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ORIGINAL RESEARCH ARTICLE

The contractile adaption to preload depends on the amount of afterload

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Abstract

Aims The Frank–Starling mechanism (rapid response (RR)) and the secondary slow response (SR) are known to contribute to increases contractile performance. The contractility of the heart muscle is influenced by pre-load and after-load. Because of the effect of pre-load vs. after-load on these mechanisms in not completely understood, we studied the effect in isolated muscle strips.

Methods and results Progressive stretch lead to an increase in shortening/force development under isotonic (only pre-load) and isometric conditions (pre- and after-load). Muscle length with maximal function was reached earlier under isotonic ($L_{max\text{-}isotonic}$) compared with isometric conditions ($L_{max\text{-}isometric}$) in nonfailing rabbit, in human atrial and in failing ventricular muscles. Also, SR after stretch from slack to $L_{max\text{-}isotonic}$ was comparable under isotonic and isometric conditions (human: isotonic 10 ± 4%, isometric 10 ± 4%). Moreover, a switch from isotonic to isometric conditions at $L_{max\text{-}isometric}$ showed no SR proving independence of after-load. To further analyse the degree of SR on the total contractile performance at higher pre-load muscles were stretched from slack to 98% $L_{max\text{-}isometric}$ under isotonic conditions. Thereby, the SR was 60 ± 9% in rabbit and 51 ± 14% in human muscle strips.

Conclusions This work shows that the acute contractile response largely depends on the degree and type of mechanical load. Increased filling of the heart elevates pre-load and prolongs the isotonic part of contraction. The reduction in shortening at higher levels of pre-load is thereby partially compensated by the pre-load-induced SR. After-load shifts the contractile curve to a better 'myofilament function' by probably influencing thin fibers and calcium sensitivity, but has no effect on the SR.

Keywords Pre-load; After-load; Contractility; Shortening; Slow force response

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Introduction

The cardiovascular system has extrinsic and intrinsic mechanisms to adapt the heart to an increased demand of blood flow. Neuroendocrine substances like epinephrine act on heart and vessels thereby increasing cardiac function.[1] However, the heart itself can adjust with an increase in heart rate[2,3] and with the Frank–Starling mechanism (FSM). Frank[4] and Starling[5] first described that an increase in ventricular end-diastolic volume caused either by an elevation in venous return or a rise in aortic resistance is followed by an immediate increase in force of contraction. This rapid response (RR) is mediated by an increased sensitivity of the myofilaments for calcium (Ca^{2+}).[6,7] If the load elevation persists a second but slower mechanism—called slow response—further increases myocardial contractility.[8,9] The mechanism of the SR depends on the sarcoplasmic reticulum Ca^{2+} handling and augmented intracellular Ca^{2+} transients.[10,11] Further experiments could show that activation of the Na^+/H^+ exchanger results in enhanced transsarcolemmal Na^+ entry followed by a $[Na^+]_i$-dependent Ca^{2+} entry via the Na^+/Ca^{2+} exchanger working in its reverse mode.[12,13]

During the cardiac contraction cycle, two different types of load—pre-load during diastole and after-load during systole—can be differentiated. Pre-load builds up during diastolic filling and stretches cardiomyocytes, whereas after-load is generated by each cardiomyocyte to produce adequate cardiac stroke work against vascular resistance. It has been shown by our group previously that pre-load elevation leads to an adaptive hypertrophy, whereas after-load elevation promotes maladaptive remodelling.[14] But the role of these load forms on the contractile response to load has not been completely understood. This is important, because pathological changes of the load types occur at various diseases.[15] In heart failure, often pre-load and after-load are increased. A selective increase in after-load is present in aortic stenosis or arterial hypertension leading to a prolonged isometric part of the contraction. Increased filling of the heart elevates pre-load, but also the isotonic part of the contraction is prolonged to generate a higher stroke volume.

In the failing heart changes in the SR calcium cycling[16] and also in myofilament, mechanics are described.[17] This could influence the adaption to mechanical load also.

The aim of this study was to investigate the contractile adaption to pre-load and after-load in the healthy rabbit and in failing human myocardium.

Methods

The investigation conforms to the principles outlined in the *Declaration of Helsinki* and *Guide for the Care and Use of Laboratory Animals* (NIH publication no. 85–23, revised 1996). The study was approved by the institutional ethics committee, and all patients provided written informed consent for the use of cardiac tissue samples. All animal procedures were approved by the government committee for animal studies and carried out according to German laws regarding the care and use of laboratory animals.

Human failing tissue

Human ventricular muscle strips were dissected from freshly explanted hearts. All procedures were in compliance with the ethical committee of Georg-August-University Göttingen. Twenty-eight end-stage heart failure patients undergoing cardiac transplantation as a result of ischaemic or dilated cardiomyopathy (22 men and 6 women, average age 49 ± 7 years, 17 ICM and 11 DCM). Unfortunately, the analysis of non-failing myocardium was not possible because of the lack of available tissue. Hearts were transported in a Krebs–Henseleit buffer with 2,3-butanedione monoxime as cardioplegic solution.[18,19]

Human atrial tissue

Six right atrial appendages were obtained from patients undergoing heart surgery who were in sinusrhyhtm (four men and two women, average age 69 ± 2 years, all undergoing coronary artery bypass graft).[20] All procedures were in compliance with the ethical committee of Georg-August-University Göttingen.

Rabbit muscle preparation

Female chinchilla bastard rabbits (1.5 to 2 kg, Charles River, Kisslegg, Germany) were heparinized and anaesthetized with thiopental sodium (50 mg/kg i.v.). Hearts were excised and retrogradely perfused with modified Krebs–Henseleit solution as described.[21]

Experimental protocol

Intact human trabeculae or rabbit papillary muscles were carefully microdissected from the right ventricle and fixed between a force transducer (Scientific Instruments) and a hook connected to a micromanipulator for length adjustment. The system is equipped with a servomotor with force-feedback function and allows cultivation of functionally intact multicellular muscle preparations for up to 48 h at 37°C with physiological protein turnover maintained.[22] Only trabecula with a diameter of 0.5 mm or below were used for experiments in order to avoid hypoxia. After wash-out of the cardioplegic solution, muscle preparations were superfused with Krebs–Henseleit solution (containing in mmol/L: 137 NaCl, 5.4 KCl, 1.2 $MgSO_4$, 1.2 NaH_2PO_4, 20 HEPES, 10 glucose, 0.25 $CaCl_2$; pH adjusted to 7.4 with NaOH) and electrically stimulated (baseline 1 Hz, amplitude 3 to 5 V; stimulator Scientific Instruments type STIM2). Force measurements were carried out at 37°C and at 1.25 mmol/L $[Ca^{2+}]_o$. After a 60 min equilibration period, the experiments were performed, according to the following protocols:

(1) The muscles were stretched, and the contraction model was switched every 30 s from isotonic to isometric and back. This was done till the length at which maximum isometric steady-state twitch force was reached (L_{max}). The isotonic shortening and the isometric developed force were analysed.
(2) Preparations were stretched progressively over 30 min to the length at which maximum steady-state twitch force was reached ($L_{max\text{-}isometric}$). The muscle diameter was determined, and the muscle was released to 88% of $L_{max\text{-}isometric}$. After 30 min, the muscle was suddenly stretched to 98% of $L_{max\text{-}isometric}$ and developed force or the isotonic shortening was measured. After

mechanical stabilization, the muscle was released to 88% $L_{max\text{-}isometric}$, and the protocol was repeated. Alternating one stretch was done under isotonic and the other under isometric conditions.

(3) The SR was studied by the same protocol as given above (2), beside that the muscles were released to slack conditions and the stretch was done from slack to 98% of $L_{max\text{-}isometric}$.

(4) The SR was studied by the same protocol as given above (2), beside that the muscles were only stretched to a resting tension where isotonic shortening was maximal ($L_{max\text{-}isotonic}$ in human 3.5 mN/mm^2 and in rabbit 11 mN/mm^2).

(5) Muscles were stretched to $L_{max\text{-}isometric}$ under isotonic conditions and were allowed to stabilize for 30 min. Afterwards, the contraction was switched to the isometric contraction mode, and the developed tension was recorded. The change in developed force after 10 min was normalized to the developed force immediately after switch to the isometric contraction.

Mathematical methods

Force values were transferred to tension by normalizing to the cross-sectional area of a preparation, which was calculated assuming an elliptical cross-section using the formula Cross-sectional area = $D_1/2 \times D_2/2 \times \pi$, with D_1 and D_2 representing width and thickness, respectively. Gene and protein expression were analysed using unpaired Student's *t*-test, with values of $P < 0.05$ considered statistically significant.

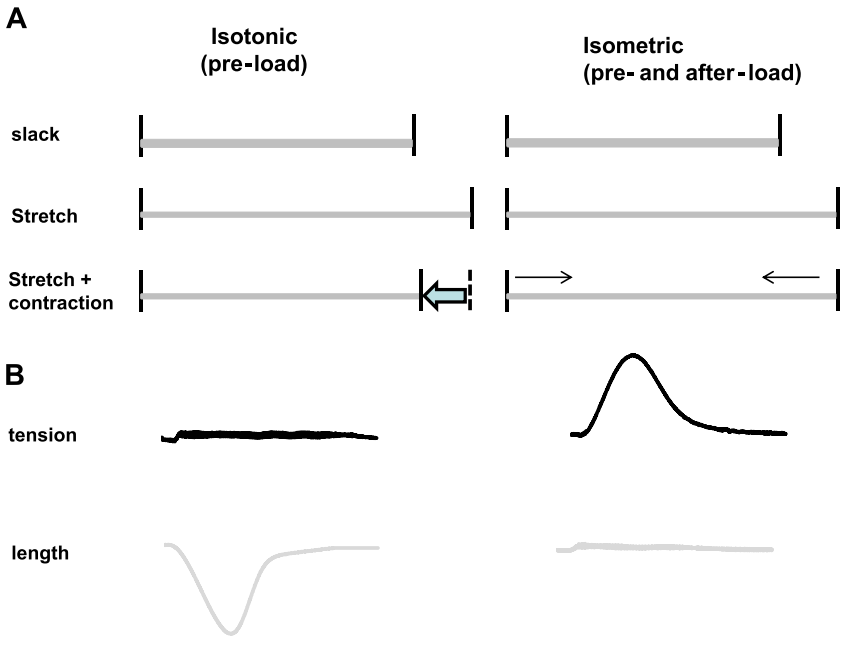
Results

The length-dependent activation differs under istonic vs. isometric conditions

To analyse the role of pre- and after-load on the contractile performance of the heart, we used the model of isolated muscle strips from rabbit nonfailing and human failing myocyardium. Therefore muscles were stretched, which lead to an increase in pre-load. The muscles where electrically stimulated under either isotonic or isometric conditions (*Figure 1A*). Isotonic contraction allowed a shortening of the muscles and after the contraction, the muscles were restretched to the original length again. Because the tension is unchanged under isotonic contraction (*Figure 1B*), only pre-load but no after-load acts on the muscle. Under isometric conditions shortening is not possible, and therefore tension is increased. Therefore, under isometric conditions, after-load produced during the contraction in addition to the pre-load induced by stretch is present.

We first investigated the length-dependent activation in isolated muscle strips under isometric and isotonic conditions.

Figure 1 (A) Schematic picture of muscle length and contractile function under isotonic (shortening) and isometric conditions (increase in tension). (B) Example of the change in length (light grey) and tension (dark grey) under isotonic vs. isometric conditions.



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The muscle length with maximal contractile performance (L_{max}) was reached earlier under isotonic conditions ($L_{max\text{-}isotonic}$) compared with isometric conditions ($L_{max\text{-}isometric}$; *Figure 2A and B*). In muscle strips from human failing myocardium, the muscle shortening under isotonic conditions increased to 6.9 ± 0.9% at $L_{max\text{-}isotonic}$ and with a further increase in pre-load decreased again by −42 ± 4% to 4.0 ± 0.6% at $L_{max\text{-}isometric}$ ($P < 0.01$; *Figure 3A*). In contrast, the developed force under isometric conditions was 5.7 ± 0.5 mN/mm^2 at $L_{max\text{-}isotonic}$ and increased further to 9.2 ± 0.9 mN/mm^2 at $L_{max\text{-}isometric}$ (61 ± 7%, $P < 0.01$; *Figure 3B*). This can also be observed in rabbit nonfailing myocardium ($L_{max\text{-}isotonic}$ to $L_{max\text{-}isometric}$: isotonic shortening −46 ± 6%, isometric developed force 57 ± 13%) and human nonfailing atrial myocardium ($L_{max\text{-}isotonic}$ to $L_{max\text{-}isometric}$: isotonic shortening −49 ± 7%, isometric developed force 51 ± 8%; *Figure 3A and B*).

These results show that the contractile response to pre-load is modulated by the amount of after-load. After-load leads to a shift in the length-dependent contractile response to longer muscle length, indicating that after-load per se improves the contractility of the heart.

Figure 2 (A) Example of isometric (black) and isotonic (grey) contractions at different muscle length. (B) Example of the length-dependent activation under isotonic (light grey) and isometric (dark grey) conditions (diastolic tension F_{dia} = black).

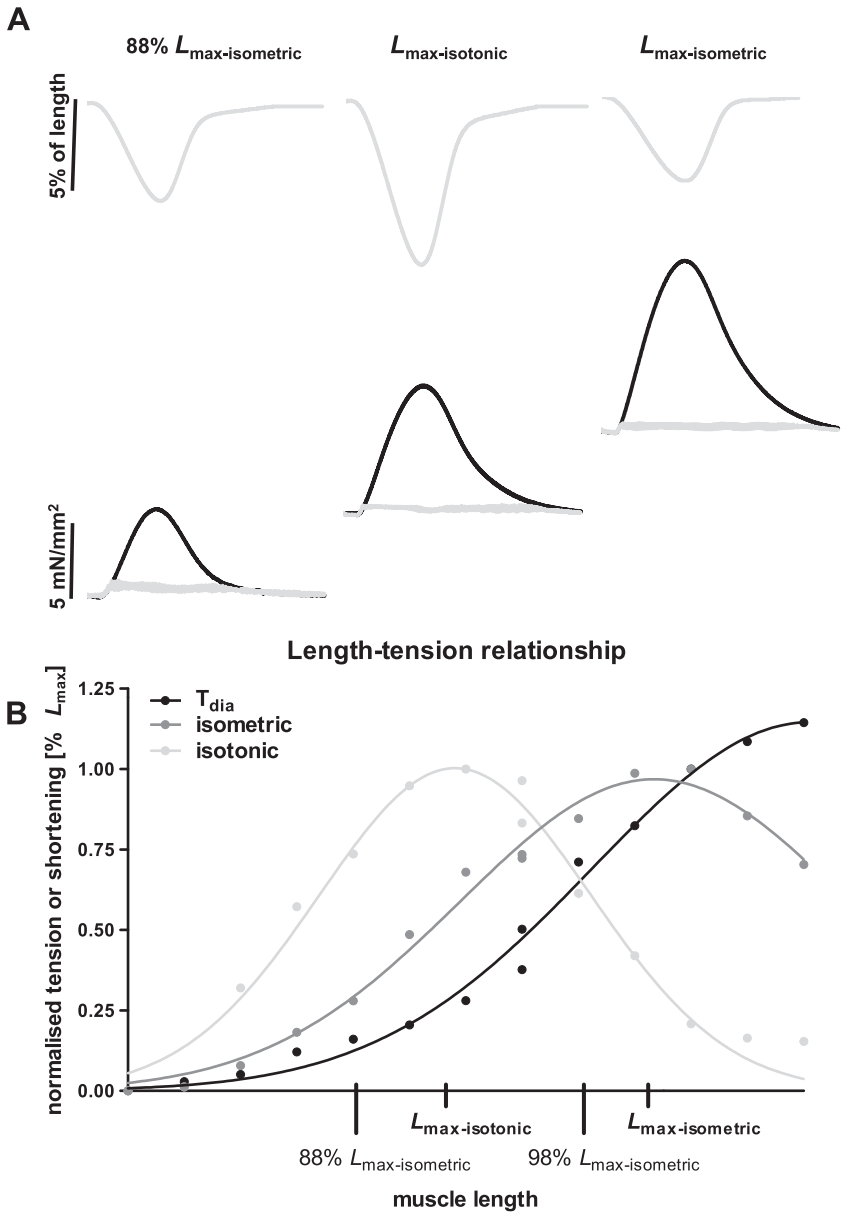

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Figure 3 (A) Percentage of muscle shortening at $L_{max\text{-}isometric}$ normalised to $L_{max\text{-}isotonic}$ in rabbit (■, n = 7), human ventricular failing (■, n = 10) and human atrial nonfailing (■, n = 6) muscle strips (each $P < 0.01$ vs. $L_{max\text{-}isotonic}$). (B) Percentage of muscle shortening at $L_{max\text{-}isotonic}$ normalised to $L_{max\text{-}isometric}$ in rabbit (■, n = 7), human ventricular failing (■, n = 10) and human atrial nonfailing (■, n = 6) muscle strips (each $P < 0.01$ vs. $L_{max\text{-}isometric}$).

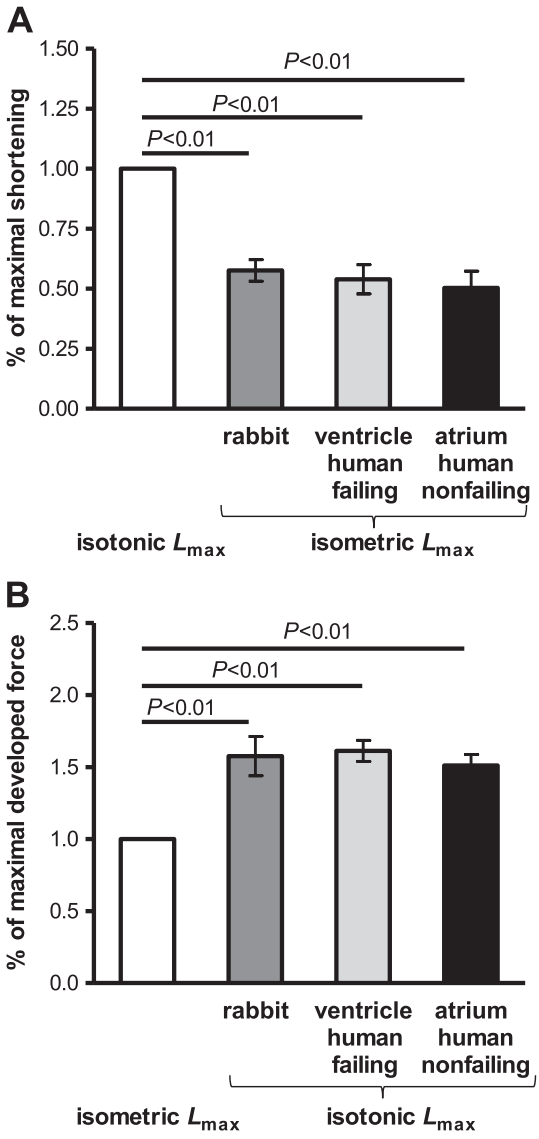
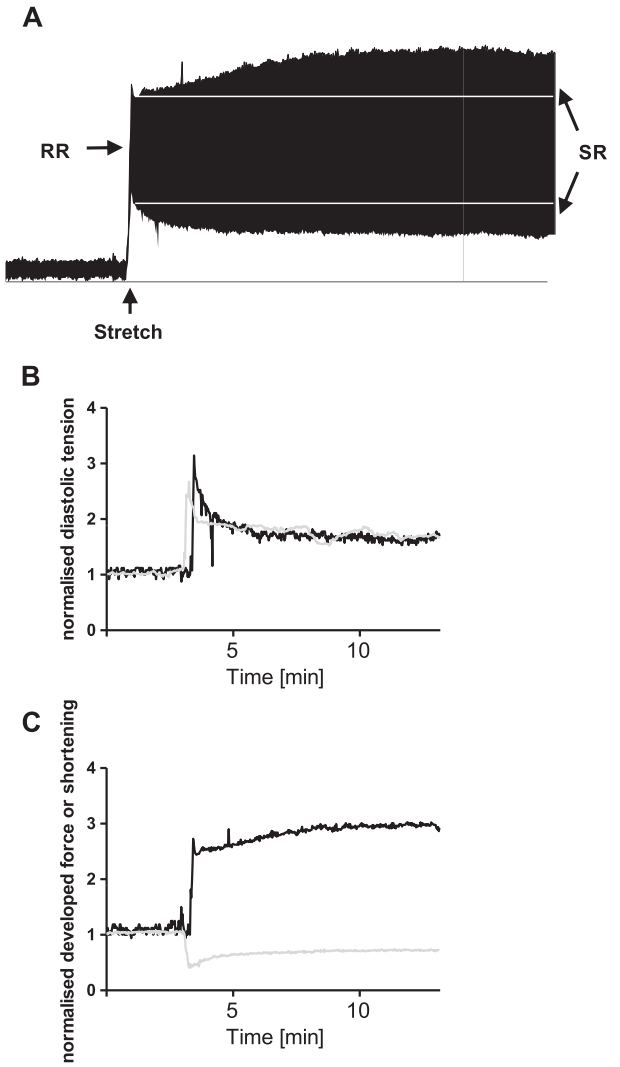


Figure 4 (A) Example of the slow force response (SR) under isometric conditions after stretch from 88% to 98% $L_{max\text{-}isometric}$; (B) normalised diastolic tension under isometric conditions (black) and isotonic conditions (grey) during the SR; (C) normalised developed tension under isometric conditions (black) and normalised muscle shortening under isotonic conditions (grey) during the SR.



Slow response is independent of after-load

We then were interested in the role of after-load on the SR and therefore studied the role of the SR and RR under isotonic and isometric conditions.

The established protocol[13] for SR uses a fast stretch from 88% $L_{max\text{-}isometric}$ to 98% $L_{max\text{-}isometric}$ (*Figure 4A*). This protocol shows an increase in RR (rabbit: 207 ± 13%; human: 222 ± 12%) and SR (rabbit: 30 ± 2%; human: 21 ± 2%) after stretch under isometric conditions (*Figure 5A–D*). Because of the stretch above $L_{max\text{-}isotonic}$, a rapid decrease of shortening can be seen under isotonic conditions (rabbit: 57 ± 5%; human: 58 ± 5%; *Figure 4C*, *5A and B*). This is followed by a SR (rabbit: 51 ± 4%; human: 36 ± 3%; *Figure 4C*, *5C and D*). The SR under isotonic conditions (human: 36 ± 3%) seems to be higher compared with isometric conditions (human: 21 ± 2%, $P < 0.05$ vs. isotonic), but the slow decline in diastolic tension must be taken in account (*Figure 4B*). This decline leads to a decrease in force development under isometric conditions and because the muscle length comes closer to $L_{max\text{-}isotonic}$ to an increase in shortening under isotonic conditions. Therefore, the large SR under isotonic conditions is at least partly derived from a reduced diastolic tension. We therefore

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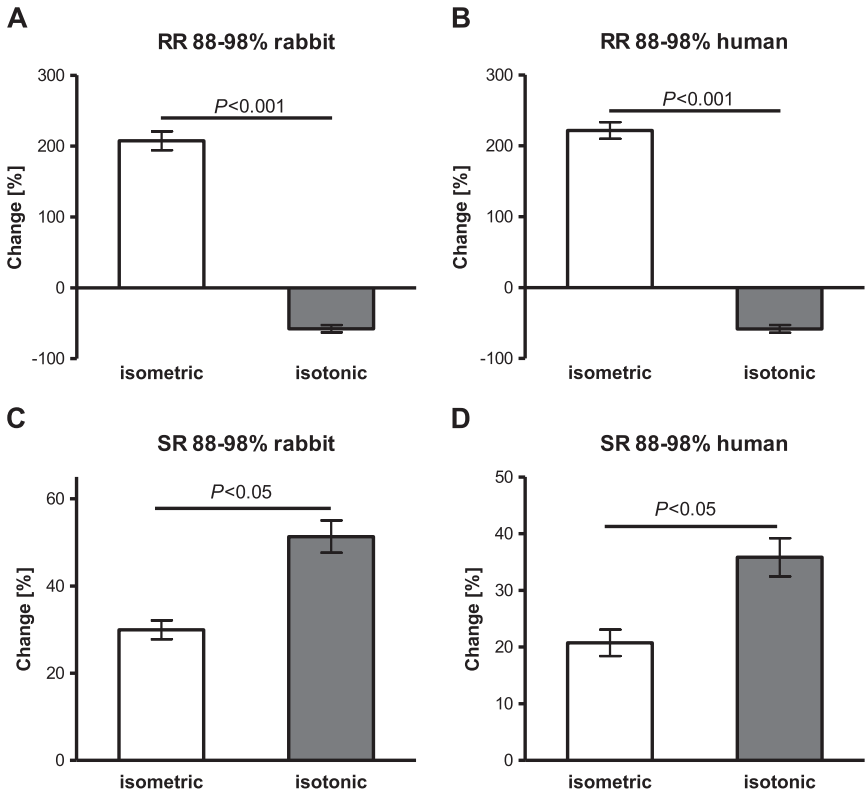
Figure 5 Rapid response (RR) and slow response (SR) after stretch from 88% to 98% $L_{max\text{-}isometric}$: (A) RR under isometric (□) and isotonic conditions (■) in rabbit muscle strips (each $n = 7$, $P < 0.001$ isotonic vs. isometric); (B) RR under isometric (□) and isotonic conditions (■) in human failing muscle strips (each $n = 6$, $P < 0.001$ isotonic vs. isometric); (C) SR under isometric (□) and isotonic conditions (■) in rabbit muscle strips (each $n = 7$, $P < 0.05$ isotonic vs. isometric); (D) SR under isometric (□) and isotonic conditions (■) in human failing muscle strips (each $n = 6$, $P < 0.05$ isotonic vs. isometric).



calculated the individual reduction of diastolic tension and the increase in muscle shortening (*Table 1*). After stretch from 88% to 98% $L_{max\text{-}isometric}$, diastolic tension decreased by 18 ± 2% in rabbit and by 16 ± 2% in human failing muscle strips. This decrease in diastolic tension alone would have lead to an increase in muscle shortening by 23 ± 3% and 16 ± 2%, respectively. Furthermore, the 'real' SR was also calculated by the measured SR minus the calculated effect of the shift in diastolic tension. The calculated SR under isotonic conditions is than 28 ± 6% in rabbit and 20 ± 3% in human muscle strips and hence not significantly different from the SR under isometric conditions (rabbit: 29 ± 3%, human: 21 ± 2%, *Table 1*). Because pre-load is elevated comparable under isotonic and isometric conditions and after-load is increased only under isometric conditions, this indicates that the SR is independent of after-load.

To prove this concept without the confounding effects of the different responses to a decrease in diastolic tension muscles were stretched from L_0 to $L_{max\text{-}isotonic}$ (*Figure 6A*). Here, the slow response was not different under isometric (13 ± 4%) and isotonic (12 ± 4%) conditions in rabbit muscle strips (*Figure 6B*) and 10 ± 4% under isometric as well as

Table 1. Calculation of the 'real' SR under isotonic conditions: The increase in muscle shortening due to the decrease in diastolic tension was subtracted from the measured SR. The now calculated SR under isotonic is not significantly regulated from the SR under isometric conditions in rabbit and human failing muscle strips after stretch from 88% to 98% $L_{max\text{-}isometric}$ (88–98%) or from slack to 98% $L_{max\text{-}isometric}$ (0–98%)

	Isotonic measured SR (%)	Decline in diastolic tension (%)	Change in shortening due to decline in distolic tension (%)	Isotonic calculated SR (%)	Isometric measured SR (%)
Rabbit 88–98%	51±4	−18±2	23±3	28±6	29±3
Human 88–98%	36±3	−16±2	16±2	20±3	21±2
Rabbit 0–98%	146±8	−33±3	86±3	60±9	
Human 0–98%	136±13	−30±4	84±5	51±14	

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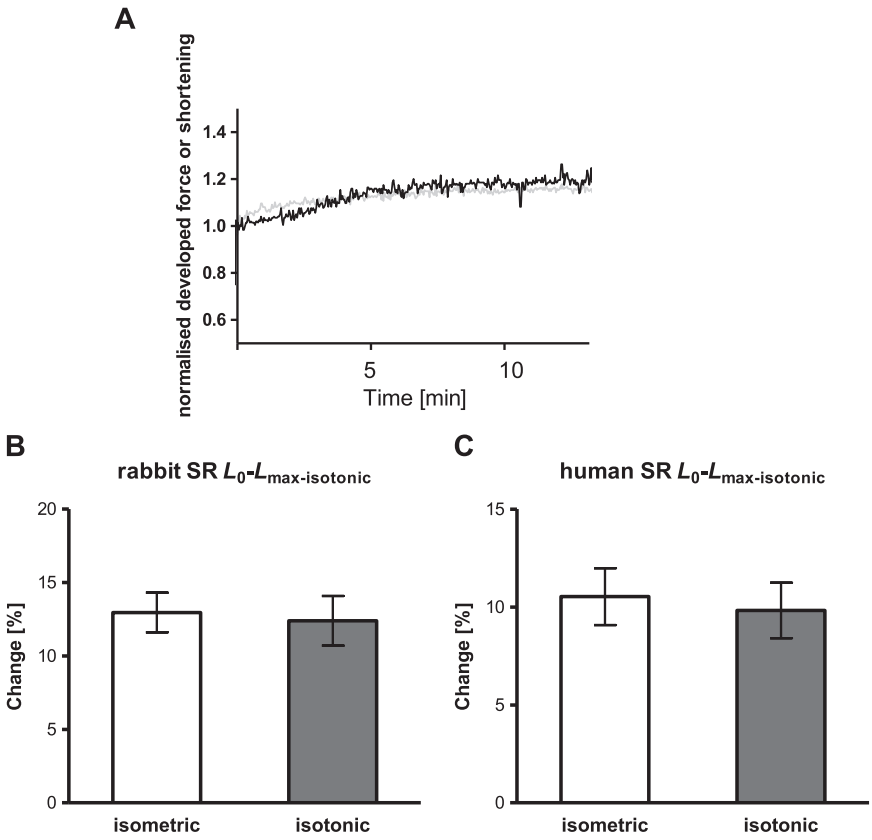
Figure 6 Slow response (SR) after stretch from slack to $L_{max\text{-}isotonic}$: (A) normalised developed tension under isometric conditions (black) and normalised muscle shortening under isotonic conditions (grey) during the SR; (B) SR under isometric (□) and isotonic conditions (■) in rabbit muscle strips (each $n = 7$, $P < 0.01$ isotonic vs. isometric); (C) SR under isometric (□) and isotonic conditions (■) in human failing muscle strips (each $n = 7$, $P < 0.01$ isotonic vs. isometric).



10 ± 4% under isotonic conditions in human failing muscle strips (*Figure 6C*). Therefore, these data indicate that pre-load is the only trigger for the SR.

As a second prove muscle strips that were stretched to $L_{max\text{-}isometric}$ under isotonic conditions and after-load was added by switching to isometric conditions. After addition of after-load, no change in isometric developed force and therefore no SR was seen (*Figure 7A–D*). These experiments also show that after-load is not involved in the SR.

Slow response compensates the reduction of shortening after stretch over $L_{max\text{-}isotonic}$

Because the SR is only pre-load dependent, we were interested to quantify the degree of contractile support by the SR under isotonic conditions at higher muscle length. Therefore, the muscle strips were stretched under isotonic conditions from slack length (L_0) to 98% $L_{max\text{-}isometric}$ (*Figure 8A and B*). The SR was 146 ± 12% in the rabbit and 135 ± 13% in human failing muscle strips (*Figure 5D*). A part of this SR is due to progressive decline in diastolic tension, thereby bringing the muscle nearer to $L_{max\text{-}isotonic}$. After subtraction of the calculated change in shortening due to the decline in diastolic tension—calculated according to the measured diastolic tension parameters and the length-tension relationship—the SR was 60 ± 9% in rabbit and 51 ± 14% in human failing muscle strips (*Table 1*). This indicates that under isotonic conditions the SR partially compensates the decline of shortening after stretch over $L_{max\text{-}isotonic}$ and that this mechanisms shows no difference between failing and nonfailing myocardium.

Discussion

The present study consistently shows that (i) the length-dependent activation is different under isotonic vs. isometric conditions; (ii) the SR depends only on pre-load but not on after-load; and (iii) there is no difference of these mechanisms between non-failing rabbit ventricular, non-failing human atrial and failing human ventricular hearts.

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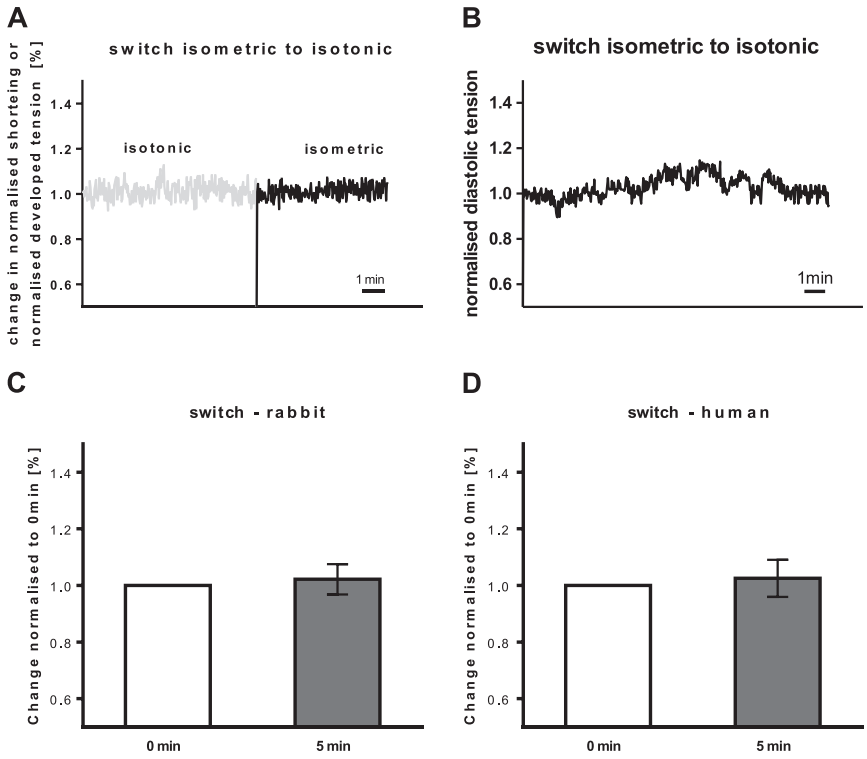
Figure 7 Change from isotonic to isometric conditions at $L_{max\text{-}isometric}$ (A) normalised muscle shortening under isotonic conditions (grey) before and normalised developed tension under isometric conditions (black) after switch from isotonic to isometric conditions; (B) normalised diastolic tension during switch from isotonic to isometric conditions; (C) change in developed force after 10 min (■) normalised to the developed force immediately after switch from isotonic to isometric conditions (□) in rabbit muscle strips (n = 6); (D) change in developed force after 10 min (■) normalised to the developed force immediately after switch from isotonic to isometric conditions (□) in human failing muscle strips (n = 6).



The length-dependent activation depends largely on type of load. The muscle length with maximal shortening ($L_{max\text{-}Shortening}$) under isotonic conditions is shorter than the muscle with maximal force development under isometric conditions ($L_{max\text{-}force}$). Iribe *et al.* analysed the length-dependent activation in isolated myocytes.[23] In contrast to our results, they found no difference on cell shortening during isotonic and isometric conditions. These cells could only be stretched to a sarcomere length of ~2.0 μm. We used intact trabeculae that could be stretched to higher sarcomere lengths. The sarcomere length at $L_{max\text{-}isometric}$ is ~2.3 μm.[24] Therefore, the technique and the amount of stretch applied to the myocytes could explain why Iribe *et al.* did not see a difference in their single-cell experiments.

There are several possible mechanisms that could explain the underlying mechanism of the difference in the length-dependent activation under isotonic vs. isometric conditions. A theoretical explanation could be that a reduced length during shortening causes a decreased length-dependent activation. Therefore, we analysed the length of the muscles at the different stretching states. The muscle length from slack (L_0) to $L_{max\text{-}isotonic}$ increased to ~114% L_0 and to $L_{max\text{-}isometric}$ to 130% L_0 (data not shown). This indicates that the muscle length at the point of maximal shortening under isotonic conditions (corresponds to muscle length at $L_{max\text{-}isometric\ -\ shortening}$ = 130% L_0 – 4% L_0 = 126% L_0) is still longer than at $L_{max\text{-}isotonic}$ (114% L_0). We therefore believe that the reduction of the muscle length during isotonic shortening is not the major mechanism for the shift of the maximal contractile response to lower muscle length under isotonic compared with isometric conditions.

Another explanation could be that the myofilament regulation is different under isotonic compared with isometric conditions. The number of force-generating cross-bridges is depending on the cytoplasmic Ca^{2+} and the cooperative activation of the thin filament by strong binding cross-bridges, which are both increased by load.[25] In the normal heart, the isometric phase is followed by an auxotonic phase with myocardial cell shortening. It appears that by switching from isometric to isotonic conditions, shortening is a stimulus to deactivate the thin filaments. In skeletal muscle fibers, the reduction of strong binding cross-bridges by a repetitive isotonic shortening protocol is capable to eliminate the initial fast component of shortening.[26] Also, analysis of fibre stiffness—a parameter of strong binding cross-bridges—showed evidence for isotonic deactivation.[27]

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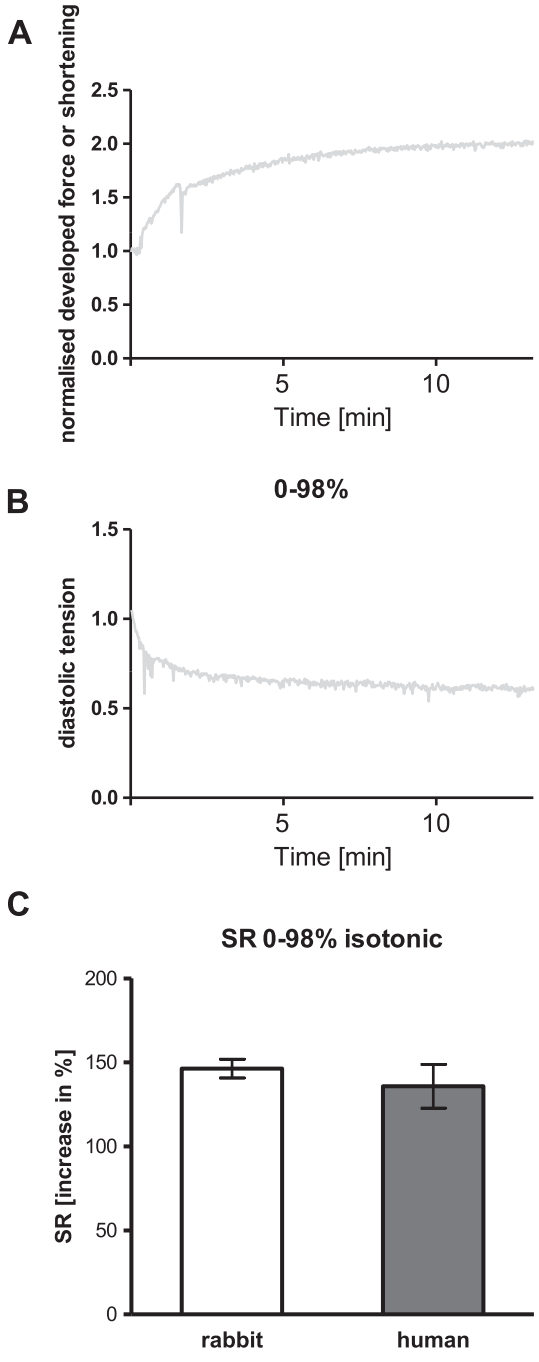
Figure 8 Slow response (SR) after stretch from slack to 98% $L_{max\text{-}isometric}$ under isotonic conditions; (A) normalised during the SR; (B) normalised diastolic tension during the SR; (C) SR in rabbit (□) and human failing muscle strips (■) in rabbit muscle strips (each n = 6, $P < 0.01$ isotonic vs. isometric).



Data from experiments using cardiac myocytes are lacking, but shortening-induced cooperative deactivation of the thin filaments might still be an explanation of the different response to increasing length under isotonic vs. isometric conditions.[28]

The binding properties of Ca^{2+} to troponin itself might also have an effect on the length-dependent activation. Yasuda *et al.* showed that the Ca^{2+} transient under isotonic conditions is higher and faster compared with isometric conditions.[29] This might be explained by either load-dependent regulation of the Ca^{2+} regulating proteins or by different binding characteristics of Ca^{2+} to the myofilaments. Because the described change was visible on a beat-to-beat basis, an involvement of the myofilaments seems to be likely. An increase in after-load without change in pre-load might lead to an increased binding of Ca^{2+} to troponin without altering the calcium transients and thereby to an increased force development. A slower diffusion of Ca^{2+} from the myofilaments might therefore be part of the mechanism of a slower cytosolic Ca^{2+} removal under isometric conditions.[29] This would lead to a slower relaxation. In our experiments, the relaxation under isometric compared with isotonic conditions was also slower (exemplary shown in *Figure 2A*).

After sudden stretch, the RR differs between isotonic and isometric conditions. Those differences can be seen after stretch over $L_{max\text{-}isotonic}$ and can be explained by different length-dependent activation. The SR is similar over the complete range of the length-dependent activation. The dependence of pre-load for the SR has also been shown in isovolumetric beating hearts[30,31] and *in vivo* volume-loaded canine hearts.[32] In this experiment, after-load is still present. In our experimental set-up, an absolute control of after-load was possible, and therefore it could be shown that after-load is not involved in the SR.

In vivo, the heart normally has an auxotonic contraction with an isometric and an isotonic component. Increased filling of the heart elevates pre-load but also prolongs the isotonic part of the contraction. Because pre-load and isotonic contraction are linked, it makes sense that pre-load has with the SR an additional mechanism of improving contractility. The SR thereby especially compensates the reduction in shortening at higher levels of pre-load.

Increased after-load shifts the contractile curve to a better 'myofilament function' by influencing thin fibers and calcium sensitivity. Also, after-load induces a small increase in pre-load.[14] Therefore, the contractile effects of increased after-load are only partially and indirectly dependent on FSM and the SR. *In vivo,* data from human hearts are not available until know.

Conclusions

This work shows that the acute contractile response largely depends on the degree and type of mechanical load. Increased filling of the heart elevates pre-load and prolongs the isotonic part of contraction. The increased pre-load increases contractility by the Frank–Starling mechanism, but

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at the same time, the increase in isotonic shortening counteracts this increase. This is not relevant at lower levels of increased pre-load, but when increased further, this leads to a gradual reduction of contractility. The SR is thereby a compensatory mechanism that especially at higher levels of pre-load compensates for the loss of contractility by the myofilaments. After-load shifts the contractile curve to a better 'myofilament function' by probably influencing thin fibers and calcium sensitivity, but has no effect on the SR.

In a clinical setting, this could imply that increased filling of the heart—as it also occurs in decompensation of heart failure—is reducing contractility by increasing pre-load above the maximal contractile point. This could contribute to the progression of decompensation. Also, these data would imply that the reduction of highly increased pre-load in decompensation is a very important mechanism to improve the contractile capacity of the heart. But it needs to be taken into account that this are acute compensatory mechanisms and it is not clear how these or other mechanisms contribute to pre-load or after-load at longer time intervals.

Conflict of interest

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