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MINI-REVIEW

Mechanobiology in cardiology: Micro- and nanotechnologies to probe mechanosignaling

Sharda Yadav[1] | **Hang T. Ta**[1,2] | **Nam-Trung Nguyen**[1]

[1] Queensland Micro- and Nanotechnology Centre, Griffith University, Nathan, Queensland, Australia

[2] School of Environment and Science, Griffith University, Nathan, Queensland, Australia

Correspondence
Nam-Trung Nguyen, Queensland Micro- and Nanotechnology Centre, Griffith University, Nathan, QLD 4111, Australia.
Email: nam-trung.nguyen@griffith.edu.au

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Abstract

The past few decades have shown significant growth in the study of mechanical effects on cellular properties. Novel methods and techniques had been developed to analyze the changes in the biophysical and biomechanical properties of cells. Recently, it has been reported that interaction between the external environment and cardiomyocytes would be essential for the function of the heart due to the importance of mechanical signaling. Physical forces play a major role in the development of cardiovascular disease. In this mini review, we discuss recent advances in technology for probing mechanobiology signals from the cardiac tissue and focus on the unmet needs and challenges to completely understand the mechanobiology of cardiac tissues.

KEYWORDS
cardiology, cell stretching, mechanobiology, mechanotransduction

1 | INTRODUCTION

Cells respond to changes in their environment. Over the past few decades, the interactions between cells and their physical environment have been extensively studied. Mechanobiology elucidates the role of mechanical signals in controlling cell behavior.[1,2] Cells are interconnected with each other as well as with extracellular matrix (ECM) by physical stimuli such as shear stress, pressure, tension, and matrix elasticity. Utilizing biomechanics to explain the biological and physiological functions at different levels is the main basis of this emerging area of mechanobiology.[3]

Abbreviations: AFM, atomic force microscopy; BRET, bioluminescence resonance energy transfer; CFTR, cystic fibrosis transmembrane conductance regulator; FRET, fluorescence resonance energy transfer; MEF, mechanoelectric feedback; NSOM, near-field scanning optical microscopy; TFM, traction force microscopy; TRP, transient receptor potential

Mechanobiology elucidates the role of these physical stimuli through mechanotransduction. Mechanobiology has become one of the major research focuses due to the ubiquitous impact that mechanical stresses impart on cell behavior such as signaling and gene expression.[4] Integrin-mediated mechanotransduction has contributed to advances in many fields mostly in stem cell differentiation and cancer progression.[5] Recently, it is also suggested that interaction between the external environment and cardiomyocytes would be essential for the function of the heart due to the importance of mechanical signaling in this vital organ.[1]

Mechanotransduction is the progression of converting physical stimuli to biochemical signals and connecting the generated signals into cellular responses.[6] The process can be divided into three parts: (i) mechanoreception—stimulus is detected, and the signal is transmitted from outside to inside the cell, (ii) intercellular signal

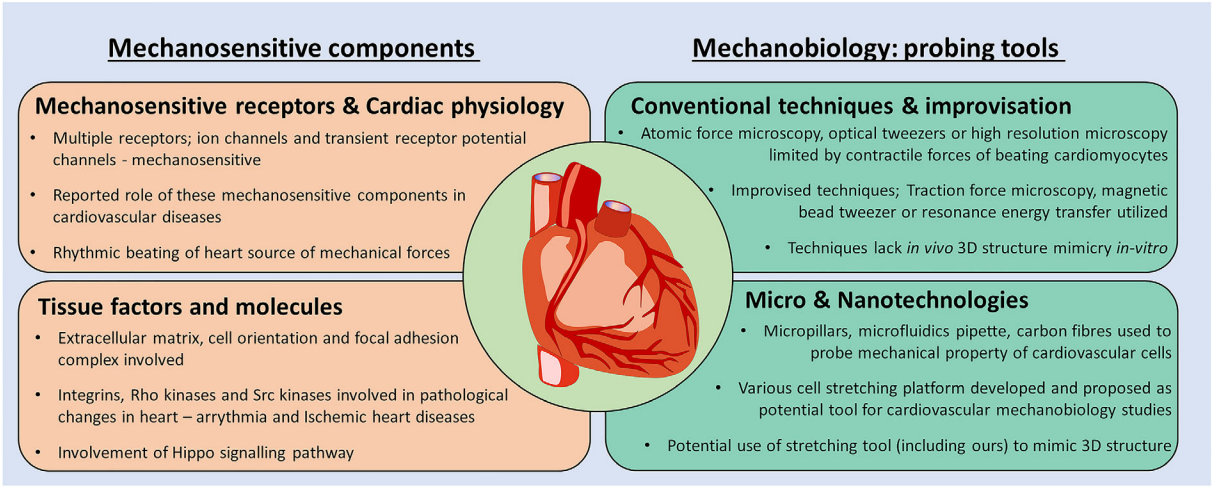

FIGURE 1 Overview of mechanosensitive components and technologies to probe them in cardiovascular tissues. In addition to conventional mechanobiological cues like ECM stiffness, cell orientation, and Rho signaling, multiple mechanosensitive receptors are present in the cardiovascular tissue, which are involved in both normal function and cardiovascular diseases. These cues have been probed by conventional techniques in mechanobiology studies and recently micro and nanotechnologies have been developed to further advance these studies

transduction—signal transduction inside the cell to generate the molecular response, and (iii) activate target—activation of protein that makes changes in cell behavior by various mechanisms.[7] Mechanical forces had been introduced as an important feature in the cellular processes and extra matrix signal processing for the regulation and function of the cells. The mechanical properties of the environment affect morphological changes, differentiation, proliferation, adhesion, growth, locomotion, and development of a cell.[8–10] The differences in these measures indicate the state of diseases that are mostly caused by changes in the mechanical and biochemical microenvironment.[11] The study of cellular mechanics in different diseases and technologies to probe this will help us to better understand the cellular behavior in the microenvironment. As the field has progressed rapidly in recent years, several reviews have been published. However, there is a lack of study that discusses the challenges associated with the available techniques for mechanobiology studies of the heart. The present review will discuss the recent advances in the technology and focus on the unmet needs and challenges to probe the mechanobiology signal from the cardiac tissue (Figure 1).

2 | MECHANOBIOLOGY INVOLVEMENT OF CARDIOVASCULAR TISSUE

2.1 | In normal physiology

The heart is one of the most prominent organs associated with mechanosensitivity. The normal physiology of heart is regulated by the mechanoelectric feedback (MEF) mechanism.[12] The cells of the heart, cardiomyocytes, are electrically excited. The electric signal is converted into mechanical stimulation.[13] This mechanical stimulation then provides feedback for electrical excitation maintaining the rhythm of the heart, hence called MEF.[14,15] Stretching of the cardiomyocytes affecting the electric signaling of the heart was reported as one of the early relationships between cells stretching and its biological impact.[14] The stretch-activated channels are also involved in the MEF mechanism. Physiological rhythm of the heart itself changes the orientation of the cardiomyocytes and arrangement of intramyocardial myocytes. This innate property makes it difficult to monitor if the changes in cells are due to normal physiology or pathological state. To overcome this problem, solutions such as concurrently monitoring mechanical and electrical changes have been applied to mechanobiology studies of cardiac cells.[16,17]

Cardiac mechanobiology involves the transduction of mechanical signals not only to biochemical signals but also to electric signals usually via ion channels.[18] Sodium channels, potassium channels, calcium channels, chloride channels, and nonspecific cationic channels also known as transient receptor potential (TRP)-type ion channels are involved in mechanosensing in the heart. These channels respond to the stimuli (both mechanical and electrical) and change their conformation to allow the permeation of ions. Kv7 potassium channel family responds to cell volume and calcium channel, cystic fibrosis transmembrane conductance regulator (CFTR) responds to stretch stimulus on the membrane and swelling, and TRP channels respond to cellular pressure. Members of TRP channel—TRPC1 and TRCP6—activate by stretching, whereas

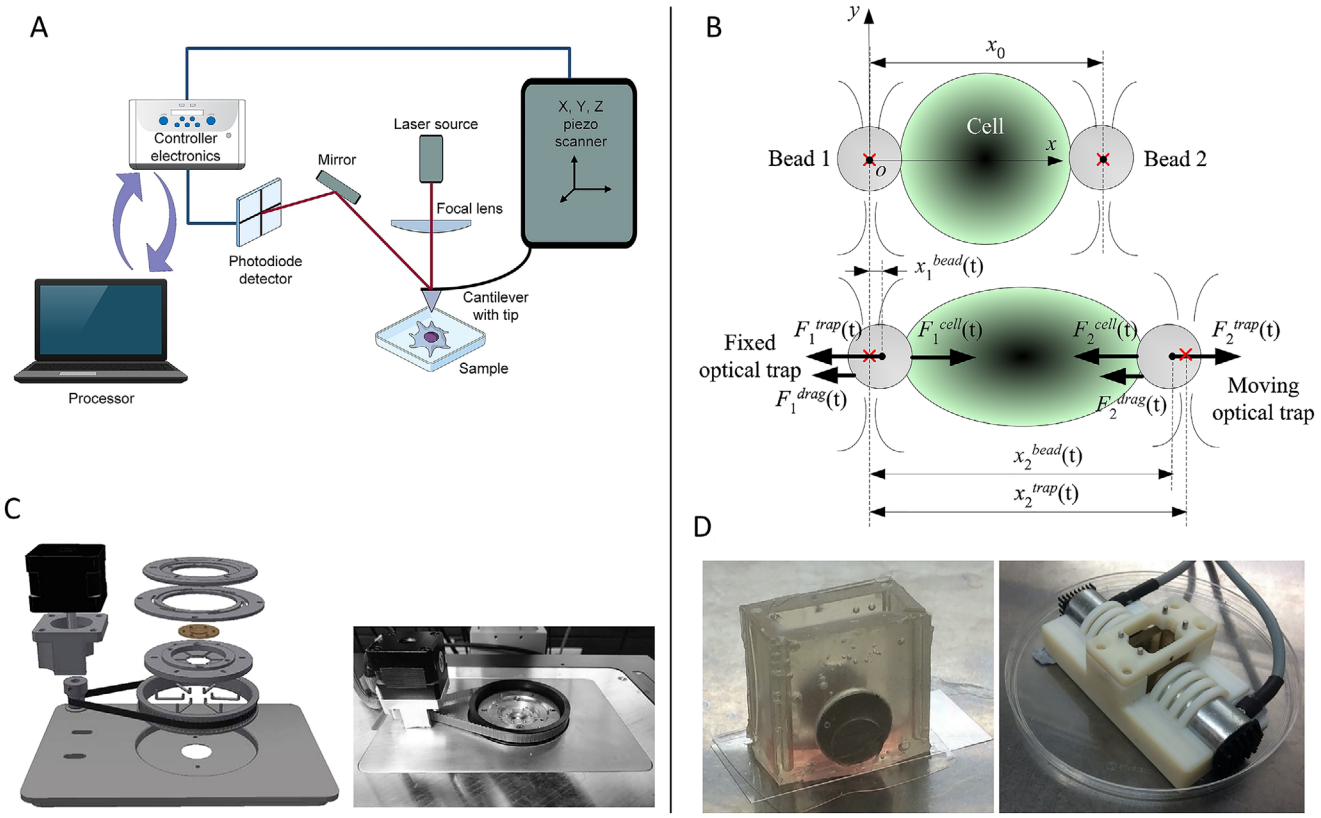

FIGURE 2 Methods for studying of mechanobiology in cardiovascular tissues: (A) A setup with AFM for measuring the tissue stiffness with a cantilever probe.[49] Copyright 2018, Elsevier. (B) Optical tweezer setup to tether and manipulate individual cells.[50] Copyright 2012, Elsevier. (C) Isostretcher setup to stretch cells using motor driven system.[51] Copyright 2016, Elsevier. (D) Electromagnetic stretching system, in which the well has enough space to introduce hydrogels for three-dimensional cell culture and stretch the cells in the presence of these hydrogels or any other additional components.[52] Copyright 2019, Elsevier

TRPV4 re-orients cells in response to this mechanical stimulus.[19–21]

In addition to the cardioselective mechanosensitive molecules, various other factors play a role in mechanotransduction in the heart. Extracellular matrix, cell orientation, and focal adhesion complex are involved in cardiac mechanosensing by usual mechanotransduction pathway, the Hippo pathway.[22,23] Molecules such as integrins, Rho kinases, or Src kinases are also involved in mechanotransduction and are associated with pathological changes in the heart such as ischemic heart diseases or arrhythmias.[12,24–26]

2.2 | In cardiovascular diseases

Involvement of mechanobiological cues—particularly, the channel responding to the mechanical stimulation—has been studied in relation to cardiovascular diseases.[27,28] The most common implication of the change in mechanobiological signals in cardiac tissue is arrhythmia. This irregular heartbeat is noted with slight changes in MEF.[29] Stretching of atrium of the heart changes the action potential (electric signaling) leading to arrhythmia. TRPV4 channel is reported to be involved in the dysregulation of the heartbeat by delaying polarization. However, further research is still warranted to develop an effective therapy for arrhythmias. TRPV4 showed involvement in hypertension and caused mechanical stimulation of cardiomyocytes via mechanobiology signal transduction pathways.[30,31] TRPV4 along with other channels such as TRPC1 and TRPC6 has demonstrated a role in cardiac hypertrophy.[18,32] Although the exact mechanism is still unknown, it has been reported that TRPC6 mediates the hypertrophy of cardiomyocytes via calcium-dependent regulatory loop.[33,34] Progressive and chronic cardiomyocytes hypertrophy is the basic cause of cardiac failure. TRPC6 is reported to be hyperregulated in the myocardial infarction. Potassium channel (K_{ATP}), another channel involved in myocardial infarction, has been shown to precondition ischemic effects in the heart in response to mechanical stretching. Similarly, calcium channel (CFTR) has shown ischemic preconditioning via osmotic swelling during regulation of cell volume.[35] These mechanosensitive molecules contribute to myocardial infarction by their ischemic preconditioning. However, the relation between

them and if the act of response to stimuli is different or a part of single mechanobiological signaling cascade are still unknown.

3 | TOOLS TO MEASURE MECHANOBIOLOGICAL SIGNAL FROM CARDIAC TISSUE

The most common techniques for probing mechanobiological cues in cardiovascular system depend on probes, tools, or nanoscale structure of materials. Atomic force microscopy (AFM), optical tweezers, and high-resolution microscopy imaging, common techniques with molecular-level sensitivity, have been used to elucidate the cardiovascular physiology or pathology (Figure 2).

3.1 | Atomic force microscopy

Although being developed for solid material analysis, AFM has been popular for biological material analysis.[36,37] Biomechanical forces are measured by bringing the cells in contact with the cantilever of the AFM. The deflection of the cantilever provides information on the interaction forces between the cells and the cantilever tip. In cardiomyocytes, normal heart beating also contributes to AFM cantilever deflection, therefore it is complex to utilize this technology for measuring changes of active forces.[38] The active vertical force of the cardiomyocytes was offset for the measurement of lateral contraction forces of the cells and subsequent stiffness measurement.[39–42] However, due to difficulty in accessing this type of force and difference caused by beating cardiomyocytes, AFM is not the method of choice for mechanobiological studies in cardiac cells.

3.2 | Optical tweezers

Optical tweezer is well known in mechanobiological studies, where a single cell is tapped between two beads.[43,44] One of the beads is fixed and the other is moved along the centroid to stretch the cell. Images taken by this approach are then analyzed to obtain the time the cell takes to return to its original shape and consequently estimating its stiffness. The stiffness of embryonic stem cells varies when they differentiate into cardiomyocytes.[45] The difference in stiffness is caused by the myofibrillar structure of cardiomyocytes. However, this phenomenon is hard to measure using the optical tweezers once the cells are in a contractile state. Typically, the force applied by an optical tweezer is less than 1 μN to avoid light damage to the cells, whereas the contractile force of cardiomyocytes is already on the order of μN, making the technology not suitable to use in contractile cardiac cells.

3.3 | High-resolution microscopy

Video-enabled high-resolution microscopy has also been utilized to measure the mechanical changes in cardiac cells. The most common microscopy-based technique is the measurement of displacement between the contraction and relaxation cycles. Although easy to gather information, analysis of data is critical in this assay as the cells loose structure to the extent that sometimes their membrane remains undefined. Furthermore, direction of contraction cannot be controlled in this setup leaving it to create algorithms with multiple assumptions for force calculations. In recent microscopic methods, labeling dyes have been used for various cell components such as calcium or fluorescent dyes for cell organelles. These dyes allow for correlating different structural parameters and hence better data interpretation. Microscopy technique has been advanced to near-field scanning optical microscopy (NSOM) for resolving topography and optical properties at a greater resolution compared to confocal microscopy. The NSOM has a resolution capacity of 40-100 nm and has been successfully deployed to investigate the contraction of a beating cardiomyocyte.[46]

Other techniques including resonance energy transfer techniques (fluorescence resonance energy transfer [FRET] and bioluminescence resonance energy transfer [BRET]), traction force microscopy (TFM),[47] and moving magnetic bead tweezer have been employed for studying mechanobiology in cardiac cells.[48] Techniques such as FRET or BRET have leveraged the single-molecule energy transfer property to measure the distance between molecules and their conformation especially for deciphering mechanisms for Adenosine Triphosphate (ATP)-sensitive potassium channels. TFM was employed as an indirect measurement tool, where the displacement of a marker was utilized to report the force exerted by the cardiomyocytes on the substrate. Moving magnetic bead tweezer was developed to overcome the limitation of the optical tweezers where the bead was magnetically manipulated along the centroid to stretch the cells avoiding the damage caused by highly focused light.

4 | RECENT ADVANCES IN CARDIAC MECHANOBIOLOGY

Although these conventional techniques are important for providing fundamental information on cardiac

mechanobiology, these techniques come with their own limitations. The cardiac tissue itself is highly unique due to its stratified nature and high viscoelasticity together with regular features of tissues such as spatial-temporal orientation and three-dimensional structure. Novel techniques have been employed to incorporate one or the other elements of the cardiac tissue. Microfluidics combined with micro/nanotechnologies has been the platform of choice in these setups.

One of these techniques is introducing micropillars to the cell culture. The deformable pillars usually made of hydrogels will bend in response to the cellular forces. This methodology was applied in monolayers of cells but does possess a potential for three-dimensional cardiomyocytes culture. These easily fabricated micropillars were used to measure the contractile forces of single cells of cardiomyocytes. The major limitation of this technique remains in matching the stiffness with physiological conditions. Microfluidics micropipette was also utilized for measuring the mechanical property of nucleus in the fibroblast harvested from an individual with cardiomyopathy. In contrast to AFM, this technique is flexible due to the tunable pressure exerted on cells and of high throughput. Another technique is attaching cardiomyocytes to carbon fibers for mechanical manipulation.[53] A micromanipulator holds the fibers and presses them against the cell membrane without damaging it. Zhang et al utilized scanning ion conductance microscopy for mechanobiological probing of cardiomyocytes to validate mathematical models.[54] The team utilized a noncontact method that measures elasticity and viscosity of the cytoskeletal structure and not the cells themselves. The results were verified by AFM and micropillars demonstrating clear correlations in mass, elasticity, and viscosity.

An approach that has been repeatedly used for measuring mechanical forces in various cell types including cardiomyocytes is cell stretching. Cell stretching can be achieved in two ways: (i) the cells are directly pulled by tethering them onto a stretching platform and (ii) the cells are stretched by pulling the surface where the cell is cultured and adheres to. The second approach of cell stretching has been gaining popularity as the surface for cell growth can be easily fabricated. Biaxial or multiaxial stretching systems are available for mostly two-dimensional cell culture, whereas efforts are ongoing to develop stretching platforms for a three-dimensional cell culture.

Motor-driven stretching system such as the isostretcher or the iris like system Cellerator has been used with endothelial cells for stretching experiments.[55] Pneumatically driven systems such as Flex I, Bioflex, or TissueTrain were also used in such experiments. We have developed a two-sided electromagnetic cell stretching system and used it for stretching various types of cancer.[52,56,57] Our simple design has the potential to add hydrogels into the system and convert it to a three-dimensional stretching system. The addition of hydrogels for cell stretching has been proposed by various researchers but has not been implemented due to limitations of the stretching device. Fredrick et al reported an attempt to stretch cardiomyocytes on a hydrogel-embedded three-dimensional culture on an isostretcher system. However, this work seems to be only a proof-of-principle experiment and have not yet reported any results of the stretching experiment.[51] Polacheck et al reported a microfluidic device capable of mimicking the tubular structure of blood vessels with the potential to incorporate different ECM materials.[58] The system depends on the stiffness of the matrix material and cannot implement external stretching as the other platforms.

5 | CONCLUSION AND FUTURE OUTLOOK

As indicated by previous literature in the field and the growing knowledge in understanding that the mechanical forces are involved in cardiovascular diseases, there is a need to further explore cardiovascular mechanobiology. The main challenge of mechanobiology research is still the limitation to replicate in vivo forces in the tissue, which is even more complicated in the heart due to its beating nature. For a complete understanding of the mechanobiology of cardiac tissues, multiple factors need to be considered. An ideal system will be capable of incorporating the striated nature, spatiotemporal arrangement, viscoelasticity, and three-dimensional structure of cardiac tissues. It is also equally important to include the capacity to alter the individual properties for studying the effects of changes in individual parameters. Different hydrogels with photoactivity such as photocatalytic degradation, changes in stiffness and viscosity have been proposed for mechanobiology research to address the above challenges. However, these concepts have not yet been applied to cardiac cells. With advances in microfluidics, the development of in vitro systems that mimic biological systems at the cellular or tissue levels could be soon a reality. The major challenge still lies in replicating the responses previously recorded on a two-dimensional system with a three-dimensional system.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORCID

Sharda Yadav https://orcid.org/0000-0002-5838-2270
Nam-Trung Nguyen https://orcid.org/0000-0003-3626-5361

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AUTHOR BIOGRAPHIES

Sharda Yadav received her PhD from QMNC at Griffith University, Australia in 2020. After receiving her PhD degree, she joined QMNC as a Research Fellow. Prior to starting her PhD candidature, she obtained her BSc degree in Medical Laboratory Technology and MSc degree in Medical Laboratory Technology in clinical Biochemistry from Manipal University, India. Her research background lies in the development of novel diagnostic technologies for the early detection of diseases. Her research interest includes uncovering the role of biophysical properties associated with the microenvironment of a tumor and cardiovascular diseases.

Nam-Trung Nguyen received his Dipl-Ing, Dr Ing, and Dr Ing Habil degrees from Chemnitz University of Technology, Germany, in 1993, 1997, and 2004, respectively. From 1999 to 2013, he has been an Associate Professor with Nanyang Technological University in Singapore. Since 2013, he has been serving as a Professor and the Director of Queensland Micro- and Nanotechnology Centre of Griffith University, Australia. He is a Fellow of ASME and a Senior Member of IEEE. His research is focused on microfluidics, nanofluidics, micro/nanomachining technologies, micro/nanoscale science, and instrumentation for biomedical applications. One of his current research interests is developing flexible and stretchable systems with bio interface.

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