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Energetic consequences of mechanical loads

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Abstract

In this brief review, we have focussed largely on the well-established, but essentially phenomenological, linear relationship between the energy expenditure of the heart (commonly assessed as the oxygen consumed per beat, oxygen consumption (VO_2)) and the pressure-volume-area (PVA, the sum of pressure–volume work and a specified 'potential energy' term). We raise concerns regarding the propriety of ignoring work done during 'passive' ventricular enlargement during diastole as well as the work done against series elasticity during systole. We question the common assumption that the rate of basal metabolism is independent of ventricular volume, given the equally well-established Feng- or stretch-effect. Admittedly, each of these issues is more of conceptual than of quantitative import. We point out that the linearity of the enthalpy–PVA relation is now so well established that observed deviations from linearity are often ignored.

Given that a one-dimensional equivalent of the linear VO_2–PVA relation exists in papillary muscles, it seems clear that the phenomenon arises at the cellular level, rather than being a property of the intact heart. This leads us to discussion of the classes of crossbridge models that can be applied to the study of cardiac energetics. An admittedly superficial examination of the historical role played by Hooke's Law in theories of muscle contraction foreshadows deeper consideration of the thermodynamic constraints that must, in our opinion, guide the development of any mathematical model. We conclude that a satisfying understanding of the origin of the enthalpy–PVA relation awaits the development of such a model.

Keywords: VO_2–PVA relation; Diastolic work; Series elasticity; Feng effect; Cross-bridge models; Muscle thermodynamics

Contents

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1. Introduction

The heart experiences loads during both systole and diastole. The temporal variation of these loads produces the pressure–volume loop, which characterises the pump function of the heart. Both systolic and diastolic loads have energetic (i.e., mechanical and metabolic) consequences that remain ill-understood, despite intensive investigation since the late 19th century (Yeo, 1885). Passive loads are borne by elastic forces arising in stretched connective tissue. Active forces arise within myocytes. They are generated and borne by the contractile filaments and the cyclic attachment and detachment of their interconnecting myosin crossbridges. These microscopic events are funded by the hydrolysis of ATP and produce macroscopic force, shortening and work. It is straightforward to measure macroscopic work or power, whereas it is less straightforward to measure the rate of ATP hydrolysis. However, that can be done (Stienen et al., 1993; de Tombe and Stienen, 2007)—either directly or via a surrogate measure (heat production or oxygen consumption (VO_2), for example). So, metabolic energy input and mechanical output of either the whole heart or isolated cardiac tissue can be assessed experimentally. Given this state-of-the-art, it is surprising that our best predictor of active cardiac energetics is, essentially, phenomenological in nature. This well-attested description is shown schematically in Fig. 1. It is attributable to Suga and co-workers (1981a, b) who revealed a linear relationship between VO_2 and pressure-volume-area (PVA: the sum of work and potential energy; see Fig. 1) in the isolated, blood-circulated, cross-perfused dog heart.

The (extrapolated) intercept of the VO_2–PVA relation (Fig. 1B) denotes the VO_2 of the empty, beating, heart. Arrest of the heart under this condition (commonly achieved by elevation of extracellular K^+ concentration or reduction of extracellular Ca^{2+} concentration) reduces VO_2 to the value indicated by *b*, the

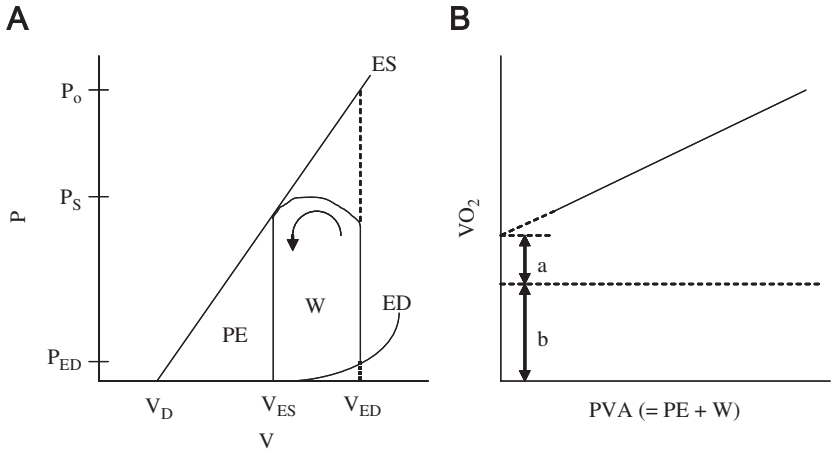


Fig. 1. Stylised representation of the energetics of the heart. (A) Pressure (*P*) as a function of ventricular volume (*V*) during a single cardiac cycle (arrow indicates direction of time); ES and ED: end-systolic and end-diastolic $P-V$ relations; V_D: dead-space volume, *W*: stroke work, PE: potential energy. (B) Oxygen consumption (VO_2) as a function of pressure-volume-area (PVA = W + PE); *a* denotes the metabolic energy cost of contractile *activation*, *b* represents *basal* metabolism. PVA can be varied by varying either PE or *W*. For example, during an isovolumetric contraction (broken line intercepting the ES relation at (V_{ED}, P_0) in (A)), $W = 0$ and PE is maximal. Note that *W* excludes the 'triangular' region between ED and the abscissa, to the left of end-diastolic volume (V_{ED}).

basal metabolism. The difference between the extrapolated intercept and b is labelled a. This value is commonly ascribed the label 'activation metabolism'—i.e., the energy expenditure, by the sarcolemmal Na^+–K^+-ATPase and the sarcolemmal and sarcoplasmic reticular Ca^{2+}-ATPases, required to restore the trans-membrane gradients of Na^+, K^+ and Ca^{2+} from their systolic to their diastolic values. But, given that the heart continues to beat, thereby causing it to change shape (Suga, 1990), some component of a must reflect the hydrolysis of ATP by actively cycling cross bridges.

2. Diastolic energetics

2.1. Diastolic work (W_D)

Diastolic work is performed as the ventricle is 'passively' inflated from its end-systolic (V_{ES}) to its end-diastolic (V_{ED}) volume (Fig. 1A). Its magnitude, determined by the quasi-triangular area lying between the abscissa and the end-systolic pressure–volume relation to the left of the dotted line-segment at V_{ED}, is given by

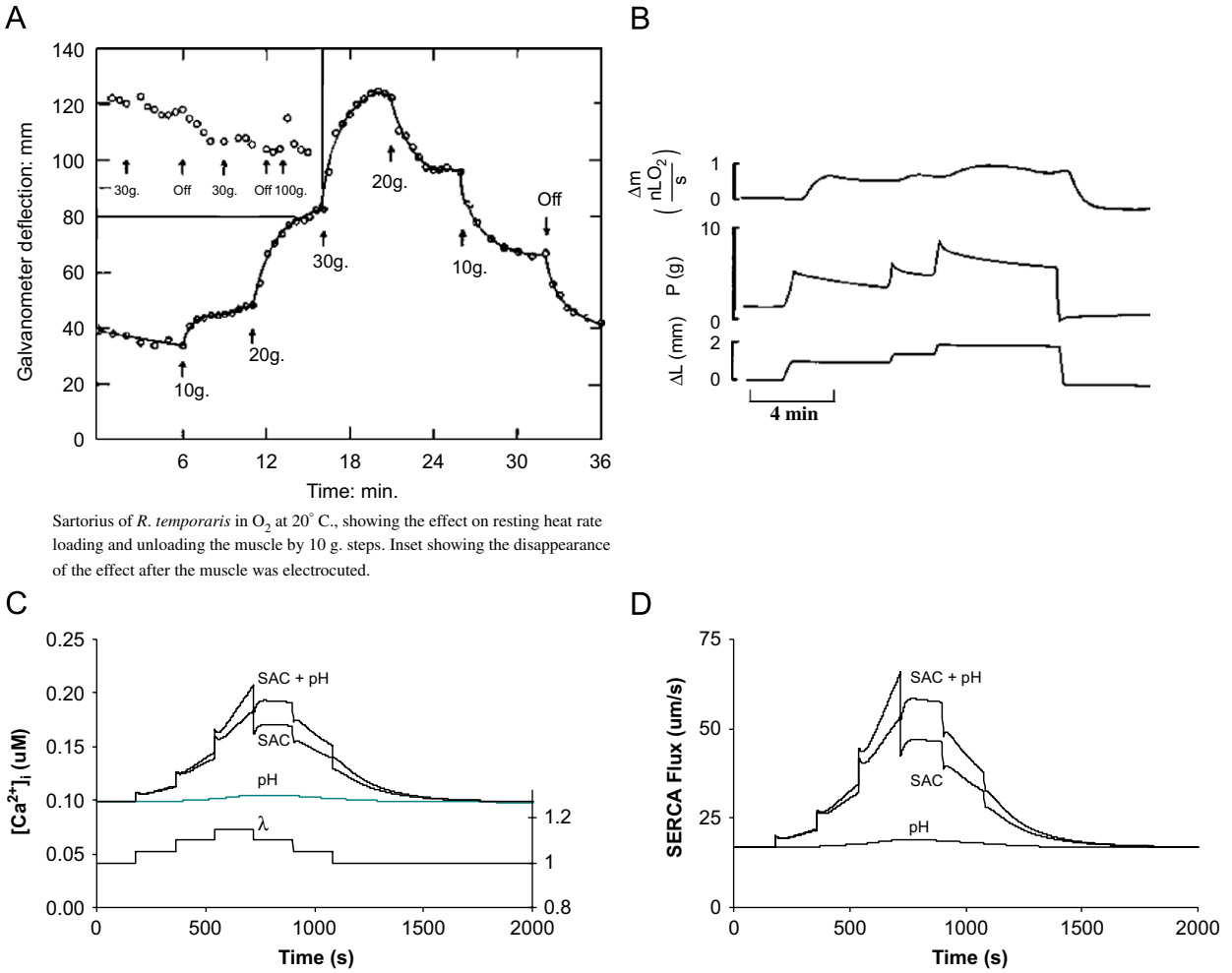
$$W_D = \int_{V_{ES}}^{V_{ED}} P_D \, dV \tag{1}$$

Diastolic work is universally excluded from the calculation of PVA. In our view, its omission is unwarranted for, clearly, *something* must provide the energy to increase the volume of the heart from V_{ES} to V_{ED}. Two possible mechanisms include the recoil of elastic structures that had been compressed during shortening, and 'ventricular filling'. Of these, the principal contributor is probably 'ventricular filling', achieved by re-capture of the kinetic energy of blood (venous return), which had been imparted by previous ejections, assisted by a pressure boost resulting from contraction of the atrium. But, regardless of the mechanism, it seems clear that the work performed in stretching the (passive) myocardium from its end-systolic to its end-diastolic volume must ultimately be funded by the expenditure of metabolic energy. In consequence, and despite its numerical unimportance, it is our contention that diastolic work (Eq. (1)) should be included in the calculation of PVA.

2.2. The Feng effect

An associated feature of diastolic metabolism arises from the effect of stretching quiescent muscle tissue on its *basal* metabolism (b in Fig. 1A). The 'Stretch Effect' was first shown, in skeletal muscle (Fig. 2A), by Feng (1932) and later, in cardiac muscle, by Gibbs et al. (1967). In both of these investigations, the metabolic effect of stretch was indexed as an increase in rate of heat production by an isolated muscle resting on a thermopile. Confirmation that the effect, in cardiac muscle, reflects the stimulation of oxidative phosphorylation is provided in Fig. 2B.

Despite numerous investigations (Loiselle, 1987; Gibbs and Loiselle, 2001; Widén and Barclay, 2005), the cause of the stretch effect remains obscure. But, given the wealth of data presented in this volume (see, for example: Iribe and Kohl, 2008; Nishimura et al., 2008; Taggart and Lab, 2008; Ward et al., 2008), it becomes an intriguing possibility that stretch may indirectly induce an increase of intracellular Ca^{2+} concentration. We tested this possibility *in silico* using the rat myocyte model recently developed by Niederer and Smith (2007). Simulations involved applying step increments of resting length (bottom trace, Fig. 2C) to the quiescent myocyte, while computing the resulting increase of $[Ca^{2+}]_i$ via reverse-mode Na^+–Ca^{2+} exchange, in response to an influx of $[Na^+]_i$ through stretch-activated channels (trace-labelled SAC, Fig. 2C). Also shown is the independent effect on $[Ca^{2+}]_i$ of Na^+-influx via stretch-sensitive modulators of pH_i: the Na^+–H^+ and HCO_3^-–Cl^- exchangers (trace-labelled pH, Fig. 2C). The individual and combined effects of these simulated stretch-induced increments of intracellular Ca^{2+} concentration on the rate of Ca^{2+} sequestration by the sarcoplasmic reticular Ca^{2+} pump are shown in Fig. 2D. The degree of qualitative agreement between the upper (experimentally measured) and lower (mathematically modelled) panels of Fig. 2 is noteworthy. Given the magnitude of these observed and simulated effects, it seems unlikely that the basal metabolic rate remains



Sartorius of *R. temporaris* in O_2 at 20° C., showing the effect on resting heat rate loading and unloading the muscle by 10 g. steps. Inset showing the disappearance of the effect after the muscle was electrocuted.

Fig. 2. Stretch effects in striated muscle. (A) Fig. 2 from Feng (1932) showing reversible increase of rate of heat production ("Galvanometer deflection") in response to elongation of passive muscle length in response to various loads (10–30 g). The inset demonstrates that the effect is of metabolic origin. [Reproduced with the permission of the Journal of Physiology and Blackwell Publishing.] (B) Fig. 1A from Loiselle (1982) showing reversible increments of rate of oxygen consumption (upper panel) and passive force (middle panel) in response to stretches (lower panel) of a rat papillary muscle of resting length 7 mm. [Reproduced with permission of The Biophysical Society]. (C,D) Simulated effects of passive stretch (normalised strain (λ): right-hand ordinate of panel (C) on intracellular Ca^{2+} concentration, *C*, and resulting rate of sequestration of Ca^{2+} into the sarcoplasmic reticulum, *D*). Traces labelled SAC show singular contribution of reverse-mode Ca^{2+} influx on the Na^+–Ca^{2+} exchanger following Na^+-influx via stretch-activated channels. Traces labelled pH show corresponding consequence of Na^+-influx via stretch-sensitive exchangers that modulate pH_i: Na^+-H^+ and Cl^--HCO_3^-. Uppermost traces show combined effects of SACs and pH-regulating mechanisms.

constant, independent of V_{ED} (and, hence, PVA). Thus, a question must be raised concerning the propriety of the horizontal line delineating region *b* in Fig. 1B.

3. Systolic energetics

Whether consideration is focussed on mechanics or metabolism, cardiac energetics is dominated by systole. Historically, numerous indices of cardiac mechanical performance have been proposed, but from the point-of-view of whole-heart energetics, it is systolic pressure–volume work that is fundamental. The phenomenological observation that metabolic energy expenditure is linearly related not to *W* (as might be expected) but to PVA (i.e., the sum of *W* and PE, Fig. 1A) is seductive. But might the phenomenon be merely coincidental?

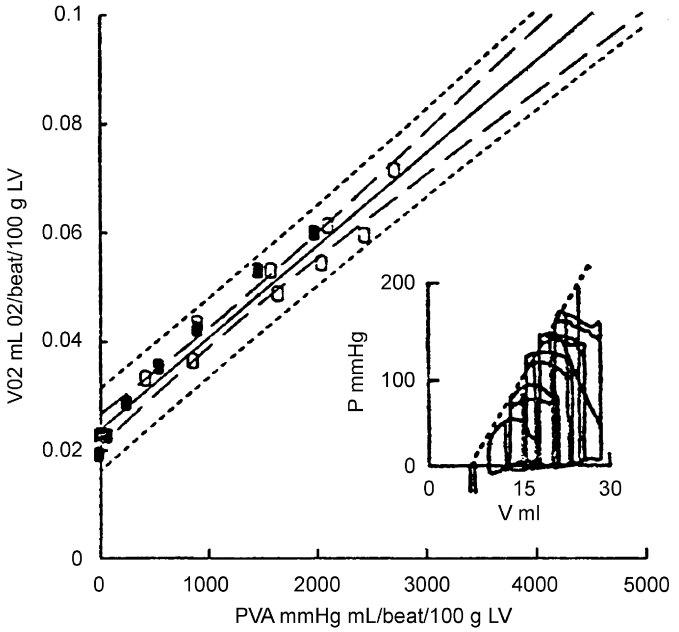


Fig. 3. Oxygen consumed per beat (normalised per 100 g of left-ventricular tissue) of an isolated, blood-circulated, cross-perfused dog heart, as a function of pressure-volume-area (PVA). Closed symbols denote isovolumic contractions; open symbols denote ejecting contractions (see inset). [reproduced from Fig. 2 of Suga et al. (1984), with permission of Federation Proceedings].

3.1. The experimental basis of the VO_2–PVA relation

An early demonstration of the linear dependence of VO_2 on PVA is shown in Fig. 3, where the narrowness of the confidence limits on the regression line is noteworthy. Note, further, that the same relationship holds for isovolumic as for ejecting contractions, despite the fact that, for the former, only the PE term obtains.

The inset of Fig. 3 reveals that the end-systolic loci of both isovolumic and ejecting contractions fall on the same straight line, independent of V_{ED}- behaviour first explored by Otto Frank (1899) (for an English translation, see Sagawa et al., 1990).

The data of Fig. 4 show that the end-systolic pressure–volume relation rotates around the dead-space volume (V_D) intercept in response to agents or interventions that change inotropic state. Rotation is counter-clockwise under increased inotropy and clockwise under decreased inotropy.

If the alteration of inotropic state occurs in the absence of a net effect on the intercept of the VO_2–PVA relation (i.e., on the sum of a and b in Fig. 1B), then the VO_2–PVA data fall on the same straight line. An example is shown in Fig. 5 where hyperthermia decreased myocardial contractility (panel A) with no effect on PVA-independent metabolism (panel B). By contrast, when hyperthermic hypo-contractility was restored by increasing the Ca^{2+} concentration in the coronary perfusate, then the pressure–volume relation rotated counter-clockwise and the VO_2–PVA relation underwent a parallel upward shift, reflecting the increased cost of Ca^{2+} clearance from the cytoplasm (panel C).

The linearity of the VO_2–PVA relation has been reported in a variety of species (Goto et al., 1988) including, most recently, the isolated working mouse heart (Kameyama et al., 1998; How et al., 2005, 2006), an example of which is shown in Fig. 6. Note that, under the 'high Ca^{2+}' perfusion condition, both the P–V (panel A) and VO_2–PVA (panel B) relationships are concave downward. Indeed, the data of panel B suggest that 'maximal' rates of VO_2 may have been reached in the hearts of these small rodents, whose 'reserve metabolic capacity' is small (Pasquis et al., 1970). Given that the rates of VO_2 (normalised per beat and per mass of heart tissue) are some four times larger than those observed in the blood-perfused dog heart (cf. Fig. 1), it is possible that saline-perfused mouse hearts are oxygen supply-limited. But, regardless of the

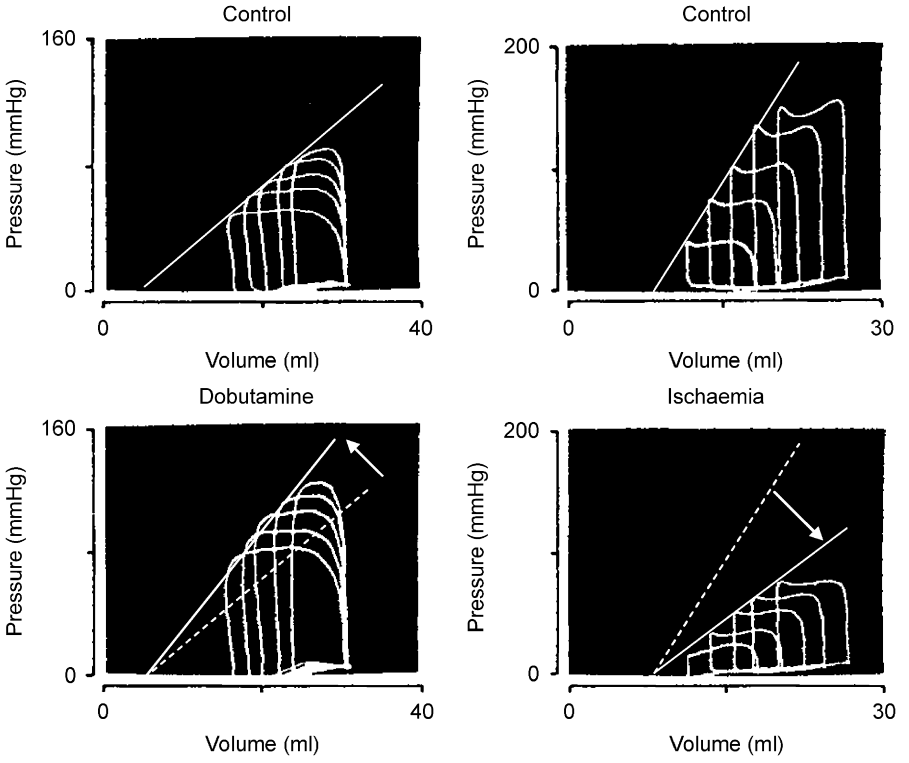


Fig. 4. Pressure–volume loops recorded from cross-perfused dog hearts under conditions of enhanced (left-hand panels) and compromised (right-hand panels) mechanical performance [Modified from Goto et al. (1986), with permission of the American Journal of Physiology].

basis of the non-linearity, it is interesting to note that although the authors emphasised the non-linearity in the mechanics panel, they disregarded it in the 'energetics' panel.

Results comparable to those detailed, above, in isolated whole hearts have been reported in studies using isolated muscle preparations. In these 'one-dimensional' equivalents of whole-heart preparations, force–length–area (FLA) substitutes for PVA. For example, Mast and Elzinga (1990) reported a linear relationship between the heat released during relaxation and FLA in rabbit right-ventricular papillary muscles. But even more germane are the results of Hisano and Cooper (1987), for these authors found a strikingly linear VO_2−FLA relation in papillary muscles isolated from ferret hearts (Fig. 7B) despite the pronounced convexity of the active force–length relation (Fig. 7A). Of note, too, is the fact that VO_2 also showed (admittedly weaker) linear dependencies upon both peak twitch force development (Fig. 7C) and force–time integral (Fig. 7D).

Figs. 3, 5 and 6, demonstrate the universality, and consequent wide-spread acceptance, of a linear VO_2−PVA relation in the intact heart. Fig. 7 reveals the phenomenon to be a property of cardiac muscle *per se*. In both the 3-D and 1-D models, an entity labelled 'potential energy' plays a key role. This entity bears a close resemblance to elastic energy (as explicitly recognised in the 'time-varying elastance' model of Suga and colleagues). The involvement of elastic forces in theories of muscle contraction has fascinating historical antecedents.

3.2. Historical antecedents of the VO_2−PVA relation

It is instructive to trace the history that precedes the concepts embodied in Fig. 1B. (In doing so, we are indebted to the brief review by Gibbs and Chapman (1985).) Of particular interest is the notion of 'potential energy' as defined in the concept of PVA, since it appears to have much in common with Hooke's Law. Indeed, early ideas of the mechanics of skeletal muscle were based on the notion that, upon excitation, muscle immediately develops (isometric) force proportional to its length. This 19th century idea has classically been

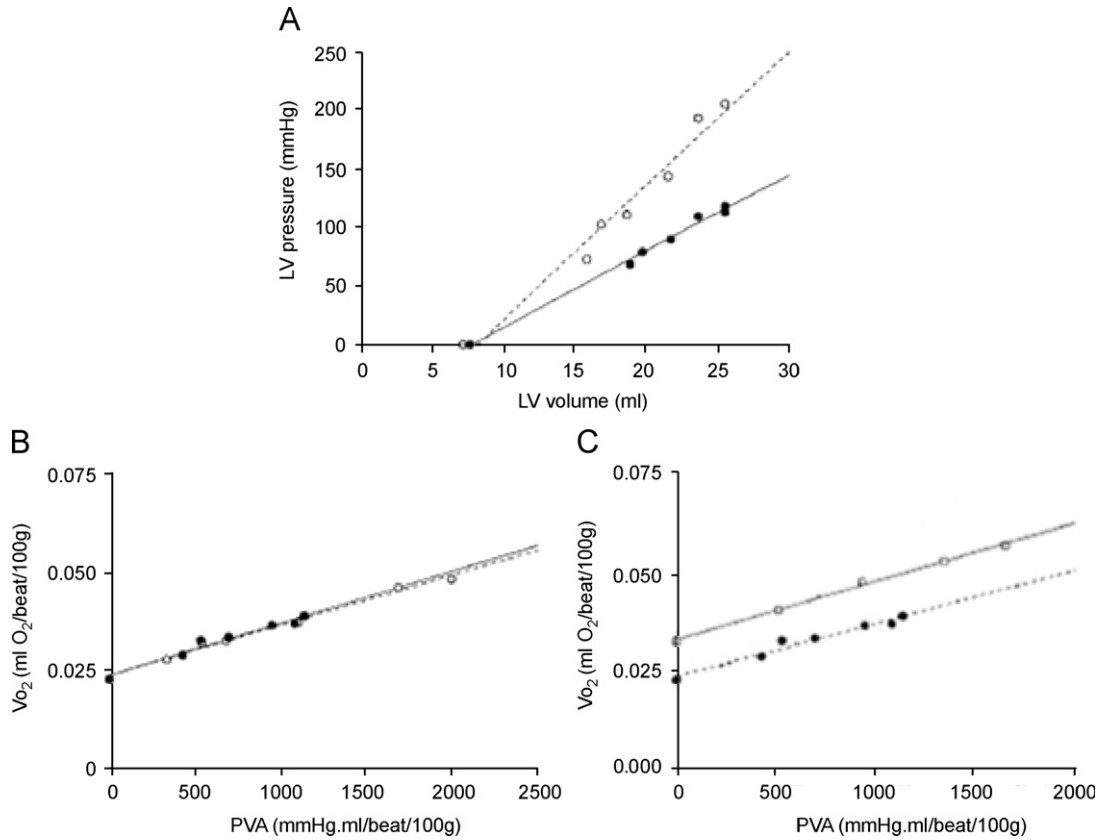


Fig. 5. Energetics of blood-perfused, cross-circulated, dog heart. (A) Left-ventricular isovolumic pressure–volume relations under normothermic (36–37 °C, open circles) or hyperthermic (40–42 °C, filled circles) perfusion. (B) VO_2–PVA relation for the data shown in (A). (C) VO_2–PVA relations for ejecting contractions under standard (filled symbols) and elevated (open symbols) extracellular Ca^{2+} concentration, respectively, during hyperthermic perfusion [adapted from Figs. 3 and 4 of Saeki et al. (2000) with permission of the American Journal of Physiology].

attributed to Eduard Weber (1846), but, in a lengthy quote (pp. 101–103), he explicitly attributed the notion to Schwann's earlier description published in *Müllers Physiology Volume II* (pp. 59–61, 1837).

According to this simple model (Fig. 8A), the activated muscle has available a fund of potential energy equivalent to $\frac{1}{2}P_0L_0$, where L_0 is the optimal length, i.e., that length which maximises the peak isometric force, P_0. Hence, according to the 1st Law of Thermodynamics, this amount of energy should be convertible into either work (shortening contraction) or heat (isometric contraction). It was not until the second decade of the 20th century that this crude model was refined by AV Hill's finding that a muscle can shorten only about $\frac{1}{3}$ of its optimal length. This result implied that the maximal energy available, $E_0 = P_0L_0/6$. Hill had the advantage that he could test this hypothesis experimentally. He must have been gratified to find that, indeed, an isolated muscle resting on a thermopile produces an amount of heat, $Q = P_0L_0/6$. However, no amount of experimental ingenuity could extract an equivalent amount of work. In fact, Hill observed that $W_{max} \approx 0.4E_0$.

In the manner that typifies the often slow advance of Science, attempts were made to salvage the 'new elastic body' theory. It was hypothesised that shortening was hampered by internal (cytoplasmic) viscosity (η) such that force (P) was diminished in proportion to the velocity of shortening (V):

$$P = P_0 - \eta V \tag{2}$$

Assuming velocity-independent viscosity, this implied that a muscle's force–velocity (F–V) relation would be linear-declining from its intercept on the ordinate (0, P_0) to an intercept on the abscissa of ($V_{max} = P_0/\eta$, 0).

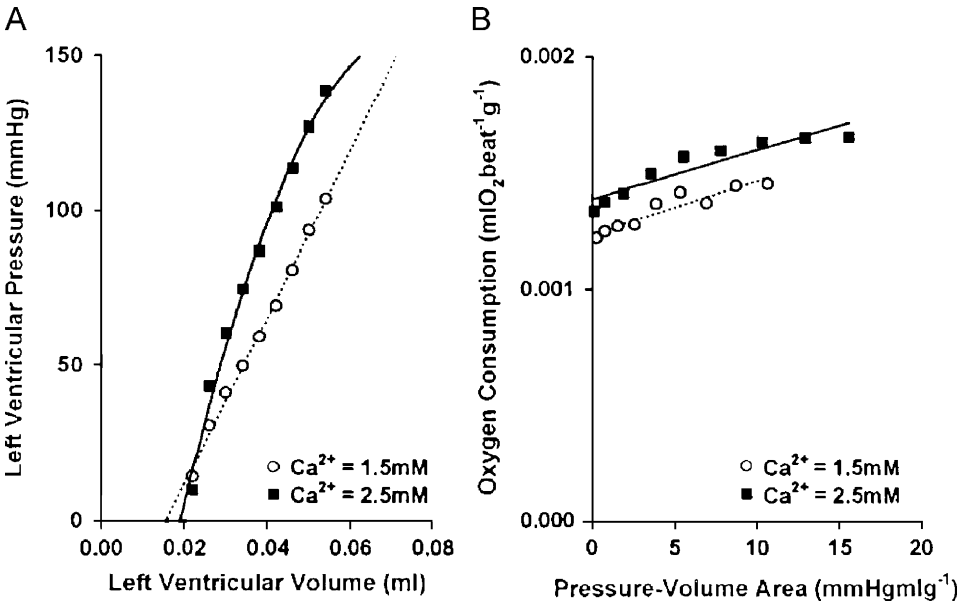


Fig. 6. Pressure–volume (A) and VO_2-PVA (B) relations of isolated, paced (4 Hz), isovolumically contracting mouse hearts, perfused with low (1.5 mM, open circles) and high (2.5 mM, closed squares) Ca^{2+}. Note the reduction of the intercept at 1.25 mM Ca^{2+} (Panel B), interpreted as a reduction of activation metabolism. Basal metabolism estimated to be about 1 $\mu L\, O_2\, g^{-1}$ per beat, thereby contributing over $\frac{2}{3}$ of the total cardiac metabolism. This may be an overestimation, reflecting the large surface-area-to-volume ratio of the mouse heart and the correspondingly large transepicardial flux of oxygen directly from the coronary perfusate to the environment (Loiselle, 1989a, b; van Beek et al., 1992; Mawson et al., 1994; Loiselle et al., 1995) [reproduced from Fig. 3 of Kameyama et al. (1998) with permission of the American Physiological Society].

But, as can be seen in Fig. 9A, careful measurements by Fenn and Marsh (1935) showed the $F-V$ relation to be decidedly non-linear; so the 'new elastic body' theory was finally interred.

In retrospect, its demise had occurred over a decade earlier, subsequent to the exemplary thermal results of Fenn (1923), which are reproduced as Fig. 9B. These results, also arising from isolated amphibian skeletal muscle, were so unexpected that it took the community of muscle physiologists many years to absorb their implication. For, contrary to earlier ideas, the amount of heat produced during an afterloaded shortening contraction *exceeded* the amount liberated in an isometric contraction. Since the 'excess heat' was some 30% of the isometric heat, it could scarcely be attributed to 'experimental error'. Indeed, appreciating the thermometric equipment available to Fenn in 1923 (working in the cellar of AV Hill's house "… where the sensitive galvanometer could be made free from the electrical disturbances which are characteristic of the laboratory in Manchester"), the quality of his experimental results remains inspirational.

Fenn's thermal results (Fig. 9B) clearly render implausible any simple 'global elastic' theory of muscle contraction. Nevertheless, it remained obvious to experimentalists that muscle contains compliant elements and that these can be separately revealed during rest and activity. This idea, first enunciated by Hill (1938), is readily conceptualised in a three-component model of the sort shown in Fig. 10A. The model consists of a contractile element (CE) in series with an elastic element (SE), both of which are in parallel with a parallel elastic element (PE). The benefit of such a conceptual model is that it allows any sort of crossbridge model to be inserted into the CE. What is less clear is the appropriateness of including an SE element in order to introduce a compliance which is dependent only on the contractile force exerted by a muscle. Legitimate arguments for the inclusion of such an SE element must centre on a compliant element that is physically in series with the contractile apparatus, i.e., the bound actomyosin crossbridge. Possible extracellular candidates include clips, ties or snares designed to hold the ends of the preparation. Intracellular candidates include titin, which spans from the *Z*-disc to the *M*-line (Labeit et al., 1997, 2003), or the protein filaments that constitute the *Z*-discs. From experiments performed using isolated skeletal muscle preparations, it appears that the

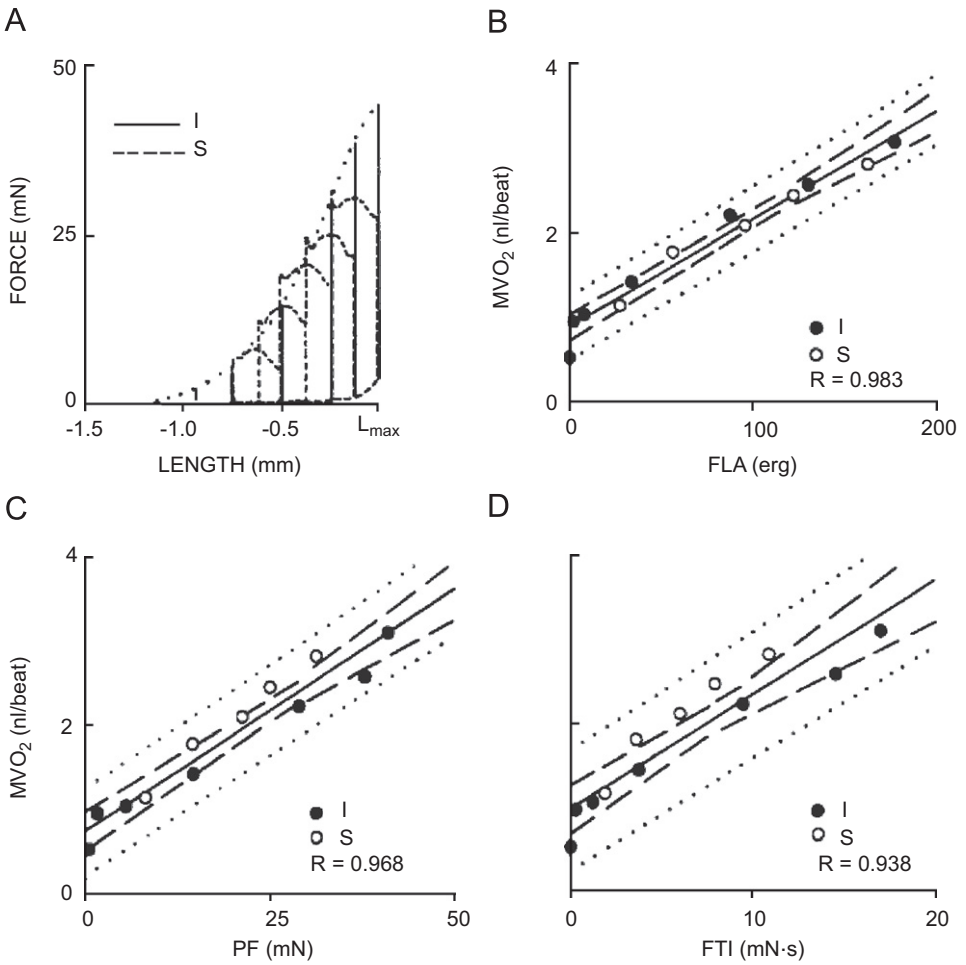


Fig. 7. Energetics of right-ventricular papillary muscles isolated from ferret hearts. (A) Twitch force as a function of muscle length; I = isometric, S = shortening contractions. (B) Per-beat oxygen consumption as a function of force–length–area. (C) Oxygen consumption as a function of peak twitch force. (D) Oxygen consumption as a function of force–time integral [modified from Fig. 3 of Hisano and Cooper (1987), with permission of Lippincott Williams & Wilkins, Baltimore].

combined compliance of such sources of series elasticity is at least an order of magnitude greater than that of the crossbridges (Ford et al., 1977; Curtin et al., 1998; Barclay and Lichtwark, 2007).

Characterising the compliance which results from stretch (or compression) of bound crossbridge heads (and perhaps compliant actin and myosin filaments) during contraction is more complex. It depends on the number of attachment points and their spatial distributions, as well as crossbridge strain. Thus, we argue that accounting for ensemble sarcomere compliance, resident in myosin crossbridge heads, requires detailed modelling of the CE. Such models of the CE can be broadly categorised into three classes: (i) continuum models which account for crossbridge kinetics based on partial differential equations, (ii) phenomenological, fitted models based on ordinary differential equations, and (iii) discrete models which stochastically represent binding and unbinding events.

The continuum modelling framework proposed by Huxley (1957) was the first significant advance on the paradigm proposed by Hill. This two-state model, which is still widely applied, explicitly accounts for the transitions between force-bearing 'bound' and non-force-bearing 'unbound' populations of crossbridges within each sarcomere. The rates of transition between states are dependent on the strain experienced by a given crossbridge head and the presence of ATP, whose chemical free energy is converted to work during the crossbridge cycle. At the level of the single crossbridge, the time-dependence of transition rates on spatial

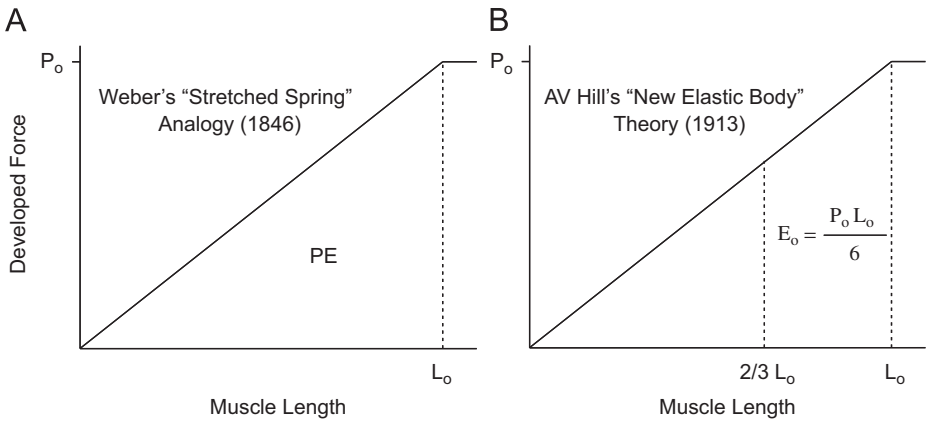


Fig. 8. Stylised diagrams of early 'stretched elastic spring' models of active muscle. (A) After Schwann (1837); a muscle activated at optimal length (L_0) can develop maximal isometric force (P_0). At shorter lengths, proportionately less force can be generated. By analogy with a stretched spring, the activated muscle has potential energy (PE) equivalent to the area under the force–length relation ($\frac{1}{2}P_0L_0$), and so should be able to produce that amount of work. (B) Hill (1913) found that a muscle could shorten to only about $\frac{2}{3}L_0$. Hence its maximal work (or energy) output would be only $\frac{1}{3}$ of that predicted by the model of Weber.

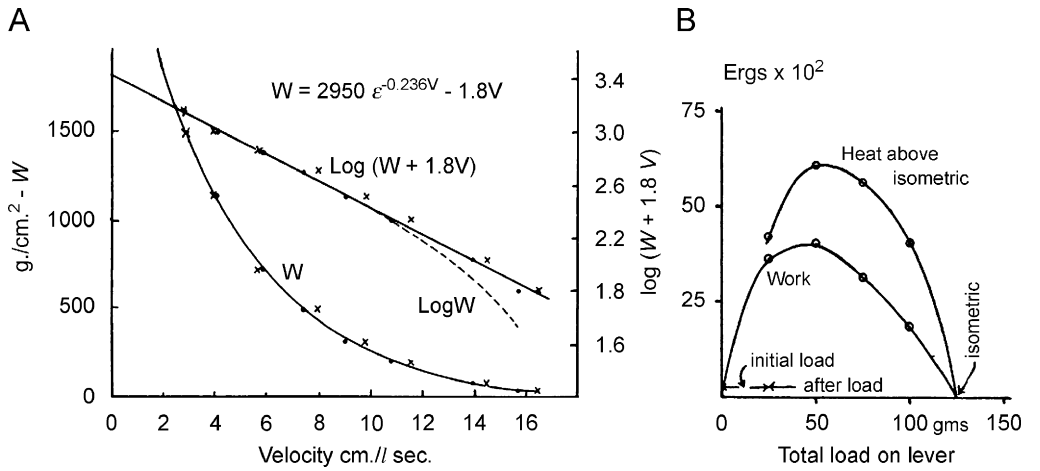


Fig. 9. (A) Fig. 3 from Fenn and Marsh (1935). (B) Fig. 2 from Fenn (1923). (Note the estimate of initial mechanical efficiency: 15.2%. This value was subsequently found to be only about one-half of the correct value, due to the retrospective discovery of a constant calibration error (Hill and Woledge, 1962)), which had previously led to overestimation of the amount of heat produced by contracting muscles.) [Figures reproduced with permission of the Journal of Physiology and Blackwell Publishing.]

crossbridge strain requires the system to be modelled as a partial differential equation. The tension generated within the CE is determined by summing the tension carried by each myosin crossbridge bound to an actin site. This formulation assumes that the source of the CE compliance resides entirely within the crossbridge head and that the actin and myosin filaments are inextensible. Within this paradigm, compliance within the sarcomere (defined as change of tension with respect to change of sarcomere length) at a given point in time is calculated as the sum of the attached crossbridges multiplied by the spring constant of an individual crossbridge head.

Thus, the central assumption, common to the entire class of sliding filament models, is that the actin and myosin filaments are inextensible. The corollary of this assumption is that each crossbridge acts as a separate force generator which is independent of the state of the other myosin heads in the half sarcomere. However, experimental evidence now indicates that both actin and myosin filaments are extensible, and may make significant contributions to the compliance (Goldman and Huxley, 1994; Wakabayashi et al., 1994) of the

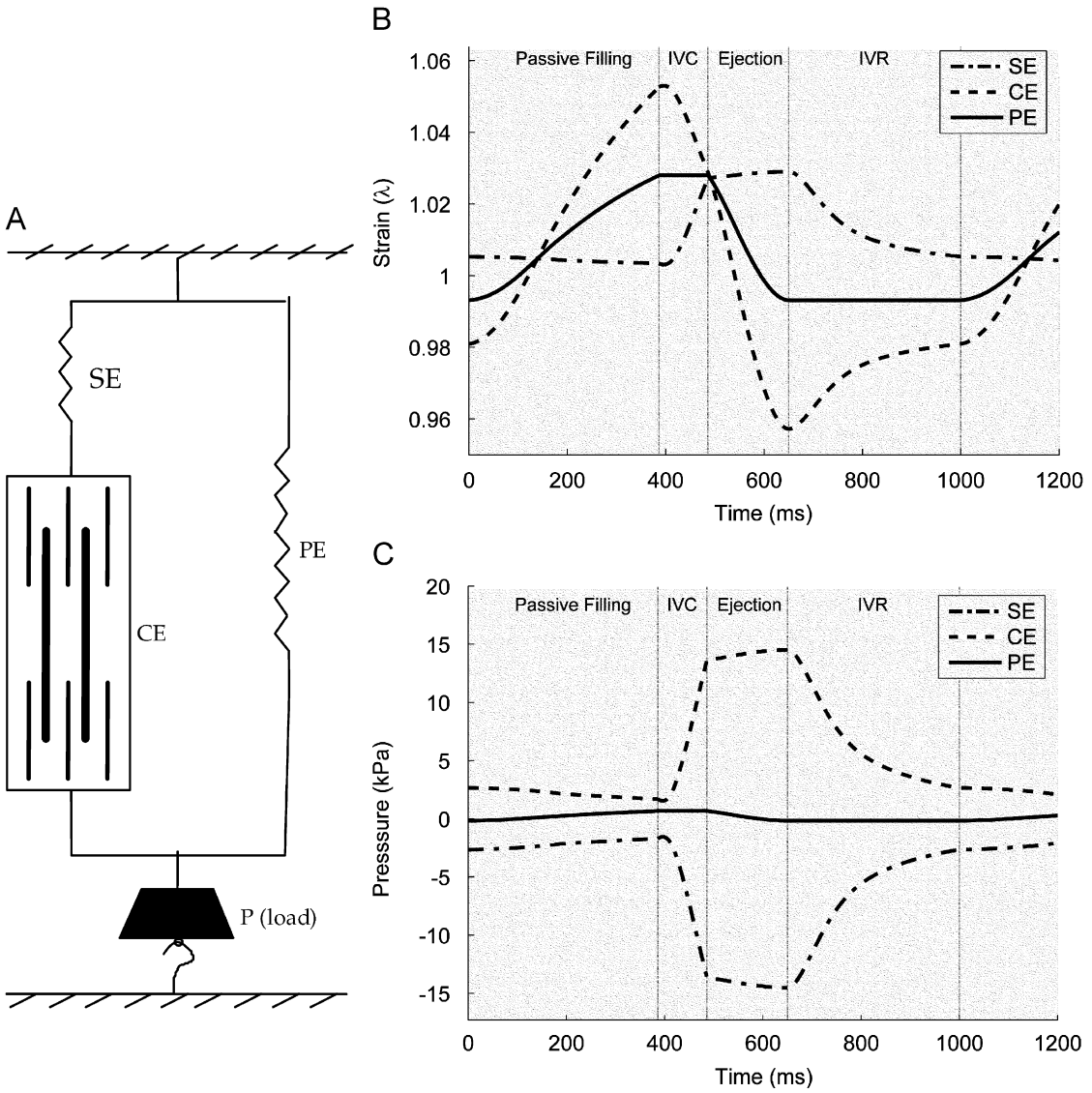


Fig. 10. (A) Three-component Maxwell model of muscle mechanics consisting of a contractile element (CE) in series with an elastic component (SE), both of which are in parallel with a second elastic component (PE). At rest, the CE is freely extensible (Jewell and Wilkie, 1958) so that passive extension of the muscle by the pre-load has two consequences: extension of the PE (with concomitant increase of resting force) and increase of diastolic length of the sarcomeres that constitute the CE. (B) Normalised strain (λ) of each of CE, SE & PE, throughout a single cardiac cycle consisting of passive filling, isovolumic contraction (IVC), ejection, and isovolumic relaxation (IVR). (C) Corresponding stresses (pressure) experienced by each of the three components.

sarcomere. Such compliance implies that there is coupling between adjacent myosin heads. This has important implications for the use of muscle models to interpret experimental data. To determine sarcomere compliance, in the presence of compliant filaments, requires summing the effects of individual compliant elements. The number and arrangement of these elements is dependent on the specific arrangements of bound crossbridge heads (see Smith et al. (2005) for details). Compliant myosin and actin filaments have been incorporated into two recently published models. Forcinito et al. (1998) applied a discrete framework to show the relationship between filament and crossbridge compliance, with stiffness depending on the distribution of attached myosin heads. Daniel et al. (1998) adopted a Monte Carlo simulation to capture the binding kinetics and thus the transient tension–length behaviour of the model. Smith et al. (2005) used their model to demonstrate the possibility of a 'tuning' relationship whereby compliant filaments increase the efficiency of transducing

chemical potential into work at high contraction velocities. The implications of such a mechanism for whole-heart contraction remain to be investigated.

The slow progress in applying these notions to the intact heart reflects the fact that, in order to solve a continuum-scale tissue-mechanics problem, the active tension generated by cellular contraction must be calculated at a large number of spatially distributed points in the model. Solving systems of partial differential or stochastic equations at each point is computationally prohibitive in this context. Zahalak and co-workers have applied a homogenisation approach by using a set of Gaussian functions to approximate the solutions of these partial differential equations, thereby reducing them to a set of ordinary differential equations. These authors have successfully applied this approach to models of both skeletal (Ma and Zahalak, 1991) and cardiac (Guccione et al., 1998) tissue. The validity of this approach, however, is questionable—as the Gaussian distribution does not provide a good fit to the solutions, particularly for perturbations distant from isometric equilibrium.

The modelling framework of Hunter et al. (1998) couples a linear, time-dependent, fading memory component with a static nonlinearity to produce a phenomenological description of tension development associated with crossbridge kinetics. The form of this fading memory model is consistent with frequency–phase relationships fitted from sinusoidal length perturbation experiments arising from a number of different muscle preparations including cardiac myocytes (Saeki et al., 1991; Kawai et al., 1993). Most recently, Niederer et al. (2006) have updated this framework via a detailed re-parameterisation suitable for rat cardiac myocytes. It is this contractile model that we have embedded in the CE component of the Maxwell model (Fig. 10A).

For the results shown in Fig. 10, we have chosen to embed a full model of left-ventricular mechanics (Niederer et al., 2006) into the CE (panel A). In order to simulate the strains (B) and stresses (C) experienced by each of the three components over a single cardiac cycle, the model was driven using a Ca^{2+}-transient prescribed by the model of Hunter et al. (1998). The SE component was modelled as a simple spring whose tension (T) as a function of normalised strain (λ) was given by

$$T = k(\lambda - 1) \tag{3}$$

where $k = 500\,\mathrm{kPa}$. The behaviour of PE was characterised by a non-linear pole-zero law (see Appendix A of Hunter et al. (1998)) and the model solved for Cauchy stresses.

As alluded above, the concept of 'series elasticity' must exclude any contribution from either the contractile filaments or the crossbridges—as explicitly recognised a decade ago by Curtin et al. (1998). Nevertheless, work must be done against the remaining series elasticity (whatever its cellular or extracellular substrate). The magnitude of this 'internal work' component is given by

$$W_{\mathrm{SE}} = \int_0^{\Delta L_{\mathrm{SE}}} F_{\mathrm{SE}}\,\mathrm{d}L_{\mathrm{SE}} \tag{4}$$

Note that, during the ejection phase, there is a steady increase in both the stress (Fig. 10C) and the strain (Fig. 10B) experienced by the SE component. A proportion of these effects arises from the progressive unloading of the PE component, as sarcomeres shorten. This, in turn, progressively increases the after-load seen by the CE, thereby increasing the work done by it in lengthening the SE component commensurately—as recognised by Alan Wong a quarter of a century ago (Wong, 1971, 1972). Conventionally, it is presumed that the 'pure elastic' energy resident in the stretched series elastic component is converted to heat during relaxation. It has already been noted (Eq. (1)) that work must be done against the parallel elastic element, as well. And, as in that case, the total amount of 'internal work' against series elasticity is quantitatively minor (probably adding only some 5% to the total). Nevertheless, it is conceptually inescapable, and we argue that it should be included in the work component of PVA.

3.3. Modelling the VO_2–PVA relation

We consider that any mechano-energetic model capable of explaining the experimentally observed VO_2–PVA relation must, at minimum, be thermodynamically constrained. This requirement involves four criteria, each of which applies to the transition between the various states which a crossbridge transits during

one complete cycle of attachment and detachment (Eisenberg and Hill, 1978; Eisenberg et al., 1980; Hill, 1989).

3.3.1. Mathematical modelling constraints

(i) Each transition, from one state to the next, must be (at least theoretically) reversible. Hence, if f_+ is the rate of transition from some (say, low force-bearing) state (S_1) to some other (say, high force-bearing) state (S_2), then there must exist a non-zero rate of back-transition (the reverse rate constant): f_-.

$$S_1 \underset{f_-}{\overset{f_+}{\leftrightarrows}} S_2 \tag{5}$$

(ii) For such a simple reaction, the forward and reverse rate constants (f_+ and f_- in Eq. (4)) must be constrained, as follows:

$$\frac{f_+}{f_-} = e^{-(G_2-G_1)/RT} = K_{eq} \tag{6}$$

where R is the universal gas constant (8.31 J mol^{-1} K^{-1}), T is the absolute temperature (K), G_i is the Gibbs free energy (ΔG) of state i (J mol^{-1}) and K_{eq} is the equilibrium constant of the transition reaction.

(iii) In order for the transition between states to occur spontaneously, the sum of the ΔG transitions over the complete cycle cannot exceed the ΔG of hydrolysis of ATP (ΔG_{ATP}):

$$\sum_i G_i \le \Delta G_{ATP} \tag{7}$$

(iv) Over a complete crossbridge cycle, the ratios of forward and backward rate constants are related to the ΔG of hydrolysis of ATP (ΔG_{ATP}) as follows:

$$\frac{\prod_i f_+}{\prod_i f_-} = e^{\Delta G_{ATP}/RT} \tag{8}$$

where

$$\Delta G_{ATP} = \Delta G^0_{ATP} + \frac{[ADP][Pi][H^+]}{[ATP]} \tag{9}$$

where $\Delta G^0_{ATP}$is the standard ΔG of ATP hydrolysis, measured under unit molar concentration of all products and reactants, and Pi signifies inorganic phosphate.

It is difficult to judge the explanatory effectiveness of any mathematical model of the crossbridge cycle purporting to explain the PVA phenomenon if it is not subject to the above constraints.

3.3.2. Examples of PVA-focussed models

A model that is based on the above constraints has been developed by Vendelin et al. (Vendelin et al., 2000, 2002; Saks et al., 2006). This model successfully demonstrates a linear relationship between the quantity of ATP consumed per crossbridge and the stress–strain area (SSA) experienced by the contractile filaments, regardless of whether the simulated contractions are isometric, isotonic or 'physiologic'. But, as the authors expressly admit, this is a consequence of the fact that they sought a set of parameters that would generate the linear relationship.

A comparable, but more subtly achieved, result has been proffered by Landesberg and co-workers ((Landesberg and Sideman, 1994, 1999, 2000; Landesberg, 1996; Landesberg et al., 2000, 2004; Levy and Landesberg, 2004, 2006; Levy et al., 2005; Tchaicheeyan and Landesberg, 2005; Yaniv et al., 2006), who have extensively explored the behaviour of a model that falls into the 'loose coupling' category, as defined by Zahalak and Ma (1990) (i.e., crossbridges can bear force in either the presence ($+Ca^{2+}$) or absence ($-Ca^{2+}$)

of calcium bound to Troponin-C). It is worth examining this model, in some detail, because of its success in mimicking a large number of experimentally observed phenomena, including the linear VO_2−PVA relation, and because it carefully distinguishes among 'double overlap', 'single overlap' and 'no overlap' regions of actin and myosin within the sarcomere. The model is of particular interest because it is not of the 'Huxley-type'. That is, force generation does *not* arise from microscopic strain in the crossbridge head, but rather from a unitary crossbridge isometric force ($\bar{F}$) (whether or not Ca^{2+} is bound to Troponin-C) diminished in proportion to *strain velocity* (V). That is,

$$F = \bar{F} - \eta V \tag{10}$$

where η is crossbridge viscosity. (Note the similarity to Eq. (3), above.) The model is not thermodynamically constrained. Specifically, it contains no reverse rate constants attributable to crossbridge cycling. Both its rate of transition (f), from the 'weakly bound' to the 'strongly bound' state ($+Ca^{2+}$), and its rate of unbinding (g), from the 'strongly bound' state ($-Ca^{2+}$), are velocity-dependent:

$$f = f_0 - f_1 V \tag{11a}$$

$$g = g_0 + g_1 V \tag{11b}$$

Landesberg and co-authors suggest that the linear form of the VO_2−PVA relation, as predicted by their model, arises exclusively from its "cooperativity mechanism", whereby the affinity for Ca^{2+} of troponin-C is determined by the number of crossbridges in the 'strong-force' configuration (whether or not Ca^{2+} is bound). Our implementation of their model finds the nature of the predicted VO_2−PVA relationship to be strongly sensitive to this cooperativity, with the apparent linearity contingent on the chosen parameterisation of the Ca^{2+} binding curve. Furthermore, the relationship was also found to deviate when we changed the Ca^{2+} transient, as might be expected, given the significance of cooperativity in the binding of Ca^{2+}. Nevertheless, the model gives rise to the experimentally testable prediction that the 'potential energy' (PE) component of PVA is proportional to the force–time integral of a twitch. But, as Vendelin et al. (2000) point out, this prediction requires that the duration of a twitch scale linearly with its peak force.

> Taking into account the SSA dependency on sarcomere length, such prolongation is required to reproduce the relationship between ATP consumption and SSA. Namely, one can roughly estimate that the maximal developed force is increasing linearly as a function of sarcomere length, and consequently, SSA is increasing with the second order of the sarcomere length. To have the same second-order increase of ATP consumption, which is the time integral of ATP consumption rate in a beat, the twitch duration has to increase linearly with respect to sarcomere length. (Vendelin et al., 2000)

The Landesberg model implicitly allows variable stoichiometry—i.e., multiple crossbridge cycles per ATP-hydrolysis event:

> The present model allows multiple stroke steps per single ATP consumption compared with Huxley's 1:1 relationship.(Page H1281, Landesberg and Sideman, 2000).

So, too, does the model proposed by Vendelin et al., where crossbridges that dissociate without hydrolysing ATP (colourfully yclept 'passenger crossbridges') appear more frequently as the afterload is reduced below about 20% of peak isometric force (Fig. 10 of Vendelin et al., 2000). These predictions resonate with that of Taylor et al. (1993), whose insights from a comparable (albeit non-thermodynamically constrained) model also suggested a contribution of variable stoichiometry to the linear dependence of enthalpy on FLA. Whether or not multiple crossbridge cycles per ATP hydrolysis event are either necessary or sufficient to explain the linearity of the VO_2−PVA relation is confounded by the fact that, in the model of Landesberg and colleagues, cycling crossbridges in the 'non-overlap region' of the sarcomere consume ATP without generating force. That is, their model accommodates both multiple force-generating events per ATP-hydrolysis event and multiple ATP hydrolysis events per force-generating event.

Before terminating this discussion, attention should be drawn to the fact that cardiac energy expenditure has been repeatedly shown to be proportional not only to FLA but also to peak force development (Gibbs, 1974, 1978; Gibbs and Chapman, 1979b; Hisano and Cooper, 1987; Wannenburg et al., 1997) and force–time

integral (Weber and Janicki, 1977; Gibbs and Loiselle, 1978; Gibbs, 1978; Gibbs and Chapman, 1979a, b; Hisano and Cooper, 1987; Loiselle, 1987; Widén and Barclay, 2006). It probably does not need stating that these three mechanical indices are mutually incommensurate (although, as argued by Vendelin et al. (2000), given a linear end-systolic pressure–volume relation, peak force and FLA are themselves linearly related—at least during isometric contractions).

3.4. A fundamental paradox

The above discussion has highlighted a number of matters, yet to be resolved, if a compelling explanation of the observed VO_2−PVA relation is to be forthcoming. We now address another issue that we, and others (Gibbs and Chapman, 1985; Gibbs and Barclay, 1995), consider to be of principal concern—namely, that the linearity of the experimental VO_2−PVA relation implies a constant mechanical efficiency. Conventionally, in muscle thermodynamics, mechanical efficiency (ε) is defined as the proportion of the net enthalpy change (ΔH) that is converted to work:

$$\varepsilon = \frac{W}{\Delta H} \tag{12}$$

where the enthalpy change, ΔH, is readily measured experimentally as the sum of work and heat (Q):

$$-\Delta H = Q + W \tag{13}$$

When dealing with the concept of PVA, it is necessary to modify the definition accordingly:

$$\varepsilon_{PVA} = \frac{W + PE}{VO_2} = \frac{W + PE}{\Delta H} \tag{14}$$

where the enthalpy equivalent of aerobic combustion of metabolic substrates by the heart is approximately 20 kJ/L. Thus, it can be seen that ε_{PVA} (Eq. (14)) exceeds ε (Eq. (12)) by the extent to which PE exceeds W. Again, one is struck by the similarity between the PVA concept and the elastic models described earlier; the 'PVA efficiency' reflects not only work output but also a potential capacity to do work that has the same unit metabolic cost as actual work output. In practice, 'PVA efficiency' (i.e., the inverse of the slope of the VO_2−PVA relation, Fig. 1B) is commonly about 0.4 (Suga, 1990), whereas maximum 'mechanical efficiency' falls in the range 0.1–0.15 (Baxi et al., 2000; Barclay et al., 2003).

Note that, in Eqs. (12) and (14), the denominators are given by the change of enthalpy (ΔH) during a single beat of the heart. But Eqs. (6)–(9) make it clear that it is the Gibbs free energy (ΔG) rather than the enthalpy (ΔH) that dictates the thermodynamic constraints. ΔG and ΔH are related by the Second Law of Thermodynamics:

$$-\Delta H = \Delta G + T\Delta S \tag{15}$$

where T is temperature and S signifies entropy. It is to be emphasised that work arises solely from ΔG, whereas heat (or its aerobic equivalent) arises both from the change of entropy, which accompanies the transition from reactants to products, and from the fraction of ΔG that is not converted into work. Hence, the more fundamental expression of efficiency is given by

$$\eta = \frac{W}{\Delta G} \tag{16}$$

where η is the thermodynamic efficiency. We are now in a position to focus on what we have labelled the 'fundamental paradox'.

At the level of the crossbridges, W (and, hence, η) must be highly variable. This can be seen by reference to Fig. 11, where crossbridge attachment at $x < h$ or detachment at $x \neq 0$ will result in the sub-optimal production of work. Such diminution of potential work is exacerbated if detachment fails to occur until $x < 0$ since now the attached crossbridge will be producing a force that is counter to the direction of the sliding filaments. It is difficult to see how, given this inherent variability of both magnitude and sign of W, thermodynamic efficiency (Eq. (16)) could be constant. But the matter is even more complicated since ΔG_{ATP} is unlikely to remain constant locally—especially at high rates of ATP utilisation (Aliev and Saks, 1993, 1994, 1997). This is readily

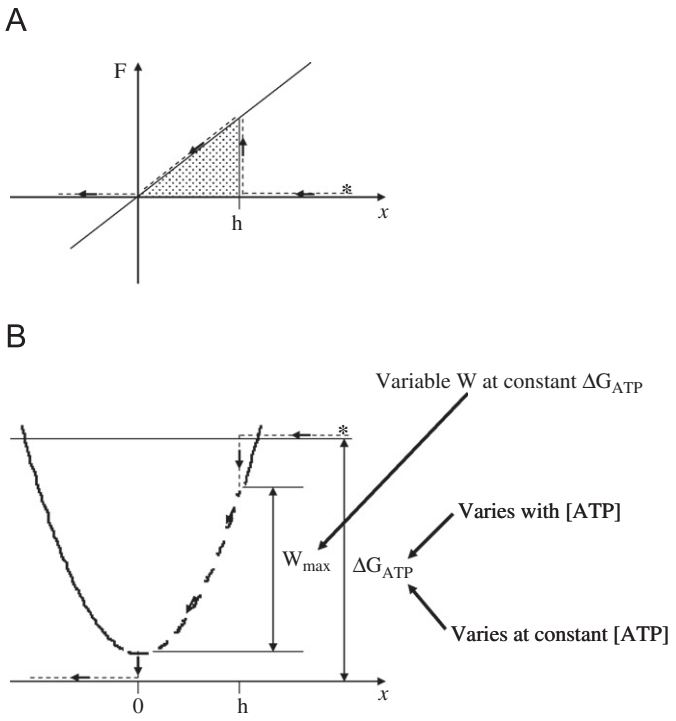


Fig. 11. Thermodynamic interpretation of Huxley's (1957) two-state model, showing the improbability that thermodynamic efficiency (Eq. (16), text) is constant. (A) Interpretation of the Hookean force (F) that arises when a crossbridge forms at displacement $+h$ from its neutral position. Shaded region denotes the maximum work (W_{max}) achievable under the conditions shown. (B) Gibbs free energy profile for a single crossbridge that attaches at $+h$ and detaches at zero, as exemplified in (A). Diagonal arrows emphasise the variability of both the Gibbs free energy of ATP hydrolysis (ΔG_{ATP}) and the work achievable from a single crossbridge cycle of attachment and detachment [modelled on Fig. 5.2 in Woledgeet al. (1985), *Energetic aspects of muscle contraction*, Academic Publishers].

appreciated by consideration of Eq. (9), recalling that, as creatine phosphate buffers ATP locally (via the MM isoform of creatine kinase, for example), the local concentration of Pi necessarily increases. Thus, ΔG_{ATP} can vary, even in the face of constant concentrations of both ATP and ADP. And, of course, the concentration of ATP *per se* can wax and wane, thereby providing a 'direct' source of variation of ΔG_{ATP}. Hence, both the numerator and denominator of the expression for thermodynamic efficiency are variable, making it even less likely that their ratio remains constant. So, unless the localised production of entropy (Eq. (15)) varies in a complementary fashion, it is difficult to see how 'PVA efficiency' (Eq. (14)) can remain constant, independent of the relative contribution of W and PE to PVA, as demanded by the constant slope of the VO_2–PVA relation. It is our conviction that only a detailed mathematical model of cardiac mechano-energetics is likely to provide an explanation of this paradox.

Editor's note

Please see also related communications in this issue by Kockskämper et al. (2008) and Zhang et al. (2008).

References

Aliev, M.K., Saks, V.A., 1993. Quantitative analysis of the 'phosphocreatine shuttle': I.A probability approach to the description of phosphocreatine production in the coupled creatine kinase-ATP/ADP translocase-oxidative phosphorylation reactions in heart mitochondria. Biochim. Biophys. Acta 1143, 291–300.

Aliev, M.K., Saks, V.A., 1994. VI-2 Mathematical modeling of intracellular transport processes and the creatine kinase systems: a probability approach. Mol. Cell. Biochem. 133/134, 333–346.

Aliev, M.K., Saks, V.A., 1997. Compartmentalized energy transfer in cardiomyocytes: use of mathematical modeling for analysis of in vivo regulation of respiration. Biophys. J. 73, 428–445.

Barclay, C.J., Lichtwark, G.A., 2007. The mechanics of mouse skeletal muscle when shortening during relaxation. J. Biomech. 40, 3121–3129.

Barclay, C.J., Widén, C., Mellors, L.J., 2003. Initial mechanical efficiency of isolated cardiac muscle. J. Exp. Biol. 206, 2725–2732.

Baxi, J., Barclay, C.J., Gibbs, C.L., 2000. Energetics of rat papillary muscle during contractions with sinusoidal length changes. Am. J. Physiol. 278, H1545–H1554.

Curtin, N.A., Gardner-Medwin, A.R., Woledge, R.C., 1998. Predictions of the time course of force and power output by dogfish white muscle fibres during brief tetani. J. Exp. Biol. 201, 103–114.

Daniel, T.L., Trimble, A.C., Chase, P.B., 1998. Compliant realignment of binding sites in muscle: transient behavior and mechanical tuning. Biophys. J. 74, 1611–1621.

de Tombe, P.P., Stienen, G.J.M., 2007. Impact of temperature on cross-bridge cycling kinetics in rat myocardium. J. Physiol. 584, 591–600.

Eisenberg, E., Hill, T.L., 1978. A cross-bridge model of muscle contraction. Prog. Biophys. Mol. Biol. 33, 55–82.

Eisenberg, E., Hill, T.L., Chen, Y.-D., 1980. Cross bridge model of muscle contraction: quantitative analysis. Biophys. J. 29, 195–227.

Feng, T.P., 1932. The effect of length on the resting metabolism of muscle. J. Physiol. 74, 441–454.

Fenn, W.O., 1923. A quantitative comparison between the energy liberated and the work performed by the isolated sartorius muscle of the frog. J. Physiol. 58, 175–203.

Fenn, W.O., Marsh, B.S., 1935. Muscular force at different speeds of shortening. Journal of Physiology 85, 277–297.

Forcinito, M., Epstein, M., Herzog, W., 1998. A numerical study of the stiffness of a sarcomere. J. Electromyogr. Kinesiol. 8, 133–138.

Ford, L.E., Huxley, A.F., Simmons, R.M., 1977. Tension responses to sudden length change in stimulated frog muscle fibres near slack length. J. Physiol. 269, 441–515.

Frank, O., 1899. Die Grundform des arteriellen Pulses. Z. Biol. 37, 483–526.

Gibbs, C.L., 1974. Cardiac energetics. In: Langer, G.A., Brady, A. (Eds.), The Mammalian Myocardium. Wiley & Sons, Inc, pp. 105–133.

Gibbs, C.L., 1978. Cardiac energetics. Physiol. Rev. 58, 174–254.

Gibbs, C.L., Barclay, C.J., 1995. Cardiac efficiency. Cardiovasc. Res. 30, 627–634.

Gibbs, C.L., Chapman, J.B., 1979a. Cardiac energetics. In: Berne, R.M., Sperelakis, N. (Eds.), The Cardiovascular System, Handbook of Physiology, vol. 1. American Physiological Society, Bethesda, MD, pp. 775–804 (Chapter 22).

Gibbs, C.L., Chapman, J.B., 1979b. Cardiac heat production. Annu. Rev. Physiol. 41, 507–519.

Gibbs, C.L., Chapman, J.B., 1985. Cardiac mechanics and energetics: chemomechanical transduction in cardiac muscle. Am. J. Physiol. 249, H199–H206.

Gibbs, C., Loiselle, D., 1978. The energy output of tetanized cardiac muscle: species differences. Pflügers Arch. 373, 31–38.

Gibbs, C.L., Loiselle, D.S., 2001. Cardiac basal metabolism. Jpn. J. Physiol. 51, 399–426.

Gibbs, C.L., Mommaerts, W.F.H.M., Ricchiuti, N.V., 1967. Energetics of cardiac contractions. J. Physiol. 191, 25–46.

Goldman, Y.E., Huxley, A.F., 1994. Actin compliance: are you pulling my chain? Biophys. J. 67, 2131–2133.

Goto, Y., Suga, H., Yamada, O., Igarashi, Y., Saito, M., Hiramori, K., 1986. Left ventricular regional work from wall tension-area loop in canine heart. Am. J. Physiol. 250, H151–H158.

Goto, Y., Slinker, B.K., LeWinter, M.M., 1988. Similar normalized E_{max} and O_2 consumption–pressure–volume area relation in rabbit and dog. Am. J. Physiol. 255, H366–H374.

Guccione, J.M., Motabarzadeh, I., Zahalak, G.I., 1998. A distribution-moment model of deactivation in cardiac muscle. J. Biomech. 31, 1069–1073.

Hill, A.V., 1913. The absolute mechanical efficiency of the contraction of an isolated muscle. J. Physiol. 46, 435–469.

Hill, A.V., 1938. Heat of shortening and the dynamic constants of muscle. Proc. R. Soc. London B 126, 136–195.

Hill, T.L., 1989. Free Energy Transduction and Biochemical Cycle Kinetics. Verlag, New York, 119pp.

Hill, A.V., Woledge, R.C., 1962. An examination of absolute values in myothermic measurement. J. Physiol. 162, 311–333.

Hisano, R., Cooper, G., 1987. Correlation of force–length area with oxygen consumption in ferret papillary muscle. Circ. Res. 61, 318–328.

How, O.-J., Aasum, E., Kunnathu, S., Severson, D.L., Myhre, E.S.P., Larsen, T.S., 2005. Influence of substrate supply on cardiac efficiency, as measured by pressure–volume analysis in ex vivo mouse hearts. Am. J. Physiol. 288, H2979–H2985.

How, O.-J., Aasum, E., Severson, D.L., Chan, W.Y.A., Essop, M.F., Larsen, T.S., 2006. Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice. Diabetes 55, 466–473.

Hunter, P.J., McCulloch, A.D., ter Keurs, H.E.D.J., 1998. Modelling the mechanical properties of cardiac muscle. Prog. Biophys. Mol. Biol. 69, 289–331.

Huxley, A.F., 1957. Muscle structure and theories of contraction. Prog. Biophys. Biophys. Chem. 7, 255–318.

Jewell, B.R., Wilkie, D.R., 1958. An analysis of the mechanical components in frog's striated muscle. J. Physiol. 143, 515–540.

Kameyama, T., Chen, Z., Bell, S.P., Fabian, J., LeWinter, M.M., 1998. Mechanoenergetic studies in isolated mouse hearts. Am. J. Physiol. 274, H366–H374.

Kawai, M., Saeki, Y., Zhao, Y., 1993. Crossbridge scheme and the kinetic constants of elementary steps deduced from chemically skinned papillary and trabecular muscles of the ferret. Circ. Res. 73, 35–50.

Kockskämper, J., et al., 2008. The slow force response to stretch in atrial and ventricular myocardium from human heart: Functional relevance and subcellular mechanisms. Prog. Biophys. Mol. Biol. 97, 250–267.

Labeit, D., Kolmerer, B., Linke, W.A., 1997. The giant protein titin. Emerging roles in physiology and pathophysiology. Circ. Res. 80, 290–294.

Labeit, D., Watanabe, K., Witt, C., Fujita, H., Wu, Y., Lahmers, S., Funck, T., Labeit, S., Granzier, H., 2003. Calcium-dependent molecular spring elements in the giant protein titin. Proc. Natl. Acad. Sci. 100, 13716–13721.

Landesberg, A., 1996. End-systolic pressure–volume relationship and intracellular control of contraction. Am. J. Physiol. 270, H338–H349.

Landesberg, A., Sideman, S., 1994. Mechanical regulation of cardiac muscle by coupling calcium kinetics with cross-bridge cycling: a dynamic model. Am. J. Physiol. 267, H779–H795.

Landesberg, A., Sideman, S., 1999. Regulation of energy consumption in cardiac muscle: analysis of isometric contractions. Am. J. Physiol. 276, H998–H1011.

Landesberg, A., Sideman, S., 2000. Force–velocity relationship and biochemical-to-mechanical energy conversion by the sarcomere. Am. J. Physiol. 278, H1274–H1284.

Landesberg, A., Livshitz, L., ter Keurs, H.E.D.J., 2000. The effect of sarcomere shortening velocity on force generation, analysis, and verification of models for crossbridge dynamics. Ann. Biomed. Eng. 28, 968–978.

Landesberg, A., Levy, C., Yaniv, Y., Sideman, S., 2004. The adaptive intracellular control of cardiac muscle function. Ann. N. Y. Acad. Sci. 1015, 71–83.

Levy, C., Landesberg, A., 2004. Hystereses in the force–length relation and regulation of cross-bridge recruitment in tetanized rat trabeculae. Am. J. Physiol. 286, H434–H441.

Levy, C., Landesberg, A., 2006. Cross-bridge dependent cooperativity determines the cardiac force–length relationship. J. Mol. Cell. Cardiol. 40, 639–647.

Levy, C., ter Keurs, H.E.D.J., Yaniv, Y., Landsberg, A., 2005. The sarcomeric control of energy conversion. Ann. N. Y. Acad. Sci. 1047, 219–231.

Loiselle, D.S., 1982. Stretch-induced increase in resting metabolism of isolated papillary muscle. Biophys. J. 38, 185–194.

Loiselle, D.S., 1987. Cardiac basal and activation metabolism. Basic Res. Cardiol. 82, 37–50.

Loiselle, D.S., 1989a. The diffusive oxygen conductance of the heart. In: Paul, R.J., Elzinga, G., Yamada, K. (Eds.), Muscle Energetics, vol. 315. Alan. R. Liss, Inc., New York, pp. 529–541.

Loiselle, D.S., 1989b. Exchange of oxygen across the epicardial surface distorts estimates of myocardial oxygen consumption. J. Gen. Physiol. 94, 567–590.

Loiselle, D.S., van Beek, J.H.G.M., Mawson, D.A., Hunter, P.J., 1995. The surface of the heart leaks oxygen. News Physiol. Sci. 10, 129–133.

Ma, S.-P., Zahalak, G.I., 1991. A distribution-moment model of energetics in skeletal muscle. J. Biomech. 24, 21–35.

Mast, F., Elzinga, G., 1990. Heat released during relaxation equals force–length area in isometric contractions of rabbit papillary muscle. Circ. Res. 67, 893–901.

Mawson, D.A., Hunter, P.J., Kenwright, D.N., Loiselle, D.S., 1994. Oxygen exchange in the isolated, arrested guinea-pig heart: theoretical and experimental observations. Biophys. J. 66, 789–800.

Müller, J.P., 1837. Handbuch der Physiologie des Meuschen für Vorlesungen mit Rücksicht auf physiologische Pathologie. Band 3. Teil 2. 2 Bde. Coblenz, Germany.

Niederer, S.A., Smith, N.P., 2007. A mathematical model of the slow force response to stretch in rat ventricular myocytes. Biophys. J. 92, 4030–4044.

Niederer, S.A., Hunter, P.J., Smith, N.P., 2006. A quantitative analysis of cardiac myocyte relaxation: a simulation study. Biophys. J. 90, 1697–1722.

Nishimura, S., Seo, K., Hosoya, Y., Nagasaki, M., Yamashita, H., Fujita, H., Nagai, R., Sugiura, S., 2008. The response of single ventricular myocytes to dynamic axial stretch. Prog. Biophys. Mol. Biol. 97, 282–297.

Pasquis, P., Lacaisse, A., Dejours, P., 1970. Maximal oxygen uptake in four species of small mammals. Respir. Physiol. 9, 298–309.

Saeki, Y., Kawai, M., Zhao, Y., 1991. Comparison of crossbridge dynamics between intact and skinned myocardium from ferret right ventricles. Circ. Res. 68, 772–781.

Saeki, A., Goto, Y., Hata, K., Takasago, T., Nishioka, T., Suga, H., 2000. Negative inotropism of hyperthermia increases oxygen cost of contractility in canine hearts. Am. J. Physiol. 279, H2855–H2864.

Sagawa, K., Lie, R.K., Schaefer, J., 1990. Translation of Otto Frank's Paper "Die Grundform des Arteriellen Pulses" Zietschrift für Biologie 37: 483–516 (1899). J. Mol. Cell. Cardiol. 22, 253–277.

Saks, V., Dzeja, P., Schlattner, U., Vendelin, M., Terzic, A., Wallimann, T., 2006. Cardiac system bioenergetics: metabolic basis of the Frank–Starling law. J. Physiol. 571, 253–273.

Schwann, T., 1837. Referenced in: Weber, E., 1846. Muskelbewegung. In: Wagner's Handwörterbuch der Physiologie. Vieweg, Braunschweig, Germany, pp. 101–103.

Smith, N.P., Barclay, C.J., Loiselle, D.S., 2005. The efficiency of muscle contraction. Prog. Biophys. Mol. Biol. 88, 1–58.

Stienen, G.J., Papp, Z., Elzinga, G., 1993. Calcium modulates the influence of length changes on the myofibrillar adenosine triphosphatase activity in rat skinned cardiac trabeculae. Pflügers Archive 425, 199–207.

Suga, H., 1990. Ventricular energetics. Physiol. Rev. 70, 247–277.

Suga, H., Hayashi, T., Shirahata, M., 1981a. Ventricular systolic pressure–volume area as predictor of cardiac oxygen consumption. Am. J. Physiol. 240, H39–H44.

Suga, H., Hayashi, T., Suehiro, S., Hisano, R., Shirahata, M., Ninomiya, I., 1981b. Equal oxygen consumption rates of isovolumic and ejecting contractions with equal systolic pressure–volume areas in canine left ventricle. Circ. Res. 49, 1082–1091.

Suga, H., Yamada, O., Goto, Y., 1984. Energetics of ventricular contraction as traced in the pressure-volume diagram. Fed. Proc. 43, 0061–0063.

Taggart, P., Lab, M., 2008. Cardiac mechano-electric feedback and electrical restitution in humans. Prog. Biophys. Mol. Biol. 97, 452–460.

Taylor, T.W., Goto, Y., Suga, H., 1993. Variable cross-bridge cycling–ATP coupling accounts for cardiac mechanoenergetics. Am. J. Physiol. 264, H994–H1004.

Tchaicheeyan, O., Landesberg, A., 2005. Regulation of energy liberation during steady sarcomere shortening. Am. J. Physiol. 289, H2176–H2182.

van Beek, J.H.G.M., Loiselle, D.S., Westerhof, N., 1992. Calculation of oxygen diffusion across the surface of isolated perfused hearts. Am. J. Physiol. 263, H1003–H1010.

Vendelin, M., Bovendeerd, P.H.M., Arts, T., Engelbrecht, J., van Campen, D.H., 2000. Cardiac mechanoenergetics replicated by cross-bridge model. Ann. Biomed. Eng. 28, 629–640.

Vendelin, M., Bovendeerd, P.H.M., Saks, V., Engelbrecht, J., 2002. Cardiac mechanoenergetics in silico. Neuroendocrinol. Lett. 23, 13–20.

Wakabayashi, K., Sugimoto, Y., Tanaka, H., Ueno, Y., Takezawa, Y., Amemiya, Y., 1994. X-ray diffraction evidence for the extensibility of actin and myosin filaments during muscle contraction. Biophys. J. 67, 2422–2435.

Wannenburg, T., Janssen, P.M.L., Fan, D., De Tombe, P.P., 1997. The Frank–Starling mechanism is not mediated by changes in rate of cross-bridge detachment. Am. J. Physiol. 273, H2428–H2435.

Weber, E., 1846. Muskelbewegung. In: Wagner's Handwörterbuch der Physiologie mit Rücksicht auf physiologische Pathologie. Band 3. Teil 2. Vieweg, Braunschweig, Germany, pp. 100–123.

Weber, K.T., Janicki, J.S., 1977. Myocardial oxygen consumption: the role of wall force and shortening. Am. J. Physiol. 233, H421–H430.

Widén, C., Barclay, C.J., 2005. Resting metabolism of mouse papillary muscle. Pflugers Arch. 450, 209–216.

Widén, C., Barclay, C., 2006. ATP-splitting by half the cross-bridges can explain the twitch energetics of mouse papillary muscle. J. Physiol. 573, 5–15.

Woledge, R.C., Curtin, N.A., Homsher, E., 1985. Energetic aspects of muscle contraction. Academic Publishers, New York.

Wong, A.Y.K., 1971. Mechanics of cardiac muscle, based on Huxley's model: mathematical simulation of isometric contraction. J. Biomech. 4, 529–540.

Wong, A.Y.K., 1972. Mechanics of cardiac muscle, based on Huxley's model: simulation of active state and force–velocity relation. J. Biomech. 5, 107–117.

Yaniv, Y., Sivan, R., Landesberg, A., 2006. Stability, controllability, and observability of the "four state" model for the sarocomeric control of contraction. Ann. Biomed. Eng. 34, 778–789.

Yeo, G.F., 1885. An attempt to estimate the gaseous interchange of the frog's heart by means of the spectroscope. J. Physiol. 6, 93–121.

Zahalak, G.I., Ma, S.P., 1990. Muscle activation and contraction: constitutive relations based directly on cross-bridge kinetics. J. Biomech. Eng. 112, 52–62.

Zhang, Y., et al., 2008. Cell cultures as models of cardiac mechanoelectric feedback. Prog. Biophys. Mol. Biol. 97, 367–382.