Article title: Mechanical stress concealed force enhancement and ionic transient membrane potential and metabolism in akinesia of stress cardiomyopathy

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Keywords: apical ballooning, mechanical stretch, Ca2+ transient, energy consumption
Mechanical stress concealed force enhancement and ionic transient membrane potential and metabolism in akinesia of stress cardiomyopathy

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Abstract

Stress cardiomyopathy is a unique heart syndrome that is characterized by reversible left ventricular apical wall motion abnormalities and is commonly known as Takotsubo syndrome. In transient left ventricular apical ballooning, myocardium lengthening stress is in a high energy-demand state. The increased passive tension and force enhancement conducted asynergically are associated with severe hypokinesis on the ventricular wall and reduced the blood ejection fraction. Ventricular myocardial deformation and global longitudinal strain have significant mechanotemporal alteration characteristics. Membrane potential dominant mechanisms related to akinesia are considered from multiple effects of variation of calcium transients, myocardium metabolism, which is relative to the ST segment lift in an ECG, and in the weakness of contraction of the ventricular muscle. Ventricular filling, not pressure, determine the strengthening from stretching; thus, in stress cardiomyopathy, ventricular apical ballooning (takotsubo-shaped ventricle) strengthens the mechanical stress on the wall. Muscle fiber tolerance of lengthening is a high energy consumption process. Ventricular apical akinesia further aggravates passive tension. Depleted ATP and high inorganic phosphate inhibit Ca\(^{2+}\)-activated development, terminates the crossbridge detachment process in its early stage, and facilitates the occurrence of myogenic force enhancement. Comprehensive analysis of the above mechanisms, in lengthening stress, increased cardiac fibers energy demand, and Ca\(^{2+}\) transient variation interruption of the diastolic cycle, delayed the onset of systole and aggravated the occurrence of apical ballooning in stress cardiomyopathy.

Keywords: apical ballooning, mechanical stretch, Ca\(^{2+}\) transient, energy consumption
1. Introduction

Stress cardiomyopathy, also known as Takotsubo cardiomyopathy, apical ballooning syndrome, or broken heart syndrome, is a severe emotional or physical stress that causes heart muscle to weaken quickly and, in some cases, severely, and. A ballooning ventricular image, resembling an octopus trap pot [1], was primarily reported and named in Japan as takotsubo cardiomyopathy [2]. Emotional stress is only part of the causation of this illness, with one third of patients being physically triggered [3]. Reversible ventricular apical akinesia was characterized by hypokinesis of the apical cardiac segments with hypercontractility of the ventricle basal segments (apical ballooning). Cardiac muscle kinetic dysfunction with rarely obstructive coronary arteries is of concern for this syndrome. During the COVID-19 pandemic a higher rate of this syndrome is present. The trend of a high incidence rate is manifested as a longer length of stay in the hospital [4]; thus, stress cardiomyopathy has evolved into a unique medical term, Covidsubo (COVID-19-derived pot-shaped ventricle) [5]. Reversible left ventricular asynergy and relatively severe hypokinesis occur in anterolateral, apical, and diaphragmatic segments. In laboratory animal experiments, ventricular apical ballooning requires a large apical region spanning 50% of the ventricle where contraction is driven by the control calcium transient as well as a large (25–50%) basal region with a beta-adrenergically stimulated calcium transient [6]. Ventriculogram imaging indicated transient extensive akinesia of the apical and mid portions of the left ventricle, diaphragmatic and/or anterolateral segments, and hyperkinesis in the basal segments [7]. The elevated blood filling in the cardiac ventricle causes a large stretch in the boundary region. Lengthening stretch-induced muscle activities enhance contractile strength, which compensates for the increased mechanical load to help maintain cardiac output. When diastole-activated ventricle work obeys the Frank-Starling mechanism, apical ballooning does not always reduce the ejection fraction. However, in the clinical setting, patients suffering from apical or nonapical type were shown to present a distinct clinical phenotype. The nonapical
type have a less impaired left ventricle ejection fraction \[^{[5]}\], while in the apical ballooning type neither the apex nor the base ejects induced a lower ejection fraction.

Cardiac apical ballooning requires abnormal muscle contraction driven by transient of \( \text{Ca}^{2+} \) and a significant reduction in \( \text{Ca}^{2+} \) sensitivity in a large apical region \[^{[6]}\]. The compensated increase in the basal calcium transients does not produce apical ballooning. The direct toxicity of catecholamines, lipotoxicity, and inflammation are potential pathophysiological mechanisms in this reversible myocardial dysfunction \[^{[7]}\]. However, myocardial functional alterations during diastole, as well as pathophysiological mechanisms involved in the onset of systolic contraction, are not completely defined. Myocardial fibrosis and contraction bands in the presence or absence of overt myocyte necrosis, including sympathetic stimulation in the heart, do not explain apical ballooning \[^{[8]}\]. Myocardial hypertrophy, fibrosis, coronary microvascular dysfunction, oxidative stress and inflammation are only some of the main pathologically detectable processes.

![Figure 1 The Takotsubo and Takotsubo shape ventricle](image)

2. Mechanical stress varied membrane potentials influence on the ST-segment in ECG

Abnormalities in ECGs were shown in most Takotsubo patients and were associated with ST segment abnormalities \[^{[7, 9a, 9b, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28]}\], prolonged QT intervals \[^{[29, 30, 31, 32, 33, 34, 35]}\], tachyarrhythmias \[^{[36]}\], and more extensive
repolarization \([16, 37]\). Prolonged QTc intervals during a Takotsubo episode is associated with a high risk of cardiovascular rehospitalization were reported \([38]\). The depth and spread of T-waves and QTc duration provide increased diagnostic confidence in nonobstructive coronary patients \([39]\). The significantly prolonged precardial T wave is altered by the spatial dispersion of ventricular repolarization \([36]\), which may be associated with ST segment elevation \([30, 19]\) and probable with ST depression in aVR and chest-led PR \([36]\). In mechanically lengthening cardiac muscle fibers, the cellular membrane depolarizes in a specific pattern, which significantly lasts the decay period of the repolization phase (Figure 2) \([40]\); however, the action potential conduction velocity does not significantly change \([41]\). In a beta-receptor activation mimicking study, Takotsubo cardiomyocyte depolarization velocity was slowed down, and an enhanced late membrane influx current (I_{Na}) suppressed the efflux current (I_{to}), thus prolonging the action potential duration \([42]\), which is the basis of QT interval prolongation \([43]\).

![Figure 2](image)

**Figure 2** The cellular membrane depolarizes significantly lasts the decay period of the repolarization phase (Amar 2018, Figure 3)

In atrioventricular dissociation hearts, action potential duration (msec) has a negative relation with dP/dt\text{max} (mm Hg/sec), and an increased cytosolic Ca\textsuperscript{2+} content that intensifies the outward current carried by K\textsuperscript{+}, which is associated with the shortening of the action potential (Figure 3) \([44]\). In mechanically lengthened single myocytes,
shortening of action potential was also admitted, while contraction velocity did not synchronize with this shortening \[45\].

**Figure 3** The action potential duration associated shortening has a negative relation with dP/dt\(_{\text{max}}\) (mm Hg/sec), which relative to increasing cytosolic Ca\(^{2+}\) and intensifies K\(^+\) outward current (Drake 1982, Figure 2)

In contrast, sustained muscle stretch delayed the cytoplasmic Ca\(^{2+}\) transient decay and prolonged the cytoplasmic membrane repolarization (Figure 4a, A and B) \[46\]. A sudden release from the length-shortening contraction (rapid slacking) increased the cytoplasmic Ca\(^{2+}\) transient in the decay phase (Figure 4b, A) and prolonged the repolarization time (Figure 4b, B). This clarified the involvement of Ca\(^{2+}\) transients in lengthened cardiac muscle \[47\].

**Figure 4** The sustained muscle stretch delayed the cytoplasmic Ca\(^{2+}\) transient decay
and prolonged the cytoplasmic membrane repolarization (Lab 1984, Figure 1 and 2).

The prolonged repolarization time, which is not limited to the slacking of the stretched fibers but is also presented in active stretching fibers (Figure 5) \([48]\) is a clue that is helpful to elucidate the mechanism of abnormal ST segments and akinesia in Takotsubo cardiomyopathy.

**Figure 5** The prolonged repolarization time in slacking of the stretched fibers (Nazir 1996, Figure 5)

Ventricular apical ballooning increased the metabolic demand for depleted energy for Ca\(^{2+}\) transients, and the cardiomyocytes suffer from “metabolic insufficiency”. The disturbed spatiotemporal pattern of depolarization (and subsequent myocardial contractions) led to late activation in the cardiac ventricular wall \([49]\). Myocardial potential variations contribute to a high risk of progression to severe and deadly arrhythmic events \([50]\).

A model study was conducted to investigate the mechanism of changes in excitability at long cycle lengths (i.e., > 1,000 ms), which are responsible for various phenomena, including electrotonic inhibition, active facilitation, and the hysteresis of excitability in the ventricular muscle at slow frequencies of stimulation. Experimental studies suggested that with repetitive activity, the inward rectifier potassium current (IK1) is not a passive component of the membrane response and that the dynamics of IK1 are responsible for the changes in excitability at long cycle lengths. In the present study, we used new experimental data as the basis to modify the equations for IK1 in the...
ionic model for ventricular muscle of the Luo and Rudy (LR) model. The modified equations for IK1 incorporate an additional slow gate (s-gate), which governs the transition from a high steady-state conductance at rest to a lower conductance with repetitive stimulation. In simulation studies, electronic inhibition was seen in the original and modified LR models and was shown to depend on changes in the delayed rectifier current (IK). However, the addition of the s-gate to IK1 of the LR model extended the frequency dependence of excitability to longer length cycles and allowed for the demonstration of active facilitation and hysteresis. The inward rectifier is involved in the dynamic control of the membrane excitability. The overall results provide mechanistic explanations for heart rate-dependent excitation abnormalities that may be involved in the genesis of cardiac arrhythmias [132].

3. Instantaneous muscle tension in the lengthening stretched cardiac muscle

At the initial time of diastole, active stretch drastically increased, which was identified as the “motor break” period (Figure 6a, blue lines are left ventricle time course of pressure (top), volume (middle), and active stretch (bottom) for two cardiac cycles; blue points and dotted lines refer to the main phases of the cardiac cycles). The motor break period is further divided into rapid breaking and slow breaking on the time scale. In this 630 ms lengthening tolerance time, sustained steady stretch lasts approximately 500 ms, which is a considerable period of force enhancement occurrence. In sustained steady stretched single cardiac fiber, the force enhancement occurrence lasted approximately 390 ms (Figure 6b) [51].
As the intraventricular pressure does not increase during the whole “motor break” period, the active stretch is considered originate from blood filling volume rather than from intraventricular pressure. The muscle fibers tolerate significantly high lengthening stress in the initial time of diastole (Figure 6a from point 3 to point 4) and receive high mechanical strain. The distribution of muscle fiber strain varies with sarcomere length across the ventricle wall. Linearized fiber strain is significantly high at the beginning of the lengthening (Figure 7, with the arrow) but gradually weakens.

Figure 6 The “motor break” period in cardiac cycles (Colorado Cervantes 2019, Figure 5 and 7)

Figure 7 The linearized fiber strain significantly high at the beginning of the lengthening sarcomere across the ventricle wall (Chadwick 1983)
This strain cycle is consistent throughout the ventricular cycle\textsuperscript{[52]}. Muscle fibers tolerate instantaneously sustained stretching in the strain reduction phase. Sustained stretching activates the muscle, which was subsequently linked to the occurrence of myogenic fasciculation. In this strain cycle, cytosolic Ca\textsuperscript{2+} shifts from the uptake compartment to the release compartment, and optimum filling in the release compartment is achieved. The intensified outward current by K\textsuperscript{+} efflux produces earlier membrane repolarization, which shorts the duration of the action potential and affects the onset of muscle contraction.

The biaxial cross of the cardiac fibers is in the tenacity structure, has the capacity for tolerating higher mechanical strain rather than in the uniaxial unconstrained fibers (\textbf{Figure 8}), prevents overstretching, lowers the risk of intensified outward current, maintains Ca\textsuperscript{2+} normal transient, and protects the myofilaments from filament attachment insufficiency\textsuperscript{[53]}.

\textbf{Figure 8} The mechanical stress induced strain in biaxial cross and uniaxial unconstrained fibers in cardiac muscle (\textit{Demer 1983, Figure 4})

However, lengthening stretch-induced by cardiac fiber reorientation inevitably leads to an increase in tissue anisotropy, resulting in ventricle-pressure uncoupling\textsuperscript{[54]}. Overlengthening increased tissue anisotropy and has the risk of aggravating the ventricular akinesis. The myocardial dysfunction of McConnell’s sign, is an instance where characteristic echocardiographic finding of the right ventricle regional
dysfunction has pulmonary embolisms. Overloading presents a distinct bulge on the mid-free ventricular wall, which is associated with an increased in wall stress from high afterload that leads to an inverted Takotsubo variant [53].

In diastole, the growing ventricle longitudinal strain increased the transmural helix angle gradient and remained constant in healthy cardiac muscle, whereas the helix angle gradient became steeper in dilated infarct ventricles (Figure 9). Contractile-deficient infarcted muscle lacks long-axis shortening, and muscle fibers tolerate the extra lengthened loads. The elevated transmural helix angle gradient reflects the muscle fiber compensatory mechanism [56].

![longitudinal strain vs. helix angle gradient](image)

**Figure 9** The growing ventricle longitudinal strain induced transmural helix angle gradient in healthy and dilated infarct cardiac ventricles (*Stoeck 2021, Figure 6*)

In ventriculography analysis, global myocardial ventricle strain is the index that partially determines the deformation and the increased anisotropy on the ventricle wall; however, this index cannot distinguish the significance from different ventricle mass groups (*Table 1 by Diaz-Navarro 2021*) [57]. Geometric deformation primarily contributes to the preload, and cardiomyocytes are more lengthened and thinner, characterized by less passive stiffness [58]. In compensated hypertrophic geometries, wall thickening reduced and slowed tissue deformation, and muscle fiber disarray
minor changed circumferential and radial strain. The increase in tissue stiffness caused a more homogeneous distribution of the strain. The remarkable reduction of the active force development leads to less overall deformation \[59\]. Therefore, the reduction of global longitudinal strain is an important sign in Takotsubo cardiomyopathy diagnosis; however, other investigations suggest that this reduction does not contribute to the downward ejection fraction and does not reflect the myocardial tension state \[60\]. Nevertheless, global longitudinal strain remains a prognostic indicator in Takotsubo patients.

**Table 1** Baseline data for patients, stratified for sex

<table>
<thead>
<tr>
<th>Participants</th>
<th>Women</th>
<th>Men</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 18</td>
<td>51 ± 14</td>
<td>0.34</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71 ± 14</td>
<td>68 ± 9</td>
<td>0.20</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>122 ± 25</td>
<td>132 ± 22</td>
<td>0.08</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 11</td>
<td>82 ± 13</td>
<td>0.007</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.65 ± 0.15</td>
<td>1.96 ± 0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>54 ± 24</td>
<td>76 ± 26</td>
<td>0.001</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>108 ± 28</td>
<td>140 ± 31</td>
<td>0.0002</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>54 ± 9</td>
<td>64 ± 15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(ESV+EDV)/2 (mL)</td>
<td>81.4 ± 25.7</td>
<td>108.4 ± 27.3</td>
<td>0.0005</td>
</tr>
<tr>
<td>EF (%)</td>
<td>51 ± 8</td>
<td>46 ± 9</td>
<td>0.045</td>
</tr>
<tr>
<td>EFC (mL)</td>
<td>122 ± 36</td>
<td>160 ± 38</td>
<td>0.0004</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>94 ± 20</td>
<td>124 ± 22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GLS (%)</td>
<td>-10.76 ± 3.47</td>
<td>-9.58 ± 3.32</td>
<td>0.28</td>
</tr>
<tr>
<td>LVGFI (%)</td>
<td>32 ± 6</td>
<td>29 ± 7</td>
<td>0.044</td>
</tr>
<tr>
<td>LVGFIC (mL)</td>
<td>179.9 ± 37.5</td>
<td>235.6 ± 41.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MCF (%)</td>
<td>62.3 ± 15.7</td>
<td>55.8 ± 17.7</td>
<td>0.14</td>
</tr>
<tr>
<td>MCFC (mL)</td>
<td>105.5 ± 17.3</td>
<td>134.9 ± 20.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VAC</td>
<td>1.09 ± 0.28</td>
<td>0.92 ± 0.35</td>
<td>0.042</td>
</tr>
<tr>
<td>VACC (mL)</td>
<td>77.76 ± 22.13</td>
<td>101.34 ± 23.28</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

During sustained steady lengthening, the passive tension variation and the myofilaments-determined force enhancement are driven by cross-bridge interactions between the actin-containing thin filaments and the myosin II-based thick filaments.
In active contraction, the muscle thin filaments in the fully activated state form overlapping arrays of opposite polarity in the center of the sarcomere[61], while ramp stretch or slack muscle fiber create an overbalance in the cross-bridge interaction, which further creates an immediate response of myogenic force enhancement (please refer Figure 3A of Chiu 1982) [62]. Most enhancement responses are from myofilament compartment shortening during muscle contraction in an isometric state and from tolerating the sustained steady stretch (please refer Figure 2E of Chiu 1982) [63]. The lengthening scale determines the enhancement strengthening, while the lengthening ramp velocity determines the enhancement lasting time (please refer to Figure 5 of Chiu 1982) [62]. These further seals the trend of passive tension decay from the exponential nature of the elastic structure (springs) (Figure 10) [62]. Myocardial architecture rapid loss of elasticity at the apex in excessive dilatation Takotsubo cardiomyopathy. The relatively intact myocardium layers bear additional lengthening stretch.

Figure 10 The force enhancement response to tolerate the sustained steady stretch in an isometric state (Chiu 1982a, Figure 1)
Sarcomeres assembling in a series leads to chamber enlargement, while in the parallel the response is increased systolic stress, effectively increasing the thickness of the ventricular wall. The passive mechanical properties of the myocardium are largely determined by the tension developed by cardiac fibers, governed by the passive tension in the myocardium \[63\]. The intersarcomere force prevents large disparities in the lengths of neighboring sarcomeres, while decreasing the initial nonuniformity of the sarcomere length reduces the rate of force enhancement rise but does not decrease the peak enhanced tension. When lengthening the muscle fiber above the optimum, the sarcomere shortening velocity is significantly slowed down, and the stretched passive tension delays its decline phase \[64\]. At a constant sarcomere length, the isometric force is mostly based on the response to the Ca\(^{2+}\)-bound troponin in the myofilament overlap zone. Overlengthening expands the nonoverlapping zone and attenuates the Ca\(^{2+}\)-bound relative isometric force \[65\]. The myocyte deposit sarcomere alters the free-wall longitudinal strain in the echocardiographic images \[66\] and is the prognosticator for ventricle dysfunction \[67\]. Myosin-based regulation modulates the number of myosin motors available for interaction with the Ca\(^{2+}\)-regulated thin filaments. The folded conformation of the myosin is disrupted by the maximal Ca\(^{2+}\) activation. Stretching produces delayed activation of folded myosin motors \[63\]. In vitro pressure preload causes the myofibril A band to become shorter and wider, while sarcomere length remains mostly unchanged (Figure 11). This shortening was reduced by ATP \[68\], which suggests that the remaining lengthened ATP energy consumption process.
**Figure 11** The myofibril A band shortening and sarcomere length unchanged in pressure preload (*Shintani 2021, Figure 1c, d, e*)

In active stretched muscle, the tension variation occurs in two distinct phases: an abrupt increase that coincides with the active stretch strength and a slow increase in the force that is accompanied by cytosolic the Ca$^{2+}$ transients. The second phase is considered to actuate the spontaneous myogenic force that responds to instantaneous lengthening tolerance. Stretch-activated ionic channels play an important role in this force enhancement event [69], which is considered the energy consumption period

4. **The instantaneous energy consumption in the muscle fiber tolerating stretch**

The passive mechanical properties of the myocardium partially recovered to their initial value in the muscle bearing the sustained stretch, reflecting a series of combinations of viscous elements and spring structures in the muscle fibers. The viscoelastic load is length-independent and dominates the early diastolic restoring force [62]; however, most compounds in recovering passive tension are involved in the contraction filament- events. Muscle tension continues to rise slowly in this secondary phase [70]. This slow increase the muscle tension, raising its Ca$^{2+}$ depending on the rapid lengthening of cardiac muscle (**Figure 12**). This further generates a delayed mechanical oscillation due to a feedback mechanism of stretching [71].

![Figure 12](image)

**Figure 12** Rapid lengthening cardiac muscle increased muscle tension (*Bozler 1972, Figure 2A*)

The cardiac muscle percentage increment of the oxygen consumption/concentration
relation is correlative with its basic metabolic rate. The muscle lengthening stretch enhances the oxygen consumption and the metabolic rate (Figure 13) [72].

![Figure 13](image)

Figure 13 The lengthening stretch enhance oxygen consumption and metabolic rate in cardiac muscle (Loiselle 1982, Figure 5)

In ballooning cardiomyopathy, cardiomyocytes experience a sudden increase in reactive oxygen species and mitochondrial superoxide production and inhibit mitochondrial membrane potential [73], reducing the oxygen consumption rate and the decrease in the mechanical performance index demonstrate that stretched muscle fibers lose during natural coupling with mitochondria [74]. Inorganic phosphate, the main intracellular membrane permeable anion, is the metabolic product of ATP hydrolysis. Its release does not significantly increase at the initiation of the active stretching but enhances the subsequent process during muscle tolerance of the sustained stretching, as well as in the subsequent myogenic force enhancement occurrence period (Figure 14) [75], which mentioned high energy consumption in the sustained stretch tolerating muscles.
Figure 14 The inorganic phosphate releasing in enhanced sustained stretching cardiac muscle (*Bickham 2011, Figure 1a and 1c*).

In myofibrils identified in the lamellae imaged in 3D, glycogen granules were found outside and within the myofibrillar interior, whereas mitochondria, sarcoplasmic reticulum, and ribosomes were adjacent to myofibrils. In stretched muscle fibers, accumulated inorganic phosphate inhibited Ca\(^{2+}\)-activated development forces (active tension, Figure 15a and b) but precipitated the strengthening of passive tension, as seen in Figure 4C by Mutungi et al. in 2003. When artificially increasing ATP, the muscle fibers presented negative inotropy (Figure 15c), while depleted ATP attenuated sarcoplasmic reticulum Ca\(^{2+}\)-ATPase to retain Ca\(^{2+}\) transients, passive tension was enhanced. Accompanied by increasing sarcomere length, myogenic force enhancement is facilitated by Ca\(^{2+}\) transients at this steady-state moment, combined with a high inorganic phosphate release rate and a lasting passive tension decay that
was seen in Figures 3 and 2 by Mansfield et al. in 2012 and is accompanied by an increase in sarcomere length \(^{[77]}\).

**Figure 15** The accumulated inorganic phosphate inhibited Ca\(^{2+}\)-activated development forces in stretched muscle fibers (a and b were from Mutungi 2003, *Figure 1A and C; c, Burnstock 1983, Figure 3*).

The excessive inorganic phosphate content accelerated the passive tension decay rate and accelerated the passive tension recovery (**Figure 16b** compared to **16a**). When rapid release of the sustained stretch, muscle fiber passive tension recovery occurs in a dawdling pattern (**Figure 16c**), demonstrating that the inorganic phosphate content increases, and not only the ionic transit involved in the residue passive tension
remains [78].

a.

b.

The excessive inorganic phosphate accelerate the passive tension decay rate and passive tension recovery (Ranatunga 2002, Figure 1A, B and D)

The passive tension decay phase is the period of crossbridge detachment between myofilaments. In the sustained stretch muscle, stress causes high inorganic phosphate to terminate the crossbridge detachment process in its early stage and promote myosin-actin attachment in advance. The force enhancement curve shifts to the left on the time scale (Figure 17) [79].
Catecholamine stress is another factor influencing instantaneous energy changes in sustained stretched muscle. In impaired diastolic function patients with an abnormal cardiac angiogram in the mid-portion and apex of the left ventricular cavity, catecholamine stimulation produces a decrease in volume with an increase in diastolic pressure, and beta-receptor blockade acutely produces an increase in left ventricular volume and a decrease in left ventricular diastolic pressure \[^{80}\]. The activated beta-receptor pathway promotes ATP metabolic adenosine and the development force increase \[^{81}\], while beta-receptor coupled PKA blunts the magnitude of the passive tension and accelerates tension time constants in a titin isoform-dependent manner \[^{82}\]. The beta-receptor activation-derived inorganic phosphate to phosphocreatine ratio fluctuates in a physiological range; however, in dilated cardiomyopathy, this ratio is drastically increased \[^{83}\]. This supply–demand mismatch in ATP levels potentially leads to a state of metabolic shutdown, along with a significant decline in the

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**Figure 17** (Palmer 2020, Figure 6)
contractile functions\[84\]. In addition, the decreased viability of the cardiomyocytes occurs through cyclic AMP-mediated Ca\(^{2+}\) overload and oxygen-derived free radicals \[85\]. The activated β3 adrenergic receptor increases the L-type Ca\(^{2+}\) channel current \((I_{ca})\), decreasing the cardiac myocyte active contraction and positive lusitropic effects, regulating cardiac diastole by decreasing myofilament Ca\(^{2+}\) sensitivity and modulating myocardial stiffness through troponin I and titin phosphorylation \[86\], and alleviated cardiac dysfunction by inhibiting NADPH oxidases \[87\].

Apart from cAMP-induced release of the catalytic subunit from protein kinase, Ca\(^{2+}\) sensitivity regulation is also dependent on the beta-adrenergic controlled increase in the affinity of the myofibril for the catalytic subunit in as much as perforated cells can sustain \[88\]. Mitochondrial swelling reduces oxygen consumption, the respiratory quotient and ATP synthesis. Subsequently, the attenuated membrane potential in mitochondria collapses Ca\(^{2+}\) homeostasis, further increasing passive tension \[89\]. The population with diabetes mellitus has a low risk of Takotsubo syndrome, based on myocardium-associated neuropathy preventing the emergence of ventricular ballooning \[90\]. However, in diabetes patients, even if the heart geometry and function are normal, impaired high-energy myocardial phosphate metabolism and a decreased mean cardiac PCr/ATP ratio are notable \[91\]. This could be drawn from the study of the mechanism of those who suffered from sudden Takotsubo cardiomyopathy, which was very similar to the impaired myocardium metabolic patterns are reported in Takotsubo cardiomyopathy patients \[39\]. Ischemia-induced exacerbation of mitochondrial oxidative phosphorylation (Nayler 1982, Figure 1B) and aerobic reperfusion (95% O\(_2\) in 80 kPa) further aggravate this effect. The depletion of catecholamine reduced mitochondrial Ca\(^{2+}\) accumulation, ameliorated this exacerbation, and promoted ATP activities (Table 3) \[92\]. Hypoxia was used to evaluate mitochondrial O\(_2\) consumption and ATP production in cardiac muscle \[93\]. Glycolysis inhibited oxidative phosphorylation and decreased the magnitude of Ca\(^{2+}\) transients. The decreased intracellular pH influenced the sensitivity of the contractile proteins to Ca\(^{2+}\), thus reducing muscle active tension. ATP hydrolysis falls below the level required to pump
Ca$^{2+}$ from the myoplasm to the sarcoplasmic reticulum, slow down the cytosolic Ca$^{2+}$ transient decay phase, and delay passive tension recovery (Figure 18)\textsuperscript{94}.

Regional norepinephrine spillover from the heart and kidneys was reported in severe heart failure patients\textsuperscript{95}. The generalized autonomic storm may lead to acute ventricle dysfunction and has an important role in causing Takotsubo cardiomyopathy\textsuperscript{21}. Cardiac ATP metabolic exhaustion can partially explain the mechanism of catecholamine-induced transient neurogenic stress-related cardiomyopathy\textsuperscript{96}.

However, reduced neuronal innervation in the ventricle apical anterior, apical inferior, and lateral walls brings out apical ballooning in the treadmill exercise test because the circulation catecholamines adapt during exercises\textsuperscript{97}. The activated beta-adrenergic receptor cascades increased cyclic AMP concentration and adenylate cyclase activity and enhanced myocardial contractile force in the ballooning area\textsuperscript{98}.

In ventricle muscle, myosin isoenzymes determine Ca$^{2+}$ utilization. Fast myosin Ca$^{2+}$ ATPase activities were 3 times higher than slow myosin (Table 1)\textsuperscript{99}. The fast myosin quantity is over the slow myosin in the ventricles during growth and development, but slow myosin has high expression in aging ventricles (Winegrad 1983, Figure 4); therefore, Ca$^{2+}$-activated tension is frail\textsuperscript{1007}. Depleted ATP and high

**Figure 18** The increased Pi concentration earlier passive tension recovery in relaxation phase (Allen 1983, Figure 2B)
inorganic phosphate have a high risk of interrupting the diastolic cycle, delaying the onset of systole in Takotsubo ventricles. Once the ATP is exhausted, the myosin head region and actin start to form rigor cross-bridge attachments\textsuperscript{[101]}. The increased stiffness of the ventricle muscle reflects the development of rigor cross-bridge attachment.

The inefficient energy utilization and consequent depletion of high-energy phosphate moieties most commonly manifest as a reversible mid-systolic drop in a pulsed Doppler mid left ventricle ejection velocities and flow in the patients with left ventricular outflow tract gradients >60 mm Hg. A mid-systolic drop in systolic myocardial velocities due to obstruction and premature termination of septal contraction has been reported\textsuperscript{[102]}.

In exercising the heart, the possibility of concomitant diastolic adaptation to respond to acute stretching involves most of the sarcomeric proteins and ion channels involved in the slow force response\textsuperscript{[103]}. Cardiomyocyte autoregulation occurs only in the range of stiffness and instantaneous elastic shear modulus where cell strain is constant. Cardiomyocyte contraction remains relatively constant despite increased mechanical loading. Ca\textsuperscript{2+} transient was steady state (\textit{Izu 2021, Figure 5})\textsuperscript{[104]}.

With aortic banding with the normal ejection fraction and fractional shortening of the heart, in this high preload type cardiac muscle, the relaxation velocity increased (\textbf{Figure 19a}, \textit{Røe 2017, Figure 5A}), the time to 50% relaxation was shortened, and high passive stiffness was maintained. This was because cardiomyocytes have a rapid decline in cytoplasmic Ca\textsuperscript{2+} handling (\textbf{Figure 19b}, \textit{Røe 2017, Figure 6A}), and the Ca\textsuperscript{2+} transient magnitude and cytosolic Ca\textsuperscript{2+} in the diastole were significantly reduced (\textbf{Figure 19c, 19d}, \textit{Røe 2017, Figure 6B, 6E}). This was because of enhanced Na\textsuperscript{+}-Ca\textsuperscript{2+} exchange (NCX) and sarcoplasmic reticulum Ca\textsuperscript{2+}-ATPase (SERCA2) function, therefore lowering resting cytosolic Ca\textsuperscript{2+}\textsuperscript{[105]}. The relaxation was interrupted.
The intracellular Ca\(^{2+}\) transient time was mostly prolonged in optimally lengthened cardiac muscle cells (H7 line cells); however, stretching beyond the optimum length significantly reduced this time (Figure 20)\(^{106}\).
Passive properties of the myocardium are important to allow for proper filling of the ventricles. The lowered Ca\textsuperscript{2+} sensitivity and decreased α myosin heavy chain are related to the increase in passive tension. Passive tension was increased 2 times in 15% passive stretching in aging heart muscle, and active stress production was not significantly different \cite{107}. The myosin light chain mutation associated with restrictive cardiomyopathy noted a significant decrease in contraction structure lattice spacing (Figure 21a), which combined with significantly high passive tension (Figure 21b) \cite{108}.

![Figure 21](image)

**Figure 21** The myosin light chain mutation associated with restrictive cardiomyopathy with significantly high passive tension (Yuan 2017, Figure 4C, 4D) G protein-coupled receptor kinases (GRKs), β-arrestins and complex intracellular signals physiologically modulate beta-adrenergic receptors involved in receptor internalization in ventricle function failure. GRK2 activity and expression are significant in failing hearts \cite{109}. The downregulation of NO/sGC/PKG signaling in the myocardium due to inflammation and oxidative stress contributes to elevated passive tension of cardiomyocytes ahead of coronary microvascular endothelial dysfunction. Protein kinase G is the factor that relieves increased passive tension in overstretched cardiac fibers (Waddingham 2019, Figure 4A) \cite{110}. The nitric oxide/cGMP/PKG system comprises the most efficacious inhibitory mechanism against the PKC-dependent contractile mechanism (Asano T, Matsui T. Various pathogenetic factors revolving around the central role of protein kinase C activation in the
occurrence of cerebral vasospasm. Crit Rev Neurosurg. 1998, 13:8(3):176-187.). PKA- and PKG-dependent phosphorylation in the elastic segment of cardiac fibers, in the domain of the N2BA-titin isoform of the cardiac half sarcomere, was significantly reduced in dilated cardiomyopathy (Kötter 2013, Figure 4A), and passive tension was enhanced in lengthened cardiomyocytes in dilated cardiomyopathy (Kötter 2013, Figure 3C) [111]. PKA induces enhanced myofilament length-dependent activation through prominent myofilament targets cardiac myosin binding protein C and troponin-I, which enhances cross-bridge formation at long sarcomere lengths while accelerating cross-bridge detachment and relaxation at shorter sarcomere lengths. (Kumar M, Govindan S, Zhang M, Khairallah RJ, Martin JL, Sadayappan S, de Tombe PP. Cardiac Myosin-binding Protein C and Troponin-I Phosphorylation Independently Modulate Myofilament Length-dependent Activation. J Biol Chem. 2015, 290(49):29241-29249.). Physiology, Anrep Effect [113]. Exercise decreased passive stiffness and involved beneficial alterations in titin phosphorylation. Hypophosphorylation of the titin S11878 site in the PEVK region and hypophosphorylation of the S4010 site in the N2B region after exercise and reduces titin-based passive tension. Exercise targets titin and improves diastolic health (Figure 22) [112].
Figure 22 Hypophosphorylation titin S11878, S4010 site in PEVK, N2B region after exercise and reduces titin-based passive tension (Slater 2017, Figure 2)

The left ventricular end diastolic pressure was correlated with the L-type voltage-dependent calcium channel, Na⁺-K⁺ ATPase pump, and pCAMKII (de Las Heras 2021, Figure 5) [114]. In the acute phase of mimic Takotsubo cardiomyopathy, diastolic cardiac fiber cytosolic Ca²⁺ was elevated (Figure 23a), while mitochondrial Ca²⁺ transients and accumulation were reduced (Figure 23b). Defective Ca²⁺ handling combined with energetic deficits, such as dysregulation of glucose and lipid metabolic pathways, lead to decreases in final glycolytic and b-oxidation metabolites [115].

Even though GLUT 1 and GLUT4 expression was elevated, as reported by Godsman et al., insulin deficiency maintained a lower dP/dt, and the baseline end diastolic pressure volume relation stiffness index was increased (Waddingham 2019, Figure 2) [116]. In the cardiac cycle, the myocardial mass in diastole is larger than that in the systole [117]. During diastolic filling, the left ventricle rapidly expands at rates where viscoelastic forces impact ventricular compliance. Skinning also removes key viscoelastic elements such as membranes, microtubules, and cytosolic proteins, which is reflected in the reduced viscoelasticity of skinned preparations, as shown by a greater than proportional decrease in the stress relaxation of skinned myocytes [118].
Elasticity assessments via uniaxial extension tests are performed on healthy and infarcted tissue samples from the left ventricular rat myocardium. The stretch-shortening cycle effect is present in sarcomeres themselves. Crossbridge kinetics and noncrossbridge structures (e.g., titin and nebulin) contribute to the stretch-shortening cycle effect, which is characterized by velocity dependence. The power output increases with increasing stretch-shortening cycle effect velocity. In velocity ramp stretch single skinned fibers, energy recovery is higher in blocking the non myosin II ATPase fibers, indicating the existence of a noncrossbridge structure titin involved in the high energy consumption and the viscoelastic properties in stretched fibers. In isolated electrically driven human ventricular papillary muscles, activated beta receptor or H2-receptor pathways cause concentration-dependent increases in the force of contraction and reductions in both time-to-peak tension and time-to-half-maximal relaxation. H2 receptors cause distinct changes in the action potential configuration with increases in the height and duration of the plateau phase and an increase in the overall action potential duration, which are associated with cyclic AMP-mediated increases in calcium-dependent slow inward current. A limited release of cardiac markers was disproportionate to the extent of akinesia.

Mechanical signals include the forces of cyclic contraction and relaxation of the myocardial walls and the hemodynamic load leading to stretch of the cardiac chambers during the filling phase and increased wall stress during the contraction phase. These factors are known to regulate myocardial function, gene expression and structural appearance. Yoda1 stimulation also significantly increased the expression of Piezo1 mRNA, a divergence in the molecular mechanisms in ventricular failure. Here, we aimed to investigate interventricular differences in sarcomeric regulation and function in reduced LV ejection fraction. CaMKII activity showed an 81.6% increase in the left ventricle, and the passive stiffness was significantly higher with steeper passive tension-to-sarcomere length relationships. PKG activity was lower in ventricles. PKG administration decreased cardiomyocyte passive stiffness; distinct
changes in titin site-specific phosphorylation explained divergent cardiomyocyte stiffness modulation, and the left ventricle cardiomyocytes showed increased $\text{Ca}^{2+}$-sensitivity. Ser282 phosphorylation of cMyBP-C without any alteration in the left ventricle and Ser23/24 phosphorylation of cTnI were decreased \[^{[123]}\]. The $\text{Na}^+-\text{K}^+$ pump couples with membrane $\text{Ca}^{2+}-\text{Na}^+$ exchange, reversibly blocking the $\text{Na}^+-\text{K}^+$ pump without reducing the secondary effects of pump inhibition (avoiding intracellular Na+ and extracellular K+ accumulation), plateaus the membrane resistance much higher than at the resting potential and correspondingly increases the potential produced by the pump current \[^{[124]}\]. The depletion of ATP decreases the efficiency of the $\text{Na}^+-\text{K}^+$ pump efflux current and reduces membrane $\text{Ca}^{2+}-\text{Na}^+$ exchange. The accumulated cytosolic $\text{Ca}^{2+}$ increased the positive inotropic effect, subsequently enhancing myogenic force generation while tolerating stretch \[^{[125]}\]. The enhanced resting tension increased stiffness in $\text{Ca}^{2+}$ elevation and SERCA2a blockage maneuvers and decreased NCX1 and SERCA2a \[^{[126]}\]. HFpEF patients exhibited increased t-tubule density that resulted from both the tubule dilation and proliferation. In a mouse experimental model, $\text{Ca}^{2+}$ transient magnitude and release kinetics were largely maintained. However, impairments in diastolic $\text{Ca}^{2+}$ include reduced sarco/endoplasmic reticulum $\text{Ca}^{2+}$-ATPase activity \[^{[127]}\].

In rodent heart models, angiotensin II induced high left ventricle end-diastolic pressure and end-diastolic pressure-volume relationships \[^{[128]}\]. This myocardium passive force-length characteristic brings out contraction zones, and bands are prominent with the dehiscence of myofilaments in adjacent sarcomeres of the diastolic ventricular muscle \[^{[129]}\].

### 5. Apical ballooning in Covid-19 patients

There are a possible number of up to 4.97 million patients who widely undiscovered face the acute complications of developing TTS \[^{[23]}\]. The emergence of substantial emotional stress at the population level and respiratory infections causes stress
cardiomyopathy to play a significant role. TTS also infected young who are without prior cardiac issues. The virus effects on angiotensin-converting enzyme 2 (ACE2) receptor-expressing cells have been proposed as a possible mechanism. It is known that myocarditis is a possible sequela of COVID-19 infection. Underlying midventricular/apical edema and ballooning, the most likely diagnosis of COVID-19 vaccine-induced Takotsubo cardiomyopathy was made. Although myocarditis is a possible differential diagnosis after COVID-19 vaccination, there have been rare reports of Takotsubo cardiomyopathy after influenza vaccination, with an underlying pathophysiology of systemic inflammatory stress reaction after vaccination with a sympathovagal imbalance toward adrenergic predominance. Takotsubo cardiomyopathy confirmed by CMR after a COVID-19 vaccination has not yet been reported and may be considered a differential diagnosis in addition to myocarditis in this clinical setting. A systematic review of Takotsubo syndrome cases reported during the pandemic suggests that this syndrome was increasingly diagnosed in physical stress (mostly COVID-19 pneumonia)-triggered male patients without psychiatric/neurologic disorders. Sex and inpatient mortality primarily contributed to the automated classification of Takotsubo syndrome. Long COVID syndrome has left ventricle apical ballooning without obstructed coronary vessels, outlining an emergent need to better understand the pathophysiological mechanisms that underpin the development of cardiac complications in those with COVID-19 and long COVID syndrome. Apical ballooning and several other types of wall motion abnormalities have been classified as variants of Takotsubo syndrome. In particular, right ventricular involvement, or biventricular TTS, is not uncommon and is associated with poor in-hospital as well as long-term outcomes. Attention should be given to a variety of cardiovascular conditions related to COVID-19. TTS is one of these conditions that can be triggered by both emotional and physical impacts of the COVID-19 pandemic.
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Declarations

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