"Heart failure, whole-body insulin resistance and myocardial insulin resistance: An intriguing puzzle"

Paola Gargiulo, MD, PhD,[a] and Pasquale Perrone-Filardi, MD, PhD[b]

[a] Institute of Diagnostic and Nuclear Development, SDN Foundation, Naples, Italy
[b] Department of Advanced Biomedical Sciences, Section of Cardiology, Federico II University, Naples, Italy

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Type 2 diabetes mellitus (DM) is not only a causative factor of heart failure (HF),[1] but the co-existence of DM in HF patients is also responsible for more severe prognosis.[2] DM cause functional, metabolic, and structural alterations that ultimately generate myocardial damage and HF progression. In particular, abnormalities in contractile proteins and impaired relaxation,[3] change in substrate utilization,[4] cellular injury,[5] microvascular dysfunction,[6,7] neurohormonal, and sympathetic nervous systems activation[8,9] are main features that accompany DM in HF (Figure 1). As recently reported,[10] these alterations can be recognized not only in DM, but also in patients with insulin resistance (IR). IR is highly prevalent (up to 60%) in patients affected by HF,[11] and a complex pathophysiological interaction exists between these two conditions, since IR may represent, at the same time, cause and consequence of HF. In HF patients, not only the presence of established DM but also presence of minimal glycemic profile alteration, such as those recognized in prediabetic and newly diagnosed DM patients, can induce more aggressive form of HF.[12] Perturbation in myocardial metabolism and energetics in patients with IR is one of underlying mechanisms likely involved. Although whole-body IR is a central feature of prediabetes and DM, the insulin sensitivity of the heart in patients with DM is subject of debate. Some studies using positron emission tomography (PET) with F-fluorodeoxyglucose (FDG) reported reduced myocardial glucose uptake (MGU) during hyperinsulinemia in patients with DM;[13,14] however, other evidences documented absence of myocardial IR in patients with DM.[15] In this issue of Journal of Nuclear Cardiology, Nielsen et al[16] reported the results of their study looking at the relationship between abnormal response to oral glucose tolerance test (OGTT) that is a reliable method to test patients with possible DM,[17] and MGU, assessed by FDG-PET in HF patients without overt DM. The study is a substudy of the clinical, randomised LIVE study,[18] enrolling HF patients with reduced left ventricular ejection fraction, initiated to elucidate the effect of a glucagon-like peptide 1 analog (liraglutide) on left ventricular function. It involved 35 patients that underwent OGTT, insulin sensitivity, free fatty acid estimation, echocardiographic measurement, 18F-FDG/15O-H2O PET/CT scan. For each patient, they measured global and regional MGU, myocardial blood flow (MBF) at rest and during adenosine-induced hyperemia, and global myocardial flow reserve (MFR), as the ratio between adenosine-induced hyperaemia MBF and resting MBF. Myocardial segments were defined based on a combination of WMS and FDG-PET examinations and grouped into those who had preserved function (Wall Motion Score (WMS = 2)) and were dysfunctional viable (WMS < 2, normal FDG uptake) and dysfunctional nonviable (WMS < 2, low FDG uptake). From methodological point of view, differently from other studies exploring the role of whole-body glucose metabolism alterations on myocardial IR, authors use OGTT to stimulate MGU. During OGTT values of glycaemia and insulinemia are not stable, differently from those obtainable with hyperisulinemic-euglycemic clamp technique; however, insulin levels

Reprint requests: Pasquale Perrone-Filardi, MD, PhD, Department of Advanced Biomedical Sciences, Section of Cardiology, Federico II University, Via Pansini 5, 80131 Naples, Italy; *fpperron@unina.it*
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achieved are more physiological and, likely, more representative of a daily postprandial condition.[19]

Key finding of this study is the significant reduction of MGU in HF patients with prediabetes and newly diagnosed DM in comparison with HF patients with normal OGTT, despite similar demographic and clinical characteristics and left ventricular dysfunction, without interaction from cause of HF (ischemic or idiopathic). Furthermore, the authors demonstrated that insulin sensitivity correlated positively with MGU ($r^2 = 0.17$, $p = 0.02$).

The authors also analyzed regional MGU, MBF, and MFR. Of 560 myocardial segments evaluated, 242 segments were characterized as normally contracting (WMS = 2) and 333 as dysfunctional (WMS < 2); of dysfunctional segments, 242 were classified as viable and 91 as nonviable, by the FDG uptake definition. Segment with preserved contractility had reduced MGU in the abnormal OGTT group. Interestingly, in HF patients with abnormal OGTT, MGU is reduced in viable segments that demonstrated preserved MFR irrespective of whether they had normal or reduced function. The significance of these results relies on the demonstration that during daily life in HF patients with minor whole-body glucometabolic disturbances the myocardium is insulin resistant, suggesting that consequent reduced glucose oxidation and myocardial efficiency might contribute more aggressive to HF progression observed in IR-HF patients. Another interesting tool provided by authors is the relation between MGU and MFR. In patients with abnormal OGTT, MGU was lower in segments that had preserved MFR as compared with those that had reduced MFR ($p = 0.005$), whereas MGU did not differ in patients with normal OGTT. The authors advocated the translocation of glucose transporter 4 (GLUT-4) transport molecules to the sarcolemma to explain these results. In experimental studies,[20] insulin stimulation induces translocation of GLUT-4 to sarcolemma, augmenting cellular glucose uptake up to 20-fold. Similarly, during ischemic insult, translocation of GLUT 4 is increased to improve glucose uptake and protect myocardial cell from ischemic damage.[20] As consequence, in patients with HF and abnormal OGTT an increase of MGU is detectable in viable segments with reduced MFR in comparison with those with normal MFR, likely as compensatory response to ischemia. However, the relationship between MGU, ischemia, and insulin is complex and still far to

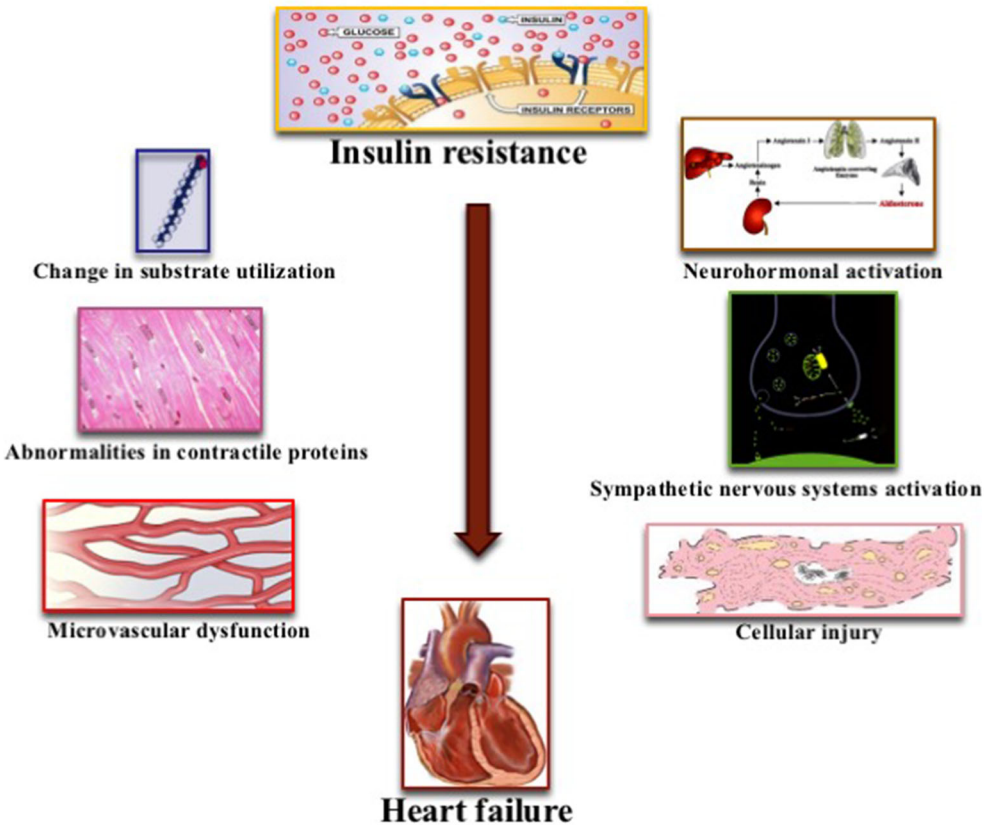

Figure 1. The complex relationship between insulin resistance and heart failure.

be completely understood.[21] In fact, in nondiabetic HF patients, insulin sensitivity is itself impaired and prediabetes and myocardial ischemia likely contribute to induce myocardial IR, suggesting the importance of interpretation of MGU in the contest of MFR and whole-body metabolism. Furthermore, as authors reported in study limitation, their attention was focalized on patients with prediabetic condition, one of the ''phenotypic'' features of IR. However, myocardial IR has been documented also in other conditions, such as hypertension,[22] strictly linked to whole-body IR. Accordingly, we could not exclude the potential summative effect of other metabolic syndrome components on myocardial IR and reduced MGU in prediabetic HF patients.

The most important question raised by the current report by Nielsen et al[16] is whether reversal of myocardial metabolic abnormalities can improve outcome. New therapeutic avenues are now opening up to test this hypothesis. An option could be represented by use of metformin, a biguanide agent acting through activation of AMP-activated protein kinase that plays an important role in insulin signaling and the metabolism of glucose and fats.[17] In prediabetic patients, metformin is considered in addition to diet and life-style modification in obese patients.[17] Data from experimental studies have suggested that administration of metformin before and during ischemia reperfusion might affect these protective pathways and preserve left ventricular function, independent of glycometabolic state.[23] Consequently, in spite of previous concerns of lactic acidosis, now it is opening the potential useful role for metformin in the setting of HF. However, in the GIPS (Glycometabolic Intervention as Adjunct to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction) III[24] in patients without DM presenting with acute coronary syndrome, the use of metformin compared with placebo did not result in improved systolic dysfunction. In addition, the TAYSIDE trial (Metformin in Insulin Resistant LV Dysfunction, a Double-blind, Placebo-controlled Trial),[25] designed to determine whether metformin can improve insulin sensitivity in patients with HF and whole-body IR, failed to demonstrate the improvement of exercise capacity and left ventricular ejection fraction in comparison with placebo, despite IR improvement.

Trimetazidine is a partial fatty acid oxidation inhibitor that inhibits 3-ketoacyl CoA thiolase, one of the enzymes of fatty acid β-oxidation, that reduces glycolysis, enhances glucose oxidation, and improves postischemic recovery.[26] The beneficial effect of trimetazidine on left ventricular function has been attributed to the preservation of intracellular myocardial high-energy phosphate levels. Trimetazidine is able to relieve symptoms, to improve the quality of life, and to increase functional capacity in patients with HF.[27] However, these data are obtained from meta-analysis based on small, unpowered studies. In addition, no data are available on effect of trimetazidine on IR at myocardial level in this specific subset of HF patients.

The study of Nielsen et al[16] present interesting data on a complex tool, the myocardial IR in specific subset of HF patients with whole-body IR, but without overt DM, providing a new piece an intriguing puzzle difficult to solve. It is not clear whether whole-body IR causes directly myocardial IR or whether HF induces myocardial IR and whole-body IR is an epiphenomenon. Beyond definition of causative relation between whole-body IR and HF, assessment of myocardial IR can be useful to select patients with more aggressive left ventricular dysfunction. However, we need prospective studies evaluating the effect of ''metabolic'' therapeutic strategy on MGU and on prognosis to elucidate the role of assessing myocardial IR in prediabetic patients.

Disclosure

No interests conflicts.

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