyopathy, which is also associated with a considerable risk.[13,14] The benefit of the β_1-adrenergic receptor agonist dobutamine for treatment of acute heart failure in peripartum cardiomyopathy is controversial. Cardiac STAT3 is part of myocardial salvage pathways[15] and its expression is reduced in peripartum cardiomyopathy patients. Mice carrying a cardiomyocyte-restricted deletion of STAT3, STAT3 knockout mice, develop peripartum cardiomyopathy. In a Basic Science article entitled '**Low STAT3 expression sensitizes to toxic effects of β-adrenergic receptor stimulation in peripartum cardiomyopathy**', Denise Hilfiker-Kleiner and colleagues from the Hannover Medical School in Germany hypothesized that STAT3-dependent signalling networks may influence the response to β_1-adrenergic receptor agonists in peripartum cardiomyopathy patients and analysed this hypothesis in STAT3 knockout mice.[16] Follow-up analyses in 27 patients with severe peripartum cardiomyopathy revealed that those not receiving dobutamine improved cardiac function, while those receiving dobutamine ended up with heart transplantation or assist devices. Of note, they displayed diminished myocardial triglyceride, pyruvate, and lactate content compared with non-failing controls. The β_1-adrenergic receptor agonist isoproterenol induced heart failure with high mortality in post-partum females, in non-pregnant females, and in male STAT3 knockout mice, but not in wild-type littermates. Isoproterenol induced heart failure and high mortality in STAT3 knockout mice by impairing fatty acid and glucose uptake, thereby generating a metabolic deficit. The latter was governed by disturbed STAT3-dependent signalling networks, microRNA-199a-5p, microRNA7a-5p, insulin/glucose transporter-4, and neuregulin/ErbB signalling. The resulting cardiac energy depletion and oxidative stress promoted dysfunction of cardiomyocytes and eventually heart failure, which could be attenuated by the β_1-adrenergic receptor blocker metoprolol or glucose uptake-promoting drugs such as perhexilline or etomoxir. The authors conclude that isoproterenol impairs glucose uptake, and induces energy depletion, oxidative stress, dysfunction, and death in STAT3-deficient cardiomyocytes mainly via β_1-adrenergic receptor stimulation. These cellular alterations may underlie the dobutamine-induced irreversible progression of heart failure in peripartum cardiomyopathy patients who frequently display reduced cardiac STAT3 expression.

Iron metabolism is important for myocardial function,[17] and iron deficiency is associated with adverse outcomes in heart failure, while iron substitution improves quality of life and results of the 6-min walking test.[18,19] However, the underlying mechanisms are incompletely understood. Intracellular iron availability is secured by two mRNA-binding iron-regulatory proteins, IRP1 and IRP2. In another Basic Science article, entitled '**Iron-regulatory proteins secure iron availability in cardiomyocytes to prevent heart failure**', Tibor Kempf and colleagues from the Hannover Medical School in Germany generated mice with a cardiomyocyte-targeted deletion of iron-regulatory proteins Irp1 and Irp2 to explore the functional implications of iron deficiency in the heart independent of systemic iron

deficiency or anaemia.[20] Iron content in cardiomyocytes was reduced in Irp-targeted mice. The animals were not anaemic nor did they show a phenotype at baseline. Irp-targeted mice, however, were unable to increase left ventricular systolic function in response to an acute dobutamine challenge. After myocardial infarction, Irp-targeted mice developed more severe left ventricular dysfunction with increased mortality. Mechanistically, the activity of the iron–sulphur cluster-containing complex I of the mitochondrial electron transport chain was reduced in left ventricles from Irp-targeted mice (*Figure 1*). As demonstrated by extracellular flux analysis *in vitro*, mitochondrial respiration was preserved at baseline but failed to increase in response to dobutamine in Irp-targeted cardiomyocytes. As shown by ^{31}P-magnetic resonance spectroscopy *in vivo*, the left ventricular phosphocreatine/ATP ratio declined during dobutamine stress in Irp-targeted mice, but remained stable in control mice. Intravenous injection of ferric carboxymaltose replenished cardiac iron stores, restored mitochondrial respiratory capacity and inotropic reserve, and attenuated adverse remodelling after myocardial infarction in Irp-targeted mice but not in control mice. The authors conclude that iron deficiency in cardiomyocytes impairs mitochondrial respiration and adaptation to acute and chronic increases in workload. Iron supplementation restores cardiac energy reserve and function in iron-deficient hearts. The clinical implications of this experimental paper are discussed in an **Editorial** by Gavin Oudit from University of Alberta in Canada.[17]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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