openheart

Hypoxia in myocardial infarction and natriuretic peptides

Olli Arjamaa

To cite: Arjamaa O. Hypoxia in myocardial infarction and natriuretic peptides. *Open Heart* 2025;**12**:e003130. doi:10.1136/openhrt-2024-003130

Accepted 27 February 2025

University of Turku Biodiversity Unit, Turku, Finland

Correspondence to
Dr Olli Arjamaa; olli.arjamaa@utu.fi

ABSTRACT

Background Mechanical stress on the heart is commonly considered the sole stimulus explaining the synthesis and release of circulating natriuretic peptides and their derivatives. While one of the most critical paradigms in cardiology is that mechanical load increases oxygen consumption, clinical studies on these peptides have neglected the relationship between mechanical stress and oxygen metabolism. At the cellular level, cardiac myocytes have a ubiquitous oxygen-sensing pathway mediated by a nuclear transcription factor, the hypoxia-inducible factor (HIF). Published studies indicate that the human myocardium starts expressing HIF during infarction. In myocardial cell cultures, natriuretic peptides are synthesised and released under hypoxic conditions through immediate and sufficient actions of HIF.

Conclusion Myocardial oxygen metabolism directly regulates the plasma levels of natriuretic peptides in heart diseases. The function of oxygen gradients should be correlated with circulating natriuretic peptides to achieve better sensitivity in plasma measurements of natriuretic peptides in myocardial infarction.

BACKGROUND

About 40 years ago, the isolation and characterisation of natriuretic peptides from the heart profoundly changed our perspective of this organ. 20 years earlier, a cell biology article had been published that showed that mammalian heart atria had small granules near atrial nuclei which, the authors concluded, were 'presumably secretory in nature'.[1] Strong cardiovascular effects (natriuresis and diuresis) of the A-type and then B-type natriuretic peptides revealed that the heart was also an endocrine organ[2] and the granules were the source of natriuretic peptides. This discovery provoked tremendous scientific activity in cardiology: the search term 'natriuretic peptide' identified more than 48 000 articles in the PubMed database in December 2024. However, there has been a failure to truly capitalise on natriuretic peptides and their derivatives in diagnosing and following up cardiac diseases. These issues stem from the fact that the results achieved on the cardiac cell physiology of natriuretic peptides have not been fully implemented, and, therefore, interpretations of their measurements in diverse cardiac conditions have varied. Nonetheless, their use has been increasing in other medical branches.

INTRODUCTION

An article that has become the cornerstone of all the clinical studies on the roles of natriuretic peptides in cardiology was published in *Nature* in the mid-1980s.[3] Its authors rapidly infused a large volume of physiological buffer solution into the circulation of a laboratory rat, more than doubling the intravascular volume. They concluded that mechanical atrial stretching (confirmed in isolated rodent hearts) was the sole stimulus that could explain the synthesis and release of natriuretic peptides, which then contributed to reducing volume overloads. However, terrestrial mammals rarely encounter such conditions; in contrast, they are at constant risk of becoming dehydrated. Since this article was published, mechanical stress has become a static paradigm in the cardiology of natriuretic peptides that can clarify all cardiac diseases, as evidenced by a recent educational article with learning objectives.[4] While wall stress represents one of the major determinants of myocardial oxygen consumption,[5 6] mechanical stress and oxygen metabolism have been disconnected in clinical studies on natriuretic peptides. According to a strong tradition since the times of William Harvey, cardiologists have looked on the heart as only a mechanical pump and have explained its function using mechanical parameters. Consequently, the cellular physiology underlying the mechanical stress has been less studied; while clearly unphysiological in the context of natriuretic peptides, mechanical stretching of the atria matched well with cardiology practice. In addition, one additional reason why the mechanical stress paradigm has robustly prevailed and has not been challenged was the transformation of physiology departments into molecular

biology departments during the 1980s and 1990s, which ended research into the in vivo physiology of natriuretic peptides. However, it is paradoxical that cardiologists whose clinical work focuses on rescuing the myocardium from hypoxic damage have neglected to study the role of oxygen metabolism in the pathophysiology of natriuretic peptides and developing drugs related to them.

HYPOXIA-INDUCIBLE FACTOR

All cells, including cardiac myocytes, must have some mechanism to respond to oxygen tension at the cellular level, which has been a critical constraint during biological evolution. Under natural selection, the ubiquitous solution to this problem has been evolving a common oxygen-sensing pathway; its functional and structural components are phylogenetically conserved across the animal kingdom. The key actor in this pathway is the hypoxia-inducible factor (HIF), a heterodimeric nuclear transcription factor that comprises a labile α subunit (α 1–3) and a stable β unit. The α subunit is regulated, whereas the β subunit is constitutively expressed. HIF-1α is rapidly oxidised under normal oxygen tension but is stabilised when cells become hypoxic, starting the expression of thousands of genes. HIF can be considered a master regulator of oxygen homeostasis to match the oxygen supply and demand in the progression, prevention and treatment of cardiovascular disease.[7] The discoverers of the HIF pathway were awarded the Nobel Prize in Physiology or Medicine in 2019.

Studies on natriuretic peptides have used in vitro methods and experimental animal models, not far from clinical cardiology, to outline how cardiac myocytes and tissues operate at the cellular level under normal and hypoxic conditions. However, their results have not been adopted or implemented in clinical studies, guidelines or influential position papers.

Interestingly, hypoxia was a direct and sufficient stimulus to induce the expression of both the A and B types of natriuretic peptide by cardiac myocytes in culture, and the responses were mediated via the HIF pathway.[8 9] When the HIF pathway was blocked in human cardiac cells cultured under hypoxic conditions, they stopped secreting brain natriuretic peptide (BNP).[10] In addition, in cultures of retinal pigment epithelium cells from a human eye in which undisputedly no stretching occurred, hypoxia induced the release of N-terminal pro-BNP (NT-proBNP) with a concomitant increase in HIF expression.[11] In pigs in which the blood flow to myocardial arteries had been surgically inhibited, hypoxia increased BNP gene expression distally from the lesions.[12]

Generally, almost all in vitro models that have been used to study the synthesis and release of natriuretic peptides (cell cultures, isolated myocytes, atrial or ventricular blocks and Langendorff perfusion system) have suffered from limited and overlooked oxygen control. Critical parameters have not been reported, and the conditions have been either hypoxic or hyperoxic and infrequently normoxic.[13 14]

CELLULAR OXYGEN

Under normal conditions, the intracellular partial pressure of oxygen near mitochondria in a myocyte is very low, with reported values ranging from 1 to 10 mm Hg.[15] It follows that large oxygen gradients occur between coronary arteries and myocytes in a healthy myocardium. When the myocardium is deprived of blood during infarction, these gradients become irreversibly disrupted and remodelling is initiated, resulting in changes in the heart's size, shape, structure and function. During infarction, gene expression in the ventricles shifts towards the fetal state and ventricles start synthesising and releasing natriuretic peptides.[2]

Previously, Lee *et al*[16] collected ventricular biopsy specimens from patients undergoing coronary bypass surgery, which were analysed for HIF-1α. HIF-1α messenger RNA was found in myocardial samples with pathological evidence of acute ischaemia or early infarction but not in those from healthy ventricles. While this study did not measure natriuretic peptides (it instead measured vascular endothelial growth factor), its results clearly showed that HIF pathway activation was among the first adaptations of the human myocardium to oxygen deficiency.

New information about the role of oxygen metabolism in myocardial infarction has emerged from studies using modern molecular biology methods. For example, single-cell gene expression has enabled the generation of an integrative map of the human heart after infarction with high spatial resolution, profiling physiological zones at different time points in affected patients.[17] More specifically, the boundary between the injured hypoxic tissue and normal tissue, known as the border zone and characterised by an oxygen gradient, can be studied with an engineered microphysiological system in a cellular environment.[18] This method provides us with a more detailed understanding of the effects of oxygen gradients in tissues, such as the expression of inflammatory cascades, compared with traditional in vitro models in which all cells are globally exposed to hypoxia. A spatial transcriptome in the border-zone-on-a-chip model demonstrated that changes induced by the oxygen gradient during myocardial infarction are distinct from those observed during uniform hypoxia.

CONCLUSION

Based on published results, hypoxia regulates the synthesis and release of both the A-type and B-type natriuretic peptides. Hypoxia is a direct and sufficient condition, and responses are intracellularly mediated via the HIF pathway. Most likely, high plasma levels of natriuretic peptides, especially NT-proBNP, found during infarction and coronary artery disease[19] relate directly to the volume of injured hypoxic tissue.[20] In the future, the

function of oxygen gradients in the myocardium should be correlated with circulating natriuretic peptides to achieve better predictive value in plasma measurements of natriuretic peptides in myocardial diseases.

Contributors OA is the sole author of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Olli Arjamaa http://orcid.org/0000-0003-1538-8602

REFERENCES

1 Jamieson JD, Palade GE. Specific granules in atrial cells. *J Cell Biol* 1964;23:151–72.
2 Goetze JP, Bruneau BG, Ramos HR, *et al*. Cardiac natriuretic peptides. *Nat Rev Cardiol* 2020;17:698–717.
3 Lang RE, Thölken H, Ganten D, *et al*. Atrial natriuretic factor--a circulating hormone stimulated by volume loading. *Nature*1985;314:264–6.
4 Eltayeb M, Squire I, Sze S. Biomarkers in heart failure: a focus on natriuretic peptides. *Heart* 2024;110:809–18.
5 Sonnenblick EH, Ross J, Braunwald E. Oxygen consumption of the heart. Newer concepts of its multifactoral determination. *Am J Cardiol* 1968;22:328–36.
6 Strauer B-E. Myocardial oxygen consumption in chronic heart disease: role of wall stress, hypertrophy and coronary reserve. *Am J Cardiol* 1979;44:730–40.
7 Semenza GL. Hypoxia-inducible factors: roles in cardiovascular disease progression, prevention, and treatment. *Cardiovasc Res* 2023;119:371–80.
8 Chun Y-S, Hyun J-Y, Kwak Y-G, *et al*. Hypoxic activation of the atrial natriuretic peptide gene promoter through direct and indirect actions of hypoxia-inducible factor-1. *Biochem J* 2003;370:149–57.
9 Weidemann A, Klanke B, Wagner M, *et al*. Hypoxia, via stabilization of the hypoxia-inducible factor HIF-1alpha, is a direct and sufficient stimulus for brain-type natriuretic peptide induction. *Biochem J* 2008;409:233–42.
10 Casals G, Ros J, Sionis A, *et al*. Hypoxia induces B-type natriuretic peptide release in cell lines derived from human cardiomyocytes. Am J Physiol Heart Circ Physiol 2009;297:H550–5.
11 Aaltonen V, Kinnunen K, Jouhilahti E-M, *et al*. Hypoxic conditions stimulate the release of B-type natriuretic peptide from human retinal pigment epithelium cell culture. *Acta Ophthalmol* 2014;92:740–4.
12 Goetze JP, Gore A, Møller CH, *et al*. Acute myocardial hypoxia increases BNP gene expression. *FASEB J* 2004;18:1928–30.
13 Palacio-Castañeda V, Velthuijs N, Le Gac S, *et al*. Oxygen control: the often overlooked but essential piece to create better *in vitro* systems. *Lab Chip* 2022;22:1068–92.
14 Tan J, Virtue S, Norris DM, *et al*. Limited oxygen in standard cell culture alters metabolism and function of differentiated cells. *EMBO J* 2024;43:2127–65.
15 Ortiz-Prado E, Dunn JF, Vasconez J, *et al*. Partial pressure of oxygen in the human body: a general review. *Am J Blood Res* 2019;9:1–14.
16 Lee SH, Wolf PL, Escudero R, *et al*. Early expression of angiogenesis factors in acute myocardial ischemia and infarction. *N Engl J Med* 2000;342:626–33.
17 Kuppe C, Ramirez Flores RO, Li Z, *et al*. Spatial multi-omic map of human myocardial infarction. *Nature New Biol* 2022;608:766–77.
18 Rexius-Hall ML, Khalil NN, Escopete SS, *et al*. A myocardial infarct border-zone-on-a-chip demonstrates distinct regulation of cardiac tissue function by an oxygen gradient. *Sci Adv* 2022;8:eabn7097.
19 Jering KS, Claggett BL, Pfeffer MA, *et al*. Prognostic Importance of NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) Following High-Risk Myocardial Infarction in the PARADISE-MI Trial. *Circ: Heart Failure* 2023;16:e010259.
20 Wan J, Xu F, Yin C, *et al*. Predictive value of HIF-1α for left ventricular remodeling following an anterior ST-segment elevation myocardial infarction. *Am J Med Sci* 2024;26:50002–9629.