REPLY: The Role of Inflammation and Gender Differences in the Pathogenesis of Cardiac Arrhythmias

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https://doi.org/10.1016/j.jacbts.2023.03.018

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We appreciate the comments from Drs Dendramis and Brugada regarding our recent review paper[1] on the role of inflammatory cytokines in the pathogenesis of cardiac arrhythmias.

It is well recognized that sex-related factors significantly impact Brugada syndrome (BrS), whose clinical disease expression is 8 to 10 times higher in men than in women.[2] Equally well known is that fever is an important precipitating factor for ventricular arrhythmias (VAs) in BrS, more commonly in males (only ~20% of cases occur in females and almost exclusively in nonreproductive periods).[3] Although it is generally accepted that fever acts by reducing the sodium current I_{Na} via temperature-dependent biophysical changes of the $Na_v1.5$ channel,[1,4] the impact of estrogens on this current seems to be minimal.[2] Therefore, it can be speculated that additional inflammation-mediated mechanisms are involved, possibly helping to explain sex differences. Indeed, cytokines are the fundamental mediators of fever, and practically all cases of fever-induced BrS and related VAs occurred in the setting of active inflammatory diseases. Moreover, cases of BrS unmasked by inflammatory processes even in the absence of fever are ever more reported,[5] and systemic and/or myocardial inflammation is newly recognized as an important arrhythmogenic substrate in BrS.[6,7] In this scenario, it is likely that the increasingly recognized electrophysiological effects of inflammatory cytokines may significantly contribute to the clinical expression of BrS, at least in part via their rapid down-regulating effects on cardiac connexin-43 expression.[1,4] Indeed, it has been demonstrated that in the BrS right ventricular outflow-tract epicardium connexin-43 expression is reduced and correlated with life-threatening VAs.[8] Nevertheless, cardiomyocytes from adult females show ~50% higher connexin-43 levels than in males,[9] due to estradiol-mediated effects also reducing VA vulnerability,[10] possibly contributing to lower susceptibility for women.

Although the above data may provide an intriguing new insight into the pathophysiology of sex-related differences in BrS, and more in general in cardiac arrhythmias susceptibility, more research is needed before sex-specific recommendations can be made.

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This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR), Progetti di Rilevante Interesse Nazionale (PRIN), and Bando 2017, protocollo 2017XZMBYX (to Drs Lazzerini and Capecchi.); Bando Ricerca COVID-19 Toscana-2021, Progetto PRECARVID (to Drs Lazzerini and Capecchi); Biomedical Laboratory Research & Development Service of Veterans Affairs Office of Research and Development, Merit Review grant I01 BX002137 (to Dr Boutjdir); National Heart, Lung, and Blood Institute 1R01HL164415-01 (to Dr Boutjdir); and the U.S. Department of Defense award number W81XWH-21-1-0424 (to Dr Boutjdir). Dr Lazzerini received a grant from Roche Italia S.p.A. outside the submitted work, in 2018. Dr Abbate has served as a consultant for Cardiol, Implicit Biosciences, Kiniksa, Novartis, Novo-Nordisk, Olatec, R-Pharm, Sanofi, and Serpin pharma, unrelated to the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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