Stretch modulation of cardiac contractility: importance of myocyte calcium during the slow force response

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Abstract

The mechanical response of the heart to myocardial stretch has been understood since the work of muscle physiologists more than 100 years ago, whereby an increase in ventricular chamber filling during diastole increases the subsequent force of contraction. The stretch-induced increase in contraction is biphasic. There is an abrupt increase in the force that coincides with the stretch (the rapid response), which is then followed by a slower response that develops over several minutes (the slow force response, or SFR). The SFR is associated with a progressive increase in the magnitude of the Ca^{2+} transient, the event that initiates myocyte cross-bridge cycling and force development. However, the mechanisms underlying the stretch-dependent increase in the Ca^{2+} transient are still debated. This review outlines recent literature on the SFR and summarizes the different stretch-activated Ca^{2+} entry pathways. The SFR might result from a combination of several different cellular mechanisms initiated in response to activation of different cellular stretch sensors.

Keywords Cardiac stretch · Calcium influx · Slow force response · Stretch-activated channels · Autocrine/paracrine response · G-coupled protein receptors

Introduction

Mechanical forces are created by the heart with every cardiac cycle as the chambers contract and relax in a highly synchronized manner throughout life. These forces influence the entire cardiovascular system and are acutely matched by intrinsic mechanisms within the myocytes that ensure cardiac output meets the metabolic demands of the body. One important regulator of cardiac myocyte force is the degree of stretch experienced by the myocytes immediately before activation. The mechanical response of the heart to myocardial stretch has been understood since the work of muscle physiologists more than 100 years ago, whereby an increase in ventricular

chamber filling during diastole increases the subsequent force of contraction. The stretch response is commonly referred to as the Frank-Starling relationship (Frank 1895; Patterson and Starling 1914). At least 3 different cellular mechanisms are involved in the Frank-Starling relationship (for review see (Allen and Kentish 1985)): (i) increased overlap between contractile protein myofilaments (Fabiato and Fabiato 1975; Gordon et al. 1966); (ii) increased Ca^{2+} sensitivity of the contractile proteins (Fukuda and Granzier 2005; Hibberd and Jewell 1982); and (iii) increased Ca^{2+} transients (the systolic rise in intracellular Ca^{2+} ($[\text{Ca}^{2+}]_i$) which activates the contractile proteins) which gradually become larger over some minutes after a stretch (Allen and Kurihara 1982; Kentish and Wrzosek 1998; Ward et al. 2008). This review will focus on the third of these cellular mechanisms since there is still debate about this aspect of cardiac regulation. The Ca^{2+} -dependent response to stretch is commonly referred to as the “slow force response” (SFR) and is thought to form the basis of the Anrep effect which describes the heart’s increase in contractility that develops following an increase in afterload (Alvarez et al. 1999; Cingolani et al. 2013; Nichols et al. 1988).

The SFR was first recognized by Parmley and Chuck (1973) in isolated cat papillary muscles subjected to axial stretch. They observed there was an immediate response to

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stretch that was then followed by a slower increase in force which took several minutes to reach completion (Parmley and Chuck 1973). They argued that the slow phenomenon was likely to be caused by changes in the degree of activation of the contractile proteins. It was later shown that the SFR was accompanied by a slow increase in the magnitude of the Ca^{2+} transients which continued for several minutes (Allen and Kurihara 1982; Kentish and Wrzosek 1998; Ward et al. 2008). Figure 1 shows a representative SFR from a rat ventricular trabecula. Table 1 provides a list of terms and definitions used in the manuscript.

Cardiomyocyte Ca^{2+} cycling

Calcium is crucial to the contractile performance of the heart, and there have been many studies investigating the cellular mechanisms that increase the Ca^{2+} transients during the SFR (Kentish and Wrzosek 1998; Shen et al. 2013; Ward et al. 2008). Excitation contraction coupling in cardiac myocytes is initiated by the depolarization-induced influx of Ca^{2+} through voltage-gated L-type Ca^{2+} channels which triggers ryanodine receptors (RyRs) of the sarcoplasmic reticulum (SR) to release Ca^{2+} . The subsequent rapid increase in cytosolic Ca^{2+} , termed the “ Ca^{2+} transient,” initiates cross-bridge cycling, force production, and contraction (Bers 2008). With each cardiac cycle, there is movement of Ca^{2+} across the sarcolemma between the cytosol and the extracellular space, and to and from the sarcoplasmic reticulum (SR) which is the Ca^{2+} store within myocytes. Ca^{2+} is also buffered in the myocyte cytosol, with movement of small amounts between the cytosol and the mitochondria and other proteins that bind Ca^{2+} . Figure 2 shows a four-compartment model of myocyte Ca^{2+} movements under steady-state conditions. Perturbations in Ca^{2+} movements between compartments results in immediate changes to the amplitude and/or the time course of the Ca^{2+} transient and the subsequent duration and magnitude of the

force developed during contraction. During the SFR, stretch triggers a net increase in Ca^{2+} movement from the external compartment to the cytosol and then to the SR. This continues for several minutes until some new steady-state is achieved.

Given the importance of L-type Ca^{2+} channels as a portal for Ca^{2+} movement from the external compartment into cardiac myocytes, it would seem obvious to assume additional Ca^{2+} entry during the SFR might, therefore, involve a stretch-related increase in L-type Ca^{2+} currents during the action potential. However, many studies of the cardiac action potential and L-type Ca^{2+} currents have shown that these are only marginally affected by stretch (Hongo et al. 1996), whereas enhancement of force and intracellular Ca^{2+} can occur even when the stretch takes place only during diastole (Allen et al. 1988) or in quiescent muscles (Ward et al. 2008). These observations suggest that the stretch-induced Ca^{2+} entry during the SFR is not associated with excitation-contraction coupling but is a result of some other continuously active mechanism that takes time to fully develop. Beat-to-beat trans-sarcolemmal Ca^{2+} flux occurs via the electrogenic $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) in cardiac myocytes (for review see (Blaustein and Lederer 1999)). NCX acts in “forward mode” during diastole to extrude Ca^{2+} , but at positive membrane potentials and when intracellular $[\text{Na}^+]$ is elevated, such as during the action potential plateau, “reverse mode” Ca^{2+} entry occurs. There is general agreement that Ca^{2+} influx via NCX operates during the SFR as a final step in some stretch-activated signaling pathway (Kockskamper et al. 2008b; Luers et al. 2005; Perez et al. 2001; Shen et al. 2013). However, there is debate about the stretch-activated cellular mechanisms upstream to NCX Ca^{2+} entry.

Whereas Ca^{2+} entry during the SFR is beneficial to healthy hearts, in some cardiac pathologies, additional Ca^{2+} accumulation can lead to Ca^{2+} overload and metabolic dysfunction. Abnormal regulation of myocyte Ca^{2+} cycling is a hallmark of failing hearts which typically have weak and poorly

Fig. 1 Representative slow force response from a rat trabecula. Panel A shows stress before, during (solid bar), and after a step increase in muscle length. Panel B shows individual Ca^{2+} transients (340/380 fura-2 ratio,

LHS) and twitches (stress, RHS) immediately after stretch (i) and following 200 s of stretch (ii) for the time points indicated by arrows in panel A

Table 1 Description of terms and abbreviations

Term and/or abbreviation	Definition
Diastolic	Interval between contraction during which the chambers are relaxed and fill with blood
Systolic	Contraction of the chambers
Cardiac myocytes	The muscle cells of the heart
Action potential	The wave of depolarization that initiates myocyte contraction
Extrasystole	An additional action potential that initiates an unsynchronized contraction
Paracrine	Substance released by the heart that regulates myocyte activity
Autocrine	Substance released by the myocytes that regulates their own activity
Superfusate	Physiological buffer solution that supplies oxygen and nutrients to the isolated muscle preparation
Inotropic	Modifying force or time course of contraction
Trabeculae	Multicellular muscle preparations (diameter ~ 300 μm and length ~ 3 mm) microdissected from within the right ventricle used for measurements of isometric force and intracellular $[\text{Ca}^{2+}]$
Sarcoplasmic reticulum (SR)	Intracellular Ca^{2+} store within myocytes that provides the bulk of Ca^{2+} for contraction
Ryanodine receptors	The Ca^{2+} release channels of the sarcoplasmic reticulum
Voltage-gated channels	Membrane channels that are opened by changes in membrane potential
TRP	A superfamily of membrane channels that is mostly permeable to monovalent and divalent cations
GPCR	Family of G protein-coupled receptors
eNOS	Endothelial nitric oxide synthase
L-NAME	<i>L</i> -arginine analogue used as an inhibitor of nitric oxide synthase

synchronized contractions (Bers 2006; Hasenfuss 1998; Ward et al. 2003). Diseased hearts may also exhibit heterogeneous contractility. This would mean some myocytes were stretched as neighboring myocytes contracted more strongly, which could contribute to abnormal Ca^{2+} homeostasis.

Potential mechanisms underlying the SFR

Stretch-activated nonspecific cation channels

An obvious candidate for the SFR would be stretch-activation of sarcolemmal ion channels that allowed either Na^+ entry, which would then permit increased $[\text{Ca}^{2+}]_i$ via $\text{Na}^+/\text{Ca}^{2+}$ exchange (NCX), or direct Ca^{2+} entry. Their activation would slowly increase SR Ca^{2+} load and result in a steady increase in Ca^{2+} transient amplitude. There have been many studies of the stretch-induced currents in isolated ventricular cells thought to be caused by the opening of mechanosensitive or stretch-activated channels (Iribe et al. 2010; Kamkin et al. 2000; Zeng et al. 2000). Localized stretch of isolated ventricular myocytes depolarized the resting membrane potential, shortening the action potential plateau and initiating extrasystoles (Isenberg et al. 2003). Voltage-clamp analysis of isolated myocytes by Isenberg et al. (2003) attributed these effects to several ion current components, suggesting different mechanosensitive or stretch-activated; ion channels were present in the sarcolemma (Isenberg et al. 2003). Stretch-activated channels (SAC) were first discovered by patch clamping in skeletal muscle (Guhray and Sachs 1984), but these channels

have never been patch clamped in adult ventricular myocytes (Zeng et al. 2000), possibly because they reside only in the t-tubule sarcolemma and are unavailable to a patch electrode. It seems possible that stretch-activated channels may act as signal-transducing mediators, enabling the transduction of the mechanical stretch into intracellular chemical responses. It is reasonable to think that the increasingly potentiated Ca^{2+} transients during the SFR could be due to the direct conduction of Ca^{2+} via these channels or to the accumulation of $[\text{Na}^+]_i$ and the subsequent activation of the NCX. With this in mind, a number of groups have tested whether the SFR can be inhibited by blockers of SAC_{NSC} . For instance, streptomycin (40–80 μM) reduced the amplitude of the SFR to stretch in both rat papillary muscles and isolated myocytes (Calaghan and White 2004b). Ward et al. (2008) also directly demonstrated that the inhibition of the SAC using streptomycin and gadolinium (Gd^{3+}) lead to a significant, but recoverable, reduction in the SFR to stretch in multicellular ventricular trabeculae from mouse (Ward et al. 2008). However, streptomycin and Gd^{3+} are both nonspecific blockers of SAC, with lesser effects on other key Ca^{2+} handling proteins (White 2006). The discovery that a peptide isolated from a spider venom (GsMTx-4) is a more potent, and specific, blocker of stretch-activated nonspecific cation channels (SAC_{NSC}) enabled the role of SAC in the SFR to be further examined (Suchyna et al. 2000). Ward et al. used GsMTx-4 in mouse trabeculae and showed a significantly reduced, nonreversible SFR, suggesting that at least some components of the SFR upon stretch was due to SAC in mouse myocardium (Ward

Fig. 2 Model of steady-state Ca^{2+} cycling. With each cardiac cycle movement of Ca^{2+} takes place between four separate compartments. These are: (i) the external compartment which represents the extracellular fluid surrounding the myocytes; (ii) the myocyte cytosol; (iii) the internal Ca^{2+} store or sarcoplasmic reticulum (SR); and (iv) the intracellular buffers (which include the mitochondria). During steady state conditions, equal

amounts of Ca^{2+} move between the compartments. The width of the red arrows shows the relative amount of Ca^{2+} movement during each cardiac cycle, with the thick arrows representing 70–90% of the Ca^{2+} , depending on the species, and the dashed arrows representing less than 2% of total Ca^{2+}

et al. 2008). In contrast, neither Gd^{3+} nor streptomycin reduced the SFR in failing human myocardium (von Lewinski et al. 2004).

A critical issue is the molecular identification of SAC_{NSC} . There is mounting evidence that members of the transient receptor potential (TRP) family of cation channels are potential candidates (Dyachenko et al. 2009; Inoue et al. 2009; Ward et al. 2008). TRP proteins form Na^+ and Ca^{2+} channels that are activated by different physical (e.g., mechanical stretch) and/or chemical stimuli that result in slow changes in intracellular Ca^{2+} homeostasis, either directly or indirectly (Liu and Montell 2015). Many TRP channels have been shown to exhibit mechanosensitivity, possibly due to their ability to undergo dynamic interactions with the various scaffolding proteins that transduce mechanical force directly to membrane channels. All members of TRP channels have been identified in the heart (Freichel et al. 2017; Hof et al. 2019). TRPC6 has been implicated in the SAC_{NSC} in ventricular cells because the current initiated by stretch was blocked by a TRPC6 antibody (Dyachenko et al. 2009). However, further studies are required to quantify, in vivo, whether TRPC channels are the targets of pharmacological blockers of stretch-activated channels.

In 2010, an ubiquitously expressed family of large membrane proteins that assemble into mechanically activated, Ca^{2+} -permeable, nonselective cation channels were identified. These are known as Piezo channels, and they are blocked by GsMTx-4 and Gd^{3+} (Coste et al. 2010). The channels are widely expressed and are important to the normal function of multiple tissues, including from the cardiovascular system (Beech and Kalli 2019). The channels display rapid voltage-dependent inactivation in patch-clamped and whole-cell mechanical assays (Coste 2012; Coste et al. 2010; Murthy et al. 2017; Wu et al. 2017). Two family members (Piezo1 and

Piezo2) have been identified, with Piezo2 being more rapidly inactivated (with a decay constant of ~ 50 ms for Piezo1). However, the channels have also been shown to become non-inactivating with excessive mechanical stimulation (Suchyna et al. 2004). Piezo2 is mainly associated with sensory perception, but Piezo1 exists throughout the cardiovascular system and is embryonically lethal in Piezo1 knock out mice (Li et al. 2014). Piezo1 would, therefore, seem a likely candidate as having a role in the SFR, but to date, this has not been shown (Ridone et al. 2019).

Paracrine/autocrine Ca^{2+} entry pathways

Another obvious mechanism that could explain the slow force increase in Ca^{2+} transients is if stretch-activated some paracrine/autocrine signaling pathway that then leads to increased myocyte Ca^{2+} influx. It has been suggested that myocyte stretch releases angiotensin II (Ang II) from cytoplasmic granules within myocytes which then acts, along with endothelin (ET-1), as part of the hypertrophic pathway (Sadoshima and Izumo 1993). Ang II is the major bioactive peptide of the renin-angiotensin pathway and is implicated in many cardiovascular diseases. At least two G protein-coupled receptors mediate Ang II function with the type 1 (AT_1) receptor predominantly expressed in the cardiovascular system (Ohtsu et al. 2006). G protein-coupled receptors are conformationally dynamic proteins that transmit ligand-encoded signals to promote multiple, yet specific, downstream signaling pathways. They are widely implicated in the control of cardiac function through action on heterotrimeric GTP-binding proteins of the $\text{G}_{\alpha\text{s}}$, $\text{G}_{\alpha\text{i}}$, $\text{G}_{\alpha\text{q/11}}$, and $\text{G}_{\alpha\text{12/13}}$ families.

ET-1 receptors are also G protein-coupled receptors that are abundant in ventricular myocytes. Both ET-1 and Ang II are synthesized by cardiac myocytes (and other cells present in the

heart) and have been implicated by some in the SFR. They are thought to act acutely by binding to their receptors and activating a signaling cascade that includes activation of the cardiac Na^+/H^+ exchanger (NHE1). Cingolani and colleagues reported an intracellular alkalosis in isolated rabbit muscle following stretch, consistent with activation of NHE1, which was blocked by the NHE1 inhibitor EIPA, as well as by angiotensin and endothelin receptor blockers (Alvarez et al. 1999; Cingolani et al. 1998). Increased NHE1 activity increases $[\text{Na}^+]_i$, leading to increased $[\text{Ca}^{2+}]_i$ via the cardiac $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX). Other studies have confirmed some, but not all, aspects of this pathway suggested to underlie the SFR. For instance, Kockskamper et al. (2008a, b) found chamber differences in the SFR. They observed NHE-dependent (but Ang II- and ET-1-independent) $[\text{Na}^+]_i$ increase in human ventricle when stretched in contrast to human atrium, which had an Ang II- and endothelin-dependent (but NHE- and NCX-independent) force increase (Kockskamper et al. 2008a). Failing human myocardium had a slow force response (SFR) to stretch but without any detectable pH_i change (von Lewinski et al. 2004). In a later study on rabbit myocardium, the same group observed a pH_i change following stretch, but occurring after the force had stabilized (Luers et al. 2005). In contrast, Shen et al. (2013) showed a steady decrease in pH during the SFR in rat trabeculae and were unable to prevent the SFR by angiotensin-1 or ET-1 inhibition (Shen et al. 2013). Nevertheless, Shen et al. (2013) found inhibitors of NHE1 reduced the magnitude of the SFR in rat ventricular trabeculae, although blockers of angiotensin and endothelin receptors were ineffective on the SFR. Shen et al. (2013) argued that proton production would increase following a stretch-dependent (or any other) increase in force and that this would be sufficient to activate the NHE-1 (Shen et al. 2013). In response, this would increase NHE-1 proton removal from the cytosol in exchange for Na^+ , increasing intracellular $[\text{Na}^+]_i$. In turn, $[\text{Ca}^{2+}]_i$ in the cytosol would increase via NCX, either by reversing the exchanger or by slowing Ca^{2+} efflux.

The involvement of paracrine/autocrine factors in the SFR was unequivocally confirmed in rat hearts using a simple bioassay system (Ward et al. 2014). This consisted of a Langendorff-perfused heart with a balloon in the LV used for pressure recording and producing LV stretch. Coronary effluent from the perfused heart was collected for 30 s following stretch by a cannula inserted into the RV. The collected effluent was then reoxygenated and used to superfuse an unstretched trabecula held at fixed (optimal) length, resulting in a steady increase in the Ca^{2+} transients and twitch force over a similar time period to the SFR. Investigation of the coronary effluent samples using liquid chromatography-mass spectrometry (Ward et al. 2014). Results from this study strongly suggested the factor(s) released by stretch were prostaglandins, with $\text{PGF2}\alpha$ as the most likely candidate. $\text{PGF2}\alpha$ applied to the superfusate of isolated trabeculae increased

Ca^{2+} transients and twitch force, with a similar time course to that of the SFR. Levels of $\text{PGF2}\alpha$ in the heart are increased by hemodynamic overload (Chazov et al. 1979; Escobar et al. 1983), and $\text{PGF2}\alpha$ has been associated with inducing cardiac myocyte hypertrophy in vitro (Vandenburg et al. 1996) and cardiac growth in vivo (Adams et al. 1996; Lai et al. 1996). $\text{PGF2}\alpha$ exerts its effects through FP prostanoid receptors that link to activation of phospholipase C- and G_q -coupled proteins, leading to inositol triphosphate-induced elevation of intracellular calcium and diacylglycerol activation of protein kinase C (PKC) (Watanabe et al. 1994). The net result of acutely applied $\text{PGF2}\alpha$ on cardiac muscle preparations is a steady increase in the amplitude of the Ca^{2+} transients and twitch force (Shen et al. 2016; Yew et al. 1998). Yew et al. (1998) proposed that the positively inotropic effect of $\text{PGF2}\alpha$ was mediated via activation of the sarcolemmal Na^+/H^+ exchanger (Yew et al. 1998), which is also implicated in the SFR (Cingolani et al. 2003; Luers et al. 2005; Shen et al. 2013; Vargas et al. 2013; von Lewinski et al. 2003).

Interestingly, both Ang II and $\text{PGF2}\alpha$ initiate signaling cascades through the activation of receptors linked to $\text{G}_{\alpha q}$. Transmission of conformational information between the AT_1 and FP receptors has been described in the presence of active $\text{G}_{\alpha q}$ in vascular smooth muscle cells (Fillion et al. 2019; Goupil et al. 2015; Sleno et al. 2017). G protein-coupled receptors (GPCRs) reportedly form a heterodimer complex in smooth muscle that allows signal integration between AT_1 and the FP receptors in the control of smooth muscle contractility (Fillion et al. 2019).

Another stretch-mediated mechanism (independent of stretch-activated channels) that has been implicated in the SFR is the activation of endothelial nitric oxide synthase (eNOS) which is localized within the caveolae of cardiomyocytes. Low concentrations of NO have inotropic effects in the myocardium through s-nitrosylation of Ca^{2+} handling proteins (Eu et al. 2000). A stretch-induced increase in Ca^{2+} transients in rat ventricular trabeculae can be prevented with inhibition of eNOS using L-NAME or in cardiomyocytes from mice lacking expression of eNOS (Petroff et al. 2001). Activation of eNOS during stretch was found to be through a phosphoinositide-3-kinase-Akt pathway.

Modeling the SFR

An important aspect of the myocardial response to mechanical stretch or strain is the identification of the sensors that initiate the response and transduce it into the biological response. Many mechanosensitive proteins have been identified, with some debating that all membrane proteins are stretch-sensitive to some extent. In isolated ventricular trabeculae, the size of the SFR is highly dependent on the nature of the muscle length change (Ward et al. 2008), as well as on SR

Ca^{2+} load, with the largest increase in force during the SFR occurring when the SR Ca^{2+} content is low (Shen et al. 2013). This suggests there may be more than one means of sensing the mechanical stimulus. Experimental evidence has come from studies performed in models that are lacking one or more key structural or anchoring components, such as deletion of β -1 integrin, for example (Babbitt et al. 2002; Shai et al. 2002). Integrins form a structural link between the myocyte cytoskeleton and the extracellular matrix. A study using magnetic beads coated with an anti- β -1 integrin antibody to stretch isolated ventricular myocytes, in conjunction with pharmacological blockers, suggested integrins were sensors of myocyte stretch (Browe and Baumgarten 2003). This has been further investigated using modeling studies to probe the cellular mechanisms underlying the mechanosensitivity of ventricular myocytes (Tan et al. 2017).

The role of SAC_{NSC} channels was investigated by Tavi et al. (1998) and Youm et al. (2006). Both models showed that Ca^{2+} permeability of the SAC_{NSC} made only a small difference to the increase in Ca^{2+} transients produced by stretch, whereas if Na^{+} permeability was removed, then the Ca^{2+} transient increase was only minimal. Niederer and Smith (2007) also developed a model of the rat ventricular myocyte which demonstrated that SAC_{NSC} was capable of producing a robust SFR. An important finding of the Niederer and Smith (2007) model was the contribution of NHE-1 to the response, even when the NHE1 was not stretch-sensitive. This was validated by Shen et al. (2013) in their investigation of the SFR (Shen et al. 2013).

Summary

This review has focused on the short-term response to myocardial stretch that takes place over several minutes, known as the slow force response to stretch. Although the SFR has been studied for almost 50 years (Parmley and Chuck 1973), there is still no single mechanism that clearly explains the steady increase in $[\text{Ca}^{2+}]_i$ that accompanies the force response. The SFR has been observed in isolated cardiomyocytes (Calaghan and White 2004a), isolated trabeculae (Kentish and Wrzosek 1998; Ward et al. 2008), papillary muscles (Cingolani et al. 1998), isolated perfused hearts (Ward et al. 2014), and in vivo (Todaka et al. 1998; von Anrep 1912). It is also present across many different species, suggesting it is an important physiological mechanism for increasing Ca^{2+} -dependent contractility in the heart. While the SFR is beneficial as a means of increasing mechanical performance in healthy hearts, it may also have a key role in the initiation of hypertrophic remodeling if stretch is sustained for long periods. It is therefore important that the cellular mechanisms that regulate myocyte Ca^{2+} handling in response to myocyte stretch during the SFR is fully understood.

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Compliance with ethical standards

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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