MECHANICAL phenomena in muscle are frequently interpreted by invoking cross-bridge mechanisms. These interpretations imply that tension development and shortening are brought about by the action of physical cross-links formed transiently between the interdigitating thick and thin filaments that comprise the contractile apparatus.

Recently, we have noticed a growing number of experimental observations which can be reconciled with the cross-bridge mechanism only if additional submechanisms are invoked. This increasing complexity makes us wonder whether the possibility of an altogether different and less complex mechanism ought not to be summarily dismissed.

The cross-bridge mechanism arose out of early electron micrographic observations: These showed that radial projections from the thick filaments appeared to terminate on the thin filaments. As these links were the only visible means by which interaction of filaments could take place, it was suggested that they might function as the generators of contractile force and provide the means by which actin in thin filaments could interact with myosin in the thick filaments.

This suggestion inspired a detailed exposition of cross-bridge dynamics in which each link was postulated to attach and detach many times per second, producing shortening and/or tension with each stroke. The elements of this scheme were consistent not only with the basic structure, but with the energetics, mechanics, and biochemistry of muscle as well. However, the scheme ultimately proved inadequate in light of more recent data. Which underscored the need for more elaborate structural models. One such model is shown in Figure 1A-C.

A theory of cross-bridge dynamics compatible with these newer structural features was proposed by Huxley and Simmons. It is now being accorded a great deal of attention. The scheme (Fig. 1D) assumes that the arm of the cross-bridge is compliant, and that the head, which rotates, can sustain tension. When activated, the head can attach transiently to a site on the thin filament, after which it rotates clockwise, thereby pulling on the compliant link. This pull manifests itself in tension development and/or sliding of the filaments.

There is now substantial support for the mechanism of force generation by physical cross-links; however, incontrovertible evidence for cross-bridge attachment during contraction in living muscle still does not exist. Thus it seems worthwhile to entertain other proposals, provided these are demonstrably consistent with the same body of data adduced to support the cross-bridge theory. Some of the more plausible schemes have been based on electrostatic mechanisms, but most have not shown broad consistency. On the other hand, the theory proposed by Iwazumi shows sufficient consistency that we believe it ought to be taken seriously. Because this theory is less well known than the cross-bridge theory we will devote relatively more time to discussing it.

The principle of force generation is that of a dielectric rod suspended in the electric field between the plates of a capacitor (Fig. 2A). Because the charge induced on the rod is asymmetrically distributed, there is always an attractive force tending to draw the rod further into the field of the capacitor. The dielectric rod is assumed to be the thin filament, and the capacitor is the cross-bridge. In this context more appropriately the cross-projection (Fig. 2B). By separation of charge, an electric field is generated on each projection, thereby forming a succession of force-generating sites along the thick filament. The energy required to sustain charge separation is supplied through the hydrolysis of ATP, and has been shown to be of reasonable magnitude.

The force depends on the interaction of the tip of the thin filament with the field of the local cross-projection. Other cross-projections, including those in the overlap zone along the shaft of the thin filament, have no effect on force even though they generate a field (Fig. 2C).

Variation of force can occur by four mechanisms:

1. Variation in the level of the calcium in the region near the tip. Within its working range, the higher the calcium the higher the ATPase activity and the higher the field generated. Force is proportional to the square of the local field strength. Thus the transient increase of myofila-
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FIGURE 1 A: cross-bridge configuration suggested by Huxley.9 This two-component scheme was postulated to permit the head of the cross-bridge to attach to the thin filament with the same relative orientation irrespective of interfilament spacing, which had been shown to vary with sarcomere length.5 The relative positions of the head, arm, and filaments are shown at rest in A, with the muscle stretched in B and shortened in C. Activation causes an increase of θ and φ. A power stroke is then achieved by a decrease of φ. In D the mechanism of contraction suggested by Huxley and Simmons10 is shown. This is compatible with the structure shown in A. After attaching to the thin filament, the head of the cross-bridge rotates clockwise in discrete steps, stretching the link AB to length AB' and exerting tension on the thick filament. The thin filament tends to slide leftward, giving rise to sarcomere shortening. Since filament separation varies with sarcomere length, θ does as well. Between 2.1 and 3.6 μm the variation of θ is about 25° (with AB taken as 40 nm and d varying between 16.5 and 8.5 nm). The cross-bridge force, resolved into lateral and longitudinal components, is shown for narrow and wide interfilament distances in E. Note that the longitudinal component of cross-bridge force (the force measured externally) varies with θ, as does the lateral component.

FIGURE 2 Mechanism of force generation proposed by Iwazumi.14,15 A: the principle is that of a dielectric rod suspended in the field of a capacitor. From the distribution of charge induced on the rod, it is evident that there will be a net attractive force which draws the rod further into the capacitor. B: the capacitors are the cross-projections along the thick filament. Charge is separated by ATP splitting, generating an electric field. The thin filament is always drawn further into the field, leading to translation and sarcomere shortening. C: force is generated only at the tip of the thin filament. Other capacitors in the overlap zone do not generate force because the charge they induce is distributed symmetrically along the thin filament. The distance between capacitors is 43 nm.

ment calcium during activation brings about the transient increase of tension. Relaxation occurs after calcium is withdrawn from the myofilaments: charge gradually leaks off the capacitors and cannot be replenished in the absence of ATPase activity.

2. Force induced by short range movement. In a manner analogous to that in which a voltage is induced in a coil moving in a magnetic field, a dielectric rod moving through a capacitor induces a change of voltage and field in the capacitor, which is then manifested as a change of force. This is elaborated under Transients, below.

3. Variations in force as a result of the nonuniform distribution of calcium along the thick filament. Iwazumi supposes a distribution that has a minimum at the center of the thick filaments (i.e., about the M line) and has maxima at either end (i.e., at the edges of the A band). An assumption that is consistent with available data.16-20 As a consequence of this distribution, sarcomeres which are stretched by one or more cross-projection spacings during activation will transiently generate increased tension because of movement of the tip into a region of higher calcium concentration. Conversely, long range shortening will reduce the force.

4. Longitudinal alignment of tip of thin filament with the nearest cross-projection. Since the field is highest in the immediate proximity of each projection and falls off with distance (fringe field), force will be highest when the tip is aligned with the projection, and lower at any other position. Midway between projections the field is zero, so
a tip passing through this region experiences no force. Continuous force generation during shortening is ensured because the arrangement of projections around the thick filament is helical: some tips will always be situated in the field of a projection as others pass through regions of zero field. The situation is less straightforward when the tips extend into the central 0.2 \( \mu \text{m} \) of the thick filament which is devoid of projections. However, the thick filaments go out of register on activation by several tenths of a micrometer,\(^\text{21, 22}\) enough to ensure that some filament tips will always be situated in proximity of a projection so that force can be generated.

**Differences between the Theories**

The two theories differ in three fundamental ways: (1) tension is brought about by physical links in the former and electric fields in the latter; (2) in the cross-bridge theory tension depends rather directly on the degree of overlap of thick and thin filaments; in the field theory it is unrelated to overlap, but depends on the calcium level in the region of the tip of the thin filament; and (3) the structure postulated for the cross-projection is totally different in the two theories. Given these striking differences, one might expect the evidence supporting one theory to be inconsistent with the other, but this is not necessarily the case.

**MECHANICAL VS. ELECTROSTATIC TENSION GENERATION**

That tension generation in living muscle occurs by the formation of physical cross-links between actin and myosin is a supposition drawn by inference from several types of studies. One of the best known is rigor mortis, in which electron micrographs have clearly shown physical cross-linking of thick and thin filaments. The observed linking configuration is generally thought to reflect a stage in the cycle of cross-bridge rotation.\(^\text{8}\) Thus the rigidity of rigor is considered an extreme example of the stiffness of contraction. Such a simple interpretation should be questioned since the characteristic rigidity of rigor occurs whether rigor is induced at full overlap of thick and thin filaments where cross-linking is maximal, or at no overlap where it is absent (Haselgrove.\(^\text{23}\) p. 133).

Actin and myosin also interact in vitro systems (see Weber and Murray\(^\text{24}\) for review). That similar interaction constitutes the contractile event in intact muscle has been a logical inference from these observations. The field theory also predicts actomyosin interaction in vitro. As thin filaments will be drawn into the electric field generated by the myosin heads to form an electrostatic aggregation. We see no simple way of using such biochemical evidence to distinguish between the two theories.

Other evidence for mechanical action of cross-bridges comes from elegant experiments in which fluorescent molecular probes tagged to cross-bridges are found to rotate during contraction.\(^\text{25, 26}\) The interpretation has been that the cross-bridges rotate; another interpretation is that the cross-bridges remain stationary while the probes rotate—in response to the local electric field buildup or as a result of conformational changes in the cross-bridges required to set up the field. Thus the fluorescence experiments also fail to distinguish between the two theories.

Cross-bridge motion has also been inferred from changes in the spatial distribution of x-ray reflections associated with different contractile states.\(^\text{27}\) This interpretation leads to surprising conclusions: cross-bridge motion that is independent of overlap\(^\text{28, 29}\) and independent of shortening velocity and tension\(^\text{30}\) but dependent on time after dissection.\(^\text{22}\) Another potential line of interpretation follows from events that occur during contraction; namely, axial misregistration of thick filaments\(^\text{31}\) and internal shortening. Sarcomere shortening of 20% can occur in carefully mounted single fibers contracting isometrically (Cleworth and Edman.\(^\text{27}\) plate 4). In a nonideal lattice such as muscle (but not necessarily in an ideal lattice) these events affect both the axial and equatorial reflections in a manner qualitatively similar to that of cross-bridge motion. A quantitative treatment ruling out this interpretation would be of great value.

Turning to the field theory, we see one potentially strong argument against tension generation by electric fields. As Huxley\(^\text{3}\) pointed out, a long range field cannot exist in a region where ions are abundant. as these would screen the charges involved in setting up the field. A condition necessary for the existence of a field, therefore, is that the microregion surrounding each cross-projection be devoid of high concentrations of mobile ions. Such a requirement seems at odds with the high ionic strength known to exist in muscle. However, nuclear magnetic resonance studies indicate that some fraction of muscle water behaves in a physically anomalous way,\(^\text{32-38}\) whether this fraction is simply "bound water" hydrated to muscle proteins or "structured water" which excludes ions is currently the subject of much debate. If the latter interpretation is correct, then the low ionic strength requirement could be locally satisfied despite the high average ionic strength of the sarcoplasm. It is noteworthy that a requirement for comparable myosin ATPase activity in vitro with that in vivo is low ionic strength.\(^\text{39, 40}\)

One type of experiment that potentially distinguishes between mechanical and electrostatic modes of tension generation has been carried out by Oplatka et al.\(^\text{41}\) They have shown that "ghost" myofibrils, i.e., those from which thick filaments have been effectively removed by myosin extraction, could still develop substantial tension when irrigated with myosin heads (S-1) and ATP. Their conclusion that aggregation of myosin molecules into filaments is not an obligatory feature of contraction raises the question of how isolated subfragments of myosin might be able to transmit tension mechanically by a scheme such as that outlined in Figure 1. On the other hand, thin filaments can be drawn into the field generated by S-1 heads, and thereby generate tension according to the field theory. These experiments seem worth confirming in other laboratories.

We conclude that the data most frequently cited as lending strong support to the cross-bridge theory seem consistent with both modes of tension generation. Unfortunately, neither electric fields nor tension-generating motion of cross-bridges have ever been directly demonstrated in living muscle.
TENSION VS. OVERLAP

The elegant studies of Gordon et al. have elucidated an excellent inverse correlation between developed isometric tension and degree of overlap of thick and thin filaments. This finding is frequently cited as providing strong support for a contractile mechanism in which tension is developed by independent force-generators distributed throughout the zone of overlap. However, in other experimental situations isometric tension and overlap do not correlate at all (see Force-Length Relations, below). Thus length-tension data are inconsistent, and provide little basis for distinction between the two theories.

Moreover, the inverse linear relation between tension and overlap seems less precise today on the basis of newer data. Page has found the thin filaments to be 0.1 μm shorter than earlier measurements had indicated, so that the observed length-tension curve falls to the right of that expected on the basis of the number of cross-bridges available to generate tension (Fig. 3A). Another difficulty is that the tensions failed to reach a plateau during tetanus at the longer sarcomere lengths. After a rapid rise, tension continued to rise upward, even in segments whose length had been servo-controlled. This steady increase of tension was thought at the time to be due to gradual dispersion of sarcomere length within the servo-controlled segment, and therefore was deemed artifactual. The tensions which would have existed in the absence of creep were estimated by extrapolation and plotted, as shown in Figure 3A. In more recent studies with frog semitendinosus fiber bundles, the increase of sarcomere length dispersion on contraction was found to be negligibly small at long sarcomere lengths. These studies raise the question of whether the extrapolated tensions are appropriate to use in constructing the length-tension diagram. If peak tensions are plotted instead, the correlation between tension and number of available cross-bridges becomes considerably less precise (Fig. 3A). Further study seems warranted on this subject.

CROSS-BRIDGE STRUCTURE

The third basic difference between theories lies in the postulated structure of the cross-projection. The cross-bridge was shown to comprise two subfragments, a globular region (S-1) about 15–20 nm long and a tail (S-2) about 40 nm long. The total length of 55–60 nm is sufficient for either of the postulated configurations. Electron micrographs do not distinguish clearly between them. Since the oblique S-2 arm (Fig. 1) does not show up as an entity distinct from the thick filament, electron micrographs provide no direct support for Huxley's proposal; however, the arm could be obscured if θ were small. The orientation to the myofilament axis which is generally observed is consistent with Iwazumi's interpretation.

We are accustomed to supposing that cross-bridges originate from thick filaments and terminate at the thin filaments, and most electron micrographs seem compatible with this interpretation; however, many of the ones we have examined do not appear to exclude the possibility that the projections span the better part of the gap between thick filaments, as envisioned in the field theory (cf.
In principle, some features of cross-bridge structure can also be derived by deconvolution of x-ray diffraction patterns. However, only the amplitude, but not the phase, of each diffracted order is obtained experimentally. Consequently, unambiguous determination of cross-bridge configuration is not possible. This limitation has also been an impediment in distinguishing between possible helical lay-outs of bridges along the thick filament. It appears that the size, shape, and orientation of cross-bridges have yet to be convincingly elucidated.

In summary, the present level of resolution of the basic structural and functional features of the contractile mechanism seems unable to provide the basis for excluding one or the other of the two theories; both mechanisms seem possible at this stage. We must look elsewhere to seek inadequacies in one or the other theory.

### Assumptions of the Theories

In the exposition of each theory we have seen the introduction of a considerable number of postulates and assumptions. We have listed those that are necessary to satisfy the basic structural and functional requirements of each theory as the first two items in Table 1. With regard to the cross-bridge theory these refer to the specific scheme outlined by Huxley and Simmons. Other versions of the cross-bridge theory will require alternative sets.

The satisfaction of these basic structural and functional requirements is the minimum that must be demanded of any theory. The adequacy of the theory rests on a straight-

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<td><strong>Cross-bridge theory</strong></td>
<td><strong>Electrostatic theory</strong></td>
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| **Structural** | 1. Cross-bridge has two components as in Figure 1  
2. All joints are hinge-like, allowing rotation  
3. Arm of cross-bridge is elastic; head is rigid |
| 1. Positive and negative charges separated on cross-projection by hydrolysis of ATP  
2. Effective dielectric constant of thin filament higher than water  
3. Steady state voltage at each cross-projection is function of local calcium concentration  
5. Sarcoplasm surrounding projections contains structured water which reduces local ionic strength |
| **Basic function** | 1. Upon activation bridges move toward thin filaments ($\theta$ increases)  
2. Increases of $\theta$ are coupled to increases of $\phi$, so head can maintain proper orientation for attachment to thin filament  
3. Head rotates after attachment to thin filament  
4. Energy supplied by ATP splitting during rotation cycle |
| 1. Increase of $\phi$ is coupled to increases of $\theta$ |
| **Release transients** | 1. Head rotates in several discrete steps; potential energy at each step distributed so as to fit quick release transients |
| None |
| **Stretch transients** | 1. Some mechanism to limit "slip" of sarcomere to about 40-45 nm  
2. After slip, cross-bridges form instantaneously and are greater in number than during isometric contraction |
| None |
| **Force-length relation** | 1. Calcium sensitivity of cross-bridge is length-dependent (or related assumption)  
2. Shortening during activation gives rise to structural changes in myofilaments which uncouple the muscle's force-generating ability; lengthening has the opposite effect  
3. Force per cross-bridge cycle or rate of cycling decreases with ionic strength  
4. Longitudinal component of cross-bridge force independent of $\theta$ |
| 1. Calcium concentration at tip of thin filament is a function of sarcomere length |
| **Force-velocity relation** | 1. Rate constants for cross-bridge attachment and detachment functionally dependent upon relative position of thick and thin filaments  
2. Arm of cross-bridge can support compressive loads |
| None |
| **Longitudinal stability** | 1. Higher fraction of cross-bridges recruited in sarcomeres with less overlap, or bridges "hang on" without cycling |
| None |
| **Lateral stability** | 1. Restoring force exists to balance lateral component of cross-bridge force; must vary with time, overlap |
| None |
forward explanation of a broad range of data. With regard to muscle, these should include mechanics, biochemistry, biophysics, and energetics. A consideration of all these is precluded by space allocation for this article. We consider here only the basic mechanics: mechanical transients, length-tension relations, force-velocity relations, and mechanical stability. Our objective is to identify the ad hoc assumptions required by each theory to account for these mechanical properties. These will be listed in the remainder of Table 1. The two lists should provide a useful aid in a comparative evaluation of each theory's ability to account for the basic mechanics.

TRANSIENTS

When an activated muscle is quick-released to a shorter length, the force is diminished abruptly before it begins to recover (Fig. 4A). The simultaneous diminution of force and length indicates the presence of a built-in elastic-like component. This elasticity exists over only a narrow range of length change; a quick reduction of initial sarcomere length of the order of 1-2% drops the force to zero in skeletal muscle as well as cardiac muscle. Given such a narrow working range and certain other considerations, Huxley and Simmons postulated that this elastic component resides within each cross-bridge, specifically within the arm (Fig. 1). According to this postulate, the force drops abruptly during quick release because these compliant arms recoil (Fig. 4B). The partial redevelopment of force following the release is explained by postulating either that more cross-bridges attach or that the compliant links restratch because of head rotation following the release. The latter explanation follows directly from the potential energy levels assumed by Huxley and Simmons to characterize each of the intermediate stages of rotation.

In the field theory, these force transients occur as a natural consequence of the force-generating scheme. Force drops abruptly during release because the tips of the filaments translate from positions of alignment with cross-projections, where the field is highest, to positions where field is lower (Fig. 4C). The larger the release, the farther the tip moves into the fringe field, and the lower the force. Thus the field distribution around the cross-projection shown in Figure 4C (actually its square) is described by a plot of force after release (F2 in Fig. 4D) vs. amount of release. Its shape is quantitatively similar to that actually measured (Huxley, Fig. 9).

An additional but transient diminution of force is induced by tip movement per se. Since the rod is assumed to have a high dielectric constant, its movement farther into the capacitor brings about an increase of capacitance (Fig. 4D). Because the charge on the capacitor cannot change instantaneously, the abruptly increased capacitance results in an abruptly decreased voltage and force. This decrease is transient because each projection is postulated to behave as constant voltage element (similar to a chemical battery); additional charge immediately begins to accumulate on the capacitor by ATP hydrolysis to restore the original voltage; the increasing charge and field result in the partial recovery of force seen after quick release (compare Figs. 4A and 4D).

FIGURE 4

A and B: quick-release transients as interpreted by the Huxley-Simmons theory. Rapid shortening of an activated muscle causes recoil of spring in arm of cross-bridge, thereby reducing tension (i, ii). Then, clockwise rotation of head pulls on spring and increases tension (iii). C and D: dynamics during quick release according to the field theory. The force transient has two components (bottom trace, D6). The first (broken line) arises because the tip of the thin filament translates from a position of high field within the capacitor to the lower fringe field (as illustrated in C). A second component occurs by induction: movement of the thin filament farther into the capacitor increases the capacitance (D2), giving rise to a transient decrease of force. Then the force increases as charge accumulates on the capacitor (D3) to restore the steady state voltage which existed before the thin filament had moved (D4).

With both theories the arguments used to account for releases can be turned around to account for stretches, provided these are small. For stretches continuing beyond 10-20 nm per sarcomere, elastic-like behavior terminates suddenly as the muscle "gives" or "slips." In some experimental situations but not all, abrupt increases of sarcomere length are detected as the muscle slips. The magnitude of these jumps is 40-45 nm per sarcomere. a value similar to the helical repeat spacing of cross-bridges along the thick filament.

The cross-bridge theory readily accounts for the initial portion of the response. Muscle stretch causes elastic lengthening of the cross-bridge arms, increasing the force. When the force is sufficient, the heads rotate backward and detach from the thin filaments, permitting the sarcomeres to slip to a longer length as the muscle gives. Then, some mechanism which limits the slip to 40-45 nm needs to be assumed. Also, the force would be expected to drop to zero once all bridges had detached, but in fact the force
continues to rise slightly. Cross-bridges formed just after slip must therefore instantly generate a force greater than that generated by the previous cross-links just before they were strained to the point of detachment. This requirement can be satisfied by assuming an increased number of cross-links immediately after slip despite decreased overlap, or potentiated force-production per cross-bridge just after slip.

In the field theory the initial increase is induced as the capacitance decreases (inset Fig. 4D). Then, once the contractile force can no longer sustain the increasing load, the thin filament tip slips all the way to the next region in which an electrostatic field exists. The distance between regions is equal to the cross-projection separation, i.e., 43 nm (Fig. 2C). Force is now higher because the calcium level has been assumed to be higher nearer the periphery of the A band.

FORCE-LENGTH RELATIONS

Although there is a discernible relation between developed tension and number of available cross-bridges in tetanically stimulated skeletal muscle, such a relation is less evident in other experimental situations. For example, the length-tension relation is skewed when twitches are used instead of tetani and in skinned fibers activated at submaximal calcium levels.

The cross-bridge theory accounts for these skewed curves by assuming that the cross-bridge sensitivity to calcium can depend on sarcomere length, by assigning an appropriate functional dependence. A length-tension curve of any shape can be fit. In the field theory the length-tension relation is not a fundamental property of the contractile mechanism, but a product of calcium activation levels which are assumed to vary with sarcomere length. Thus tension varies as the calcium level at the tips of the thin filaments varies. Although this assumption has not yet been tested, the experiments of Taylor et al. have shown some correlation between forces on both limbs of the length-tension curve and free calcium levels (presumably spatially averaged) in the sarcomere.

The shape of the length-tension curve is also affected by mechanical history. As shown in the experiments of Delèze, outlined in Figure 3B, he first determined the isometric length-tension relation in tetanically stimulated frog semitendinosus muscle. Then, at some length greater than optimal, he allowed isometric tension to develop, stretched the muscle (by about 10%) to a new length, and held it there for the remainder of the tetanus. This maneuver reduces the size of the overlap zone and presumably the number of tension-generating cross-bridges. The tension just after the stretch was not lower than the tension appropriate to the new length, but was generally 50–100% higher. Inappropriately high tension persisted long after stretch (note time scale in Fig. 3B). A feature also seen by workers using more modern techniques. Edman et al. recently repeated Delèze’s experiment with single fibers and plotted the sarcomere length-tension curve using isometric tensions 0.2 seconds after stretch. Between 2.0 and 3.0 μm the length-tension curve was practically flat.

Tension levels are also affected when the inverse experiment is done, i.e., when shortening replaces lengthening. Here isometric tension levels are reduced rather than increased. and the muscle is considered "deactivated." To explain the effect of previous motion. Edman favors the assumption that filament sliding causes a slowly decaying structural alteration of the myofilaments. Thus shortening produces deactivation. While lengthening produces supra-activation. In the field theory, as the sarcomere shortens the tips of the thin filaments move into a region of lower calcium concentration nearer to the center of the thick filaments, thereby reducing the tension that is subsequently generated. Lengthening has the opposite effect.

An important consideration in differentiating the two theories is the manner in which the force-length curve is affected by variations of ionic strength around the myofilaments. Decreased force at high ionic strength can be explained in the cross-bridge theory by assuming either a reduced number of cross-bridges, reduced force per cross-bridge, or some mixture of both. The first of the assumptions is in concurrence with the observed diminution of ATPase activity at high ionic strength in vitro. According to the field theory more ions are available to increase the screening effect on the field, resulting in reduced field strength and force.

Although variations in ionic strength affect the magnitude of tension, it is noteworthy that they have no effect on the shape of the length-tension relation. Some differences in shape are anticipated from the basic cross-bridge mechanism. At shorter sarcomere lengths, the cross-bridge angle (Fig. 1B and C) must be larger than at longer sarcomere lengths because sarcomere length and interfilament separation are inversely related. Consequently the longitudinal component of force generated by each cross-bridge (the force actually measured) must be lower at shorter sarcomere lengths. Since the contribution of each cross-bridge to contractile force changes with sarcomere length, some skewing ought to be evident in the force-length relation. Skew should be particularly evident at low ionic strength, where interfilament separation is largest. The skew should be small at high ionic strength. Thus differences of shape of the force-length curve at different ionic strengths are anticipated, but are not found experimentally. To explain this discrepancy a scheme must be devised by which cross-bridge force varies in such a way that its longitudinal component does not change with ionic strength.

According to the field theory the magnitude of force is hardly influenced by lateral separation of thick and thin filaments, per se. This follows because the field between the plates of the capacitor is independent of the coordinate normal to the plates. Thus the force is the same whether the dielectric rod is positioned midway between the plates, or closer to one plate than another. The invariant shape of the length-tension curve with variable ionic strength does not therefore require additional assumptions.

FORCE-VELOCITY RELATIONS

The inverse relation between force and velocity could be accounted for in the earlier version of the cross-bridge
theory by postulating that the rate constants for cross-bridge attachment and detachment were dependent on the instantaneous position of the cross-bridge relative to that of the potential attachment site on the thin filament. With this scheme the average force per cross-bridge stroke turned out to be diminished at higher velocities of shortening. The newer version of the cross-bridge theory has been shown by Julian et al. to account for the force-velocity relation with a set of assumptions analogous to those in Huxley's earlier theory. Besides space-dependent rate constants, it is also necessary to assume that cross-bridges can support compressive forces without buckling, an assumption Huxley and Simmonds believe to be consistent with their quick-release data.

In the field theory two phenomena give rise to the inverse force-velocity relation. First, each capacitor tends to maintain a constant voltage which is set by the local Ca concentration. Each time the thin filament tip enters a capacitor during shortening, it increases its capacitance, thereby transiently decreasing its voltage and field, and reducing the force (as in Fig. 4D). Steady, rapid shortening thereby results in force which is diminished substantially from the isometric level. The slower the shortening velocity the longer the dwell time within each capacitor and the longer the time available for capacitor voltage to recover toward its steady state value. Thus lower shortening velocities are associated with higher forces.

A second factor is the longitudinal position of the tips of the thin filaments relative to the cross-projections. In the isometric state (zero velocity) the filament tips tend to be aligned with the projections; they are located where the field. hence the force. is highest. During shortening, when the filaments are translating, some thin filament tips will be passing through areas of low field; consequently the force on this fraction of filaments will be lower. Thus total force is lower when velocity is higher.

STABILITY

Hill pointed out that the descending limb of the length-tension curve seemed potentially unstable: shorter sarcomeres should be able to stretch longer ones. thereby perpetuating any initial disparity of sarcomere length. and ending disastrously. In fact. longitudinal stability is present. To be stable, any theory must contain forces which tend to restore the status quo.

In the field theory longitudinal stability is achieved at any point on the length-tension curve because a shortening sarcomere always generates less force than a lengthening sarcomere. This is due first to the calcium distribution along the thick filament, and second to the induced forces (see Transients).

In the cross-bridge theory longitudinal stability could be achieved if the cross-bridges in the longer (weaker) sarcomeres were assumed to have a "hang-on" feature which prevented their detachment despite the high load. Alternatively, the sarcomeres could somehow sense the force unbalance and recruit an appropriately higher or lower fraction of tension-generating cross-bridges to restore the balance.

Muscle also shows lateral stability. X-ray diffraction data indicate that the lateral spacing between filaments is preserved as the muscle goes from rest to activation, so any lateral forces developed as a by-product of contractile forces must be counterbalanced by equal and opposite restoring forces; otherwise the filaments would fly apart or compress into a central core.

In the field theory, no lateral forces are generated during contraction. Therefore, no force is introduced which could bring about lateral instability. In the cross-bridge theory, contraction does give rise to attendant lateral forces because the cross-bridge force is applied obliquely (Fig. 1E). Unless some force is applied which is equal and opposite to the lateral component of cross-bridge force, the filaments would aggregate into a core in the center of the cross-section of the sarcomere; this does not happen.

The magnitude of such a restoring force would necessarily be highly variable from situation to situation. It must vary with time during a twitch to counterbalance the transient cross-bridge force. It must vary with sarcomere length in two different ways: First, the number of cross-bridges in the overlap zone decreases with sarcomere length, and so must the lateral component of force. Second, the cross-bridge angle, decreases with sarcomere length, so the lateral force component in each cross-bridge decreases. Thus a rather complex restoring force needs to be assumed both in intact and skinned preparations. Nevertheless, such a force must exist if the cross-bridge theory is to be adequate.

Conclusions

Table 1 represents little more than a superficial, perhaps biased, attempt at comparative evaluation of the two theories. Our purpose is not to demonstrate the superiority of one theory over another, but to reinforce the principle that the adequacy of any theory can be established only by systematic comparison of theoretical predictions with experimental data. With regard to muscle, such a comparison ought to encompass not only a broader treatment of mechanics, but muscle biochemistry, biophysics, and energetics as well. Some consistency in these areas has already been demonstrated for each of the two theories, but an evaluation commensurate with the existing volume of data has not yet appeared.

The field theory is newer than the cross-bridge theory and has not withstood the test of time; experiments designed to disprove it have not yet been carried out. It rests heavily on the assumption that the ionic strength in the vicinity of each cross-bridge is extremely low, one which most (but not all) regard as unlikely. It stands virtually alone in invoking long range electric fields to explain a biological phenomenon. It rests on interpretations of existing data which are considerably different from those generally accepted. From this vantage point, we see these as its major weak points. Its strengths are evident from Table 1.

If experience is to be a guide, both theories will eventually be found inadequate. Nonetheless, it is stimulating to speculate on which, if either, may form the basis on which future theories are built.

References

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Distribution of Coronary Artery Flow to the Canine Right Atrium and Sinoatrial Node

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SUMMARY We assessed segmental distribution of blood flow to the right atrium and the region of the sinoatrial node using microspheres (7-10 μm) in 20 anesthetized dogs. Mean right atrial flow averaged 83 ± 7 (SE) ml/min × 100 g, which was 56% of the left ventricular blood flow. The distribution of right atrial flow was not homogeneous. For example, flow to anterior right atrial segments including the segment containing the sinoatrial node was greater (105 ± 8 ml/min × 100 g) than mean right atrial flow. Following ligation of the sinoatrial node artery, perfusion of the segment containing the sinoatrial node decreased by only 36%. Relative preservation of perfusion to the sinoatrial node following sinoatrial node artery ligation may explain why ligation of the sinoatrial node artery does not alter heart rate. Furthermore, we also found that cannulation and pump perfusion of the sinoatrial node artery at pressures 10 and 50 mm Hg greater than systolic pressure did not alter the distribution of right atrial flow. Thus, because cannulation and perfusion of the sinoatrial node artery do not artifactually distort regional right atrial blood flow, we conclude that this should be a useful method for evaluating responsiveness of the sinoatrial node to various interventions.

THE SINOATRIAL node with its dominant effect on cardiac pacemaker function occupies a prominent position in the control of heart rate in man and many animals. Located in close proximity to the dominant atrial artery, the sinoatrial node artery is easily accessible for experimental interventions. In numerous studies of the pharmacology of sinoatrial node automaticity, the sinoatrial node artery is used to deliver drugs, hormones, and other chemical agents to the sinoatrial node. The responses of the sinoatrial node to these interventions must be related to the pattern and extent of perfusion of the atrium from the sinoatrial node artery and other atrial arteries.

Ligation of the sinoatrial node artery has been shown not to alter the rate of sinoatrial node discharge. In addition, the response of the sinoatrial node to pharmacological interventions is quantitatively different with various experimental methods for sinoatrial node artery perfusion. To find an explanation for these observations we assessed total and regional atrial blood flow under a variety of conditions: during normal perfusion, after transient occlusion of the sinoatrial node artery, and during various methods of sinoatrial node artery perfusion.

Methods

PREPARATION OF ANIMALS

Twenty adult mongrel dogs of both sexes weighing 15-25 kg were anesthetized with intravenous α-chloralose (50 mg/kg) and urethane (500 mg/kg). The dogs were ventilated via auffed endotracheal tube with room air and supplemental oxygen using a volume respirator adjusted to maintain normal arterial blood gases and pH. Periodically the lungs were hyperinflated to prevent atelectasis. The left chest was opened. a cannula was placed in the left atrium for injections of microspheres, and the chest was closed. Catheters were placed in the brachial and right and left femoral arteries for withdrawal of reference arterial blood samples and measurement of pressure. Arterial pressure was measured with a Statham P23Db strain gauge leveled at the midchest. The electrocardiogram was recorded from standard limb leads and heart rate was calculated with a tachometer. All signals were recorded on a direct-writing recorder. A right thoracotomy was performed and the right coronary artery and its distal branch supplying the region of the sinoatrial node (hereafter referred to as the sinoatrial node artery) were identified. If the sinoatrial node artery did not arise from the right coronary, the dog was not included in the study. This occurred in 5% of the dogs studied. All dogs were treated with heparin, 500 U/kg, iv.

SINUS NODE ARTERY CANNULATION AND PERFUSION

In 17 dogs the sinoatrial node artery was cannulated with polyethylene tubing (outside diameter = 0.09-0.21 cm).
Molecular mechanisms of contraction.
M I Noble and G H Pollack

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