J. Physiol. (1962), **160**, *pp.* 483–493
With 2 *text-figures*
Printed in Great Britain

INTRACELLULAR Na AND K CONCENTRATIONS OF RABBIT ATRIA, IN RELATION TO THE ACTION OF QUINIDINE

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(*Received* 11 *August* 1961)

Atrial muscle has been found to have a resting potential 10–20 mV lower than that of ventricular or skeletal muscle, and it has been suggested (Burgen & Terroux, 1953) that acetylcholine increases K permeability, allowing the resting potential to hyperpolarize towards the K equilibrium potential, on the assumption that the intracellular K is not much less in atrial muscle than in ventricular or skeletal muscle. Trautwein & Dudel (1958) observed that in the presence of ACh the potential after anelectrotonic pulses tended towards a value which they thought to be close to the K equilibrium potential, but their experiments were performed on quiescent isolated dog atrial strips and their calculations of K equilibrium potential were based on the intracellular K of fresh cat ventricle estimated by Robertson & Dunihue (1954). Rayner & Weatherall (1957) estimated K fluxes, K content and inulin space in rabbit atria, and the figures they provided allowed a rough calculation of the probable limits of intracellular K concentration (Vaughan Williams, 1959*a*). In the present experiments the Na and K content, and the rate of exchange of ^{24}Na, have been determined in normal atria and in atria which had been exposed for 2 hr to quinidine. These results have been used to calculate values for the probable limits of the extracellular sodium space, the intracellular Na and K concentrations, and the rate of uptake of ^{24}Na by the muscles.

METHODS

The apparatus has already been described (Goodford & Hermansen, 1961). 92 rabbits were stunned, their hearts removed, and the atria dissected free of all non-muscular tissue under a stream of oxygenated modified Locke's solution (Vaughan Williams, 1955) at room temperature (*ca.* 15° C). In order to standardize the procedure as much as possible all the dissections were done by one of us. The tip of the left atrium was pierced by a platinum hook attached to a thread, and to remove excess fluid the atria were drawn by the hook rapidly back and forth over a sheet of black Perspex until they no longer left a trail of droplets behind them. This trailing procedure always preceded the weighing of each pair of atria.

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A second weighing agreed with the first within 2–3 mg, if the atria were again immersed in solution and the trailing procedure was repeated.

A group of 11 atria, taken at random from each batch of rabbits used, was placed in dry pots immediately after dissection and trailing, and weighed. This group was designated 'fresh atria.'

All other pairs of atria were placed immediately after dissection and trailing in pots containing about 4 ml. of oxygenated Locke's solution which had been previously weighed together with the hook and thread. The pot was reweighed, and the difference constituted the 'fresh weight' of the atria. After weighing, the right atrium was pierced by a second platinum hook mounted in Perspex, so as to be in contact with two platinum electrodes also fixed in the Perspex nearby. The left atrium was suspended by the thread on a spring, against which the atria could contract (Goodford & Hermansen, 1961). The mounted preparation was held under a stream of oxygenated Locke's solution at room temperature until exactly 10 min had elapsed since the rabbit was stunned, and was then placed in a 250 ml. bath at 31° C into which 5% CO_2 and 95% O_2 was bubbled and through which a stream of fresh Locke's solution flowed at a rate sufficient to replace the original solution approximately every 20 min. All atria were driven throughout the experiments at a frequency of 180/min.

Atria were allowed to beat for various periods in control solution in groups distributed as follows:

(*a*) 1 hr controls (11 atria); removed and weighed after beating for 60 min.

(*b*) '3 hr' controls (30 atria); subdivided into four groups—
(1) removed after beating for 180 min (9);
(2) transferred at 180 min to control solution containing ^{24}Na, and removed after 1 min (7);
(3) transferred into ^{24}Na from 180–183 min (7); and
(4) transferred into ^{24}Na from 180–195 min (7).

(*c*) 4 hr controls; transferred to ^{24}Na at 180 min and removed after a further 60 min (6).

A second series of atria were treated in exactly the same way except that the solutions (both non-radioactive and radioactive) from 1 hr onwards contained in addition quinidine sulphate 6 mg/l. The numbers of atria in the corresponding groups of the quinidine series were:

(*d*) '3 hr' quinidine (28), subdivided into
(1) 60 min control + 120 min quinidine, non-radioactive, (8);
(2) 60 min control + 120 min quinidine + 1 min radioactive (7);
(3) 60 min control + 120 min quinidine + 3 min radioactive (7); and
(4) 60 min control + 120 min quinidine + 15 min radioactive (6).

(*e*) 4 hr quinidine; 60 min control + 120 min quinidine + 60 min radioactive (6).

After removal from the bath each preparation was trailed, weighed in a small glass pot to give the 'wet weight', and dried to constant weight in an oven at 105° C. It was then ashed in 1 ml. conc. nitric acid (Analar, sp.gr. 1·42) and 1 ml. perchloric acid (Analar, sp.gr. 1·70) at 130° C until dry. The drying and ashing were also carried out on samples of the radioactive Locke's solution. Counting of radioactivity was done on the dry ashed samples in an end-window Geiger G-M 4 counter, and the ashing was then repeated. Glass-distilled water 3 ml. was added to each sample when dry and cold, and the Na and K contents were estimated by comparison with standard NaCl and KCl solutions in a Beckman DU spectrophotometer employing an oxygen-acetylene flame.

The radioactivity of each sample was expressed as the relative activity

$$\mathrm{R} = \frac{\text{specific activity of Na in muscle}}{\text{specific activity of Na in radioactive Locke's solution}}$$

after appropriate corrections to both the counter and spectrophotometer readings.

Statistical treatment. Mean values have been expressed with their standard errors. The significance of differences has been indicated on a 'probability' scale such that a small value

of P represents a highly significant difference. Standard deviations of arithmetically combined quantities have been calculated as follows:

Quantity	S.D.
A	a
B	b
$A \pm B$	$(a^2+b^2)^{\frac{1}{2}}$
AB	$(a^2B^2+b^2A^2)^{\frac{1}{2}}$
$\ln A$	a/A

The slow phase of ^{24}Na uptake shown in Fig. 2 was extrapolated linearly to zero time according to the equation $y = mt+a$, where m = gradient and a = intercept on the y axis at $t = 0$; and the variance of this intercept has been calculated from the variance of the individual observations according to the equation

$$V = v\left(\frac{1}{n}+\frac{\bar{t}^2}{S(t-\bar{t})^2}\right),$$

where V = variance of intercept,
v = variance of all the individual observations,
n = number of points on the straight line, and
t = time of each observation, so that $S(t-\bar{t})^2$ is the sum of squares of deviations of t.

RESULTS

Dry weight. The first problem was to estimate the extent to which constant base-line conditions had been established from which radioactive fluxes and any changes produced by quinidine could be calculated. Since the measurements of ^{24}Na exchange, from which the extracellular space was to be calculated, extended over 1 hr, it was important to know whether any significant net changes in dry weight or in Na, K and H_2O content of the atria might be taking place during this time. The procedures described enabled these changes to be estimated independently. Goodford (1959), in a previous set of experiments under similar conditions, had found that atria which had been beating for 1 min had a dry weight of 161·3 g/kg wet wt., and atria which had been beating for 1 hr had an identical dry weight. All the atria in Goodford's experiments had been set up in Locke's solution at 35° C and allowed to beat, but in the present series measurements were made in addition on 'fresh' atria, i.e. which were set aside immediately after dissection at room temperature, and had not, therefore, been beating in warm solution at all. In this group the dry weight was 168·2 ± 2·1 g/kg fresh wt. The dry weight of atria allowed to beat for 1 hr, expressed as g/kg of original fresh wt, was 154·1 ± 1·3. The difference of 14·1 g/kg between the fresh and 1 hr groups was significant ($P < 0.001$). Atria allowed to beat for 3 hr, however, lost only a further 2·6 g/kg fresh wt. in the control series and 1·8 g/kg in the quinidine series; these additional losses were not significant ($P < 0.6 > 0.5$ and $P < 0.8 > 0.7$ respectively). During the fourth hour there were also small insignificant losses of dry weight, similar in both series. From this evidence it would appear that there was an immediate loss, largely in the first

minute after the atria started beating, of about 14 g/kg fresh wt. (or 7 % of the dry weight) of some solid material (perhaps debris from the dissection, red blood corpuscles, plasma, etc.). Thereafter there may have been a small but steady loss of about 1 %/hr, too small to reach the level of statistical significance, and unaffected by quinidine. From the point of view of the loss of dry weight material, therefore, it has been concluded that the changes detected, being small and similar in the two series, could not have affected significantly any of the factors from which the calculations of intracellular Na and K concentrations have been made.

Loss of water and K. During the first hour there was a mean loss of 0·068 g/kg fresh wt. (or 1·77 m-mole) of K, and a mean loss of 20·3 g/kg fresh wt. of water. If the K had been lost as isotonic solution it would have been accompanied by 11·6 ml. H_2O, leaving a loss of 8·6 ml./kg unaccounted for, which is less than the accumulated standard error of the measurements from which the loss was deduced (Table 1). There was thus no significant difference between the K contents of the fresh atria ($65{\cdot}64 \pm 0{\cdot}59$) and of the 1 hr groups ($66{\cdot}15 \pm 0{\cdot}84$) when expressed as m-mole K/kg wet wt. (i.e. the resultant weight after the losses had occurred), since the K loss was balanced by an equivalent water loss. Either group could, therefore, have been taken as a control for calculating changes in K content. As mentioned above, however, the dry weight/kg fresh wt. at 1 hr was significantly different from the dry weight of fresh atria, but not from the dry weight at 3 and 4 hr. For this reason the measurements made on the 11 atria which had been beating in control solution for 1 hr were taken as the base-line controls.

The atria beating in control solution for 3–3¼ hr lost a further 72·0 ml. H_2O/kg fresh wt., and 7·8 m-mole K, in comparison with the 1 hr group, and these differences were statistically significant. The K lost must have come from inside the muscle fibres, for if this amount of K had been lost as extracellular fluid it would have been accompanied by 1·44 l. H_2O. If the K was lost as isotonic K, it would have been accompanied by 52·0 ml. H_2O, leaving a loss of 20 ml. H_2O in association with unidentified material, an amount greater by a third than the accumulated standard error. Similarly there was a small, but statistically significant, loss of K and water from 1–3 hr in the quinidine series, of 3·42 m-mole K and 53·7 ml. H_2O respectively. Moreover the difference between these K losses in the two series of 4·38 m-mole (7·8–3·42) was significant ($P < 0{\cdot}02 > 0{\cdot}01$, with standard errors as given in Table 1; since this included the standard error of the 1 hr sample, from which both individual differences were calculated, twice, the true significance was $P < 0{\cdot}001$).

The control atria were thus losing K and water faster than those in quinidine. Admittedly the difference in the resultant K contents at 3 hr

of the control (62·94 ± 0·59 m-mole/kg wet wt.) and quinidine series (66·43 ± 0·62) was only 6·6 %, and showed that quinidine, after acting in fairly high concentration for 2 hr, so far from producing a change in the K content of the atria, enabled the normal K content to be preserved. Nevertheless, the fact that so small a difference was statistically significant indicated that measurements had been made on an adequate number of atria.

TABLE 1

Time (hr)		Change in K content (m-mole/kg fresh wt.)	Change in H_2O content (g/kg fresh wt.)	Additional H_2O (g/kg fresh wt.)	Estimated extracellular space (ml./kg fresh wt.)
0–1	C*	$-1·77 \pm 1·24$	$-20·3 \pm 11·3$	$-8·6 \pm 14·0$	—
1–3	C	$-7·80 \pm 1·24$	$-72·0 \pm 12·4$	$-20·0 \pm 15·0$	434 ± 9
1–3	Q	$-3·42 \pm 1·29$	$-53·7 \pm 12·9$	$-30·9 \pm 15·5$	420 ± 6

Losses of K and H_2O from 1 kg of fresh muscle. The H_2O loss not accounted for as isotonic K (= 'additional' H_2O) could not have introduced a serious error into the estimate of extracellular space.

* C = control, Q = quinidine.

These results, with the accumulated standard errors, have been summarized in Table 1. Some conclusions regarding the stability of conditions in the two series may be drawn from the evidence. During the first hour there was a significant loss of about 7 % of some unidentified solid material. There may also have been a loss of rather less than 2 m-mole isotonic KCl, and less than 10 ml. of additional water/kg. From 1 to 3 hr the atria were losing isotonic KCl at about 4 m-mole/hr in the control series, and less than 2 m-mole/hr in the quinidine series, plus some additional loss of 10 to 15 ml./hr of water in both series.

A steady loss of water over 1 hr could have introduced an error into the estimate of the extracellular space, and so of the intracellular K. The magnitude of the maximum amount of such an error can be obtained from Table 1. The greatest loss unaccounted for as isotonic KCl was from the quinidine 3 hr sample of 30·9 ± 15·5 ml. H_2O/kg over 2 hr, giving limits of 7·75 and 23·25 ml./hr. Even the upper of these limits is only 5 % of the estimated extracellular space. It has, therefore, been concluded that net changes of H_2O and K did not introduce any serious error into the estimate of the extracellular space or intracellular K concentration.

Na and K content. The Na and K contents of the various groups of atria, expressed as m-mole/kg wet wt., have been plotted in Fig. 1. The K content of the quinidine series was unchanged throughout, but there was a small but significant fall in the K content of the control series between 1 and 3 hr. The Na contents similarly varied very little, and there was a small increase of Na content of the control series, corresponding to the K loss.

The variation between the individual Na observations, however, was greater, so that this rise in Na content was not statistically significant.

Exchange of ^{24}*Na*. The exchange of ^{24}Na between radioactive solution and the atria immersed in it is illustrated in Fig. 2. There was an initial rapid exchange when the atria were transferred to the radioactive solution and this was followed by a slower phase of uptake. Observations on atria immersed for 1 and 3 min indicated that almost 50 % of the muscle sodium had exchanged within the first 2 min, and showed no significant difference between the control atria and those treated with quinidine. If the initial rate had been maintained, more than 95 % would have exchanged by

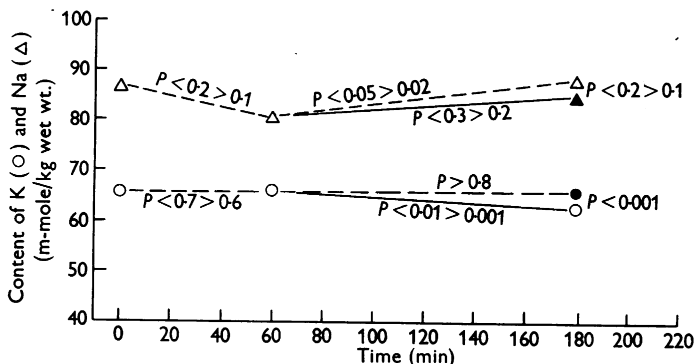

Fig. 1. Effect of quinidine on K and Na content. Exposure to quinidine (solid points) prevented the small but highly significant loss of K observed in the control atria (open points). The *P* figures show the significance of the differences between the points indicated. There was a small gain in Na in the control atria corresponding to the loss of K, but it was not statistically significant.

15 min (dotted line in Fig. 2). In fact, however, the specific activity of the atria was only 76 % of that of the bathing solution at 15 min and 83 % after 1 hr. There was again no statistically significant difference between the two series.

Calculation of the extracellular space. The results have been used to determine the proportion of the atrial sodium which exchanged so rapidly that it approached an equilibrium with the bathing solution before the 15 min observations, and which might be the sodium in the extracellular space. The proportion could not exceed the 76 % which was actually observed to have exchanged at 15 min, but this figure would include some exchange which had also been taking place at the slower rate within the first 15 min. This was corrected for by assuming a linear regression for the slower rate and extrapolating back to the moment of immersion in tracer solution (solid and interrupted lines, Fig. 2), and calculating the intercept and its standard error. Although the regressions were slightly different in the

control and quinidine series, the intercepts were almost identical (top of Table 2), suggesting that the proportion of muscle sodium exchanging rapidly was similar in each series. The sodium content and water content of the groups were also similar (Table 2), and the extracellular water was calculated on the assumption that the rapidly exchanging sodium was dis-

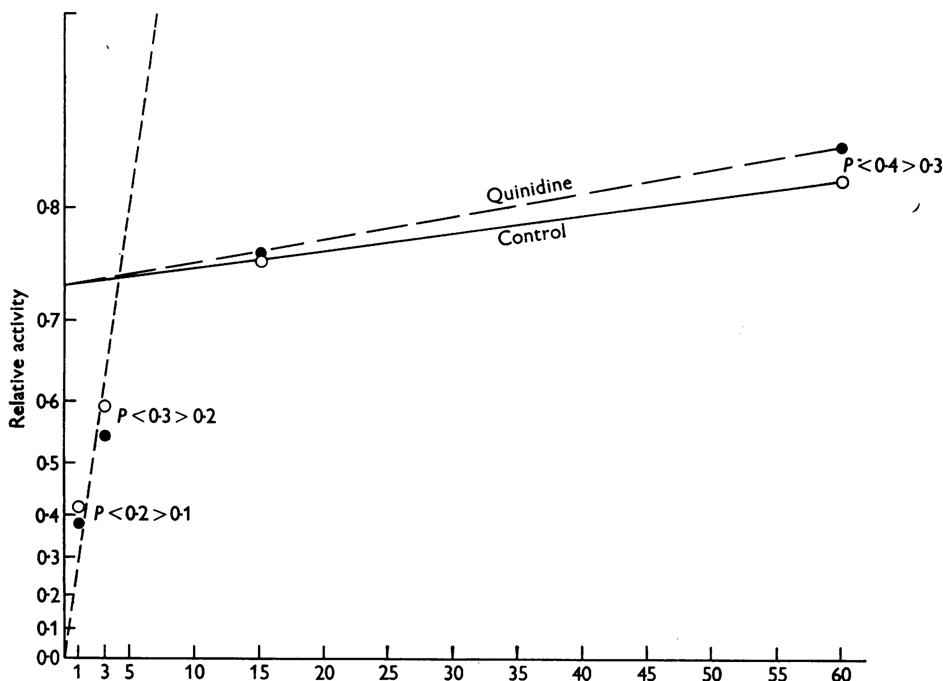

Fig. 2. Exchange of ^{24}Na. Ordinate, ratio of the specific activity of the sodium in whole atria (i.e. intracellular + extracellular sodium) to the specific activity of the sodium in the bathing solution. Abscissa: time after transfer to radioactive solution. ○, control series; ●, quinidine series. Extrapolation of fast phase (dotted line) implies that the rapid part of exchange would have been complete within 15 min. Extrapolation of slow phase to zero time suggests that the proportion of the total sodium from which the slow exchange started was similar in the two series. The *P* values show the significance of the differences between the points indicated.

solved in it in free solution at the same concentration as in the bathing fluid. (The Na in the bathing solution was 150 mM). Barclay, Hamley & Houghton (1960) estimated the extracellular space of rat atria at 21–25 %, and the space of guinea-pig atria has been put at 26 % by Goodford & Lüllmann (1962). Rayner & Weatherall (1957) found the inulin space of rabbit atria to be 441 ml./kg wet wt., agreeing with the figures of 434 and 420 ml./kg wet wt., which we have found in control and quinidine-treated atria respectively. It has been pointed out that different values can be

obtained for the extracellular space when different methods have been used to dry muscles, so that it is important to use the same drying method when determining the extracellular space and when determining the sodium and potassium contents.

TABLE 2

Observations and calculations of various properties of atria which had been beating in control solution for 180–195 min or in control solution for 60 min and in quinidine 6×10^{-6} for 120–135 min

	Control	Quinidine
Rapidly exchanging Na (%)	73·91 ± 0·71	73·90 ± 0·76
Na content (m-mole/kg wet wt.)	88·09 ± 1·52	85·20 ± 0·93
K content (m-mole/kg wet wt.)	62·94 ± 0·59	66·43 ± 0·62
Water content (g/kg wet wt.)	831·3 ± 1·8	833·1 ± 1·8
Extracellular water (g/kg wet wt.)	434·0 ± 8·6	419·8 ± 6·3
Intracellular water (g/kg wet wt.)	397·3 ± 8·8	413·3 ± 6·6
Intracellular Na concn. (mM)	57·87 ± 5·2	53·80 ± 3·5
Na equilibrium potential (mV)	24·61 ± 2·21	26·50 ± 1·62
Intracellular K concn. (mM)	152·41 ± 1·08	155·15 ± 1·02
K equilibrium potential (mV)	85·83 ± 0·61	86·29 ± 0·49

Intracellular sodium. About 57 % of the water and 25 % of the muscle sodium have still to be considered, and might be intracellular since this sodium exchanged much more slowly with the radioactive solution. The intracellular concentration of sodium would then be about a third of the concentration in the bathing solution, and the sodium equilibrium potential would be 24·61 ± 2·21 mV for the control atria and 26·5 ± 1·62 mV for those treated with quinidine. In a previous paper (Vaughan Williams, 1958*a*) it was suggested that the overshoot of normal atria was less than the sodium equilibrium potential, but approached more closely towards it if the resting potential was hyperpolarized by acetylcholine, thus increasing the availability of the mechanism carrying depolarizing current (Weidmann, 1955). It is of interest, therefore, that the calculated equilibrium potential is a few millivolts higher than the mean overshoot of normal atria, but similar to the values observed in the presence of ACh. Similarly, the calculated K equilibrium potential agrees well with the observed upper limit for the resting potential when hyperpolarized by ACh.

DISCUSSION

Antifibrillatory drugs raise the threshold to stimulation of cardiac muscle, and prolong the effective refractory period. The suggestion that the latter effect could be due to a prolongation of the duration of the action potential was not borne out by the evidence (Wedd, Blair & Gosselin, 1942; Vaughan Williams, 1958*b*; Szekeres & Vaughan Williams, 1962). Burn (1960) considered the possibility that, even if quinidine had little effect at normal frequency the action potential might be prolonged under the special condition of high-frequency excitation, when the action poten-

tials were short, as seen in fibrillation. West & Amory (1960), however, found the reverse to be true. At high frequencies the action potential was not prolonged, and it was not until the frequency had been dropped (by destruction of the pace-maker) below the spontaneous frequency that a significant prolongation of the action potential by quinidine could be demonstrated. Even then the prolongation of repolarization was only a small fraction of the increase in the effective refractory period.

Antifibrillatory drugs have in common the property of greatly slowing the rate of rise of the action potential, and reducing conduction velocity. It may be, therefore, that they interfere in some way with the mechanism by which depolarizing charge is carried across the membrane. This would explain not only the prolongation of the effective refractory period, because repolarization would have to proceed further before sufficient carrier was available to permit the development of a self-propagating current, but also the increase in threshold, since the inactivation of carrier would be analogous to accommodation. A decrease in the rate of depolarization could be produced in several ways, for example by a fall in the resting diastolic potential (Weidmann, 1955), but none of the antifibrillatory drugs studied affected the resting potential. This accords well with the present finding that quinidine did not change the intracellular K; on the contrary the control atria showed a slight fall in intracellular concentration over 3 hr, but not those in quinidine. It has been suggested on other grounds (Vaughan Williams, 1958*a*, 1959*b*) that the metabolic factors controlling ionic transfer and contraction may share a common energy source. The atria in quinidine were beating less vigorously than the controls, and may thus have had more energy available for conserving the intracellular K.

Another reason for a slower rate of rise of the action potential, if this be due to inward Na current, could be an inhibition of the Na extrusion process, with a resultant intracellular accumulation of Na and reduced concentration difference across the membrane. The evidence presented here has shown that it is probable that the intracellular Na was not changed at all by quinidine (Table 2). The tenfold reduction in the rate of rise produced by 2 hr exposure to quinidine (Vaughan Williams, unpublished) cannot, therefore, be attributed to an accumulation of intracellular sodium. Any group of compounds able to block excitation without being energetically 'expensive' by increasing ionic fluxes or causing non-specific metabolic inhibition has some general interest. Interference with depolarization in the absence of any net change in intracellular cationic concentration may account for the low toxicity of antifibrillatory agents and their close relations, local anaesthetics. A substance with specific activity of this kind could perform admirably as an inhibitory transmitter in the

central nervous system, and for this reason the high antifibrillatory activity of serpajmaline is of special interest (Vaughan Williams & Szekeres, 1961).

SUMMARY

1. The Na and K content, and the rate of exchange of ^{24}Na were determined in normal atria, and in atria which had been exposed to quinidine 6×10^{-6} (w/v) for 2 hr.

2. From the results the extracellular sodium space was calculated to be $434 \pm 8{\cdot}6$ ml./kg wet wt. and the intracellular Na and K concentrations to be $57{\cdot}87 \pm 5{\cdot}2$ mM and $152{\cdot}41 \pm 1{\cdot}08$ mM respectively in atria which had been beating in control solution for 3 hr. The corresponding figures for atria exposed to quinidine were $419{\cdot}8 \pm 6{\cdot}3$ ml./kg wet wt., $53{\cdot}80 \pm 3{\cdot}5$ mM and $155{\cdot}15 \pm 1{\cdot}02$ mM.

3. The calculated Na and K equilibrium potentials were $24{\cdot}61 \pm 2{\cdot}21$ and $85{\cdot}83 \pm 0{\cdot}61$ mV in the controls, and $26{\cdot}50 \pm 1{\cdot}62$ and $86{\cdot}29 \pm 0{\cdot}49$ mV in the quinidine series.

4. The small loss of potassium in the control series as compared with treated atria was statistically significant ($P < 0{\cdot}001$), and it was apparent that quinidine, so far from changing intracellular K, actually enabled the original concentration to be maintained.

5. It was concluded that the antifibrillatory action of quinidine could not be attributed to the production of changes in intracellular concentrations of either Na or K.

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