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A Re-Appraisement of Key Aspects of Ventricular Excitation and Contraction - a

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SUMMARY

Electricity is electrons moving. As the electron is the sub-atomic particle embodying electrical energy, it can hardly be possible for cardiac electrophysiology not to involve electrons. Depolarisation of the cardiac ventricles was attributed to net electron loss and repolarisation to electron generation by mitochondria.

ABSTRACT

As the electron is the sub-atomic particle embodying electrical energy, it can hardly be possible for cardiac electrophysiology not to involve electrons. This problem was approached by a focus on the changes in electric charge throughout the cardiac ventricular cycle. Depolarisation involved a rapid net loss of diastolic total negative charge. This loss of negative charge upon depolarisation was attributed to outflow of electrons in excess of sodium ion (Na^+) ingress through sodium channels. Depolarisation was followed by a period of net total positive charge during the calcium transient attributed to calcium ion (Ca^{2+}) release to cause contraction, and subsequent Ca^{2+} uptake by the sarcoplasmic reticulum. Repolarisation as a result of potassium ion (K^+) outflow was found to cause intracellular K^+ depletion not compatible with a steady state. Repolarisation was attributed to electron generation during oxidative phosphorylation by mitochondria. A one way process of electron generation and subsequent loss and dissipation as heat is postulated.

Keywords: Electrons; Ions; Depolarisation; Repolarisation; Negative Charge; Heart

INTRODUCTION

The purpose and direction of this paper is to call attention to the apparent lack of consideration in text books and the literature that electrophysiology involves electricity. All electrical phenomena involve electricity, defined as electrons moving. Electron flow is a basic aspect of organic chemistry [1]. It is therefore necessary to describe electrophysiological events in terms of the movement of the electrons as well as movement of other charged particles. Positive ions, for instance, are atoms and molecules lacking one or more electron, giving them a net positive charge. Negative ions are atoms and molecules with one or more extra electron. Electrons continuously move in exchanges between ions. The purpose of the present paper is an attempt to describe excitation and contraction of ventricular cells in terms of electron movement in addition to the presently accepted aspects of these phenomena.

METHODS

All data are taken from published accounts in the world literature. The review adopts the philosophy of transformative research, defined as research that causes a major change in thought patterns concerning an area of scientific endeavor [2]. In this case the addition, to the knowledge of electrophysiology in terms of positively charged ionic movements, of thought about the complementary role of negative charge carried by electrons.

RESULTS AND DISCUSSION

The interpretation of the conventional depiction of cardiac excitation in figure 1 will be reviewed in terms of the movement of electrons that produce the ventricular action potential.

The nature of the cellular material through which electrons flow

Detailed descriptions of the passage of electrons through various forms of matter are readily available, but the type of matter concerned in living cells, including heart ventricle, is highly relevant in the present context. The structured water of the intracellular gel is what enables magnetic resonance to image soft tissue by detecting differences in proton resonance depending on their micro-environment; the structuring is heterogeneous [3]. Sackmann [4] has pointed out how nature invented rational engineering designs several billion years ago and quotes as an example, proton powered rotating motors enabling bacteria to search for food or escape dangers. The importance of protons in life systems is well recognized and their activity determines pH. During cell respiration (oxidative phosphylation) electrons are separated from protons; electrons are released from NADH and FADH2). In mitochondria and bacteria, oxidative phosphorylation depends on generation of an electrochemical proton gradient (i.e., proton-motive force) across the inner membrane, with electron transport, proton pumping, and ATP formation occurring simultaneously. Increased mitochondrial membrane potential decreases respiration while decreased potential has the opposite effect [5]. Phosphorylation potential controls respiration solely via phosphorylation (rather than by controlling NADH supply). Noble M [6] attempted to bring electrons also into the picture of physiology. Essentially, all living organic cells feature

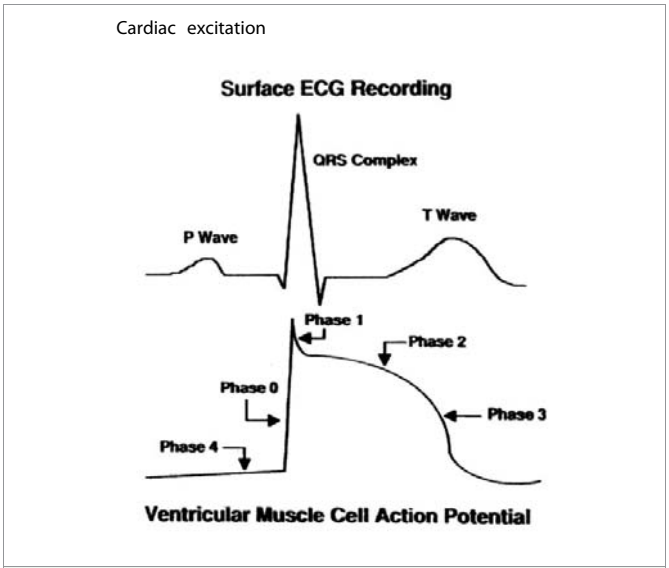

Figure 1: Cardiac excitation is commonly experienced by a recording on the surface of the body of the Electrocardiogram (ECG) (upper panel). This the pattern of emission of electrons from the heart that reach the skin and can be recorded with a volt meter. The pattern is affected by interactions between the emissions from different parts of the heart and attenuation through body tissues. The P wave of the ECG emanates from the atria and will not be considered in this paper. The corresponding pattern from inside a single ventricular cell (the Action Potential (AP) is shown in the lower panel and shows that the upstroke (phase 0) corresponds to the QRS complex of the ECG and the slow down stroke to the T wave.

negative trans-membrane potentials that reflect the net negative charge of the cell cytoplasm, which is in a gel form (as described by Dujardinin [7] in 1835, when it was called protoplasm) in which the water is structured [8]. There have been more recent discussions of cell membrane structure and function [9]. The excess of free electrons in resting cells, over and above those circling around atomic nuclei, may be created by the expulsion of protons [10].

Electrical behavior can be studied in isolated axons filled with electrolyte solution, e.g., Baker et al [11], so that it has been argued that a theory based on mitochondrial generation of electrons must be wrong, as electrons cannot travel through electrolyte. However, intracellular molecules are known to interact via electron flow [1]. Another erroneous conclusion follows from the fact that electrical behavior can be studied in isolated cell-free patch clamps, e.g., Hamill et al [12]. There is no source of electrical energy in such isolated membranes separated from the cell bodies; the electricity has to be supplied through the experimenters' apparatus that is equally capable of enabling study of the electrical properties of non-biological material. This is valuable data, but in living cells, electrical energy is produced by cellular energy transfer along with the other forms of energy that are required for the tissues' functions. Denis Noble's classic equivalent electrical circuit diagram for the Purkinje fiber [13] incorporated batteries, suggesting to myself that the batteries are mitochondria generating electrons. As established in the previous paragraph, the cell interior has, in any case, been disproved to consist of liquid electrolyte.

Electricity is defined as electrons moving. The phenomenon of electricity generation is commonplace in the modern life of humans, who convert various forms of energy into electrons, transport the electrons through lengths of electrically conducting material (with losses in the form of heat) to all locations at which a form of energy is required (movement, light, heat etc). Electrons also have wave-like properties, approaching the speed of light (C), but the mass, though only $9.10938215(45) \times 10^{-31}$Kg (3 orders of magnitude less than the atomic unit of a proton) precludes electrons from actually reaching the speed of light; nevertheless they behave in some ways like photon beams. In addition, according to Newton's second law, Electromotive Force (EMF) equals mass times acceleration (F = ma), so that a = EMF/ m. Consequently the acceleration of an electron during a change of EMF is 1000 times that of a proton and 10,000 times that of the smallest ions, such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and chloride (Cl^-). Living cells have a negative trans-membrane potential, e.g., algae, amoeba, bacteria, plants, animals. It is postulated that life on earth, because of natural selection, adopted these mechanisms billions of years ago during evolution. In other words, the outcome of evolution is the natural selection of preference for moving electrons, if possible, to moving ions, because the latter are approximately 10,000 times the mass and therefore inertia of the electron, e.g., a chloride ion only carries the same electric charge as an electron, but has 10,000 times the mass. Therefore, unless chloride, or other negatively charged particle, is essential for a required function, electrons are preferred by natural selection for the movement of negative electric charge.

Evidence compatible with cellular generation of electricity (electrons moving)

When one passes a current from the positive pole of a battery to the negative pole through an impedance, and measure the current with an ammeter, one is actually observing the movement of electrons from the negative pole to the positive pole, and, by registering the current signal upside down, one is recording the electron flow. When salts are dissolved in water, the induced electric current of electrolysis consists of ion movements, some with positive charge (electron(s) missing from the atoms), some with negative charge (with extra electron(s). Living cells by contrast can be analyzed by nuclear magnetic resonance and magnetic resonance imaging, proving that the intracellular material is not liquid but a gel with electric field patterns that allow the presence of electrons and movements of electrons; we need to describe the electrical phenomena in terms of electrons as well as in terms of protons and ions.

Why did unicellular organisms evolve a gel interior and negative trans-membrane potential?

The trans-membrane potentials (the potential difference between the cell gel interior and the extracellular milieu) in unicellular organisms are the highest found, usually around -100 mV. The evolutionary pressure for this arises from the fact that unicellular organisms live in a liquid-water-based electrolyte medium, the composition of which cannot be controlled by the organism. As the cell is at considerable risk of non-survival, one can expect an evolutionary change that provides protection for the cell interior. First there is the need for a protecting membrane composed of material of low electrical conductivity. By accumulating an excess of free electrons over and above those in the atoms, the cell exerts a field force across the membrane of 12,500V/ mm in the case of a trans-membrane potential of -100 mV. The other important feature of the evolving cell membrane is the double leaflet structure which has been reviewed by Lombard [9]. If the inter-leaflet space is subjected to an electric field force of 12,500V/ mm, all charged bodies, i.e., protons and ions will be excluded from the inter-lammellal space, creating a very large increase in membrane resistance to further insulate the cell from the external electrolyte.

Is it likely that cells in multicellular organisms would generate negative trans-membrane potentials by a mechanism different to that of unicellular organisms? In the modern knowledge of intracellular gel structure, the answer is obviously, "No". Half a century ago, before this knowledge was obtained, the intracellular material was assumed to be liquid electrolyte - the cytosol. In the multicellular organism, the external medium is of controlled composition - the extracellular fluid.

The Nernst equation $Ecell = E^0cell - (RT/ nF) \ln Q$, states that the trans-membrane potential at any one time during a cell cycle, such as in a cardiac ventricular cell, is the trans-membrane potential in the stable state, e.g., for a ventricular cell, the diastolic potential, E^0cell, minus $(RT/ nF) \ln Q$, in which the only variable is n, the number of electrons lost.

The negative membrane potentials were compatible with a balance of ions between the intracellular and extracellular ion compositions, but the high intracellular K^+ concentration is due to binding of K^+ to the protein matrix [14]. There is not enough ATP based energy for the sodium pump (which is under the control of intracellular Na^+ concentration, not extracellular K^+ concentration) to generate this difference in K^+ concentration [15,16]. We should logically now favour the idea that the electron accumulation of the gel causes the electric field force across the membrane, rather than that the membrane itself generates the electric field force [17].

Electrical dynamics: electrically imposed depolarisation

The electrically excitable mammalian heart is unique in that the

trans-membrane potential shows cyclic changes of depolarisation and repolarisation that continue for a lifetime. Therefore, this is the best example to examine the role of electrons in dynamic changes, which have to achieve a steady state of electrons, protons and ions for any given physiological state. In a multicellular organism, such as a mammal, the relatively controlled composition of extracellular fluid provides a much less threatening environment for the cell than the uncontrolled milieu of the unicellular organism. Nevertheless the cell interior must be protected from uncontrolled calcium ion intrusion, which would precipitate the phosphate-based energy system. Even so, a rapid depolarisation and repolarisation is possible in order to achieve advanced functions not available in the unicellular case. These depolarisations and repolarisations constitute the subject of electrophysiology as applied to nerve axon [18] and the heart [13]. Denis Noble [13] adapted the principles of Hodgkin & Huxley to cardiac cellular electrophysiology. It is worthy of note straight away, that Denis Noble recognized that cardiac cells showed electrical function (1) in being a capacitance (2) the cell membrane being a semiconductor and a variable resistance and (3) supplied electricity as in batteries. These principles stand firm today when one thinks of these phenomena in terms of electrons as well as in terms of ions; the main addition is to think in terms of negative polarity as well as positive polarity.

The nature of the rapid depolarisation in a ventricular heart cell

In figure 2, the upper trace is copied from an internet textbook showing a typical ventricular heart cell action-potential in which the resting negative trans-membrane potential rapidly changes from -80 to -90 millivolts (mV) to approximately +30mV. Such a sudden switch of EMF is characteristic of a short circuit, and this is because this cell would not depolarise at all except that it is engulfed in a travelling wave of depolarisation reaching it through the ventricular tissue which functions like a syncytium. Alternatively, depolarisation is triggered by an artificial electric stimulus from a pacemaker. When one visualizes the trace upside down, one obtains a tracing proportional to the amount of intracellular negative charge. The units of charge can be determined in coulombs by integrating the net current flows with respect to time. However, precise calibrations of net current and normalizations for capacitance are difficult and do not alter the principle in the diagram, because the waveforms of net current are the same as the first time derivative of voltage (dV/ dt). One now realises that the short circuit imposed event has caused a great loss of intracellular electrons, i.e., discharge of the capacitance and acquisition of positive cell charge. Charged particles can move through the cytoplasm. An example is the movement of calcium ions from the sarcomere ends into the centers, when released by the activation of ryanodine receptors of the Sarcoplasmic Reticulum (SR) by trigger Ca^{2+} entering from the T tubules upon depolarisation. Thus charged particles, including free electrons, are able to move within the gel and between the gel and the exterior in accordance with local controlling electrical and chemical conditions, which are complex and heterogeneous.

What is measurable during the rapid depolarising current?

The changes in charge in figure 3 constitute a net outward negative charge current. The net inward current (with conventional polarity) can be measured electronically from an intracellular electrode, but the traces are very noisy owing to the very small magnitudes in the range of pico-amps. However, this disadvantage can be overcome by electronic differentiation of the trace of charge drop during depolarisation, as the electron outflow rate is obtained from the first time derivative of the action potential trace. Figure 3, from the same source as figure 2, shows that the action potential is accompanied by the trace proportional to the net negative (electron) charge outflow rate (obtained from the first time derivative of the action potential). Data sent privately by Aria Verkerk shows that, with the dV/ dt method in a human ventricular cell, outward electron flow peaks in 1.5 ms or less. The outward electron movement is in excess of the net movement when positive charges move in the opposite (inward) direction. These are assumed to be sodium ions (Na^+) because the current is Na^+ dependent and there is much evidence for the opening of (Na^+) channels during this rapid, conventionally inward, current [19]. These channel openings are compatible with Weidman's measurement [20] of a drop in electrical resistance. During this time (followed by recovery during the plateau). With the opening of channels and a drop in electrical resistance, electrons will flow out in excess of any inward Na^+ flow because they have 10,000 times the acceleration of Na^+, being one ten thousandth of the mass. Intracellular Na+ concentration can be measured with a sodium-sensitive electrode

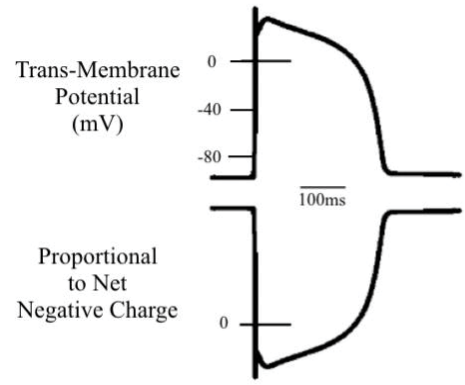

Figure 2: He upper trace is copied from an internet textbook showing a typical ventricular heart cell action-potential, as in figure 1, lower trace (AP). The lower trace here shows the corresponding net negative charge content of the intracellular space (gel).

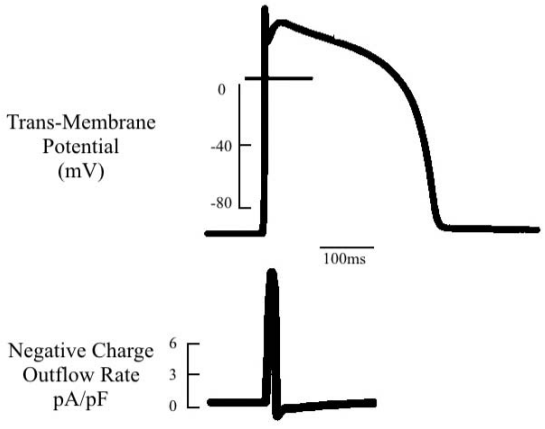

Figure 3: The upper trace is the same as that of figure 2. The lower trace shows the net outflow of electrons during upstroke of the AP that cause depolarisation (loss of electron charge).

but the method [21] has failed to show a depolarisation spike. This could easily be due to poor frequency response of the measuring system or to the very small magnitude of the signal. The method shows that there is an increase in intracellular Na^+ with increased average Ca^{2+} release which stimulates sodium-calcium exchange (NCX), causing an increase in intracellular Na^+, requiring an increase of sodium pump activity [21,22] over approximately 10 minutes. The transmembrane electric field force of the polarised ventricular cell is 10,000 volts/ mm, sufficient to exclude all charged particles from the interlamellal space of the sarcolemma. At the peak of the rapid Na^+-dependent fast inward current, it momentarily drops to zero and then increases to 3,500 volts/ mm. Thus Na^+ ions and protons briefly enter the interlamellal space, the former opening the Na^+ channels and the latter releasing the Ca^{2+} bound to the inner leaflet [23-25]. This part of the argument leaves us with 1. Imposed depolarisation occurs as a result of an excess of negative charge outflow over positive charge inflow, a fact; 2. This causes a rapid depletion of intracellular electrons, a fact; 3. The rapid depolarising current is Na^+- dependent, a fact; 4. An inflow of Na^+ to the intracellular compartment during the rapid depolarising current has not, possibly cannot, be demonstrated, and therefore remains a phenomenon of unknown magnitude; 5. Electrons dissipate as heat, a phenomenon common to all electrically powered circuits.

Consideration of the Need for a Steady State

If the cardiac cell is to continue a very large number of cycles, there must be a steady state. With physiological adaptation, there will be a transient adjustment until a new steady state is achieved that balances with the new demand, e.g., the response to adrenaline. An electron steady state is always achieved within a beat because the cell is supplied with electrons until negative charge reaches its diastolic value, corresponding to the diastolic trans-membrane potential. The ease of acquisition results from a one way system, electrons supplied and dissipating and new electrons being supplied to replace them. This is not the case with ions which, after changing compartments, have to be replaced by an equal and opposite reverse movement of the same ions, e.g., in a steady state, Ca^{2+} entering as L - type Ca^{2+} current is in balance with Ca^{2+} exit by Na^+/ Ca^{2+} exchange [26]. Thus, if the cell acquires additional Na^+, as occurs during the cardiac action potential through the Na^+/ Ca^{2+} exchange, they have to be pumped out again requiring additional energy consumption by the Na^+/ K^+ ATPase (sodium pump). The same has to be true when some Na^+ enter the cell during the rapid depolarising current via a sodium channel. Such pumping to achieve a Na^+ steady state is not required if the Na^+ are entering the sarcolemma at zero trans-membrane electric field force and forced out again when the field force returns with opposite polarity (after the "spike", Weidmann [20]), with no energy requirement for sodium pumping. One could then speculate on the role of the Evolutionary Law of Natural Selection on the advantage of electrons with 10,000 times the acceleration of Na^+.

Excitation Contraction Coupling

Another problem concerning ion movements in heart cells results from the need for a rise in intracellular calcium (Ca^{2+}) concentration sufficient for activation of contraction. Part of the process of maintaining a Ca^{2+} steady state also involves energy consumption, this time by the Sarcoplasmic Reticulum (SR) Ca^{2+} activated ATPase (calcium pump) and possibly sometimes also a sarcolemma Ca^{2+} pump.

The mechanism of repolarisation

A much more difficult puzzle is the question of how a potassium ion (K^+) steady state is achieved, if the conventional theory is correct that repolarisation is effected by K^+ ion outflow. The requirement of a steady state for ions demands that there be an equal and opposite inflow. This cannot be achieved by the Na^+/ K^+ATPase which is controlled by intracellular Na^+. This is clear from the records of Kronhaus et al. [27], demonstrating the very slow rate of decay of increased extracellular K^+ (Figure 4) in which there is no sign of any acceleration of sodium pumping. The slowness of the process of K^+ equilibrium that is influenced by the static membrane potential was demonstrated by Hodgkin and Keynes [28]. The other factor leading to the conclusion that the sodium pump is not able to maintain a potassium steady state, if repolarisation is due to K^+ outflow, is that the energy required to maintain the essential K^+ steady state is not available [15,16]. Re-supply of electrons by cell metabolism is postulated to cause repolarisation; this is an intracellular mechanism that is dependent on potassium ions, distributed within the protein matrix of the gel that permits the existence of electrical fields and conductivity.

There is a dilemma with the apparent outward positive current during final repolarisation back to the diastolic trans- membrane potential

If one just looks at the action potential in figure 2 upper trace, or rigs one's apparatus to record net current (conventional positive polarity), the plateau shows an apparent net outward positive current when, as has been asserted above, there is Ca^{2+} entry via the L-type Ca^{2+} channel and Na^+ entry via the Na^+/ Ca^{2+} exchange. The conventional view seems to be that there is, at the same time as this cation inflow, an even greater efflux of K^+. Surely positive ions repel

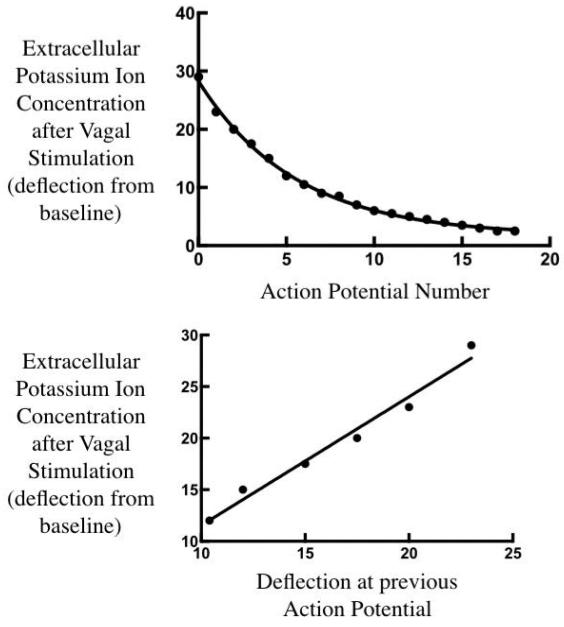

Figure 4: Rate of decay of extracellular potassium ion concentration (K+) plotted from the record of Kronhaus et al, 1978. Upper panel: single exponential decay per beat. Lower panel: Plot of each concentration against that of the previous beat. There is no stimulation of an increased movement to the intracellular space by speeding up of the sodium pump which remains at the previous rate.

each other in the interlamellal space? Whether one supposes that it is unlikely that this would be the case, or whether one speculates about opposite polarity ion channels in the cell membrane, insulated from one another in the dynamic of the constant molecular movement membrane, it might be worth considering a simpler explanation: The intracellular structured gel electric charge "pool" begins during the plateau with an excess of positive charges and positive trans-membrane potential, and is then being "filled" with positive ions: Ca^{2+} from the exterior via the Ca^{2+} channel, Ca^{2+} from the interior by the Ca^{2+} transient and Na^{+} from the exterior by the Na^{+}/ Ca^{2+} exchange (NCX); at the same time the cell metabolism is filling the same pool with delivered electrons. If there is a flat action potential plateau or a flat- topped square-wave voltage clamp depolarisation, the charge flow rates of the exchanging inputs are equal. If, as in the more usual case (Figure 2), there is a slow declining action potential signal, the delivery rate of supply of electrons exceeds the sum total of the positive charge inputs. The competing positive charge versus negative charge sub-hypothesis predicts that addition of positive charges will prolong the delay in filling the intracellular gel with electrons, i.e., will prolong the action potential duration. When one allows heart ventricular muscle to shorten, there is an additional release of intracellular calcium ions from the SR and an increase in Na^{+}/ Ca^{2+} exchange with additional positive charge gain because $3Na^{+}$ go in for each Ca^{2+} out; this gain in positive charge delays the final repolarisation [29]. This is an important result because the effect of the increase in intracellular positive charges occurs within a single cycle. Delay in final repolarisation is also induced by slower ways of increasing intracellular positive charge, e.g., when protons are added [30]. According to Narbonne & Koss [31] there are multiple K^{+} channels (at least 4) expressed in individual myocytes throughout the myocardium. However, handling of K^{+} by all these channels is not clear, as K^{+} movement is not measured or timed. The hypothesis concerning ion balance in the intracellular gel could be tested further, and more directly, by performing the "Jalife experiment" [32] on a ventricular cell, because the hypothesis predicts that intracellular injection of electrons in this case will shorten and intracellular injection of positive ions, or withdrawal of electrons, will lengthen the duration of the action potential. The dilemma of the apparent outward positive current during final repolarisation back to the diastolic trans-membrane potential. It will be noted that potassium channel blockade does not affect the final repolarisation in the experiments of Corriero, Spitzer & Giles [33], even though the conventional explanation for this final repolarisation, also repolarisation in nerve axon and skeletal muscle, is an outward current carried by potassium ions. The final repolarisation can be changed by changing the gene controlling a K^{+} channel Miake [34] but this is like looking at a difference between two strains of animal. One wants to know the effect of blocking the K^{+} channels in a given preparation, as in Cordeiro et al. [33] experiments. This hypothesis that repolarisation is effected by electron generation can be disproved by finding an extracellular K^{+} concentration transient in a ventricular cell during repolarisation that fully accounts for the change in membrane potential. Experiments designed to test these hypotheses could enhance insights in the field of electrophysiology.

CONCLUSION

Ventricular ddepolarisation involves a rapid net loss of diastolic total negative charge. This loss of negative charge upon depolarisation is measured as the rapid inward current implying a net outflow of electrons in excess of sodium ion (Na^{+}) ingress through sodium channels. Depolarisation was followed by a period of net total positive charge during the calcium transient attributed to calcium ion (Ca^{2+}) release to cause contraction, and subsequent Ca^{2+} uptake by the sarcoplasmic reticulum. Repolarisation as a result of potassium ion (K^{+}) outflow would cause intracellular K^{+} depletion not compatible with a steady state. Repolarisation was attributed to electron generation during oxidative phosphorylation by mitochondria. A one way process of electron generation and subsequent loss and dissipation as heat is postulated.

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