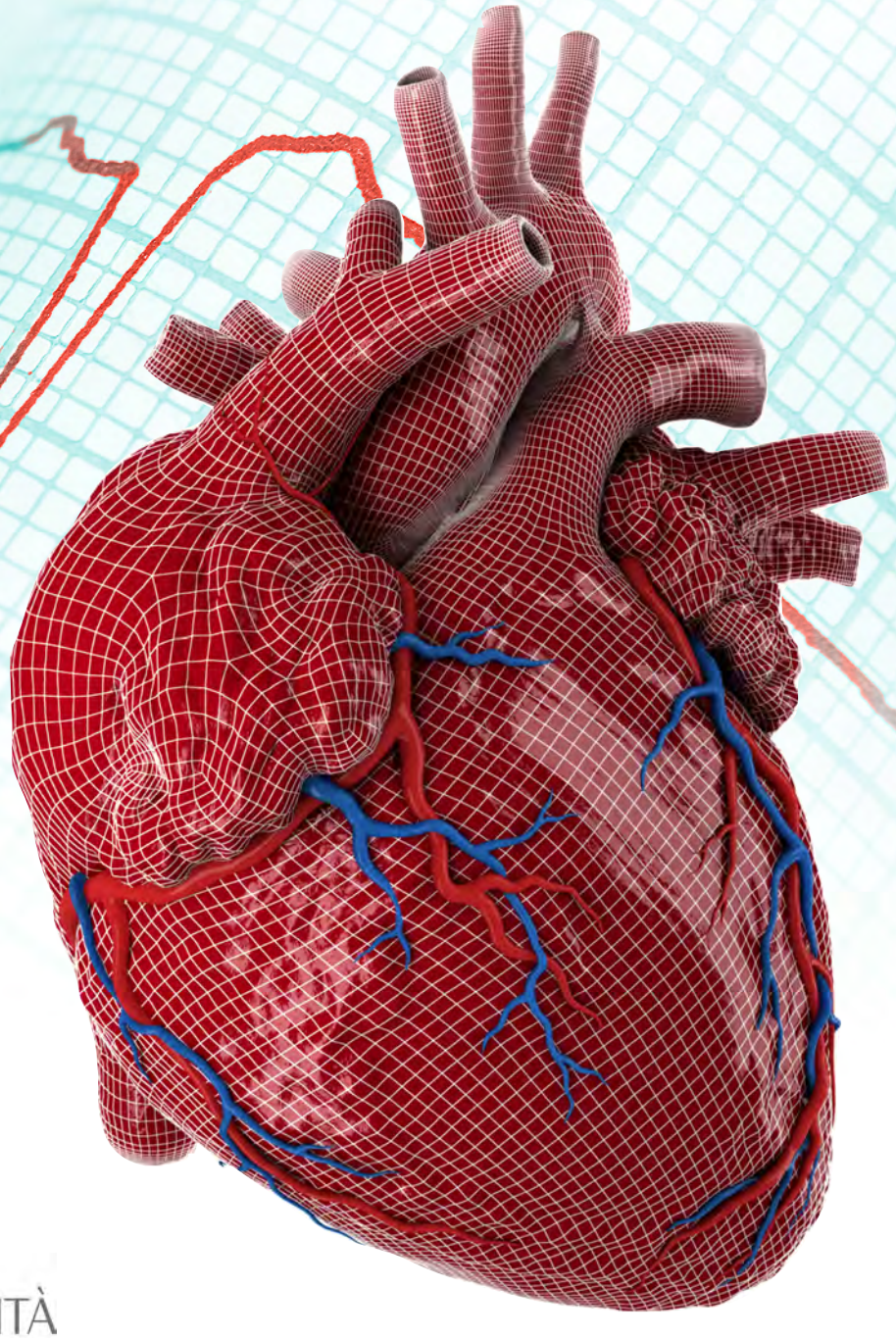
Cardiovascular Science



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Acute coronary syndrome (ACS):
A focus on inflammation and heart attack

The excellent work of the Department of Cardiological Sciences of the Fondazione Policlinico Agostino Gemelli, Universita' Cattolica del Sacro Cuore, in Rome is explored here when it comes to vital research in the field of acute coronary syndrome (ACS), with a focus on inflammation and heart attack

The Department of Cardiological Sciences of the Fondazione Policlinico Agostino Gemelli, Universita' Cattolica del Sacro Cuore, in Rome, is a major clinical and research institute that is devoted to the care of patients and research – including acute coronary syndrome (ACS). Our group gained significant international importance in 1994 with Prof Maseri, when we published the first clinical paper on inflammation and myocardial infarction (heart attack), opening the way to the research in this field and changing the whole perception of these syndromes. Furthermore, these studies opened the way to the novel therapeutic use of cytokines in ACS, as shown recently in Boston by Ridker and collaborators in the CANTOS study.

The evidence in favour of a role of in inflammation in ACS (a definition including all mechanisms of myocardial infarction) led us to the search for the more probable causes, including cytokines and infections. Although the infection hypothesis did not survive the negative pieces of evidence, the role of inflammation and cytokines gained an increasing interest over time. Our previous findings that IL-2 and IL-1 RA were involved in infarction were, therefore, followed by a number of research projects in this field by our group, that is by me and Prof Liuzzo, which concerned the role of further cytokines as IL-17 in ACS. The interest of these studies is related on one hand, to the unacceptable death toll and disability associated with infarction and on the other hand, to the need to develop novel treatment and prevention strategies, therefore, we are focusing now much more on advanced and promising fields, such as micro-RNA, small non-coding RNA that may be used to "correct", "enhance" or "modulate" biological mechanisms that are not working properly. For more information on these areas, please refer to the three references at the end of this article.[1-3]

Similarly, we are also working on long-noncoding RNAs, where we are searching for information at the genomic level to modify at its beginning the possible derangements that may occur. We presented this data in July 2018 at the "Academy of Cardiology" Congress in Boston and at the Italian Congress of Cardiology. The interest of this line of research is the possibility to "enter in" and modify the mechanisms of the body, therefore, creating the potential of changing all treatment mechanisms.

The third field of innovation in clinical research is related to the role of microbiota in cardiovascular disease. The derangement of the microbiota is a novel finding in the field of cardiology but is already considered as a major risk factor for cardiovascular disease. At the Fondazione Policilico Gemelli Hospital, Catholic University, a number of studies are ongoing in this field. Our group is searching for a common background of a number of conditions that may be associated with microbiome derangement, including psoriasis, rheumatoid arthritis, myocardial infarction and inflammatory bowel disease. Although apparently different, these conditions represent different forms of the same disease that depends on an overproduction of microbiome or

more commonly, altered permeability of the bowel membrane. Resolving the complex problems associated with the microbiome might significantly reduce the burden of several diseases in cardiology and at our institute, we have designed a number of studies designed to better address these conditions and to develop novel treatments for them.

Intestinal microbiota encompass about 800 species of different bacteria with more than 7,000 [18] spices, the most common anaerobic are *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Fusobacterium*, *Clostridium e Lactobacillus*, while the aerobic are Gram-negative species, (as *Escherichia coli e Salmonella spp*.) and Gram-positive (as *Enterococcus*, *Staphylococcus e Streptococcus*).

Intestinal post-partum bacterial colonisation of the gut is essential for innate and acquired immune defence and allows the immune system to develop tolerance toward microbic antigens. The interaction among microbes, epithelial cells and the immune system is largely due to research on microbic signalling in the intestinal lumen, based on pattern recognition receptors (PRRs), as Toll-like receptors and the NOD isoforms of the NOD-like receptors (NLR). This stimulus brings us to the activation of NF-κB, that, in turn, stimulates the release of a large number of cytokines, such as TNF-α, IL-1β, IL-6 e IL-12).

Another mechanism is linked to the activation of lipopolysaccharides (LPS) that may have a significant role in the growth of lesions in organs from a distance, furthermore elevated levels of plasma LPS could be linked to intestinal lesions and bacterial translocation.

Microbiota and heart failure (HF)

Patients with heart failure (HF) develop a reduction in cardiac output, increasing tissue congestion and peripheral vasoconstriction. This, in turn, may reduce the intestinal epithelium leading to malnutrition and cachexia. There are more microbic cells in the intestine and added to this, human cells and microbial cells contain millions of genes. In HF, in a body that is already “under attack”, the burden of an excessive gut microbiota overgrowth may represent a significant increase in the risk of death and disability. In Rome, my group is searching for innovative treatment of such patients, using a different approach to reduce death and disability and the human and social costs associated with disability and death.

References

1. MiR-21 role in aspirin-dependent PPARα and multidrug resistance protein 4 upregulation. Massimi I, Alemanno L, Guarino ML, Guerriero R, Frati L, Biasucci L, Pulcinelli FM.Res Pract Thromb Haemost. 2018 May 17;2(3):596-606. doi: 10.1002/rth2.12104. eCollection 2018 Jul.

2. Platelet miRNA-26b down-regulates multidrug resistance protein 4 in patients on chronic aspirin treatment (https://www.ncbi.nlm.nih.gov/pubmed/30015780). La Rosa G, Biasucci LM, Mandolini C, Massimi I, Copponi G, Pulcinelli FM, Crea F. J Cardiovasc Med (Hagerstown). 2018 Oct;19(10):611-613.

3. Platelet microRNAs are not modulated by systemic heparin in acute coronary syndromes (https://www.ncbi.nlm.nih.gov/pubmed/26351939). Mandolini C, Copponi G, Marini G, Vergallo R, Biasucci LM, Crea F. Clin Chem Lab Med. 2016 Jan;54(1), these studies may lead to a different and more “biological” ways of treatment.

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Cardiovascular science: Novel advances in ischemic heart disease (IHD)

Novel advances in ischemic heart disease (IHD) are placed under the spotlight here by Luigi Marzio Biasucci MD from Fondazione Policlinico Universitario A Gemelli who specialises in cardiovascular science

During the last 20 years, several novel findings have considerably changed the conceptual framework of ischemic heart disease (IHD), moving the interest of clinicians and scientists from simple pathophysiological concepts as stenosis, incrustation, cholesterol, to novel and more advanced findings that may better explain the mechanisms of disease and, in turn, the more effective and focused treatments.

The first evidence in this area was produced at the end of the last century, when different groups in Europe and USA (such as Maseri in Rome, Libby and Ridker in Boston) challenged the old and mechanistic theories that considered myocardial infarction as the results of "incrustation" of the arteries and found coronary inflammation as one of the major causes of IHD (Liuzzo NEJM 1994, Biasucci Circulation 1996, Ridker NEJM 1997). Since then, a large body of evidence has confirmed the inflammatory hypothesis and paved the way to further hypotheses.

Cytokines and infarction

The pivotal role of cytokines in the pathogenesis of infarction is now well-established and the current research in the field focuses on the possible application of cytokines in this area. In Rome, our recently published work consists of 60 papers about the role of inflammation and cytokines. Overall, 6,993 papers on the role of cytokines in IHD have been published according to website www.pubmed.gov.

Recently, a publication by Ridker and Coll increased the interest of the researcher concerning the role of cytokines in IHD, as the authors demonstrated that interleukin-1 inhibition can reduce the risk of death and reinfarction in the CANTOS trial, not at the expense of increased adverse events and without an expected or a significant reduction in cases of pulmonary cancer.

Microbiome and cardiovascular diseases

Recent findings suggest that gut microbiome is involved not only in intestinal diseases but also in IHD, heart failure, rheumatoid arthritis and psoriasis; our group (Biasucci and Coll, Curr Cardiol Rep. 2017) underlines peculiar aspects of the phenomenon: oxidative stress and autophagy; DAMPS and TLR-4 signalling activation; different macrophages lineage and the contribution of NLRP-3 inflammasome; adaptive immune system. A possible explanation is the evidence that increased bowel permeability may allow the translation of a gut microbiome product into circulation.

MicroRNA: Non-coding RNA and cardiovascular disease

microRNA can be defined as small ribonucleic acids (RNAs) that negatively regulate gene expression on the post-transcriptional level by inhibiting mRNA translation or promoting mRNA degradation. Several studies demonstrated that miRNAs dysregulation have a key role in the disease process and, probably, in every step, from formation to destabilisation.

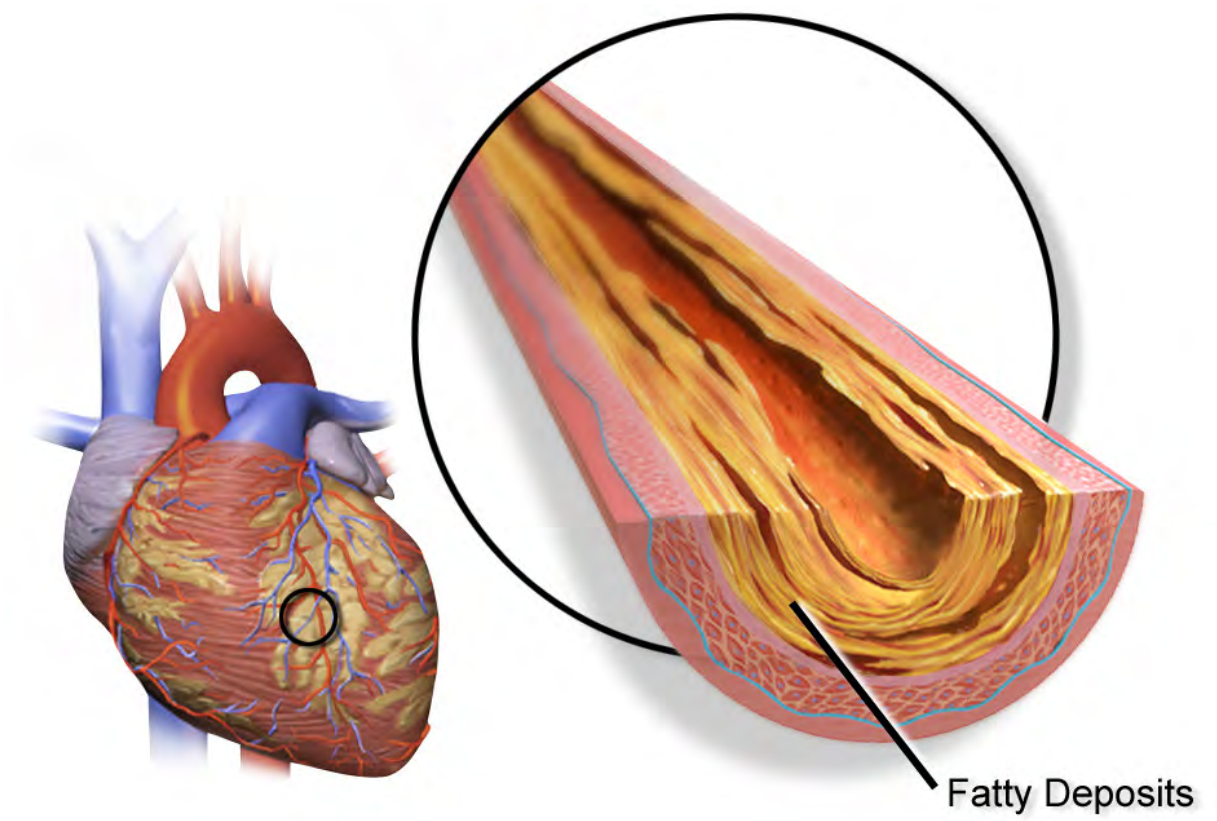

Image: Blausen.com staff (2014)

Several types of data in the available literature suggest a possible therapeutic application of miRNA modulation, in particular, dysregulated miRNAs can be modulated in the disease process, antagonising up-regulated miRNA and increasing down-regulated miRNAs. Therefore, miRNAs, although they have been largely used as biomarkers, may also represent a therapeutic option.

Long non-coding RNA are long RNAs – transcripts of more than 200nt not encoding for proteins, (lncRNA) and represent a challenging new class of epigenetic regulators. LncRNAs are deeply involved in cardiac development and pathophysiology but their mechanisms are still unknown.

As platelets are anucleated cellular fragment, they represent an ideal scenario to unlock ncRNAs undiscovered functions. And they may represent a further novel approach for cardiovascular diagnosis and treatment.

References

Correlation between CD4+CD28null T lymphocytes, regulatory T cells and plaque rupture: An Optical Coherence Tomography study in Acute Coronary Syndromes and Epicardial adipose tissue microbial colonization and inflammasome activation in acute coronary syndrome. Ruggio A, Pedicino D, Flego D, Vergallo R, Severino A, Lucci C, Niccoli G, Trani C, Burzotta F, Aurigemma C, Leone AM, Buffon A, D'Aiello A, Biasucci LM, Crea F, Liuzzo G, Int J Cardiol. 2018 Sep 7.

Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. N Engl J Med. 2017 Sep. 21;377(12):1119-1131.

Where Does Inflammation Fit? Biasucci LM, La Rosa G, Pedicino D, D'Aiello A, Galli M, Liuzzo G. Curr Cardiol Rep. 2017.

Biasucci LM, MicroRNA and myocardial infarction: a mystery turning into glory? J Am Coll Cardiol. 2013 Sep 10;62(11):999-1001.

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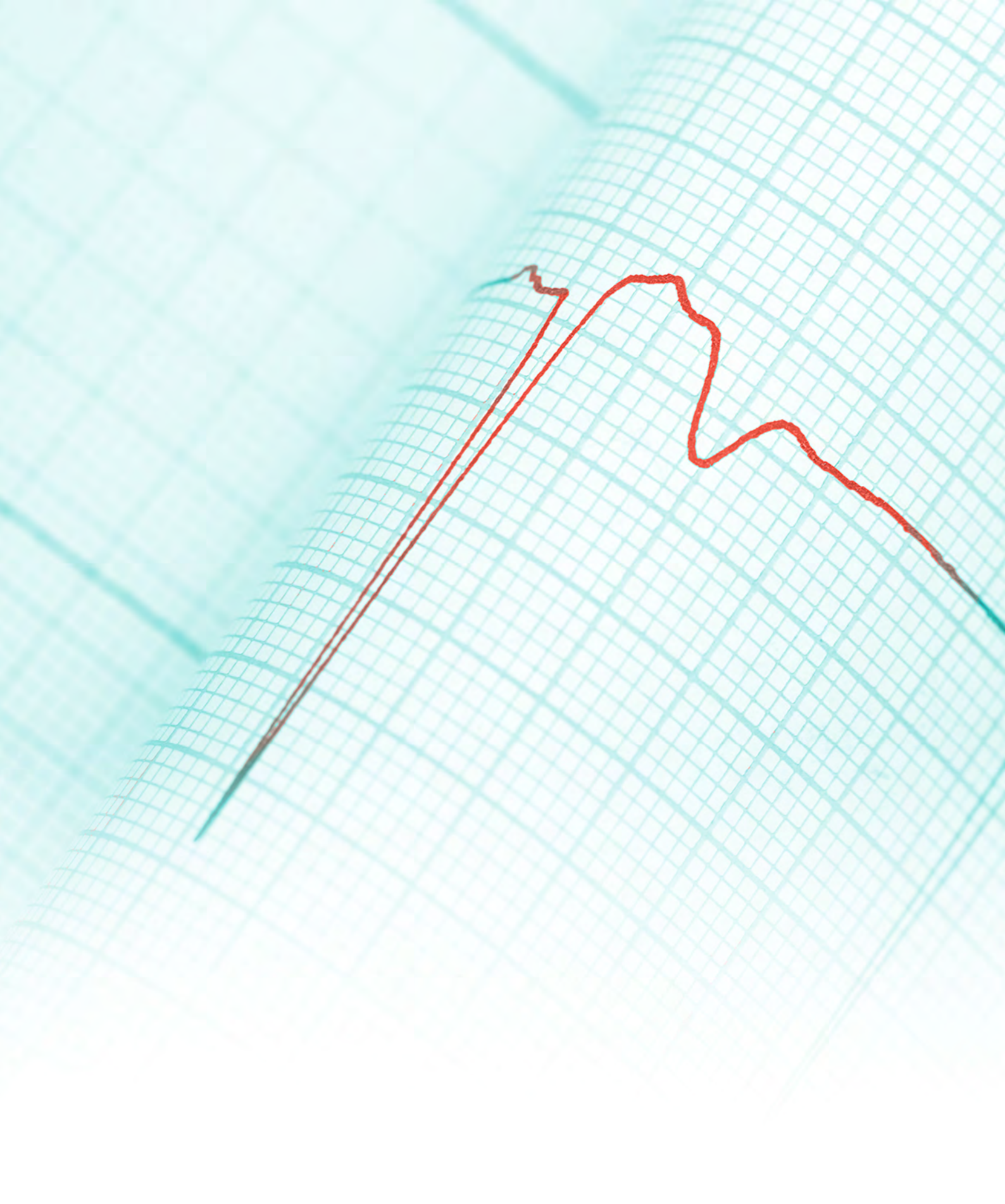

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