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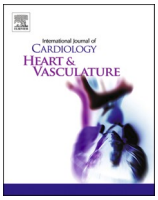

Editorial

Recent highlights from the *International Journal of Cardiology Heart & Vasculature*: Basic and translational research

The *IJC Heart & Vasculature* is dedicated to publishing a range of manuscript types that report on structural and functional cardiovascular pathology, imaging techniques and disease mechanisms. Of the topics covered by the journal, "Basic and Translational Research" tops the list, yet submissions that fall into this category make up only a small fraction of the published articles. A total of 280 original articles were published in the IJC *Heart & Vasculature* in 2022 and 2023, of which 9 could be categorized as basic and translational research papers, equating to around 2–4 %. The mechanistic and pathophysiological insights gained from such "bench" studies are, however, invaluable additions to the clinical data arising from the invasive, registry, Mendelian randomization or imaging studies that make up the bulk of the published papers. We want to spotlight these 9 basic and translational studies published in 2022–2023, which in their way advance our understanding of cardiovascular pathophysiology and provide potential new therapeutic and diagnostic opportunities and perspectives.

1. Insights into culprit pathways driving myocardial inflammation

Sterile inflammatory signaling is a common feature of many cardiovascular diseases such as heart failure [1] and atrial fibrillation (AF). The relationship is often causal and multidirectional. While clinical studies are by their nature often associative, basic investigations can unravel the temporal and causal interaction between inflammatory triggers and various disease states.

In a rat model of hypertension-driven atrial cardiomyopathy, Bukowska et al. [3] reported that atrial remodeling in adult spontaneously hypertensive rats (SHR) was accompanied by transcriptional upregulation of endothelin-1 (ET-1) and the endothelin ET_A receptor. ET-1 receptor antagonists are undergoing a revival and are under clinical investigation in patients with vasospasm and microvascular angina [4,5]. The study by Bukowska et al. examined whether the ET-1 receptor antagonist macitentan targets atrial remodeling, thereby reducing the susceptibility to AF in adult SHR. The α_1-adrenoceptor blocker doxazosin, used as an antihypertensive control, significantly lowered systolic blood pressure compared to the untreated group, while macicentan did not. However, macicentan suppressed left atrial ET-1 content and unlike doxazosin also attenuated NFkB phosphorylation and transcription of the vascular adhesion molecule VCAM-1. Macicentan comparably attenuated the levels of other oxido-inflammatory markers such as atrial 8-isoprostane, ICAM-1 and IL-8, along with reduced activation of mitogenic kinases. Neither agent notably affected major Ca^{2+}-handling proteins or structural remodeling. This study suggests that targeting the ET-1 system in hypertension may provide a degree of blood pressure-independent cardioprotection on top of classic antihypertensive approaches that modulate for example the renin-angiotensin-aldosterone system (RAAS). In addition, it appears that the contribution of ET-1 to atrial cardiomyopathy is largely restricted to pathways of inflammation, while structural and Ca^{2+}-handling remodeling are primarily attributable to mediators such as angiotensin II, among others. This insight importantly uncouples mechanisms of inflammatory signaling from structural changes, which are often considered as a causal continuum. One could argue that the concept that targeting inflammation could prevent all key components of AF-promoting atrial remodeling [2] is unrealistic one, and further work is clearly required to dissect the upstream drivers of inflammation and their specific therapeutic value. Nevertheless, this study provides important insights into the evolution of secondary atrial cardiomyopathy due to hypertension.

Maroofi et al. [6] examined physical exertion rather than pharmacological intervention to improve inflammatory cardiomyopathy. Exercise-based training programs are an important part of a multimodal management of cardiovascular diseases and cardiomyopathies [7–9]. Although high-intensity regimes lower inflammatory burden for example in patients with combined adiposity and heart failure [7], the underlying molecular mechanisms are poorly understood. Key focus of the investigation by Maroofi et al. was the contribution of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase receptor B (TrkB), which appear to provide organ protection in non-neuronal systems including the heart. Rats were fed either normal diet (ND) or Western diet (WD) for 12 weeks, and subjected to treadmill running either in a moderate-intensity continuous training (MICT) paradigm, high-intensity interval training (HIIT) or no exercise, to mimic a sedentary (SED) lifestyle. The six groups of rats were compared for cardiac function, visceral adiposity and myocardial expression of IL-18 and heme-oxygenase (HO)-1 as surrogate markers of inflammation and antioxidant defense, respectively. Both training paradigms comparably improved the cardiometabolic status in the WD rats, whereas HIIT showed the exclusive ability to boost HO-1 levels and counteract BDNF depletion. It appears that more pain brings more gain in terms of exercise-induced cardioprotection. Although a recent plethora of studies have compared the benefits of HIIT versus other training regimes, this report provides new molecular insight into the potential underlying mechanisms and verifies BDNF-TrkB as a candidate target for pharmacological approaches in patients not amenable or suited to intense physical exercise.

The study by Haj-Yehia et al. [10] identified a hitherto unknown inflammatory mechanism of CD47 related to the phagocytic activity of

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neutrophils after acute MI. CD47 functions as a kind of "don't eat me" signal and hence its surface expression negatively regulates phagocytosis. CD47 blockade was previously found to reduce post-MI injury through enhanced macrophage-mediated phagocytosis. The impact on neutrophil infiltration and function, which critically direct the early aftermath of acute MI, has not been studied. In the here reported mouse model of acute MI, the authors applied an anti-CD47 antibody as a ventricular bolus injection 5 min prior to reperfusion. The 24-h infarct size was reduced by this treatment. A potential direct effect of CD47 deletion on cardiomyocyte death was excluded with elegant accompanying experiments in Langendorff-perfused wildtype and $CD47^{-/-}$ mouse hearts, and with an *in vitro* model of simulated hypoxia-reoxygenation in cardiomyocytes treated with the anti-CD47 antibody. The 3D visualization of neutrophil infiltration using light-sheet fluorescence microscopy showed that despite the lowering of infarct volume after CD47 blockade, the number of infiltrated neutrophils did not differ between the groups. With a comprehensive panel of functional assays, the authors could show that part of the cardioprotection afforded by the anti-CD47 antibody was attributable to a boosted ability of neutrophils to phagocytose apoptotic cardiomyocytes. Unlike other anti-tumor therapies, which are frequently associated with cardiotoxicity [11,12], CD47-targeting approaches that augment macrophage-mediated removal of tumor cells might cause less harm to the heart and may even exert a cardioprotective effect after MI.

2. Candidate mechanisms and targets identified in clinical specimen provide impetus for further directed research

Stroke is one of the most detrimental complications associated with AF, and thromboembolic risk is aggravated by advancing age and comorbidities such as cancer and valve dysfunction [13–16]. The arrhythmia *per se* could also directly contribute to stroke by causing atrial blood stasis and thrombosis. Increasingly, the underlying atrial cardiomyopathy, encompassing structural, inflammatory and functional remodeling, is recognized to drive thromboembolic risk independently of prevalent AF, and to support a hypercoagulant phenotype. Pala et al. [17] sought to dissect the systemic profile of stroke patients with and without AF. Blood was collected within 72-h of symptomatic stroke and assessed by aptamer array. An initial aptamer cohort encompassed n = 10 per group, and candidate biomarkers were verified in 111 patients in total of the Crypto-AF sub-study cohort. Perhaps unexpectedly, relatively few – 46 – of the total 1,310 proteins measured did differ between the two groups, and of the 4 validated in the larger cohort, only dipeptidyl peptidase 7 (DPP7, also referred to as DPP2) emerged as a biomarker differentiating between AF and non-AF after stroke. The difference in circulating DPP7 was marginal, but robust. The authors critically discuss the limitations and implications of their findings and consider their study as a hypothesis-generating basis for further validation and research.

Moratal et al. [18] similarly explored the phenotype of circulating monocytes and the extent and time-course of macrophage polarization after MI in the context of type-2 diabetes (T2D). In patients with acute MI, circulating cardiac biomarkers show a distinct kinetic profile [19] that might be related to the injury and repair processes occurring in the infarcted heart. The rationale of the study by Moratal et al. was that T2D aggravates the risk of MI and subsequent in-hospital mortality. Immune cells are a critical feature of MI-triggered injury and repair, proper orchestration of which requires a dynamic phenotypic plasticity of monocytes and macrophages. The authors hypothesized that in patients with TD2, a defective or a delayed macrophage polarization could impair timely resolution of the inflammatory phase after MI. Circulating monocytes were collected from male patients with or without T2D on days 1, 3 and 5 after MI and were either assessed directly by flow cytometry or differentiated *in vitro* toward pro- or anti-inflammatory macrophages by standard protocols. Monocyte subtype phenotyping by flow cytometry identified no clear differences between T2D and controls, although when all time-point data were pooled, the T2D group showed a higher fraction of non-classical $CD14^{+}CD16^{+}$ monocytes. The key and somewhat unexpected observation of this study was that the presence of T2D affected neither the extent nor the kinetics of pro- and anti-inflammatory macrophage polarization *in vitro*. These results clearly warrant further exploration and validation, particularly regarding the fate and function of cardiac macrophages *in situ*, either resident or newly accumulated post-MI.

3. Implementation of novel techniques and standardization of established approaches to advance understanding and clinical management of progressive cardiac diseases

Recent clinical imaging and optical coherence tomography-based studies published in this journal implicate culprit plaque-derived lipids and cholesterol cargo in coronary events and their consequences [20–22]. In a preclinical approach, Cortenbach et al. [23] applied a novel multiplex immunohistochemistry technique to map immune cell subsets at different stages of human coronary artery disease, with around 10 samples each reflecting 4 stages of progressive thickening and atheromatous plaque manifestation. The authors established 2 panels encompassing a total of 11 markers of adaptive and innate immune cells that were assessed by semi-automated analysis in whole plaques and specific plaque regions. Although the major finding was that the type of immune response shows no substantial difference during plaque development, this elegant study yet provides a first comprehensive mapping of immune cell subtypes across coronary plaques, and importantly presents the applicability of multiplex immunohistochemistry for assessing the features and unique characteristics of progressing disease states.

The study by van Bavel et al. [24] assessed exercise-induced cardiorespiratory parameters after atrio-ventricular (AV)-block in dogs. The model is suitable to screen for efficacy of pro-and anti-arrhythmic drugs, profile drug safety and assess the effect of new devices during the course of post-block contractile, electrical and structural remodeling. Mongrel dogs were subjected to a moderate treadmill exercise protocol at 4 time-points: at baseline (in sinus rhythm), on day 2 after AV-block, when remodeling is initiated, and after 3 and 6 weeks when remodeling is progressing and partially completed. All dogs could absolve the exercise protocol at baseline and after 3 and 6 weeks, but half of the assessed animals failed to complete the run on day 2. In all animals, atrial rate was higher and exercise-induced stroke volume increased, but failed to compensate for the AV-block induced bradycardia and so cardiac output was consistently lower after AV-block. Critically, arrhythmic events were most frequently evoked by exercise training on day 2 after AV-block, together with the lowest respiratory capacity and venous blood desaturation and acidification. The authors concluded that dogs with limited remodeling after AV block have reduced cardiorespiratory fitness and exercise tolerance. Stringently standardized preclinical models are required for evaluating new cardiovascular device technologies, and robust physiological data obtained from such models is needed to feed AI-based algorithms and machine learning. The authors propose that testing and optimization of new device therapies, such as the emerging nanotechnologies [25] in the canine AV-block model might ideally be performed on day 2 after AV-block when cardiorespiratory fitness is most compromised, and improvements in cardiac function and exercise tolerance due to new cardiac device properties are most insightful. One strength of the study by van Bavel et al. is that it was performed in both male and female dogs. Sex has a profound impact on sinus rhythm heart rate, as demonstrated by intra-operative, high resolution mapping [26]. Female patients displayed more areas of conduction disorders and low voltage potentials [26], in a wider sense, females are less frequently implanted with cardiac devices, but more frequently suffer post-implantation complications with need for re-intervention [27]. The requirement to specifically consider sex and gender aspects in experimental designs and clinical

guideline formulation was highlighted by an accompanying editorial [28].

4. Molecular basis of expected and unexpected cardiotoxic adverse drug reactions

Patients with schizophrenia are at heightened risk of sudden cardiac arrest and higher mortality after such an event. This does not appear to be related to an elevated cardiovascular burden associated with the psychiatric disorder [29]. Whether psychotropic medication contributes to the risk of cardiac arrest and mortality remains uncertain. One preclinical study by Kreifels et al. [30] assessed in a rabbit model the additive and mechanistic nature of long-QT-syndrome (LQTS) in response to a trio of commonly used psychotropic drugs. The authors had previously documented QT-prolongation in the LQT2-rabbit model for the so-called cuddling chemical oxytocin. This is frequently prescribed to psychiatric patients to improve social fears, empathy and emotions. The authors were concerned about possible additive adverse reactions when oxytocin is combined with antidepressants or antipsychotics. Using an elegant experimental design coupling *in vivo* ECG with *ex vivo* Langendorff-perfused hearts and isolated cardiomyocytes, the authors demonstrated that acute application of oxytocin on top of fluoxetine, as a representative antidepressant, or risperidone, an antipsychotic, further aggravated QTc- and APD-prolongation, compared to monotherapy. The additive nature of the interaction could be attributed to differential effects of the individual compounds on repolarizing ion currents [31]: fluoxetine and risperidone both reduced the HERG-carried I_{Kr} current, while oxytocin suppressed additional K^+-currents (I_{Ks} and I_{K1}), further compromising the weakened repolarization reserve. Although preclinical, this study highlights acquired LQTS as a potential adverse reaction to a frequent combination of treatments that should be prescribed with great caution.

In cardiomyocytes the Na^+/Ca^{2+}exchanger (NCX) plays a key role in the regulation of physiological Ca^{2+} homeostasis. However, NCX dysfunction could promote the development of arrhythmias by supporting the occurrence of early and delayed afterdepolarizations (EADs/DADs) [32]. Although NCX inhibition is protective against arrhythmic events at the single cardiomyocyte level, the *in vivo* feasibility of this approach is not established. Bögeholz et al. [33] presented a proof-of-concept study in which heterozygous $NCX^{-/-}$ and wildtype mice were compared for ventricular arrhythmia initiation and perpetuation in response to programmed ventricular stimulation (PVS) and isoprenaline. The two groups did not differ in terms of PVS-triggered initiation of ectopic beats, but the $NCX^{-/-}$ mice were less susceptible to isoprenaline-induced premature ventricular complexes. However, $NCX^{-/-}$ mice showed a shortened ventricular refractory period and a significantly prolonged duration of inducible ventricular tachycardia episodes, pointing to the formation of arrhythmia-maintaining re-entrant circuits. Whether inhibition of NCX could (or should) be therapeutically exploited in patients remains to be determined.

5. Outlook

The above discussed studies exemplify that basic science and translational studies are important additions to clinical reports, often providing the mechanistic basis that could explain the observations made in patients, and fostering further systematic translational research. We would highly welcome a larger proportion of basic and translational reports in future issues of the journal.

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Disclosures

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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