EDITORIAL

Introduction to the Special Issue: Relevance of Endocrine and Metabolic Disorders in Heart Failure: From Pathophysiology to Therapeutic Approach

Chronic Heart Failure (CHF) represents a major and growing health problem. It has been estimated that its prevalence is of 1–2% in the western world, with an incidence of 5–10 per 1000 persons per year [1]. Besides the "epidemic" proportions of CHF prevalence, its relevance derives from the impact on health-care costs (around 2% of total health care budget) [2], which are mainly determined by hospitalizations for acute decompensated heart failure. The annual number of CHF related hospitalisations, in fact, has been shown to be increasing [3], with a rate of rehospitalisation of 50% within 6 months of discharge [4], mostly related to worsening of previously diagnosed HF [5].

Over the last decades, whether no progress has been registered in the therapy of CHF patients with preserved left ventricular systolic function, the use of drugs blocking renin-angiotensin-aldosterone system and sympathetic nervous system activity has allowed to greatly improve the treatment of CHF patients with reduced left ventricular systolic function [6, 7]. These classes of drugs are able to inhibit the main neuro-hormonal systems leading to left ventricular remodelling and left ventricular systolic dysfunction [6]. Furthermore, the prognosis of CHF patients with reduced left ventricular systolic function has been also improved by the introduction of new antiremodelling strategies such as cardiac resynchronisation therapy and the use of ivabradine for heart rate control as well as by the possibility of preventing sudden death with implantable cardioverter defibrillators [7]. However, despite all these therapeutical progresses, CHF patients' prognosis still remains poor [8].

Among the factors contributing to the persistence of poor CHF prognosis, there is growing evidence about the role of comorbidities, which can modify the natural history of CHF both favouring its onset and influencing its progression [9]. In this setting endocrinological, metabolic, nutritional and immunological disorders could play a relevant pathophysiological role. This special issue of Endocrine, Metabolic and Immune Disorders – Drug Targets will focus on these abnormalities in the attempt of stating what has been already shown and what still needs to be clarified by future researches.

The first reviews illustrate the relationship between thyroid function and CHF [10-12]. Thyroid hormones can exert relevant effects at cardiac and vascular level, by influencing heart rate, myocardial excitability as well as inotropic and lusitropic status, systemic vascular resistance and blood pressure. In their review, Gencer and coll. have analysed the data coming from longitudinal studies exploring the relationship between thyroid disorders and the occurrence of heart failure events [10]. On the other hand, the possible different role played by subclinical hypothyroidism in elderly patients has been discussed by Pasqualetti and coll. [11]. In the review of Triggiani and Iacoviello, the prognostic significance and the therapeutical approach to the deficiency as well as to the excess of thyroid hormones in CHF patients have been reviewed [12]. Moreover, the role of amiodarone therapy in causing thyroid disorders as well as the possible difficulties in therapeutic management of these forms have been depicted [12].

Also diabetes and chronic heart failure are conditions strictly related to each other. Dei Cas and coll. [13] have described the pathophysiological mechanisms by which, in diabetic patients, a defect in ventricular contractile function can be observed independently of coronary artery disease and hypertension. This condition, defined as diabetic cardiomyopathy, is largely determined by hyperglycaemia and insulin resistance which act synergically and potentiate each other. Although the pathophysiologic effects of these conditions in CHF patients have been established, there are controversies about the best therapeutical approach to diabetes in patients with CHF as stated by the review.

Diabetes plays, therefore, a relevant role in the onset and progression of HF, whereas the contribution of obesity is more complex. Despite its unfavourable effect on the occurrence of coronary heart disease, essential hypertension, heart failure and atrial fibrillation, several studies have shown the so called "obesity paradox" [14]. In patients already affected by cardiovascular disease, including HF, those with overweight and obesity showed a better prognosis when compared with lean patients with the same cardiovascular disease.

However, independently of body fat, a better CHF prognosis is related to the presence of a higher lean body mass. This topic has been reviewed by Zamboni and co-workers [15] who focused on the two conditions characterised by a reduced lean mass, i.e. sarcopenia and cardiac cachexia. In particular, the last one represents a harmful condition, which is caused by the imbalance between catabolic and anabolic status. Immune activation and inflammatory response have been recognised as the principal causes of this imbalance [15], but other factors such as abnormalities in GH/IGF-1 axis [17], the reduction of testosterone levels [18] and secondary hyperparathyroidism [19] have been identified as responsible for an increase in the catabolic forces. The therapeutic use of both GH and testosterone has been proposed even though the beneficial effects have not been yet definitively demonstrated [17, 18].

In the review of Poudyal and Brown and in that of Pretorius, two relevant nutritional aspects concerning CHF have been discussed [20, 21]. The first highlighted the possible role in CHF patients of n-3 polyunsaturated fatty acids (PUFA) intake. PUFA have been suggested to exert cardioprotective effects and their administration has been proposed as a useful treatment for CHF patients [20]. However, the studies evaluating the benefit of PUFA supplementation in improving heart failure prognosis have been characterised by non univocal results. Another emerging nutritional aspect related to CHF is that of changes in dietary patterns in developing countries. In particular, lifestyle changes related to urbanisation in South Africa have been described as well as their effects on the prevalence of cardiovascular risk factors and incidence of CHF [21].

Finally, in the last review, Giagulli and coll. [22] have described both the pathophysiological mechanisms and the therapeutical approach to a not infrequent condition observed in CHF male patients: the erectile dysfunction (ED).

In conclusion, endocrinological, metabolic, immunological and nutritional disorders can deeply influence pathophysiology and natural history of CHF. This issue will focus on these disorders, highlighting the possible therapeutical approach as well as the answers that should be addressed by the future studies.

REFERENCES

[1] Mosterd, A. and Hoes, A.W. Clinical epidemiology of heart failure. *Heart*, **93**, 1137-1146.

[2] McMurray, J.J.; Petrie, M.C.; Murdoch, D.R. and Davie, A.P. (1998) Clinical epidemiology of heart failure: public and private health burden. *Eur. Heart J.* **19**, P9-16.

[3] Fang, J.; Mensah, G.A.; Croft, J.B. and Keenan, N.L. (2008) Heart failureerelated hospitalization in the U.S., 1979 to 2004. *J. Am. Coll. Cardiol.*, **52**, 428-434.

[4] Butler, J. and Kalogeropoulos, A. (2008) Worsening heart failure hospitalization epidemic we do not know how to prevent and we do not know how to treat! *J. Am. Coll. Cardiol.*, **52**, 435-437.

[5] Gheorghiade, M.; Zannad, F.; Sopko, G.; Klein, L.; Pina, I.L.; Konstam, M.A.; Konstam, M.A.; Massie, B.M.; Roland, E.; Targum, S.; (2005) Acute heart failure syndromes: current state and framework for future research. *Circulation*, **112**, 3958-3968.

[6] Mann, D.L. (1999) Mechanisms and Models in Heart Failure. A Combinatorial Approach. *Circulation*, **100**, 999-1008.

[7] McMurray, J.J.; Adamopoulos, S.; Anker, S.D.; Auricchio, A.; Böhm, M.; Dickstein, K.; Falk, V.; Filippatos, G.; Fonseca, C.; Gomez-Sanchez, M.A.; Jaarsma, T.; Køber, L.; Lip, G.Y.; Maggioni, A.P.; Parkhomenko, A.; Pieske, B.M.; Popescu, B.A.; Rønnevik, P.K.; Rutten, F.H.; Schwitter, J.; Seferovic, P.; Stepinska, J.; Trindade, P.T.; Voors, A.A.; Zannad, F.; Zeiher, A.; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax J.J.; Baumgartner, H.; Ceconi, C.; Dean, V.; Deaton, C.; Fagard, R.; Funck-Brentano, C.; Hasdai, D.; Hoes, A.; Kirchhof, P.; Knuuti, J.; Kolh, P.; McDonagh, T.; Moulin, C.; Popescu, B.A.; Reiner, Z.; Sechtem, U.; Sirnes, P.A.; Tendera, M.; Torbicki, A.; Vahanian, A.; Windecker, S.; McDonagh, T.; Sechtem, U.; Bonet, L.A.; Avraamides, P.; Ben Lamin, H.A.; Brignole, M.; Coca, A.; Cowburn, P.; Dargie, H.; Elliott, P.; Flachskampf, F.A.; Guida, G.F.; Hardman, S.; Iung, B.; Merkely, B.; Mueller, C.; Nanas, J.N.; Nielsen, O.W.; Orn, S.; Parissis, J.T.; Ponikowski, P.; ESC Committee for Practice Guidelines. (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur. J. Heart Fail.*, **14**, 803-869.

[8] Levy, D.; Kenchaiah, S.; Larson, M.G.; Benjamin, E.J.; Kupka, M.J.; Ho, K.K.; Murabito, J.M. and Vasan, R.S. (2002) Long-term trends in the incidence of and survival with heart failure. *N. Engl. J. Med.*, **347**, 1397-1402.

[9] Metra, M.; Zacà, V.; Parati, G.; Agostoni, P.; Bonadies, M.; Ciccone, M.; Cas, A.D.; Iacoviello, M.; Lagioia, R.; Lombardi, C.; Maio, R.; Magrì, D.; Musca, G.; Padeletti, M.; Perticone, F.; Pezzali, N.; Piepoli, M.; Sciacqua, A.; Zanolla, L.; Nodari, S.; Filardi, P.P.; Dei Cas, L. and Heart Failure Study Group of the Italian Society of Cardiology. (2011) Cardiovascular and noncardiovascular comorbidities in patients with chronic heart failure. *J. Cardiovasc. Med.* (Hagerstown), **12**, 76-84.

[10] Gencer, B.; Collet, T.H.; Virgini, V.; Auer, R. and Rodondi, N. (2013) Subclinical thyroid dysfunction and cardiovascular outcomes among prospective cohort studies. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 4-12.

[11] Pasqualetti, G.; Togninis.; Polini.; Caraccio. and Monzani, F. (2013) Subclinical Hypothyroidism and Heart Failure Risk in Older People. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 13-21.

[12] Triggiani, V. and Iacoviello, M. (2013) Thyroid disorders in Chronic Heart Failure: from prognostic role to therapeutic management. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 22-37.

[13] Dei Cas, A.; Spigoni, V.; Ridolfi, V. and Metra, M. (2013) Diabetes and chronic heart failure: from diabetic cardiomyopathy to therapeutic approach. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 38-50.

[14] De Pergola, G.; Giagulli, V.A.; Nardecchia, A.; Castiglioni Minischetti, M. and Silvestris, F. (2013) Obesity and Heart Failure. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 51-57.

[15] Zamboni, M.; Rossi, A.; Corzato, F.; Bambace, C.; Mazzali, G. and Fantin, F. (2013) Sarcopenia, Cachexia and Congestive Heart Failure in the Elderly. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 58-67.

[16] Fiore, G. (2013) Neuroimmune-mediated pathways in the course of chronic heart failure. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 68-75.

[17] Arcopinto, M.; Bobbio,E.; Bossone, E.; Perrone-Filardi, P.; Napoli, R.; Saccà, L. and Cittadini, A. (2013) The GH/IGF-1 axis in chronic heart failure. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 76-91.

[18] Giagulli, V.A.; Guastamacchia, E.; De Pergola, G.; Iacoviello, M. and Triggiani, V. (2013) Testosterone deficiency in male: a risk factor for heart failure. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 92-99.

[19] Altay, H. and Colkesen, Y. (2013) Parathyroid hormone and heart failure: Novel biomarker strategy. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 100-104.

[20] Poudyal, H. and Brown, L. (2013) The role of n-3 polyunsaturated fatty acids in human heart failure. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 105-117.

[21] Pretorius, S. (2013) The impact of dietary habits and nutritional deficiencies in urban African patients living with heart failure in Soweto, Soweto Africa – A Review. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 118-124.

[22] Giagulli, V.A.; Moghetti, P.; Kaufman, J.M.; Iacoviello, M. and Triggiani, V. (2013) Managing erectile dysfunction in heart failure. *Endocr. Metab. Immun. Disord. Drug Targets*, **13**, 125-134.

Massimo Iacoviello
(*Guest Editor*)
Department of Emergency and Organ Transplantation
University Hospital of Bari
Address: piazza Giulio Cesare 11, 70121
Bari, Italy
Tel/Fax: 0039 080 5478796
E-mail: massimo.iacoviello@cardio.uniba.it

Vincenzo Triggiani
(*Guest Editor*)
Endocrinology and Metabolic Diseases
Interdisciplinary Department of Medicine
University of Bari "Aldo Moro"
School of Medicine, Policlinico
Bari, Italy
Tel/Fax: 0039 080 5478814
E-mail: v.triggiani@endo.uniba.it