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# The Role of Microtubules in Heart Failure

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**Abstract**

Heart failure (HF) is a complex pathological state in which cardiac performance fails to match perfusion demand, commonly preceded by an enlargement of the heart known as cardiac hypertrophy. Pathological changes in the microtubule network (MTN) organization have been shown to increase cellular stiffness and lead to contractile dysfunction of cardiomyocytes. In this narrative review, we are focusing on the role of the microtubule and also its mechanism in the heart, especially in HF. We conducted literature research for published articles carried out from 2012 to 2022. Microtubules are polymers that serve as structural elements with the shape of long, rigid tubes that are highly dynamic. The stiffness of the myocardium is largely influenced by the MTN. Through various methods, the MTN is remodeled during cardiac hypertrophy and HF. Targeting microtubules for the treatment of HF might become a new approach to improve the outcome. While colchicine inhibits various microtubule-dependent cellular in interphase cells and proliferation, it needs further study for the safety of the adjusted dosage. Manipulating detyrosination of microtubules might be useful for restoring the function of failing myocytes although there are still very limited data on this.

## Introduction

Heart failure (HF) is a complex pathological state in which cardiac performance fails to match perfusion demand, commonly preceded by an enlargement of the heart known as cardiac hypertrophy and characterized by an increase in myocyte size during an absence of cell division. It may be considered a compensatory or adaptive process, as a response to pressure or volume overload. Most patients with HF have impaired relaxation of the left ventricle and increased filling pressures. Aiming to increase cardiac output by decreasing afterload or reinforcing myocardial force production is a treatment strategy for individuals with HF and a reduced left ventricular ejection (HFrEF) [1], [2], [3]. With every heartbeat, these cells transfer contractile stress mainly via cytoskeleton fiber components (actin, microtubule, and intermediate filaments). Actin acts as the driver of cell motility, whereas microtubules arrange chromosome segregation in cell division, however mature cardiomyocytes are neither motile nor proliferative. Instead, their cytoskeleton is uniquely adapted to meet the needs of a long-lived, constantly working muscle cell. Most actin is organized into sarcomeric units that participate in the sliding filament model of contraction, but the adopted roles of the microtubules have stayed relatively obscure [4], [5]. If any of these connections are missing, anomalous or unbalanced, further mechano-dynamic behavior of the cardiomyocyte is affected.

Microtubules are hollow 25 nm diameter tube polymers of $\alpha\beta$-tubulin dimers that form a complex network throughout the cytoplasm, they can run tens of microns, and are the stiffest of the cytoskeletal filaments. Pathological changes in the microtubule network (MTN) organization have been shown to increase cellular stiffness and lead to contractile dysfunction of cardiomyocytes [4], [5], [6].

Inconsistencies have been associated with the severity of disease stimulus required to cause microtubule proliferation, raising the doubt of relevance in human HF [7]. Hitherto, therapeutic interventions targeting microtubules for the treatment of cardiovascular disease have been concentrated on the depolymerization of cardiac microtubules using colchicine administration, which has been found to enhance myocardial function in many murine, feline, and canine models of HF [8]. What's promising too is a reduction potential of microtubule detyrosination using a genetic approach, which softens cardiomyocytes

and improves contractile kinetics [7]. Yet it is unclear whether these benefits are conferred due to underlying changes regarding myocardial mechanics. Therefore, understanding the molecular determinants of hypertrophy may reveal a novel focus for HF prevention [2], [3]. This review will summarize recent advancements, how experimental techniques are shedding mechanistic clarity in microtubule functions and mechanics, as well as offer our standpoint on the captivating points for future research.

## Methods

Narrative Review is the method used in this study. We conducted a literature search for published articles carried out from 2012 to 2022. The literature came from various database namely *Pubmed* and *Google Scholar* based on agreed criteria from the authors. The selection of studies was done and agreed on by three reviewers, screening for duplicates was done automatically using the citation manager software *Mendeley*. There were no limitations on the type of study, but only English and Indonesian were included.

## Microtubule Fundamentals

Microtubules is a non-covalent multitasking polymers that serve as structural elements in most eukaryotic cells with a shape of long, rigid tubes with a diameter of 25 nm that are both polarized and highly dynamic [5], [9], [10]. They exhibit cycles of growth, shortening, and regrowth while this energy-consuming process is called dynamic instability [9]. The dynamic instability features allow microtubule tips to explore the volume of a cell, continuously searching for and binding to intracellular structures and also necessary for interplay between the tubulin and actin cytoskeletons. Cytoskeleton is an integrated filamentous protein network that gives cells their shape, facilitates their movement, organizes their cytoplasm, and builds the spindle needed to segregate genetic material [10]. Polarity is essential to the movement of motor proteins on the microtubule surface and also the root of differences in the kinetics of subunit addition and loss at the two microtubule ends [9].

Microtubules are made of the protein tubulin, arranged in linear stands called protofilaments [9]. Usually, a microtubule contains 13 protofilaments assemble laterally to form a hollow cylinder, each of which is assembled from a head-to-tail arrangement of $\alpha/\beta$-tubulin heterodimers to form a polar protofilament with a-tubulin exposed on one end and b-tubulin on the other [9], [10].

Microtubules grow by adding GTP-bound $\alpha\beta$-tubulin heterodimers to their ends. Incorporation into the microtubule facilitates GTP hydrolysis (Figure 1), resulting in the growing tip being capped by GTP-tubulin while the microtubule lattice consists primarily of GDP-tubulin [11]. If the cap is lost, a microtubule shrinks rapidly from its plus end [5]. Exposing GDP-tubulin at the tip results in catastrophe, the switch from growth to shrinkage. The transition from shrinkage to growth is called rescue. Due to the highly dynamic instability, the formation of long filaments can be reorganized on the timescale of minutes [11].

## Microtubule-based Transport in the Heart

Microtubules are stabilized in particular sites by the search and capture process, resulting in preferred delivery pathways. This delivery system helps to develop, sustain, and remodel specific domains in cardiomyocytes [12]. Below, we focus on the microtubule-based transport at the dyad, intercalated disc, and local translation. The microtubule-based transport at the dyad, intercalated disc, and local translation are discussed in detail below.

### *Microtubules-based transport at the dyad*

Interfibrillar structures at the Z-disc are associated with microtubules, which regulate the transport and placement of several essential components relating to E-C coupling. In myocytes, the sarcoplasmic reticulum (SR) and T-tubule membranes are widely dispersed throughout the cell and make frequent contact at the Z-line in formations known as dyads [13]. Dyads facilitate Ca2+ influx from the T-Tubule, which quickly prompts Ca2+ release from adjacent junctional SR stires, maintaining effective excitation-contraction coupling. As a result, the synthesis and stability of dyads and their maladaptive remodeling in response to cardiac stress can be facilitated by microtubule transport [5].

To keep the dyad stable, T-tubules must be attached to the junctional SR in a suitable manner when they are first created. Membrane tubulation in the dynamic SR is powered primarily by kinesin and dynein motility [14]. A physical link between the SR and microtubules is known to help shape the junctional SR specialized ends. SR and T-tubule membranes may be brought into proximity by microtubule-dependent membrane motility, allowing structural proteins such as junctophilin-2 (JPH2), which directly connects T-tubule and SR membranes, and associated Ca2+ channels to stabilize dyads [15].

Dysfunctional dyads are a typical HF symptom, and it appears that pathological remodeling of the MTN

and the consequent loss of JPH2 are at least partially responsible [5], [16]. Furthermore, Microtubule-mediated misregulation of JPH2 results in T-tubule disruption and calcium mishandling, and lowering microtubule density can restore dyad structure and enhance ventricular function, suggesting a causal role for microtubules in the misregulation of E-C coupling in disease [8].

### *Microtubules-based transport at the intercalated disc*

Another interesting area with known clinical value and rising reliance on microtubules is the intercalated disc. The intercalated disc is a specific junction between cardiomyocyte ends that allows for physical and electrical coupling. Desmosomes, adherents, and gap junction complexes are three distinct transmembrane complexes in the disc [5], [17]. Desmosomes link to desmin intermediate filaments, adherens junctions attach to the actin cytoskeleton, and gap junctions offer an electrical connection between adjacent cells through connexin 43 proteins that create low resistance channels [5]. It has been shown that connexin is rapidly downregulated during myocardial infarction, resulting in a loss of protein localization to the intercalated disc [8].

It is microtubule traffic that keeps the intercalated disc's primary components working. Microtubules transfer oligomers of connexion to the intercalated disc through motor-based transport, with the support of EB1 and p150 glued attaching of the microtubules' growing end to adherens junctions via N-cadherin [18]. Disorganization of intercalated discs is linked to changes in the microtubule cytoskeleton, which is similar to HF's dyads dysfunction [19]. Interfering with the intercalated disc interaction eliminates connexin 43 accumulation at the intercalated disc, which happens in response to oxidative stress [20]. Several cardiac disorders are characterized by oxidative stress, including ischemic heart disease, cardiac hypertrophy, and HF. A research done by Goldblum *et al*. found that A drastic, pathogenic change in the MTN of cardiac myocytes was caused by oxidative stress, which resulted in an increase in cellular stiffness and contractility [6].

### *Microtubules based transport and local translation*

The MTN appears to be the main organizer of mRNA distribution and localized translation in cardiac and skeletal muscle, according to many independent studies. Kinesin1 has a role in active, microtubule-based transport, which is critical for the distribution of mRNAs and ribosomes. The global rate of protein translation in cardiomyocytes increases in response to hypertrophic stimulation. A surprising finding is that redistribution of the MTN and enhanced expression of kinesin 1 can occur simultaneously with the redistribution of mRNA and ribosomes to the ends of cardiomyocytes. A cardiomyocyte's growth is inhibited if microtubule transport is disturbed, even while global synthesis rates still increase [21]. This study suggests that the MTN-dependent location of protein synthesis is a critical predictor of the insertion of new sarcomeres and cardiac hypertrophy.

## Microtubule Role in Cardiomyocyte Mechanics

The buckling of microtubules at short wavelengths that match sarcomeric periodicity is caused by the contraction of cardiomyocytes. Buckling is caused by crosslinking of longitudinal microtubules with transverse desmin intermediate filaments at the sarcomere Z-disc. Based on the amount of microtubules in a healthy myocardium and their high inherent stiffness, microtubule buckling is expected to offer resistance equivalent to around 20% of the cardiac contractile force [22].

For the MTN to mechanics, detyrosination, a mechanical coupling that links microtubules, intermediate filaments, and the contractile machinery, is required. Stiffness in the myocardium is largely influenced by the MTN during the cardiac cycle of 1.8–2.1 nm sarcomere length [23]. The viscoelastic characteristics of the crosslinking contact between microtubules, intermediate filaments, and myofilaments is short and confined in strength. The interconnection may be promoted by microtubule–intermediate filament crosslinkers such as plectin and kinesin, the strength of which can be regulated by detyrosination, or direct interconnection [5]. As a result of the MTN's viscoelastic structure, it is highly dependent on the amount of lengthening or shortening, which might have significant ramifications for cardiac function during exercise. When the heart rate is raised during exercise, the rate of diastolic filling rises to maintain stroke volume [23]. This circumstance produces a setting in which viscoelastic forces may restrict cardiac stretch and stroke volume, and patients with diastolic HF often have lower end-diastolic volumes despite increasing diastolic pressures during exercise [24]. Various pathological processes in dilated, ischemic, and hypertrophic cardiomyopathies seem to coincide on changes to the MTN that increase its contribution to myocardial stiffness [5].

## Microtubule Remodelling in HF

Chronic pressure overload leads to cytoarchitectural changes in the heart characterized

by structural remodeling of the muscular, vascular, and extracellular matrix components of the myocardium [1]. During cardiac hypertrophy and HF, the MTN is significantly remodeled and acts as a double-edged sword. On the one hand, a proliferated and stable MTN is essential for the development of cardiac hypertrophy in response to stressors, yet upon chronic stress densified MTN can also contribute to contractile dysfunction in HF [2], [7].

Consequent to the densification of microtubule and intermediate filament, organization and loss of actomyosin content often occurs in advanced HF. Given their abundance in the cell, it is far in all likelihood that microtubules may mediate the hypertrophic reaction through more than one pathway. For example, microtubules assist in shipping sarcomeric mRNAs for nearby translation and incorporation into myofibrils, which can be crucial for constructing new sarcomeres for the duration of hypertrophic growth [2].

## Autoregulation of Tubulin

The growth rate of microtubules is fixated by the concentration of free tubulin ready for polymerization, therefore, an increase in free tubulin levels will essentially densify the MTN. However, cells carry on a brake to this feedforward mechanism via tubulin autoregulation, under a detectable increase in soluble $\alpha\beta$-tubulin concentration, they trigger degradation of tubulin mRNAs via a process termed tubulin autoregulation. As a result, if free tubulin levels decrease, autoregulation is relaxed to increase mRNA stability and restore free tubulin levels [5], [25].

Autoregulation has been shown to operate on all detectable tubulin isoforms in cardiomyocytes. Renowned stabilizing factors in the heart include detyrosination, acetylation, and microtubule-associated protein 4 (MAP4) binding. Stabilization is sufficient to induce pathological remodeling and impair cardiac function. While there is extensive proof that destabilizing microtubules can dull the hypertrophic reaction, it stays an open inquiry regarding whether destabilization could reverse established cardiac remodeling, and whether such a treatment might be endured [2], [5], [26]. Whether hypertrophic or dilated in morphology, end-stage HF shares a surprisingly overlapping proteome. A dominant feature is the increased expression of cytoskeletal proteins, particularly intermediate filaments, and microtubules. We suspect that like other aspects of cardiac remodeling these changes may originally be adaptive, to protect a heart under high mechanical stress, but turns out maladaptive when it progressed [7].

## Microtubule Stabilization in Cardiac Stress

As pressure overload persists, both MAP4 abundance and dephosphorylation increase. MAP4 dephosphorylation promotes microtubule binding, which in turn stabilizes the MTN for subsequent densification. The increased microtubule lifetime then promotes detyrosination and acetylation by upregulating the available substrate for enzymatic transformation. With advanced HF and chronic overload, a distinct upregulation of intermediate filaments occurs that as well stabilizes the MTN through crosslinking and protection against depolymerisation [5], [26]. A recent study by Yu *et al*. [27] evidently suggests that microtubule-affinity regulating kinase 4 (MARK4) regulates cardiomyocyte contractility by promoting phosphorylation of MAP4, which facilitates the access of vasohibin 2 (VASH2) a tubulin carboxypeptidase (TCP)-to microtubules for the detyrosination of $\alpha$-tubulin [27]. This study described the detyrosination of microtubules (dTyr) in cardiomyocytes is finely tuned by MARK4 to regulate cardiac inotropy and identify MARK4 as a promising therapeutic target for improving cardiac function after myocardial infarction. Hence, we could argue, data support targeting the MARK4–MAP4–VASH2 axis for the conservation of cardiac function after ischaemic injury [7], [26], [27].

To sum up, the multiple mechanisms can concurringly contribute to the pathological remodeling of the MTN. This includes: transcriptional initiation of tubulin isoforms, MAPs as well as modifying enzymes; autoregulation of tubulin content; and microtubule stabilization, which eventuates through intermediate filaments, MAPs, and enzymatic and oxidative transformation of tubulin [2], [5], [26], [27].

## Targetting Microtubule in Heart Disease

The cardiomyocyte microtubules enable their on-demand regulation of cardiomyocyte mechanics, excitation-contraction coupling, conduction, and growth through their dynamicity and interconnectivity [5]. Targeting microtubules for the treatment of cardiovascular disease might become a new approach to improving the outcome of cardiovascular diseases [5], [28].

The MTN-failing cardiomyocytes were dense and heavily detyrosinated, which led to increased cardiomyocyte stiffness and impaired contractility, and these features were independent of disease origin [29]. Microtubules undergo a switch in mechanical behavior between low-resistance sliding and high-resistance buckling that promotes the buckling behavior and

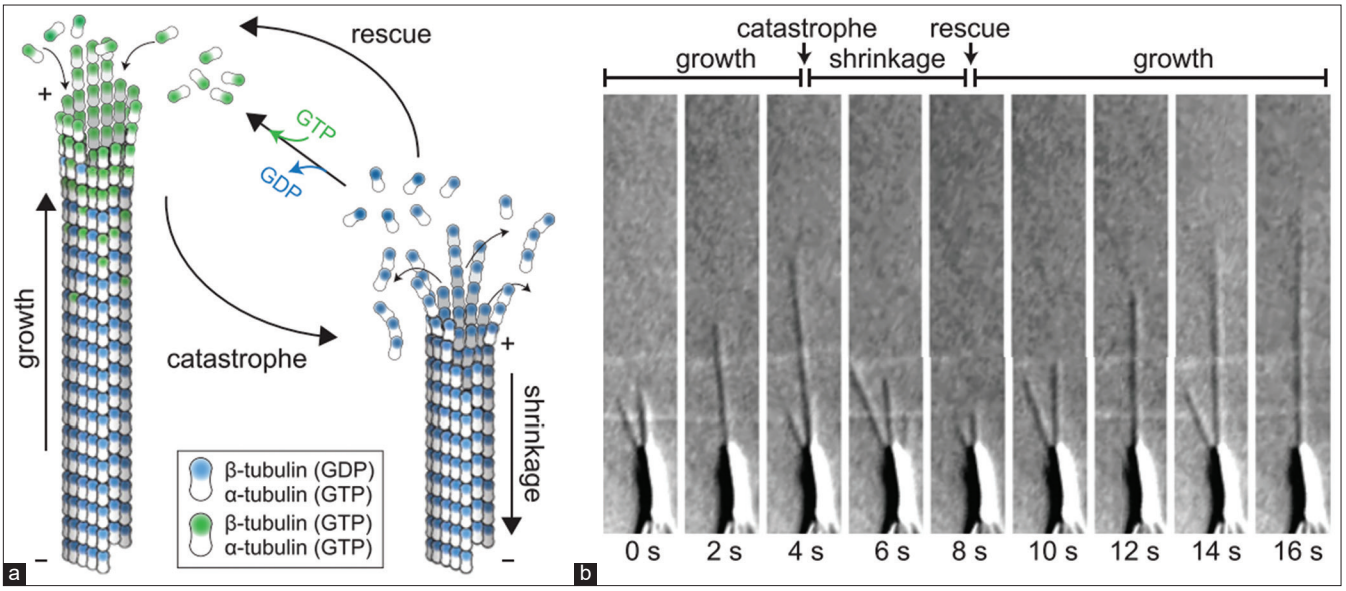



*Figure 1: (a) Microtubules grow by the addition of GTP-tubulin (green) to their ends. (b) DIC images from a time series of microtubules growing from an axoneme [11]*

crosslinking of cytoskeletal networks, increasing viscoelastic resistance to sarcomere shortening and stretch which contributes to viscoelastic resistance that impedes myocyte motion in HF [7]. It is often found in suppressed determination, that microtubules accommodate the contraction by sliding past each other rather than buckling as the sarcomere is shortened. This disrupted microtubule-sarcomere interaction allowed the sarcomere to shorten faster and decrease overall stiffness [7], [22].

Colchicine is an anti-mitotic that works by blocking mitotic cells in metaphase, binds to soluble tubulin then forms tubulin-colchicine complexes that prevent elongation of the microtubule polymer by binding to the ends of microtubules. Low-concentration colchicine would arrest microtubule growth while promoting microtubule depolymerization at high concentrations [30]. It binds with high affinity to β-tubulin and inhibits tubulin assembly into microtubule and also disassembly of a preformed microtubule. Colchicine inhibits various microtubule-dependent cellular in interphase cells and proliferation [31].

In an animal study with induced myocardial infarction, an appropriate dose of colchicine was reported could improve cardiac performance in myocardial infarction, improve survival rates, and inhibit excessive tubulin polymerization in the infarcted area to reduce HF development and inflammatory response [32]. Colchicine inhibited the accumulation of inflammatory cells, the increase of pro-inflammatory cytokines and chemokines, and also the increase of NLRP3 inflammasome components (NLRP3, ASC, caspase-1) after MI [9], [32]. Non-failing myocytes treated with colchicine showed an increase in shortening amplitude and contractile velocities [7]. Although the safety of the use of colchicine in long-term achieved and seen in gout patients who are treated with colchicine (0.5–1.0 mg daily), there is a significant dose difference that needs to be considered and studied before being used as a treatment for HF considering the maximum dose of colchicine can be consumed by human [5], [28].

dTyr, is an enzymatic cleavage of a C-terminal tyrosine residue from α-tubulin, facilitating interaction with intermediate filaments that complex with the sarcomere and altering myocyte stiffness, contractility, and mechano signaling[33]. In a genetic study with cultured human cardiomyocytes, found that Adenoviral overexpression of tubulin tyrosine ligase (AdV-TTL) decreases the density of dTyr-MTs and the proportion of total MTs that were detyrosinated. It also slightly drops the overall MT density compared to the control group. TTL overexpression also significantly increases the shortening amplitude and velocity in myocytes and also increased relaxation velocities. On a stiffness measurement, it was reported a large reduction in viscoelasticity compared to control. Targeting microtubule detyrosination specifically does not require microtubule depolymerization or changes to the $Ca^{2+}$ transient to accelerate cardiomyocyte relaxation [34]. Genetic manipulation of dTyr/Tyr balance represents a potent and specific tool to modulate contractility in human myocytes [7].

Parthenolide (PTL) is a sesquiterpene lactone that blocks the action of the TCP and decreases the fraction of detyrosinated a-tubulin *in vitro*, which catalyzes the removal of the C-terminal tyrosine from α-tubulin and already have advanced to Phase I human clinical trials [7], [35], [36]. PTL treatment significantly reduced the frequency of $Ca^{2+}$ waves and prevented the elevation in resting calcium concentration following high-frequency stimulation. It is reported that targeting microtubule detyrosination reduces detrimental calcium signaling and stress-dependent arrhythmogenesis in the *Duchenne muscular dystrophy* heart [35]. However, in 2006 Kurdi

*et al*. reported that PTL causes oxidative stress in cardiac myocytes by inducing superoxide formation by mitochondrial and NADPH oxidase in a dose-dependent manner [37]. Chen *et al*., reported that 10 μM PTL could suppress detyrosination in cardiac and skeletal muscle without grossly disrupting MT density, while 10 μM colchicine broadly depolymerizes microtubules. In failing myocytes, both colchicine and PTL robustly improved shortening amplitude and velocity, increased the speed of relaxation, and restored ~40–50% of lost function [7]. Due to very limited data and study, further study regarding the effect of PTL on cardiomyocytes is needed to conclude the use and safety of PTL.

## Conclusion

Microtubules are polymers that serve as structural elements with the shape of long, rigid tubes that are highly dynamic. The stiffness of the myocardium is largely influenced by the MTN. The MTN is remodeled by numerous mechanisms during cardiac hypertrophy and HF. Targeting microtubules for the treatment of HF might become a new approach to improve the outcome. While colchicine inhibits various microtubule-dependent cellular in interphase cells and proliferation, it needs further study for the safety of the adjusted dosage. Manipulating dTyr might be useful for restoring the function of failing myocytes although there are still very limited data on this.

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## Author Contribution

SL was involved in the idea and design of the paper. Authors SL, NA, AJ, and HK drafted the article; critically revised the text for key intellectual content; and approved the final version to be published. SL was involved in the final approval of the published edition.

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