Sexual dimorphism of psychological stress-induced susceptibility to ischemic heart disease: is the king naked?

Vincenzo Lionetti[1,2] and Fabio A Recchia[1,3,4]

[1] Scuola Superiore Sant'Anna, Pisa, Italy
[2] UOSVD Anesthesia and Intensive Care Medicine, Fondazione Toscana Gabriele Monasterio, Pisa, Italy
[3] Institute of Clinical Physiology, National Research Council, Pisa, Italy
[4] Aging & Cardiovascular Discovery Center, Lewis Katz School of Medicine at Temple University, Philadelphia. USA

Co-Corresponding Authors:

Vincenzo Lionetti, MD, PhD: vincenzo.lionetti@santannapisa.it
Fabio A. Recchia, MD, PhD: fabio.recchia@ifc.cnr.it

Chronic psychological stress, a common trait of modern life worldwide, arises from prolonged exposure to perceived threats that exceed coping capacity and can cause anxiety and cardiovascular diseases (CVDs) (1). Sustained psychological stress is now widely recognized as a risk factor for ischemic heart disease in patients of both sexes with pre-existing coronary artery disease, but studies on its sex-biased effects on multiple cardiovascular regulatory systems, including the neuroendocrine and autonomic nervous systems, are still at an early stage (1). Women suffer more from anxiety-related disorders than males (1), and sex differences in cardiac susceptibility to regional myocardial ischemia-reperfusion injury (IRI) in stressed subjects, regardless of cardiovascular risk factors, remain an intriguing topic.

Cairns et al. explored such complex area of cardiovascular pathophysiology and, in this issue of the Journal (2), provided compelling evidence of sexual dimorphism in contractile recovery after regional myocardial reperfusion in rodents subjected to chronic restraint stress (CRS), a well-established model of non-social stress. Their study in adult male and female Wistar rats show that sex-dependent mediators of chronic psychological stress response shape the myocardial microenvironment and cardiac cell tolerance to IRI. These novel findings may help explain gender disparities in cardiovascular reactivity to mental stress. The first aspect that deserves attention is relative to findings in the control groups, not subjected to CRS: the elevated plus maze, a simple anxiety assay for rodents, revealed sex differences in age-matched control rats, despite similar circulating adrenocorticotropic hormone (ACTH) and corticosterone levels. Female rats exhibited a greater propensity for exploration, albeit with lower risk-taking tendency. They also spent significantly less time in the two closed arms of the maze, suggesting reduced anxiety-related behavior that aligns with previous findings (3). Moreover, the nociceptive sensitivity of control animals was lower in females than males. Beyond the genetic influence of sex chromosomes, sexual dimorphism can also be attributed to different gonadal hormones secretion. Although estrous cycle changes were not precisely tracked in seven-week-old gonad-intact animals, unstressed female rats may have been in estrus, as indicated by to their lesser anxiety and higher pain threshold (3). Baseline plasma estradiol levels in females, indeed, were similar to males, while estradiol-to-progesterone ratio was lower in females due to higher progesterone levels. Lower plasma brain-derived neurotrophic factor (BDNF) levels in females support this interpretation, as fluctuations of BDNF and estradiol are remarkably similar during the estrous cycle (3-4). Although myocardial BDNF levels remained undetermined, the results by Cairns et al. in the context of heart-brain communication are relevant, as circulating BDNF levels might reflect their concentration in brain tissue. Since circulating BDNF might be a biomarker of anxiety disorders (4) and CVDs (5) in women, studying the link between estradiol and BDNF could help us comprehending sex-biased mental stress-induced myocardial ischemia. Surprisingly, ex vivo Langendorff preparations of control hearts of either sex revealed no significant differences in cardiac function, except for a marked reduction in coronary blood flow in female hearts, which may depend on smaller epicardial coronary arteries relative to males. Such an effect would not be consistent with previous ex vivo observations showing similar resting coronary blood flow in age-matched males and females (6). Unfortunately, the mechanism behind sex differences in resting coronary

blood flow at similar heart rates and controlled levels of left ventricular end-diastolic pressure remains unclear in the study by Cairns et al. and deserves further investigation.

Particularly noteworthy are the authors' findings in rats subjected to CRS. Consistent with prior findings (3), female rats exhibited greater resilience to the anxiety-inducing and pain-sensitizing effects of restraint compared to males, whereas, different from a prior study in Wistar rats (7), males displayed increased exploratory behavior and nociception following restraint. The historical predominance of male animals in pre-clinical studies renders such contradicting findings more apparent and may be influenced by CRS protocol, circadian rhythm, and restraint placement. Consequently, the comprehension of regulatory mechanisms of sex-biased brain-to-heart communication under stress is essential. Despite a consistent increase in urinary corticosterone excretion during CRS (8), it is conceivable that the resilience of gonad-intact females may be related to mild adrenal insufficiency, resulting in low circulating corticosterone and elevated ACTH, increasing the risk of cardiovascular diseases. Female rats attempted to mitigate stress-induced corticosterone depletion by increasing progesterone production, a precursor to cortisol. Unlike progesterone, however, higher self-perceived stress reduced plasma estradiol levels, as found also in humans, an alteration that may prevent the activation of cardioprotective genes in myocardium. In fact, the overall pattern of hormonal alterations in stressed females was associated with a unique systemic inflammatory response compared to male and controls, characterized by elevated plasma levels of tumor necrosis factor-alpha (TNF-α) and tissue inhibitors of metalloproteinase type 1 (TIMP-1), despite a slight reduction in pro- and anti-inflammatory interleukins, some of which might induce stress-like effects (9). CRS is known to increase TNF-α levels (9), which indirectly promotes TIMP-1 expression and mimics classic ischemic preconditioning in the early reperfusion phase. A noteworthy finding by Cairns et al. was the exclusive occurrence of these changes in stressed female rats, hinting at the involvement of sex-specific epigenetic mechanisms. While a decrease in plasma interleukins might suggest a protective role for systemic TNF-α against the ischemia-like effects of CRS, elevated circulating levels of cardiac troponin T indicate that myocardial damage still occurred. Higher TNF-α levels may reduce BDNF expression, contributing to higher incidence of CVDs (5). However, the authors proposed that myocardial sensitivity to IRI might be independent of BDNF, as its plasma levels remained unchanged under stress. In fact, when isolated and perfused hearts were subjected to regional IRI, female hearts exhibited impaired post-ischemic functional recovery compared to male and control hearts. Therefore, chronic psychological stress may render female hearts more vulnerable to damage following a heart attack, despite BDNF-induced stress resilience (10). Although the tissue expression levels of the BDNF and its receptors remained undetermined in the study Cairns et al., several possible explanations can be proposed. One possibility is that the estradiol deficiency observed in female rats contributes to increased TNF-α levels, which can cause robust reactive oxygen species-induced mitochondrial dysfunction and larger myocardial injury during IRI. Additionally, the deregulation of the hypothalamic-pituitary-adrenal axis (HPA) may selectively impair cardiac ability to cope with stress, leading to reduced myocardial tolerance to injury. Conversely, the stressed male rats with testosterone depletion, which are generally less stress resilient due to decreased systemic levels of BNDF,

displayed lower cardiac vulnerability to IRI, possibly because of HPA and inflammatory profile more similar to control rats (Figure 1).

In conclusion, while BDNF has been widely hailed as one of the “kings” of in vivo cardioprotection (5, 10) by mediating adaptive neuronal-cardiac communication under stress (10) and regulating cardiac contraction and relaxation (10) through tropomyosin kinase receptor B, the findings by Cairns et al. suggest that the role of this mediator in sex-biased cardioprotection is more nuanced than previously thought. They also prompt the development of targeted interventions addressing the specific myocardial needs of stressed fertile women, regardless of their stress resilience.

Grants: This work was in part supported by the Ministry of University and Research, National Recovery and Resilience Plan, project MNESYS (grant PE0000006) – A multiscale Integrated Approach to the Study of the Nervous System in Health and Disease (grant DN. 155311.10.2022) to V.L and by the NIH grant R01 HL151345 to F.A.R.

Disclosures: The authors declare that the editorial was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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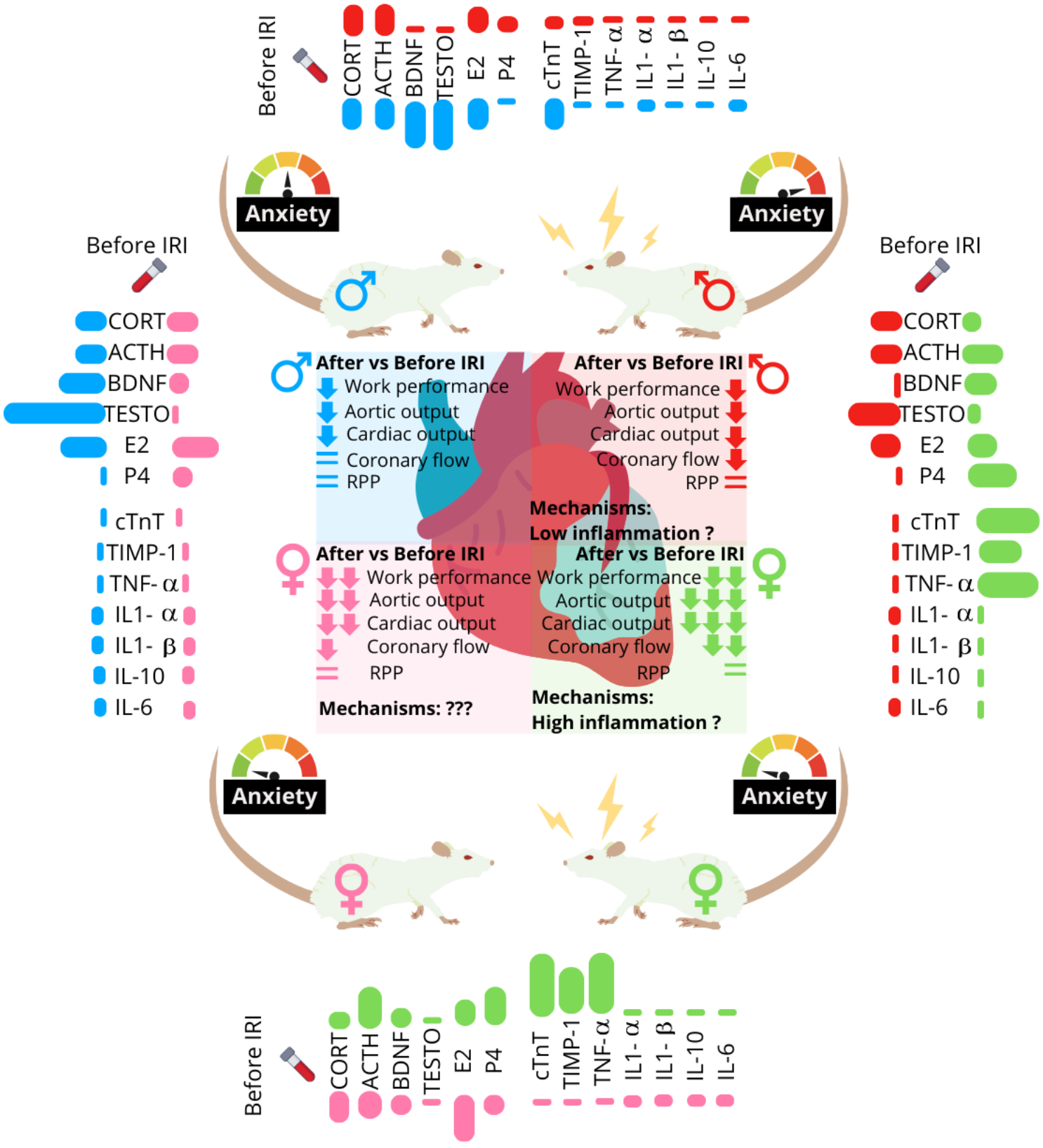
Figure legend

Figure 1. Overview of sex-biased changes in baseline plasma mediators and ex vivo heart function after regional ischemia-reperfusion injury in unstressed and stressed Wistar Rats. ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; cTnT, cardiac troponin T; CORT, conrticosterone; E2, estradiol; IL, interleukin; IRI, ischemia-reperfusion injury; P4, progesterone; RPP, rate pressure product; TESTO, testosterone; TIMP-1, tissue inhibitors of metalloproteinase type 1; TNF-α, tumor necrosis factor-alpha TNF-α.


Before IRI
CORT
ACTH
BDNF
TESTO
E2
P4
cTnT
TIMP-1
TNF- α
IL1- α
IL1- β
IL-10
IL-6
Anxiety
Anxiety
Before IRI
CORT
ACTH
BDNF
TESTO
E2
P4
cTnT
TIMP-1
TNF- α
IL1- α
IL1- β
IL-10
IL-6
Before IRI
CORT
ACTH
BDNF
TESTO
E2
P4
cTnT
TIMP-1
TNF- α
IL1- α
IL1- β
IL-10
IL-6
After vs Before IRI
Work performance
Aortic output
Cardiac output
Coronary flow
RPP
After vs Before IRI
Work performance
Aortic output
Cardiac output
Coronary flow
RPP
Mechanisms:
Low inflammation ?
After vs Before IRI
Work performance
Aortic output
Cardiac output
Coronary flow
RPP
Mechanisms: ???
After vs Before IRI
Work performance
Aortic output
Cardiac output
Coronary flow
RPP
Mechanisms:
High inflammation ?
Anxiety
Anxiety
Before IRI
CORT
ACTH
BDNF
TESTO
E2
P4
cTnT
TIMP-1
TNF- α
IL1- α
IL1- β
IL-10
IL-6