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COMMENTARY
Why the study of the effects of biological sex is important

Georgios Kararigas[1,2], Ute Seeland[1,2], Maria Luisa Barcena de Arellano[1,2], Elke Dworatzek[1,2] and Vera Regitz-Zagrosek[1,2]

[1]*Institute of Gender in Medicine (GiM), Center for Cardiovascular Research (CCR), Charité University Hospital, Berlin, Germany*
[2]*German Centre for Cardiovascular Research (DZHK), partner site Berlin, Germany*

Abstract
Biological sex significantly affects the presentation, outcome of treatment and progression of disease. However, the role of sex has yet underestimated consequences for physiology and pathology. We put forward that a better understanding of the effects of sex in pathophysiology and the underlying mechanisms is necessary. This may facilitate the identification of targets that respond to specific therapies, thereby contributing towards a more appropriate and individualised medical care for both men and women.

Key words
- biological sex
- pathophysiology
- preclinical and clinical research
- treatment

There is no doubt that sex affects the presentation, outcome of treatment and progression of disease. In the case of cardiovascular diseases, for instance, men suffer at younger ages than women from coronary artery disease and more often develop systolic heart failure or aortic aneurysms. Women are more frequently affected by heart failure with preserved ejection fraction, long QT-syndromes and Tako-tsubo cardiomyopathy. Women also exhibit a more favourable remodelling under pressure overload and a better survival with heart failure. These differences between men and women are mediated by sex-specific pathophysiological mechanisms, including the development of hypertrophy, fibrosis, inflammation and vascular remodelling. Consequently, sex-specific regulation of these mechanisms may lead to major differences between men and women following surgical interventions, such as coronary artery bypass graft and aortic valve replacement. However, the role of sex has yet unrecognised and underestimated consequences for physiology and pathology. Therefore, we put forward that further research is necessary. Impact on the medical field and direct potential for exploitation of such innovative research activities are guaranteed in drug development and by the integration of findings into guidelines on optimal management for disease prevention and treatment in both men and women.

Worldwide, many organisations are recognising the importance of studying sex differences and that the inclusion of sex into study designs increases scientific quality. In fact, considering sex may be critical to the interpretation, validation and extrapolation of research findings [1]. The Institute of Medicine (IOM) in the USA has stated that the understanding of biological differences related to sex is necessary for the optimal treatment of humans. Leading scientific journals have raised concerns about the under-representation of females in animal studies and clinical trials and advocate for the consideration of sex-specific aspects by researchers, agencies and journals [2]. The National Institutes of Health (NIH) of the USA, through its Office of Research on Women's Health (ORWH) has been sponsoring research to detect sex differences in neurological and rheumatic diseases, in cancer and cardiovascular disease. Importantly, the NIH adopted in 2014 a policy requiring the consideration of sex as a biological variable in preclinical research [3]. The Food and Drug Administration (FDA) in the USA also requires sex-specific data on drug metabolism, pharmacokinetics and pharmacodynamics for all new drugs. Integration of sex in research and innovation is an objective of Horizon 2020, which is the biggest European Union (EU) Research and Innovation programme ever. This concerns all parts of Horizon 2020 and many steps of the Research and Innovation cycle, such as disclosing the sex of animals in experiments, thereby taking into account sex in the research process, when developing concepts and theories, formulating research questions, collecting and analysing data.

Interestingly, it is rather common practice to exclude female animals from experimental designs on the basis of putative complex physiology leading to high variability. However, it was recently shown that variability is not

Address for correspondence: Georgios Kararigas, Institute of Gender in Medicine (GiM), Center for Cardiovascular Research (CCR), Charité University Hospital, Hessische Str. 3-4, 10115 Berlin, Germany. E-mail: george.kararigas@charite.de.

higher in females than males, even when females have a proper hormonal cycle [4]. In contrast, differences in temperature by housing may increase variability [5], a factor that may not be always accounted for. There is also currently debate whether animal models represent human sex differences accurately. Indeed, as with every other animal model and experimental setup, models for the study of sex differences have their limitations. However, several animal models of myocardial infarction, vascular disease, myocardial hypertrophy, or heart failure, for example, exhibit major differences between males and females that reflect sex differences in humans. These models have so far offered valuable insight into sex differences arising at the molecular and cellular level from the control of gene transcription, intracellular signalling, organelle function, and crosstalk between heart, skeletal muscle, adipose tissue and the immune system. Accordingly, we put forward that animal models have an important role in the investigation of sex differences that may lead to translational approaches, considering that results should be interpreted with caution and the model-inherent limitations are not neglected.

The study of sex is expected to have important socioeconomic implications. Therapies are designed using mainly male subjects. However, there are a number of differences in the way that men and women react to the same therapies. As a consequence, therapies applied in one of the two sexes might not have the expected effects. This leads to non-effectively-treated patients clogging up health systems and their budgets. Therefore, a better understanding of sex-specific (patho)physiological mechanisms represents an invaluable and strong foundation for the development and establishment of sex-specific therapeutic approaches. The impact on economies of such strategies, together with a detailed description of individual biological variation in connection with environmental factors that influence the development of disease, might be of great dimensions and at the same time this could lead to a more appropriate treatment of the diseased alleviating pain and suffering.

Sex differences have consistently been confirmed throughout a large spectrum of experimental and clinical studies, in different species and pathophysiological conditions. This strongly suggests that sex differences represent important biological phenomena that need further investigation. The examples stated above support the notion that a more careful consideration of sex differences will improve our understanding of frequent diseases and will subsequently lead to improved therapies. In particular, a better understanding of sex differences in cardiovascular pathophysiology will facilitate the identification of targets that respond to specific therapies, thereby contributing towards a more individualised medical care. At present, the development of new cardiovascular drugs has reached a plateau after years of continuous progress [6]. We believe that an improved understanding of sex-specific disease mechanisms and therapeutic targets will ameliorate this situation towards more efficient treatments for both men and women.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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