hearts

MDPI

Editorial

Preface to Hearts Special Issue "Nutrient Deficiency and Drug Induced Cardiac Injury and Dysfunction"

I. Tong Mak * and Jay H. Kramer *

Department of Biochemistry and Molecular Medicine, The George Washington University Medical Center, Washington DC, WA 20037, USA

* Correspondence: itmak@gwu.edu (I.T.M.); phyjhk@gwu.edu (J.H.K.)

Received: 30 October 2020; Accepted: 1 November 2020; Published: 3 November 2020

check for updates

Keywords: cardiac injury/contractile dysfunction; micronutrient deficiency; macromineral deficiency or imbalance; impact by cardiovascular and/or anti-cancer drugs; systemic inflammation; oxidative/nitrosative stress; antioxidant defenses; supplement and/or pathway interventions

Cardiac injury manifested as either systolic or diastolic dysfunction is considered an important preceding stage that leads to or is associated with eventual heart failure (HF). Due to shifts in global age distribution, as well as general population growth, HF is the most rapidly growing public health issue, with an estimated prevalence of approximately 38 million individuals globally, and it is associated with considerably high mortality, morbidity, and hospitalization rates [1]. According to the US Center for Disease Control and The American Heart Association, there were approximately 6.2 million adults suffering from heart failure in the United States from 2013 to 2016, and heart failure was listed on nearly 380,000 death certificates in 2018 [2]. Left ventricular systolic heart failure means that the heart is not contracting well during heartbeats, whereas left ventricular diastolic failure indicates the heart is not able to relax normally between beats. Both types of left-sided heart failure may lead to right-sided failure. There have been an increasing number of studies recognizing that the deficiency and/or imbalance of certain essential micronutrients, vitamins, and macrominerals may be involved in the pathogenesis of cardiomyopathy/cardiac injury/contractile dysfunction. Essential micronutrients may include, but are not limited to, water soluble B vitamins such as thiamine and vitamin C, fat-soluble vitamins (A, E, D, and K), carnitine, Coenzyme Q10, and taurine (a conditionally essential amino acid), as well as microminerals such as selenium, zinc, copper, cobalt, and chromium. Many of the listed micronutrients are co-factors of metabolic reactions, and their deficiency would disturb myocardial substrate metabolism and energy utilization. Notable macrominerals include magnesium, calcium, potassium, and iron. Iron is essential for the development of normal red blood cells and healthy immune function, whereas iron deficiency is one of the most widespread nutritional deficiencies in the world and is associated with heart failure [3]. However, iron can also be a pro-oxidant mineral [4], especially during transfusion therapies that induce tissue iron-overload. Vascular endothelium may be impaired, and the risk for heart attack and stroke may be increased.

In addition to poor dietary intake, certain nutrient deficiencies, especially of magnesium leading to hypomagnesemia, may be caused by excessive alcohol intake, the antiretroviral drug treatments [5] of HIV/AIDS patients, or anticancer therapeutics such as epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) [6] and cisplatin. Anticancer drugs may cause kidney injury and dysfunction, leading to the malabsorption of Mg and renal Mg wasting. Mg plays a key role in modulating neuronal excitation, endothelial function, and cardiac contraction by regulating several ion channels, including those of K and Ca; Mg is also a key co-factor for mitochondrial ATP production. As such, Mg deficiency may contribute to the pathogenesis of cardiac arrhythmias (QTc or QT interval prolongation, and Torsade de pointes tachycardia) and dysfunction [7].

Though nutrient deficiency independently predicts adverse clinical outcomes in patients with HF, it remains unclear if any chronic nutrient deficiency-induced cardiac injury/dysfunction is readily reversible. Thus far, no consistent nutritional supplementation has been recommended as a rescue strategy against cardiac injury/dysfunction. It is noted that many micronutrients have antioxidant properties (e.g., vitamins E and C, selenium, and Coenzyme Q10). Mg is a natural calcium blocker, and its elevated intake above normal levels may also produce antioxidative and anti-inflammatory effects in vivo [8].

The purpose of this Special Issue is to provide a platform for recent experimental or clinical research that may shed new light on nutrient/mineral deficiencies or adverse drug effects that may directly or indirectly impair cardiac function. Common mechanistic parameters may involve systemic oxidative/nitrosative stress, neurogenic inflammation, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, oxidative/antioxidant gene up-regulation, and/or compromised antioxidant defenses, all may serve as prognostic mediators/events linked to induced cardiac injury/dysfunction. The ultimate goal is to search for a better understanding of the complex interactions and molecular mechanisms contributing to cardiac injury/dysfunction and potential effective mitigating interventions.

It would be an understatement to suggest that the current COVID-19 pandemic has not had a negative impact on potential contributors to this issue. As of this writing, we anticipate publishing at least six manuscripts within this issue in the areas of magnesium deficiency-induced neurogenic inflammation and cardiac dysfunction, iron overload pathology and cardiac dysfunction, taurine deficiency-mediated cardiomyopathy, vitamin A signaling in cardiovascular diseases, clinical studies related to chemotherapy-induced pediatric cardiomyopathy, and the impact of activating oxytocin-expressing neurons on experimental pressure overload heart failure. Needless to say, the Special Issue guest editors are truly grateful for the contributions from these authors, and we continue to encourage other scientists with shared interests in this broad but important field of study to contribute to this Special Issue.

Funding: This work was supported by multiple grants throughout the years, including USPHS NIH grants RO1-HL-62282, 1R21NR012649, 1R21HL108311, R21-HL-125038, RO1-HL66226, and by a grant from George Washington University McCormick Genomic & Proteomic Center.

Conflicts of Interest: The authors declare no conflict of interest. The sponsors had no role in conceiving the writing of this editorial, and in the decision to publish.

References

1. Ziaeian, B.; Fonarow, B.Z.G.C. Epidemiology and aetiology of heart failure. *Nat. Rev. Cardiol.* **2016**, *13*, 368–378. [CrossRef] [PubMed]
2. Virani, S.S.; Alonso, A.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Delling, F.N.; et al. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association. *Circulation* **2020**, *141*, e139–e596. [CrossRef] [PubMed]
3. Von Haehling, S.; Ebner, N.; Evertz, R.; Ponikowski, P.; Anker, S.D. Iron Deficiency in Heart Failure. *JACC Heart Fail.* **2019**, *7*, 36–46. [CrossRef] [PubMed]
4. Kramer, J.H.; Spurney, C.F.; Iantorno, M.; Tziros, C.; Chmielinska, J.J.; Mak, I.T.; Weglicki, W.B. d-Propranolol protects against oxidative stress and progressive cardiac dysfunction in iron overloaded rats. *Can. J. Physiol. Pharmacol.* **2012**, *90*, 1257–1268. [CrossRef] [PubMed]
5. Mak, I.T.; Chmielinska, J.J.; Spurney, C.F.; Weglicki, W.B.; Kramer, J.H. Combination ART-Induced Oxidative/Nitrosative Stress, Neurogenic Inflammation and Cardiac Dysfunction in HIV-1 Transgenic (Tg) Rats: Protection by Mg. *Int. J. Mol. Sci.* **2018**, *19*, 2409. [CrossRef] [PubMed]
6. Mak, I.T.; Kramer, J.H.; Chmielinska, J.J.; Spurney, C.F.; Weglicki, W.B. EGFR-TKI, Erlotinib, Causes Hypomagnesemia, Oxidative Stress, and Cardiac Dysfunction. *J. Cardiovasc. Pharmacol.* **2015**, *65*, 54–61. [CrossRef] [PubMed]

7. Kramer, J.H.; Spurney, C.; Iantorno, M.; Tziros, C.; Mak, I.-T.; Tejero-Taldo, M.I.; Chmielinska, J.J.; Komarov, A.M.; Weglicki, W.B. Neurogenic inflammation and cardiac dysfunction due to hypomagnesemia. *Am. J. Med. Sci.* **2009**, *338*, 22–27. [CrossRef] [PubMed]
8. Mak, I.T.; Kramer, J.H.; Chen, X.; Chmielinska, J.J.; Spurney, C.F.; Weglicki, W.B. Mg supplementation attenuates ritonavir-induced hyperlipidemia, oxidative stress, and cardiac dysfunction in rats. *Am. J. Physiol. Integr. Comp. Physiol.* **2013**, *305*, R1102–R1111. [CrossRef] [PubMed]