



Editorial

A Molecular (Not Very Becoming) Picture of Stressed Arteries and Heart, with Some Therapeutic Hope

Maria G. Barderas ^{1,*} and Fernando de la Cuesta ^{2,3,*}

¹ Department of Vascular Physiopathology, Hospital Nacional de Paraplégicos (HNP), SESCAM, 45071 Toledo, Spain

² Department of Pharmacology and Therapeutics, School of Medicine, Universidad Autónoma de Madrid, 28029 Madrid, Spain

³ Instituto de Investigación Sanitaria del Hospital Universitario La Paz (IdiPAZ), 28029 Madrid, Spain

* Correspondence: megonzalez@sescam.jccm.es or marucitos@hotmail.com (M.G.B.); fernando.delacuesta@uam.es (F.d.l.C.)

This Special Issue has focused on molecular mechanisms (vascular calcification, endothelial dysfunction, cardiac remodelling, inflammation, oxidative stress, etc.) and pathophysiology of cardiovascular diseases (CVD), with the goal in mind of contributing to a better understanding of their development, providing insights to guide the design of future, more personalized, medicine. As early as in 2001, CVD were recognized as the largest single cause of mortality on the planet [1]. Today, despite the huge growth of pathophysiology knowledge and advances in molecular mechanisms, prognosis, diagnosis, and treatment; CVD remains at the world's top rank of all human death causes. In fact, the impact of CVD is growing and has reached pandemic proportions, mainly due to the great incidence of its comorbidities—obesity, diabetes and sedentary lifestyle, among others—in the global population [2].

Contributions to this Special Issue have been numerous, with eight original articles and four reviews being accepted for publication. These cover a wide molecular range of both vascular and cardiac pathophysiology very nicely, with an interesting focus on the implications of diabetes. There are three studies which base their major findings on comprehensive proteomic analyses, highlighting the huge technical capabilities of this approach [3–5]. Besides, two of the original articles offer interesting data supporting the therapeutical benefits of two hypoglycaemic drugs on left ventricular remodelling and cardiac dysfunction: the GLP-1 agonist DMB [5] and the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin [6], shedding light on the implication of parkin-mediated mitophagy in their mechanism of action.

Endothelial relevance in the pathophysiology of CVD has been reinforced depicting an innovative link with calcification since one study has shown that poor endothelial function, led by nitric oxide (NO) impairment, contributes with classic pro-calcifying stimuli to trigger arterial calcification [3]. Furthermore, a systematic review on the impact of uremic toxins present with Chronic Kidney Disease on endothelial function, pinpoints an increase in inflammation, oxidative stress, leukocyte migration and adhesion, cell death and a thrombotic phenotype upon uremic conditions [7]. Additionally, an original article included in this issue has interestingly shown that unilateral acute renal ischemia-reperfusion (I/R) injury causes a cardiomyocyte Ca²⁺ cycle dysfunction, thereby impairing cardiac function [8]. These two contributions have brought the cardio-renal continuum into the hereby sketched molecular picture. Besides, a review publication has outlined the major mechanisms involved in Abdominal Aortic Aneurysm (AAA), a difficult-to-diagnose latent CVD, including inflammation, smooth muscle cells' apoptosis, and the degradation of the extracellular matrix [9].

As the major outcome of vascular stenosis, due to underlying atherosclerosis within the coronary arteries, myocardial infarction (MI) is the major contributor to CVD-associated



Citation: Barderas, M.G.; de la Cuesta, F. A Molecular (Not Very Becoming) Picture of Stressed Arteries and Heart, with Some Therapeutic Hope. *Int. J. Mol. Sci.* **2023**, *24*, 3870. <https://doi.org/10.3390/ijms24043870>

Received: 8 February 2023
Accepted: 13 February 2023
Published: 15 February 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

mortality and morbidity. Interestingly, the 1-year follow up of serum biomarkers after MI has shown an increase in the glial damage biomarker: glial fibrillary acidic protein (GFAP), but no changes in the neuronal damage biomarker: neurofilament light chain (NfL) [10]. Given that cognitive impairment after MI has been already described, this study suggests a pivotal contribution of glial cell damage in existing post-MI alterations of the central nervous system. A comprehensive vision of the clinical utility of classic and novel biomarkers of MI has been additionally included in the current Special Issue [11]. A protective role in the stress-induced cardiac remodelling of the dedicator of cytokinesis 10 (Dock10), a guanine exchange factors (GEF), has been also demonstrated [12], and paves the way for novel potential therapeutic interventions.

The contribution of diabetes mellitus (DM) to the pathophysiology of aortic valve stenosis (AS) has been thoroughly reviewed and evidences that diabetes has a detrimental effect on the quality of life and survival of AS patients [13]. Likewise, type 1 diabetes mellitus is hereby reported to impair rat cardiomyocyte contractility in the left and right ventricular free walls [14]. These two manuscripts have highlighted a substantial contribution of DM to the development and progression of heart dysfunction and show a potentially higher risk of heart failure in diabetic patients, led by mechanisms directly affecting the aortic valve and heart ventricles.

Altogether, this Special Issue adds substantial aspects to the molecular picture of arterial and cardiac stress-induced pathological processes, reinforcing key mechanisms, and outlining some new ones. Although the resulting picture is, certainly, far from becoming, some therapeutical hope arises from the novel targets described and the pharmacological interventions investigated.

Author Contributions: M.G.B. and F.d.I.C. jointly reviewed all the papers included in the Special Issue, extracted and discussed the main conclusions of all contributions, wrote the manuscript and proof-read its final version. All authors have read and agreed to the published version of the manuscript.

Funding: F.d.I.C. received funding from: Talent Advanced Researchers' Grant from Comunidad Autónoma de Madrid (2019-T1/IND-13794) and Knowledge Generation ' Grant from Spanish Ministry of Science and Innovation (PID2021-126274OB-I00).M.G.B. received funding from: Instituto de Salud Carlos III through the projects PI18/00995, PI21/00384, and co-funded by the European Union, Sociedad Española de Cardiología, 2020, Grant PRB3 (IPT17/0019—ISCI-SGEFI/ERDF), Junta de Comunidades de Castilla-La Mancha (JCCM, co-funded by the European Regional Development Fund, SBPLY/19/180501/000226, SBPLY/21/180501/000078 (new SBPLY/21/180225/000035)). These results are aligned with the Spanish initiative on the Human Proteome Project (SpHPP).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Pearson, T.A.; Blair, S.N.; Daniels, S.R.; Eckel, R.H.; Fair, J.M.; Fortmann, S.P.; Franklin, B.A.; Goldstein, L.B.; Greenland, P.; Grundy, S.M.; et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* **2002**, *106*, 388–391.
2. Benjamin, E.J.; Virani, S.S.; Callaway, C.W.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Chiuve, S.E.; Cushman, M.; Delling, F.N.; Deo, R.; et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* **2018**, *137*, e67–e492. [[CrossRef](#)]
3. Van den Bergh, G.; De Moudt, S.; Van den Branden, A.; Neven, E.; Leysen, H.; Maudsley, S.; De Meyer, G.R.Y.; D'Haese, P.; Verhulst, A. Endothelial Contribution to Warfarin-Induced Arterial Media Calcification in Mice. *Int. J. Mol. Sci.* **2021**, *22*, 11615. [[CrossRef](#)]
4. Güran, A.; Ji, Y.; Fang, P.; Pan, K.T.; Urlaub, H.; Avkiran, M.; Lenz, C. Quantitative Analysis of the Cardiac Phosphoproteome in Response to Acute β -Adrenergic Receptor Stimulation In Vivo. *Int. J. Mol. Sci.* **2021**, *22*, 12584. [[CrossRef](#)] [[PubMed](#)]
5. de Freitas Germano, J.; Sharma, A.; Stastna, M.; Huang, C.; Aniaq, M.; Aceves, A.; Van Eyk, J.E.; Mentzer, R.M., Jr.; Piplani, H.; Andres, A.M.; et al. Proteomics of Mouse Heart Ventricles Reveals Mitochondria and Metabolism as Major Targets of a Post-Infarction Short-Acting GLP1Ra-Therapy. *Int. J. Mol. Sci.* **2021**, *22*, 8711. [[CrossRef](#)]

6. Song, Y.; Huang, C.; Sin, J.; Germano, J.F.; Taylor, D.J.R.; Thakur, R.; Gottlieb, R.A.; Mentzer, R.M., Jr.; Andres, A.M. Attenuation of Adverse Postinfarction Left Ventricular Remodeling with Empagliflozin Enhances Mitochondria-Linked Cellular Energetics and Mitochondrial Biogenesis. *Int. J. Mol. Sci.* **2021**, *23*, 437. [[CrossRef](#)]
7. Harlacher, E.; Wollenhaupt, J.; Baaten, C.C.F.M.J.; Noels, H. Impact of Uremic Toxins on Endothelial Dysfunction in Chronic Kidney Disease: A Systematic Review. *Int. J. Mol. Sci.* **2022**, *23*, 531. [[CrossRef](#)]
8. Junho, C.V.C.; González-Lafuente, L.; Navarro-García, J.A.; Rodríguez-Sánchez, E.; Carneiro-Ramos, M.S.; Ruiz-Hurtado, G. Unilateral Acute Renal Ischemia-Reperfusion Injury Induces Cardiac Dysfunction through Intracellular Calcium Mishandling. *Int. J. Mol. Sci.* **2022**, *23*, 2266. [[CrossRef](#)]
9. Stepien, K.L.; Bajdak-Rusinek, K.; Fus-Kujawa, A.; Kuczmik, W.; Gawron, K. Role of Extracellular Matrix and Inflammation in Abdominal Aortic Aneurysm. *Int. J. Mol. Sci.* **2022**, *23*, 11078. [[CrossRef](#)]
10. Traub, J.; Grondey, K.; Gassenmaier, T.; Schmitt, D.; Fette, G.; Frantz, S.; Boivin-Jahns, V.; Jahns, R.; Störk, S.; Stoll, G.; et al. Sustained Increase in Serum Glial Fibrillary Acidic Protein after First ST-Elevation Myocardial Infarction. *Int. J. Mol. Sci.* **2022**, *23*, 10304. [[CrossRef](#)] [[PubMed](#)]
11. Stătescu, C.; Anghel, L.; Tudurachi, B.S.; Leonte, A.; Benchea, L.C.; Sascău, R.A. From Classic to Modern Prognostic Biomarkers in Patients with Acute Myocardial Infarction. *Int. J. Mol. Sci.* **2022**, *23*, 9168. [[CrossRef](#)] [[PubMed](#)]
12. Segal, L.; Etzion, S.; Elyagon, S.; Shahar, M.; Klapper-Goldstein, H.; Levitas, A.; Kapiloff, M.S.; Parvari, R.; Etzion, Y. Dock10 Regulates Cardiac Function under Neurohormonal Stress. *Int. J. Mol. Sci.* **2022**, *23*, 9616. [[CrossRef](#)]
13. Mourino-Alvarez, L.; Corbacho-Alonso, N.; Sastre-Oliva, T.; Corros-Vicente, C.; Solis, J.; Tejerina, T.; Padial, L.R.; Barderas, M.G. Diabetes Mellitus and Its Implications in Aortic Stenosis Patients. *Int. J. Mol. Sci.* **2021**, *22*, 6212. [[CrossRef](#)]
14. Khokhlova, A.; Myachina, T.; Volzhaninov, D.; Butova, X.; Kochurova, A.; Berg, V.; Gette, I.; Moroz, G.; Klinova, S.; Minigalieva, I.; et al. Type 1 Diabetes Impairs Cardiomyocyte Contractility in the Left and Right Ventricular Free Walls but Preserves It in the Interventricular Septum. *Int. J. Mol. Sci.* **2022**, *23*, 1719. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.