Interactions of Lanatoside C and Potassium on Atrioventricular Conduction in Rabbits
By Yoshio Watanabe, M.D., and Leonard S. Dreifus, M.D.

ABSTRACT
Intra-atrial, intranodal and His-Purkinje conduction times were determined in perfused rabbit hearts. In one series, the concentration of lanatoside C was increased by 0.4 mg/liter every 30 minutes, in the presence of normal (4.5) or high (7.5) K+ in the perfusion fluid. At high (K+) the glycoside produced a greater increase in intra-atrial and His-Purkinje conduction times but caused a smaller increase of intranodal conduction time than at normal (K+). Second-degree A-V block always occurred intranodally, but the incidence was lower with high (K+). In another series, (K+) was increased by 3 mm every 30 minutes, in the absence or presence (0.4, 0.8 or 1.2 mg/liter) of lanatoside C. No difference was seen between hearts treated with lanatoside C and those untreated at the level of (K+) producing failure of conduction. At all levels of glycoside, conduction delay caused by high (K+) was greatest within the atria, less in the His-Purkinje system and insignificant within the A-V node. Intra-atrial and His-Purkinje block were observed but never an intranodal block. It is concluded that (1) cardiac glycoside and high (K+) primarily affect different regions of the A-V conducting system, and (2) aggravation of glycoside-induced A-V block by high (K+) may result from additional intra-atrial and His-Purkinje block rather than from further depression of intranodal conduction. Electrophysiological mechanisms underlying these interactions were also discussed.

ADDITIONAL KEY WORDS
intranodal conduction  His-Purkinje conduction  second-degree A-V block
intra-atrial conduction  perfused rabbit heart

Although the literature contains many reports concerning the interrelationship of cardiac glycosides and potassium, some clinical (1-4) and experimental (5-8) papers dealing with the specific interaction in atrioventricular (A-V) transmission report divergent and confusing conclusions. Several investigators reported that potassium improved A-V conduction in digitalized patients (2); others observed further depression (1, 4). Friedman and Bine, using embryonic duck hearts, demonstrated the protective effects of potassium against digitalis-induced A-V block (5). Fisch and his co-workers hypothesized that potassium may improve A-V conduction in the presence of incomplete digitalization but aggravate A-V block when toxic amounts of glycoside are present (3, 6). Since we have previously demonstrated that cardiac glycoside and potassium primarily affect different portions of the A-V conducting system, and (2) aggravation of glycoside-induced A-V block by high (K+) may result from additional intra-atrial and His-Purkinje block rather than from further depression of intranodal conduction. Electrophysiological mechanisms underlying these interactions were also discussed.

Methods
The experiments were carried out in isolated, perfused rabbit hearts, using techniques of isolation and perfusion reported previously (11). We used a modified Chenoweth's solution of the following composition in millimoles per liter: NaCl, 119.8; KCl, 4.5; CaCl2, 2.4; MgCl2, 2.1; NaHCO3, 25.0; and dextrose, 10.0. The perfusion fluid was saturated with 95% O2 plus 5% CO2, and was recycled through the heart.

A ventricular electrogram was recorded by two small surface electrodes attached to the right
ventricular apex and the left ventricular base. A small bipolar electrode with an interelectrode distance of 1 mm was attached adjacent to the S-A node to record an atrial electrogram. The preparation was driven at a constant rate by square-wave pulses of twice threshold intensity through a bipolar stimulating electrode placed near the recording atrial electrode. The rate of stimulation in individual hearts was set 10 to 15 beats/min higher than the intrinsic sinus rate. Glass microelectrodes were used to record transmembrane potentials from various regions of the A-V junction, particularly from perinodal atrial fibers and fibers in the distal NH (node-His) region. The potentials were amplified by a neutralized input capacity amplifier and Tektronix amplifiers. A Grass camera was used to photograph tracings on a Tektronix oscilloscope.

In this way we identified three components of the total A-V interval: (1) intra-atrial conduction time ($A$), the interval between the activation of the S-A nodal area and depolarization of the perinodal atrial fibers; (2) intranodal conduction time ($N$), the interval between depolarization of perinodal atrial and distal NH fibers; and (3) His-Purkinje conduction time ($HP$), the interval from depolarization of distal NH region to the onset of the ventricular electrogram.

In the first series of experiments, ten hearts were perfused with a normal potassium concentration (4.5 mM), and ten other hearts were perfused with a high potassium concentration (7.5 mM). After a control period of 30 minutes, desacetyl lanatoside C was added to the perfusate of both groups in a concentration of 0.4 mg/liter. The concentration was increased every 30 minutes in increments of 0.4 mg/liter until either second-degree A-V block occurred or the heart was perfused for at least 30 minutes with a solution with a glycoside concentration of 1.6 mg/liter. Obviously the actual concentration of lanatoside C should be slightly lower than these figures after prolonged perfusion, although the amount of glycoside taken up by the rabbit heart is probably small.

In the second series of experiments, the effects of increased potassium concentrations on A-V transmission were studied in four groups of five hearts each, differing only in the amount of glycoside administered. Group I received no lanatoside C. In groups 2, 3, and 4, lanatoside C was added to the perfusate in initial concentrations of 0.4, 0.8, and 1.2 mg/liter, respectively. Potassium concentration in the perfusate was then increased by 3 mM every 30 minutes in every group, until either failure of atrial response or second-degree A-V block was observed.

Comparison of the amount of cardiac glycoside or potassium administered by the end of individual experiments was made in terms of concentration-duration index. This index for lanatoside C (mg • liter$^{-1}$ • h) was calculated by adding the products of the concentration of lanatoside C (in mg/liter) and the duration of perfusion (in hours) for each period of perfusion at different concentrations. Likewise, the concentration-duration index of potassium (mM • hr) was calculated by adding the products of the potassium concentration (in mM) and the duration of perfusion (in hours) for each period of perfusion at different concentrations.

In both series of experiments, repeated determinations of intra-atrial, intranodal, and His-Purkinje conduction times were made. When second-degree A-V block developed, serial records were obtained from each heart to study where propagation failed as well as the A-V conduction ratios. Mean conduction times during the control period were compared with the conduction times immediately before the termination of the experiment in individual hearts, and the changes were statistically analyzed in each group using paired Student's t-test (Tables 1 and 2). Statistical comparison between the two groups was made by unpaired t-test, unless otherwise specified.

Results

Effects of Increasing Lanatoside C Concentration in the Presence of Normal vs. High Potassium

In six of the ten hearts perfused with normal potassium concentration (4.5 mM), a stepwise increase in the concentration of lanatoside C caused second-degree A-V block (Table 1). The block developed at a glycoside concentration of 0.8 mg/liter in one heart, at 1.2 mg/liter in two hearts, and at 1.6 mg/liter in the other three. The remaining four hearts perfused with a fluid with a normal potassium concentration did not develop second-degree A-V block after 2 hours of perfusion with lanatoside C with final concentration of 1.6 mg/liter. The concentration-duration index of lanatoside C in the normal potassium group was $1.52 \pm 0.17$ mg • liter$^{-1}$ • h (mean ± standard error). In the second group of ten hearts perfused with a solution having a high potassium concentration (7.5 mM), only one heart developed second-degree A-V block at a glycoside concentration of 1.6 mg/liter. The other nine hearts maintained 1:1 A-V transmission after 2 hours of perfusion with lanatoside C with this final concentration. The concentration-duration index of lanatoside C was calculated by adding the products of the concentration of lanatoside C (in mg/liter) and the duration of perfusion (in hours) for each period of perfusion at different concentrations.
TABLE 1

Changes in Conduction Time in Isolated, Perfused Rabbit Hearts Caused by Lanatoside C when Potassium Concentration was Normal or High

<table>
<thead>
<tr>
<th>K Concentration (mM)</th>
<th>Rate of Atrial Stimulation (beats/min)</th>
<th>Concentration-Duration Index of Lanatoside C (mg • liter⁻¹ • hr⁻¹)</th>
<th>Incidence of 2nd Degree A-V Block</th>
<th>Conduction Time* (msec)</th>
<th>% Change</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (4.5)</td>
<td>151.0 ± 6.56</td>
<td>1.52 ± 0.17</td>
<td>6/10</td>
<td>Control 31.8 ± 8.65</td>
<td>+ 28.7%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lanatoside C 38.3 ± 9.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HP 36.7 ± 3.24</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A-V 96.2 ± 3.63</td>
<td></td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>High (7.5)</td>
<td>159.7 ± 6.29</td>
<td>1.95 ± 0.05</td>
<td>1/10</td>
<td>Control 40.5 ± 4.74</td>
<td>+ 78.1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lanatoside C 44.7 ± 4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HP 46.0 ± 1.28</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A-V 96.9 ± 1.81</td>
<td></td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

A = intra-atrial, N = intranodal, HP = His-Purkinje, and A-V = total atrioventricular conduction time. These conduction times were measured during control period (Control) and immediately before the development of second-degree A-V block or at the termination of experiment (lanatoside C).

* Mean of 10 hearts ± standard error.

† Calculated by paired Student's *t*-test.

in this group was 1.95 ± 0.05 mg • liter⁻¹ • h. This was significantly different (P < 0.05) from the same index in the normal potassium group (1.52 ± 0.17). The incidence of second-degree A-V block (6 of 10 vs. 1 of 10) was also significantly different between these two groups at 5% level, by direct calculation of probability (Fischer). Hence, in the presence of high potassium concentration, the heart appears to tolerate a higher dosage of cardiac glycoside without the failure of A-V conduction.

Changes in the A-V conduction time produced by lanatoside C showed certain differences when normal and high potassium groups were compared (Table 1). The rate of atrial stimulation and the A-V conduction time during control perfusion were similar for both groups. With normal concentration of potassium, lanatoside C prolonged the A-V interval from 98.2% to 133.0 msec. This was predominantly due to a significant increase (by 78.1%) of the intranodal conduction time (P < 0.01). The intra-atrial and His-Purkinje conduction times were also slightly prolonged but the changes were not significant (P > 0.05 and P > 0.1, respectively). In contrast, in the presence of high concentration of potassium, lanatoside C at higher dosages yielded a smaller increase (47.0%) in the intranodal conduction time.

The difference between the increase in the intranodal conduction time when the potassium concentration was normal or high was not statistically significant. However, it should be noted that, in those hearts that developed second-degree A-V block, the intranodal conduction time immediately before the onset of block had to be used for statistical analyses. On the other hand, the intra-atrial and His-Purkinje conduction times were also significantly prolonged by lanatoside C (P < 0.01) in those hearts perfused with solution with a high concentration of potassium. The increase in the His-Purkinje conduction time was significantly different between the normal group and that with high concentration of potassium (P < 0.05). Although prolongation of the total A-V interval by the glycoside was similar during normal and high potassium perfusions, conduction was depressed only within the A-V node in the former but moderate conduction delay was produced in all three portions of the A-V transmission system in the latter.

In addition to the seven hearts (six in group 1 and one in group 2) that showed failure of A-V transmission, we also studied records of second-degree A-V block obtained from five
hearts in an earlier series of experiments (9). Of these 12 hearts, lanatoside C caused failure of propagation only within the A-V node (N and NH regions) in nine hearts perfused with normal and two with high concentration of potassium. In one heart, perfused with high concentration of potassium, the glycoside caused both intranodal and intra-atrial block. Except for the instances of 2:1 A-V conduction, the glycoside commonly produced type I (Wenckebach type) second-degree A-V block, with progressive prolongation of the A-V interval (9). We compared conduction ratios of these instances, in terms of normal and high concentration level of potassium. In nine hearts perfused with normal concentration of potassium, a total of 531 conducted beats were recorded but 232 beats were blocked, yielding a ratio of conducted beats to blocked beats of 2.29:1. This implies that roughly every third beat is blocked in episodes of Wenckebach periodicity in the presence of normal potassium. On the other hand, in three hearts perfused with a high concentration of potassium, 310 conducted beats were recorded and 59 beats were blocked. The ratio of 5.25:1 implies that only every sixth beat is blocked. Hence, each episode of Wenckebach periodicity is generally longer in the group with high concentration of potassium than in the group with normal concentration.

In one heart perfused with a solution having a normal concentration of potassium, lanatoside C produced an intermittent ventricular tachycardia which interrupted the periods of second-degree A-V block. Two other hearts in the group with normal concentration of potassium were excluded from the study, as the glycoside, in a concentration of 1.6 mg/liter, caused ventricular fibrillation before termination of the experiment. Neither ventricular tachycardia nor fibrillation was observed in the group with high concentration of potassium.

EFFECTS OF INCREASING POTASSIUM CONCENTRATION WITH AND WITHOUT LANATOSIDE C

In this series of experiments, potassium concentration in the perfusate was increased by an increment of 3 mM every 30 minutes. Group 1 received no glycoside, but groups 2, 3, and 4 received 0.4, 0.8, or 1.2 mg/liter of lanatoside C, respectively, at the beginning of control perfusion. Each group consisted of five hearts. The end-point of an experiment was either a failure of atrial response with stimuli 10 x stronger than the diastolic threshold requirement during the control period, or the development of second-degree A-V block in the presence of successful atrial response (Fig. 1). As seen in this figure, lanatoside C in varying concentrations does not appear to facilitate failure of atrial response or of A-V transmission caused by increasing concentrations of potassium. Failure of atrial response commonly occurred at a potassium level of 13.5 mM and usually resulted in a slower sinus rhythm taking over the control of the atria.

The prolongation of conduction time in individual portions of the A-V transmission system caused by high concentration of potassium is compared in the four groups (Table 2). Lanatoside C in concentrations of 0.4-1.2 mg/liter did not reduce the total potassium concentration required to produce failure of either atrial response or 1:1 A-V conduction. In all four groups, the total A-V
LANATOSIDE C AND POTASSIUM ON A-V CONDUCTION

Changes in Conduction Time in Isolated, Perfused Rabbit Hearts Caused by High Concentration of K, in the Absence and Presence of Lonatoside C

<table>
<thead>
<tr>
<th>Concentration of lonatoside C (mg/liter)</th>
<th>Rate of atrial stimulation* (beats/min)</th>
<th>Concentration-duration index of K* (mM &quot; hr -1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>163.2 ± 6.66</td>
<td>9.97 ± 1.14</td>
</tr>
<tr>
<td>0.4</td>
<td>156.8 ± 9.89</td>
<td>8.85 ± 1.56</td>
</tr>
<tr>
<td>0.8</td>
<td>164.8 ± 7.53</td>
<td>9.49 ± 1.10</td>
</tr>
<tr>
<td>1.2</td>
<td>168.6 ± 9.38</td>
<td>10.71 ± 0.38</td>
</tr>
</tbody>
</table>

Conduction time* (Control) and High concentration of K:

Control

<table>
<thead>
<tr>
<th>A</th>
<th>N</th>
<th>HP</th>
<th>A-V</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0 ± 2.85</td>
<td>33.6 ± 1.72</td>
<td>36.2 ± 2.69</td>
<td>94.8 ± 2.65</td>
</tr>
<tr>
<td>30.2 ± 4.71</td>
<td>37.6 ± 5.01</td>
<td>39.2 ± 1.93</td>
<td>107.0 ± 7.71</td>
</tr>
</tbody>
</table>

High concentration of K

<table>
<thead>
<tr>
<th>A</th>
<th>N</th>
<th>HP</th>
<th>A-V</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.8 ± 12.66</td>
<td>37.8 ± 1.86</td>
<td>59.6 ± 7.30</td>
<td>154.2 ± 18.41</td>
</tr>
<tr>
<td>58.8 ± 9.14</td>
<td>45.6 ± 9.68</td>
<td>59.6 ± 6.41</td>
<td>163.6 ± 19.56</td>
</tr>
</tbody>
</table>

% Change

+119.5 + 13.3 + 67.7 + 59.4 + 96.8 + 17.8 + 52.4 + 56.6 + 93.7 + 11.6 + 58.2 + 49.9 + 166.7 + 11.9 + 43.2 + 60.4

P < 0.05

In five hearts (two without and three with lonatoside C), occasional failure of A-V transmission developed in the presence of regular activation of the S-A nodal region at a potassium concentration of 13.5 mM (Fig. 1). In these instances, conduction failure was located between the S-A and A-V nodes (or within the atria) in three hearts and below the A-V node (probably in the His-Purkinje system) in the other two. Failure of propagation within the A-V node was not observed in these 20 hearts perfused with solutions having a high concentration of potassium. In these instances, conduction failure was noted in the SA region, however, the action potential of A-V nodal fibers and the ventricular electrogram were not recorded following every other atrial beat.

In summary, the results of this study confirm the previous observations (10). Statistical comparison of all the variables listed in Table 2 between any two groups showed no significant difference.

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Examples of intra-atrial block (top) and subnodal block (bottom) due to a high concentration of potassium. SA, electrogram from the S-A nodal region; V, ventricular electrogram. A (atrial) and NH (node-His) represent transmembrane potentials of an atrial fiber near the A-V node and of a distal NH fiber, respectively. Voltage calibration applies only to transmembrane potentials. See text for discussion.

stimuli, due to intra-atrial block. In this instance, recording of transmembrane potentials from various portions of the right atrium showed that excitation of the S-A nodal region induced by electrical stimuli was propagated only 6 to 7 mm toward the A-V node and then became less in the blocked beats. On the other hand, the lower portion of Figure 2 shows an example of subnodal (His-Purkinje) block caused by high concentration of potassium. Stimulation of the S-A nodal area is followed by a full depolarization of the distal NH fiber close to the His bundle, indicating that normal intranodal conduction is maintained. However, ventricular excitation does not occur after the third and the seventh action potentials, resulting in 3:2 and 4:3 conduction ratios below the A-V node. The bizarre and progressively widened ventricular electrogram suggests a marked delay in His-Purkinje conduction.

Discussion

Our previous studies have demonstrated that lanatoside C almost selectively depresses conduction across the A-V node, with little delay in intra-atrial and His-Purkinje transmission (9). In another series of experiments, high concentration of potassium was shown to slow intra-atrial and subnodal conduction (10). Potassium in high concentrations appeared to provide protective action for intranodal conduction rather than to produce any deleterious effects (10). Similar effects of potassium were reported earlier by Fues de Carvalho and Langan (12). These observations suggest that elevated concentration of potassium may counteract the depressing action of cardiac glycosides on intranodal transmission, but could cause additional conduction delay above and below the A-V node. The present study supports these concepts.

In the hearts perfused with a high concentration of potassium (7.5 mM), the incidence of second-degree A-V block due to lanatoside C was one out of ten, a significantly lower incidence than the six out of ten experiencing block at a normal concentration of potassium (4.5 mM). Furthermore, lanatoside C at high dosages appeared to produce a smaller increase of intranodal conduction time (47.0%) with high concentration of potassium than with normal concentration (78.1%), although this difference was not statistically significant (Table 1). The development of second-degree A-V block was not necessarily preceded by a more marked prolongation of the intranodal conduction time. This fact may explain a higher incidence of A-V block in the group with normal concentration of potassium, with no significant difference in the prolongation of the intranodal conduction time between the groups with normal and high concentrations of potassium. Even when second-degree A-V block developed, the ratio of conducted beats to blocked beats was higher (5.25:1) in the higher concentration group than in the normal group (2.29:1), implying less frequent occurrence of propagation failure in the former. Thus, high concentration of potassium in the perfusate protected against depression of intranodal conduction by lanatoside C.

On the other hand, a stepwise increase in potassium concentration prolonged the intra-atrial and subnodal conduction times notably, both with and without lanatoside C (Table 2). Most commonly (15 out of 20 hearts), the atrial muscle became inexcitable, resulting in
failure of atrial response, before second-degree A-V block occurred (Fig. 1). In the remaining five hearts, however, failure of A-V transmission developed at a potassium concentration of 13.5 mM. The block was never within the A-V node, being within the atria in three hearts and below the A-V node in the other two. This is in sharp contrast to the exclusively intranodal block produced by the glycoside. Nevertheless, despite its protective effect on intranodal conduction, high concentration of potassium can cause prolongation of A-V interval (first-degree A-V block) or failure of propagation (second-degree A-V block).

The contrasting effects of cardiac glycosides and potassium on specific regions of the A-V transmission system can be explained by the following electrophysiological findings. We have demonstrated that the characteristically low amplitude and upstroke velocity of the action potentials from N region of the A-V node are further decreased by lanatoside C. The rate of depolarization in NH fibers also appeared decreased. Hence, greater decrease and failure of propagation may result within the A-V node. In contrast, high concentration of potassium was shown to cause a significant increase in the action potential amplitude of the N and NH fibers (10). This effect is most likely responsible for the apparent protection of intranodal conduction by perfusion with a solution having a high concentration of potassium against the depressing action of lanatoside C (Table 1).

On the other hand, several investigators reported some decrease in the amplitude of the action potential and the rate of depolarization in Purkinje fibers caused by cardiac glycosides (13-15). These changes could lead to a slower conduction velocity in this tissue. However, prolongation of the His-Purkinje conduction time by lanatoside C was not significant in the presence of normal concentration of potassium (Table 1). Different experimental conditions in earlier reports as compared to this study may explain this discrepancy. Nevertheless, the depressing effect of the cardiac glycoside on His-Purkinje conduction appears minor. High concentration of potassium also was shown to decrease the resting potential of Purkinje fibers (16). Prolongation of the His-Purkinje conduction time with occasional subnodal block produced by high concentration of potassium (Table 2, Fig 2) can be explained on this basis. When a large amount of glycoside is administered in the presence of elevated concentrations of potassium, minor depressing effect of glycoside on His-Purkinje conduction may be superimposed on the more marked depression of conduction by potassium. A significant prolongation of the His-Purkinje conduction time by lanatoside C in the group with high concentration of potassium (Table 1) probably resulted from this interaction. Additive effects of lanatoside C and high concentration of potassium on ventricular action potentials were also reported earlier (17).

Regarding intra-atrial conduction, DeMello and Hoffman reported that high concentration of potassium caused loss of excitability in ordinary atrial muscle when action potentials were still recorded from the sinus and A-V nodes as well as other specialized fibers of the atria (18). The selective sensitivity to potassium of the atrial specialized tissues and atrial muscle fibers resulted in “sinoventricular conduction” in the absence of electrocardiographic P waves (18). More recently, Sano et al. showed that so-called sinoatrial block due to high concentration of potassium was actually intra-atrial block (20). Our present results are in agreement with these reports. On the other hand, cardiac glycoside produced no change in the size and shape of atrial action potentials at a dose engendering a positive inotropic effect (21). The action potential amplitude was decreased only at toxic levels of strophanthin associated with decreased contractility. Hence, significant prolongation of intra-atrial conduction time by lanatoside C seen only in the group with high concentration of potassium (Table 1) can be attributed to the effect of potassium alone. Evidence that cardiac glycoside itself does not markedly depress intra-atrial and His-Purkinje conduction is also supplied in our second series of experiments, as potassium-induced
prolongation of conduction time in these regions did not show a significant difference between hearts with or without lanatoside C (Table 2).

Some considerations must be given to the underlying ionic movements responsible for these electrophysiological effects of cardiac glycoside and potassium. Various cardiac glycosides, in addition to their effects suggesting a reduction of inward sodium current during phase 0 depolarization (17, 22, 23), have been shown to cause a loss of intracellular potassium (24, 25). The effects of altered extracellular potassium concentrations on intracellular potassium appear more complex (26). However, it can be argued that the net flux of potassium in media with high concentration of potassium may depend upon the balance between a decreased driving force for the outward potassium movement (due to decreased transmembrane gradient) and an increased membrane conductance to potassium (gK). Following elevation of the extracellular potassium concentration, a steady state of potassium flux may be re-established at a higher intracellular potassium concentration. On the other hand, high concentration of potassium decreases the sodium current during phase 0 depolarization through a reduction of transmembrane resting potential (27). Hence, it appears that cardiac glycoside and high concentration of potassium show opposite effects on intracellular potassium concentration while possessing similar action on sodium current during rapid depolarization.

Based on these and other observations, it is postulated that a change in net potassium flux rather than in excitatory sodium current may play a major role in controlling the action potential characteristics and conduction within the A-V node, particularly in the N region. A more detailed discussion of this concept has been presented elsewhere (28). Nevertheless, the interactions of cardiac glycoside and potassium on A-V conduction may be explained as follows:

Cardiac glycoside causes a loss of intracellular potassium, which adversely affects the action potential and conduction within the A-V node. High concentration of potassium could antagonize this action by preventing this loss of potassium. This could improve intranodal conduction. In the atrial and His-Purkinje fibers where excitatory sodium current dominates the depolarization process during phase 0, high concentration of potassium decreases the upstroke velocity of the action potential and slows conduction. Similar but apparently minor action of cardiac glycoside on these fibers could be superimposed on such potassium effect, and may further depress conduction. When conduction across the most crucial N region of the A-V node is improved by elevation of potassium concentration, second-degree A-V block due to glycoside may be prevented or abolished. The A-V interval may also be shortened, provided that intra-atrial and His-Purkinje conduction delay caused by high concentration of potassium does not negate the improvement in intranodal conduction. Previous experimental (5) and clinical (2) studies reporting beneficial effect of potassium administration on digitalis-induced A-V conduction disturbances appear to be in keeping with this explanation.

In the present study, lanatoside C in concentrations of 0.4 to 1.2 mg/liter did not facilitate second-degree A-V block produced by high concentration of potassium (Fig. 1, Table 2). In contrast, Fisch et al. (7) reported that smaller amounts of potassium were required to produce A-V block in digitalis-intoxicated animals than in undigitalized animals. A more rapid elevation of the plasma potassium level following infusion of this cation in digitalis-intoxicated animals was suggested as a possible mechanism (7). Indeed, the often transient nature of various electrophysiological effects (3, 8) suggests that the rate of change is more important than absolute values of extracellular potassium concentration in this interaction.

This concept of the rate of change in potassium concentration in intact animals can be combined with the results of the present study to explain how digitalis-induced A-V block is aggravated by potassium administration (1, 3, 4, 7). If intranodal conduction is
severely depressed by "toxic" doses of cardiac glycoside, the beneficial effect of elevated potassium concentration may be insufficient to restore 1:1 conduction across the crucial N region of the A-V node. Thus, intranodal block may continue. On the other hand, if infusion of potassium in "digitalis intoxication" really causes an unusually rapid elevation of plasma potassium concentration (7), this would result in additional conduction delay and block within the atria or His-Purkinje system, or both. In this regard, the observations of Fisch et al. (3) can be validated: potassium may aggravate A-V block in digitalis-intoxicated patients but may improve A-V conduction in patients receiving smaller amounts of glycoside.

Since cardiac glycosides increase diastolic depolarization in His-Purkinje fibers (13-15), and since the resultant loss of membrane potential could cause a decreased rate of phase 0 depolarization and slower conduction velocity (29), suppression of automaticity by high concentration of potassium may sometimes improve His-Purkinje conduction (30). However, it has been pointed out that, in the presence of severe conduction disturbance in the more proximal portion of the A-V transmission system (e.g., A-V node), such suppression of His-Purkinje automaticity may result in the abolition of subsidiary pacemakers and ventricular standstill (31). This is another reason why great caution must be exercised in the administration of potassium in patients with A-V block and possible digitalis excess.

Finally, it should be emphasized that potassium probably does not further depress intranodal conduction, even in digitalis-intoxicated hearts. Furthermore, the individual behavior of intra-atrial, intranodal and His-Purkinje transmission must be precisely defined in any future discussion of A-V conduction disturbances.

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