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Are PIEZO1 channels a potential therapeutic target for heart failure? Getting to the heart of the matter

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1. Introduction

Heart failure is a final pathway of many cardiovascular diseases [1]. It is characterized by high intra-cardiac pressure, low cardiac output, structural and functional cardiac abnormalities or combinations of these. It is a common problem, with a calculated lifetime risk of about 20%, increasing with comorbidities such as hypertension. It is associated with poor prognosis and a mortality of 6% per year or more, depending on the type of heart failure. It is age-related, so it is a particularly major challenge for societies that have high survival rates into old age. There are medical and device therapies but their benefits can be modest or lacking, most notably in the increasing problem of heart failure with preserved ejection fraction. Symptoms that matter most to patients are often unaddressed [2]. New therapeutic options are therefore of potential interest. An important yet mysterious aspect is the heart's intricate relationship with mechanical force, which changes in disease and has profound effects on the heart's gene expression and function [3, 4]. Could better understanding of this biology lead to transformative new treatments? The relationship is thought to be mediated partly or wholly by special ion channels that detect force and transduce it into cellular change [3, 4]. The molecular identities of the channels have been difficult to determine [3, 4] but a breakthrough occurred with PIEZO proteins, named after the Greek word for pressure.

2. PIEZOs in cardiovascular biology

Discovery of the two PIEZOs (PIEZO1 and PIEZO2) [5] was recognised in the 2021 Nobel Prize for Physiology or Medicine. These proteins assemble as trimers to form large Ca^{2+} permeable non-selective cationic channels of 114 (3×38) transmembrane segments each [6]. They respond in milliseconds to mechanical stimuli, generating depolarizing ionic currents and cytoplasmic Ca^{2+} elevations, which are both profound modulators of cell function. These channels are exquisitely sensitive to and apparently selective for activation by mechanical force: so-called professional force sensors [6]. They present opportunities for transformed understanding of the heart and potentially new therapeutics achieved through their modulation [6-8]. PIEZO1 in particular is noted for its roles in cardiovascular physiology and disease [8]. Specifically regarding the heart, there is evidence for functions of PIEZO1 in human cardiac microvascular endothelial cells, mouse and human cardiac fibroblasts, mouse cardiac myocytes, zebrafish and human cardiac valve formation and mouse cardiac remodelling [9-16].

3. Cardiac myocyte PIEZO1 in remodelling of the murine heart

Cardiac myocyte (cardiomyocyte)-specific deletion of PIEZO1 in mice has no obvious phenotypic effect or causes left ventricular hypertrophy, fibrosis and decreased ejection fraction, indicating no role of PIEZO1 in cardiomyocytes or a role in preserving normal cardiac structure and function [10, 12]. The relevance increases with age [10]. It might seem surprising, therefore, that genetically-engineered overexpression of cardiomyocyte PIEZO1 induces severe cardiac hypertrophy and arrhythmias, also increasing with age [10]. This

suggests that PIEZO1 needs to be just right – a little of it acting physiologically to protect the heart and too much damaging the heart. Neurohormonal mediators of unwanted cardiac remodelling such as angiotensin II, cell stretch and myocardial infarction or pressure overload in mice increase PIEZO1 expression [10-12, 16]. Cardiomyocyte-specific deletion of PIEZO1 strikingly protects against pressure overload-induced cardiac remodelling [11, 12] and loss of ejection fraction [12]. Downstream signalling of PIEZO1 to the CAMK2-HDAC4-MEF2 pathway is suggested [11].

These data suggest that cardiomyocyte PIEZO1 is part of a process that increases heart muscle function when the muscle is damaged or faced with abnormal demand because of pathologies or ageing processes such as valve disease, vascular stenoses or arterial wall stiffening. Such a mechanism may have evolved for survival benefits in the medium-term, serving to maintain organ blood supply despite the risks of long-term fundamental cardiac restructuring. In many modern societies, with their long lifespans and frequent vascular disease, it may ultimately contribute to a person's demise as the heart fails to cope despite or because of its adaptive capabilities.

4. Expert opinion

The mouse data outlined above raise the question of whether PIEZO1 antagonism could be a route to new therapies for heart failure, but more research is needed. For various reasons, genetic deletion studies do not necessarily indicate what would happen in therapeutic situations. Small-molecule, biological and depletion approaches of medical therapies usually reduce rather than completely remove the effect of a gene. Such attenuations could be advantageous here, paving the way to blunted PIEZO1 excess while sparing PIEZO1 physiological functions (Figure 1). To test such concepts experimentally, we would need to discover suitable PIEZO1 antagonists and investigate their effects in small and large animal models of different types of heart failure that incorporate risk factors and comorbidities, particularly in treatment protocols and measuring biomarkers that are relevant to clinical settings. We would then need to progress promising antagonists to human trials, guiding their design to the most relevant disease situations. A therapeutic window may need to be established through dosing studies that quantify potential adverse effects.

Human genetic studies provide only tantalising clues so far. PhenoScanner analysis of UK Biobank data suggests 3.6×10^{-20} probability of *PIEZO1* variation associating with the term "heart failure". More detailed analysis is needed, including deeper insight and information on heart failure subtypes and the disruptive or protective nature of variants. Genetic differences in different human populations should be considered because *PIEZO1* gain-of-function variants are much more common in some populations, notably peoples of current or recent African ancestry (at least partly because of advantage conferred by malarial protection) (see [13] for references to background information). About a third of these people carry such *PIEZO1* mutations, which conceivably drive PIEZO1 into excess and increase heart failure risk. Consistent with this hypothesis, recapitulated human *PIEZO1* gain-of-function mutation in mice induces cardiac hypertrophy and fibrosis [13].

PIEZO1 is not specific to the heart [6] but may rather be an almost ubiquitous force-sensing cassette of many cell types throughout the body. In part this could be beneficial for a PIEZO1 antagonist strategy because PIEZO1 is also in cardiac fibroblasts, where it drives the release of inflammatory and remodelling factors [13, 15]. The role of this PIEZO1 in models of heart failure is unknown, but its inhibition is expected to be protective against adverse cardiac remodelling. However, PIEZO1 antagonists might also have concerning extra-cardiac effects. PIEZO1 loss-of-function mutations are associated with a rare form of lymphedema [17], so a potential unwanted effect of antagonists is fluid retention, which can already be a problem in heart failure patients. These familial genetic studies of lymphedema also show us that the complete absence of PIEZO1 can be compatible with life and that its partial loss (due to haploinsufficiency or heterozygous disruptive mutation) can lack obvious adverse effects at least in early adult life [17]. Therefore, antagonism of physiological PIEZO1 might not be a major problem until there is at least 50% channel inhibition (Figure 1), a percentage estimated based on its potential equivalence to the effect of *PIEZO1* haploinsufficiency.

There could be challenges despite this positive perspective however, particularly in old people, in whom heart failure is most common and treatments are often considered. Genetic deletion of PIEZO1 in endothelium is associated with physical exercise limitations [18], which are already troubling in heart failure. PIEZO1 has important functions in heart valves, bone, skeletal muscle, immunity and beyond, so PIEZO1 antagonists might reduce heart valve function, bone and muscle strength and resilience against infection, accentuating pre-existing weaknesses already found in some heart failure patients. These are a few examples relating to known PIEZO1 functions. There could also be other PIEZO1 functions that are not yet identified. Ways forward in this situation could be to pay particular attention to such risks when investigating PIEZO1 antagonists in animal models and deciding on dosing regimens. Other ways forward could be to better understand PIEZO1 channels specifically in cardiomyocytes and cardiac fibroblasts because they may have specific features that enable their preferential antagonism – particularly the new PIEZO1 channels that arise in cardiac stress, of which we know relatively little [10-12, 16]. Abundance of PIEZO1 channels is normally low in cardiomyocytes (based on studies of young rodents), which may be why we so far lack information on the specific properties of these channels. Even for the enhanced (new) PIEZO1s of stressed cardiomyocytes, however, we lack electrophysiological or other biophysical knowledge.

5. Summary

This is a new field of research in an important disease area of increasing concern. The data published so far are notable for their quality and potential. Figure 1 suggests a hypothesis for how PIEZO1 antagonism might work in heart failure. Careful testing of such ideas and their clinical relevance will be important as we go forwards. A preliminary report suggests that it is possible to discover PIEZO1 antagonists [19] but much more work is needed to progress this aspect.

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Declaration of interests

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• of interest to readers

•• of considerable interest to readers

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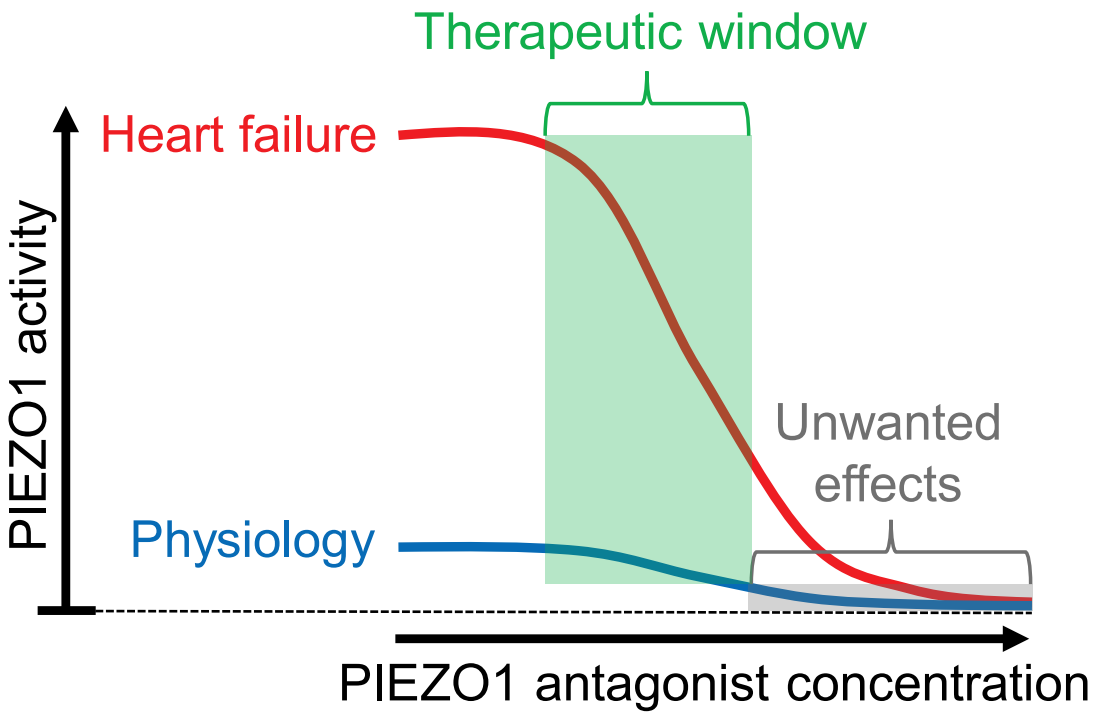

Figure 1 Hypothesis for PIEZO1 and PIEZO1 antagonist therapy in heart failure. PIEZO1 expression or activity is low in the absence of disease (i.e., Physiology) but elevated in the heart when there is sustained stress and heart failure. PIEZO1 antagonist inhibits the excess PIEZO1, leading to therapeutic benefit. Physiological PIEZO1 is inhibited but unwanted effects occur only at supra-therapeutic antagonist concentrations when there is more than 50% PIEZO1 inhibition.