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ECG Changes After Rabbit Coronavirus Infection

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Abstract: This study examines the electrocardiographic (ECG) changes following rabbit coronavirus (RbCV) infection. We have shown that infection with RbCV results in the development of myocarditis and congestive heart failure and that some survivors of RbCV infection go on to develop dilated cardiomyopathy in the chronic phase. Serial ECGs were recorded on 31 RbCV-infected rabbits. Measurements of heart rate; P-R interval; QRS duration; QTc interval; and P-, QRS-, and T-wave voltages were taken. The recordings were also examined for disturbances of conduction, rhythm, and repolarization. The acute and subacute phases were characterized by sinus tachycardia with depressed R- and T-wave voltages as well as disturbances of conduction, rhythm, and repolarization. In most animals in the chronic phase, the sinus rate returned to near-baseline values with resolution of the QRS voltage changes. The ECG changes observed during RbCV infection are similar to the spectrum of interval/segment abnormalities, rhythm disturbances, conduction defects, and myocardial pathology seen in human myocarditis, heart failure, and dilated cardiomyopathy. Because animals often died suddenly in the absence of severe clinical signs of congestive heart failure during the acute phase, RbCV infection may increase ventricular vulnerability, resulting in sudden cardiac death. RbCV infection may provide a rare opportunity to study sudden cardiac death in an animal model in which the ventricle is capable of supporting ventricular fibrillation, and invasive techniques monitoring cardiac function can be performed. Key words: coronavirus, myocarditis, heart failure, ECG.
Viral infection of the heart can lead to myocarditis, dilated cardiomyopathy, progressive heart failure, and sudden cardiac death (1,2). Myocarditis is thought to develop in approximately 2 to 5% of patients following acute viral infection (3,4). The diagnosis of viral myocarditis is problematic due to the lack of definitive clinical signs and the paucity of sensitive diagnostic tests (1). Diagnosis can be further complicated by the variable time course of progression of viral myocarditis, with clinically unapparent viral infection (even early in childhood), potentially resulting in dilated cardiomyopathy weeks, months, or even years later (5). Rapidly accumulating evidence based on nucleic acid hybridization and other molecular techniques supports the hypothesis that cardiotropic viruses play an important role in the pathogenesis of myocarditis and dilated cardiomyopathy (6–10). Difficulties inherent in diagnosing and studying the pathogenesis of viral myocarditis have prevented an accurate assessment of the prevalence of virus-induced heart disease in the human population.

Animal models of viral myocarditis offer a valuable opportunity to study the complex interactions between virus and host with respect to both viral infection and the pathogenesis of virus-induced myocarditis and dilated cardiomyopathy. An appropriate animal model could provide useful clinical diagnostic markers for the disease and serve as a model for potential therapeutic intervention once the natural history of the infection is known. A good model should induce a reproducible spectrum of disease clinically similar to that observed in humans. Recently, our laboratory has described a model of viral myocarditis, congestive heart failure (CHF), and dilated cardiomyopathy in rabbits infected with rabbit coronavirus (RbCV). The RbCV model of myocarditis and dilated cardiomyopathy has been divided into acute, subacute, and chronic phases based on duration of survival after infection, clinical signs, and pathologic findings (11–13). Survivors of RbCV infection (chronic phase) have been further categorized into those exhibiting slight myocyte hypertrophy and those with moderate hypertrophy based on myocyte diameter measurements (13). The mechanism of death after infection is unclear, especially early in infection.

Electrocardiographic (ECG) changes associated with viral infection of the heart have been studied in animal models, primarily coxsackie B and encephalomyocarditis viruses in mice (14–17), although the effects of western equine encephalitis virus, influenza A virus, and pseudorabies virus infections in the heart have also been described (18–20). In an effort to further evaluate and characterize the RbCV model system, this study was designed to describe the ECG and pathologic changes associated with RbCV infection.

**Methods**

**Animals and Viral Infection**

Pathogen-free male New Zealand White rabbits (*Oryctolagus cuniculus*) (2.5 to 3.0 kg) were purchased from a commercial supplier (Robinson Services, Winston-Salem, North Carolina). All RbCV-infected rabbits were housed singly in biohazard containment cubicles at room temperature (21 to 24°C), given tap water ad libitum, and fed 150 g/day of a commercial rabbit diet (Agway, Grandville Milling, Creedmoor, North Carolina). Control rabbits were housed singly in a room separate from the infected rabbits. Thirty-one animals were inoculated intramuscularly with 0.2 mL of a RbCV stock containing $10^3$ to $10^4$ rabbit infectious dose/mL and observed daily for clinical signs of infection as previously described (12,13).

This study was approved by the Institutional Animal Care and Use Committee and was conducted in accordance with The Guide for Care and Use of Laboratory Animals (U.S. Department of Health and Human Services, NIH 86-23, revised 1985) and the guiding principles of the American Physiological Society. The University of North Carolina Animal Facility is fully accredited by the American Association of Laboratory Animal Care.

**Pathologic and Morphometric Studies**

Moribund animals (acute and subacute phases), survivors of RbCV infection (chronic phase), and uninfected controls were euthanized as previously described (12,13). The hearts, lungs, and livers of all animals were removed, weighed, and fixed in 10% phosphate-buffered formalin and processed as previously described (11,12,13). The mechanism of death after infection is unclear, especially early in infection.

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tal group or phase of infection. Morphometric measurements of the ventricular areas and wall thickness of the hearts of all animals were performed as previously described (13). Myocyte fiber diameters of all rabbits in the chronic group were measured as previously described (13).

**ECG Studies**

Serial ECGs were performed on 31 rabbits infected with RbCV and on six uninfected controls. ECGs were recorded using a direct ink recorder (Grass model 7B, Grass Instrument Company, Quincy, Massachusetts). Surface electrodes were preamplified by an alternating current-coupled ECG preamplifier (Grass model 7P4G) and a companion pen-driven direct current driver amplifier (Grass model 7DAG). Alternatively a three-channel microcomputer-augmented cardiograph II digital transmitter/recording unit (Marquette Electronics Inc., Milwaukee, Wisconsin) was used. With the Grass polygraph, leads I, II, III, V1, V2, V4, and V6 were recorded at 50 mm/s with the recorder calibrated to 1.0 mV/20 mm. With the microcomputer-augmented cardiograph I, leads I, II, III, aVR, aVL, aVF, V1, V2, V4, and V6 were recorded at both 25 and 50 mm/s, with the recorder calibrated to 1.0 mV/10 mm.

Unanesthetized rabbits (infected and controls) were held in an upright, slightly elevated position while ECGs were taken. All rabbits were acclimated to the recording procedure by collecting baseline ECGs daily for 5 days prior to infection. After infection, ECGs were recorded twice daily from day 3 through 12 and then at weekly intervals through day 30 on all animals surviving infection. Five chronically infected animals were observed through day 70 postinfection, and three surviving animals were observed through days 83, 97, 120, 130, 160, and 200 postinfection. ECGs were recorded on control rabbits through day 200 at the same intervals as infected animals.

ECG parameters measured included heart rate; PR interval; QRS duration; QT interval; and P-, QRS- and T-wave voltages. All measurements were made in lead II by two investigators (LKA, BLY) blinded to the animal’s experimental group or phase of infection, and a mean of four sinus-conducted beats was reported. The QT interval was corrected (QTc) for heart rate using three previously described methods. To assess whether the formulae commonly used to correct QT interval in humans and other species might be appropriately applied to rabbits, we plotted QTc as calculated by Bazett’s formula [QTc = QT/√(RR)] (22), by Van de Water et al.’s formula [QTc = QT - 87 (60/HR - 1)] (23), and the by the formula of Fredericia ([QTc = QT/(1 + √RR)] (24) against the RR intervals from normal rabbits over the range of heart rates available (160 to 300 by increments of 10 beats/min, 150 sets of RR vs. QTc intervals total; QTc = corrected QT interval, QT = QT interval, RR = RR interval, and HR = heart rate). In the rabbit, the various regression-corrected QTc values are more useful than the uncorrected data, although Bazett’s formula is also of some value for correcting changes based on heart rate (25). We subsequently utilized the correction formula resulting in the flattest slope (Van de Water) to assess the effect of infection on the QT interval, and verified the effect of infection by comparing QT intervals measured at similar heart rates before and after infection. In addition, ECG recordings were examined for disturbances of conduction, rhythm, and repolarization. All ECGs were interpreted by an investigator (BWK) not present at their recording and blinded to the animal’s experimental group or phase of infection.

**Statistical Analysis**

ECG measurements are presented as mean ± standard deviation (for continuous variables; for discrete variables, number affected/percent affected). Differences between baseline ECG measurements and those made during the course of infection were identified by a paired t-test (26). Comparisons of ECG parameters measured in animals that developed chronic myocarditis (survival > 12 days postinfection) with moderate versus slight myocyte hypertrophy were made by a two-sample t-test (26). A one-way analysis of variance was used to evaluate the statistical significance of differences in ECG measurements among the acute, subacute, and chronic groups.

**Results**

**Mortality and Course of RbCV Infection**

Of the 31 rabbits inoculated with RbCV stock, 10 (32%) died during the acute phase (days 2–5), and 7 (23%) died during the subacute phase (days 6–12) of infection. Fourteen animals (45%) survived into the chronic phase of infection and were euthanized and necropsied. Animals that died during the acute phase of infection often did so sud-
denly, without showing severe or moderate signs of heart failure. Clinical signs consistent with CHF (weakness, dyspnea, anorexia) were present in all animals that died during the subacute phase. All animals surviving into the chronic phase of infection were clinically asymptomatic at the time of euthanasia.

**Pathologic Findings**

Gross and microscopic findings in animals dying during the acute and subacute phases or sacrificed during the chronic phase were similar to those previously described (11,12,13).

The AV node was available for examination in five of the rabbits that died during the acute phase and four rabbits that died in the subacute phase. All of the AV nodes examined had evidence of edema and contained small to moderate numbers of macrophages and Anitschkow cells, and rarely a few heterophils—findings not present in any of the six control rabbits. Alteration of cellular architecture of the AV nodal tissue was always minimal, despite extensive degeneration in the adjacent myocardium (Fig. 1A–D). The AV nodes of six rabbits euthanized during the chronic phase were available for examination. All were unremarkable except for the presence of a few scattered lymphocytes.

**Morphometric Analysis**

Ventricular area and wall thickness measurements in animals during each phase of infection were consistent with earlier studies (12,13). Morphometric analysis of the hearts of animals surviving into the chronic phase of infection revealed

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**Fig. 1.** Histologic changes in the AV node and in the surrounding myocardium following rabbit coronavirus infection. (A) AV node on day 6 with infiltrate of histocytes and edema. Bar = 50 μm. (B) A high-power view of panel A. Bar = 25 μm. (C) Myocardium adjacent to AV node on day 6 as shown in panels A and B. Focal necrosis of myocytes with interstitial edema, histocytes, and heterophils. Bar = 25 μm. (D) The junction of the muscular and membranous portions of the interventricular septum in the vicinity of the AV node and His bundle on day 12. The myocardium has increased cellularity characterized predominantly by lymphocytes. The myocardium also contains two foci of necrosis and mineralization. Bar = 500 μm. All sections were stained with hematoxylin–eosin. AV, atrioventricular.
Table 1. Mean Baseline Electrocardiographic Measurements From 31 Infected Rabbits and 6 Control Rabbits

| Parameter          | Mean ± SD       | Range          |
|--------------------|-----------------|----------------|
| PR interval*       | .066 ± .007     | (.056-.08)     |
| QRS interval       | .036 ± .007     | (.02-.05)      |
| QT interval        | .139 ± .011     | (.12-.16)      |
| QTc interval§      | .273 ± .022     | (.23-.32)      |
| QTc interval¶      | .190 ± .012     | (.17-.24)      |
| P voltage||       | .098 ± .034    | (.04-.18)      |
| QRS voltage        | .388 ± .10      | (.22-.60)      |
| T voltage          | .252 ± .096     | (.10-.50)      |

* Duration in seconds.
† Mean ± SD.
‡ Range of measurements.
§ QT interval corrected for heart rate using Bazett’s formula (QTc = QT/(RR) (22).
¶ QT interval correction proposed by Van de Water et al. [QTc = QT – 87 (60/HR - 1)] (23).
|| Voltage in mV.

myocyte hypertrophy, characterized as slight (18.8 ± 0.75 μm, n = 9) or moderate (22.6 ± 1.7 μm, n = 5) as described previously (13). No animals had severe myocyte hypertrophy (>26 μm) in this study.

Baseline and Control ECG Findings

ECGs recorded prior to infection in the 31 rabbits and 6 control animals (days 0–200) demonstrated normal sinus rhythm with a mean heart rate of 232 ± 24 and 216 ± 18 beats/min, respectively. No significant differences were found between the two groups, and no disturbances of rhythm or conduction were observed in either group of animals. The baseline ECG parameters (Table 1) measured were consistent with previously reported values (22,27,28).

To assess whether the formulae commonly used to correct QT interval in humans and other species might be appropriately applied to rabbits, we plotted QTc as calculated by Bazett, Fredericia, and Van de Water versus RR intervals from normal rabbits over a wide range of heart rates to determine the effect of heart rate (RR interval) on QT interval (Table 2). To assess the correction of the QT interval at various heart rates, we also plotted the QTc by the various methods versus RR interval and constructed a linear regression line through the points. Over the range of heart rates available in normal rabbits, the Van de Water formula appeared superior to Bazett’s or Fredericia’s in correcting the QT interval, and the slope of the Van de Water line was closest to 0 (data not shown).

To verify that the QT interval did indeed prolong during RbCV infection and that this finding was not an artifact caused by inappropriate QT correction, QT intervals measured during periods of similar heart rates before (QTb, HRb) and after (QTa, HRa) RbCV infection were compared where available using the paired t-test. In nearly every instance in which such comparisons were available before and after infection in an individual animal, the QT was longer at a given heart rate postinfection (P < .001 by one-tail, paired t-test) (Table 3).

ECG Findings in the Acute Phase

The acute phase of RbCV infection (n = 31) was characterized by sinus tachycardia in 74% of the animals, with the fastest mean heart rates recorded on day 3 postinfection (277 ± 32 beats/min, P < .001 vs baseline). R-wave voltages were slightly depressed throughout the acute phase in 16% of the animals, reaching their nadir on day 3.

Table 2. QT Interval Correction in Rabbits

| HR Range | N(Obs)* | AVG QT† | AVG HR | VdwW‡ | Bazett|| Fredericia|
|----------|---------|---------|--------|-------|-------|-------|-------|
| <200     | 92      | 138.35  | 176.70 | 195.64| 237.25| 198.18|
| 200–220  | 78      | 133.88  | 204.18 | 195.88| 246.88| 201.32|
| 220–240  | 114     | 135.74  | 225.75 | 199.61| 263.27| 211.10|
| 240–260  | 66      | 133.08  | 244.62 | 198.73| 268.65| 212.56|
| 260–280  | 44      | 126.74  | 263.72 | 193.94| 265.70| 207.60|

* Number of observations.
† in milliseconds.
‡ Using van de Water et al. method (23).
§ Using Bazett method (22).
∥ Using Fredericia method (24).
Table 3. QT Interval Prolongation Associated With Rabbit Coronavirus Infection

| Animal Number | QTB† | HRb† | HRb/QTb† | QTP‡ | HRp‡ | HRp/QTp‡ | (HRb/QTb)-(HRp/QT) |
|---------------|------|------|----------|------|------|----------|---------------------|
| 41            | 140  | 290  | 2.07     | 130  | 290  | 2.23     | -0.16               |
| A59           | 110  | 260  | 2.36     | 110  | 260  | 2.36     | 0.00                |
| 1304          | 100  | 260  | 2.60     | 140  | 260  | 1.86     | 0.74                |
| A56           | 130  | 250  | 1.92     | 160  | 250  | 1.56     | 0.36                |
| 62            | 160  | 200  | 1.25     | 160  | 200  | 1.25     | 0.00                |
| X83           | 140  | 280  | 2.00     | 150  | 280  | 1.87     | 0.13                |
| 1293          | 110  | 220  | 2.00     | 140  | 220  | 1.57     | 0.43                |
| 1301          | 120  | 280  | 2.33     | 130  | 280  | 2.15     | 0.18                |
| 1301*         | 150  | 200  | 1.33     | 170  | 200  | 1.18     | 0.16                |
| 1302          | 120  | 320  | 2.67     | 130  | 320  | 2.46     | 0.21                |
| 1302*         | 130  | 260  | 2.00     | 140  | 260  | 1.86     | 0.14                |
| 14            | 120  | 260  | 2.17     | 150  | 260  | 1.73     | 0.43                |
| 14*           | 140  | 240  | 1.71     | 140  | 240  | 1.71     | 0.00                |
| 14*           | 130  | 220  | 1.69     | 140  | 220  | 1.57     | 0.12                |
| 21            | 150  | 200  | 1.33     | 160  | 200  | 1.25     | 0.08                |
| 53            | 140  | 200  | 1.43     | 150  | 200  | 1.33     | 0.10                |
| 53*           | 140  | 230  | 1.64     | 150  | 230  | 1.53     | 0.11                |
| 71            | 150  | 260  | 1.73     | 170  | 260  | 1.53     | 0.20                |
| 84            | 150  | 190  | 1.27     | 150  | 190  | 1.27     | 0.00                |
| X88           | 150  | 240  | 1.60     | 160  | 240  | 1.50     | 0.10                |
| 1299          | 130  | 210  | 1.62     | 160  | 210  | 1.31     | 0.30                |
| 1300          | 150  | 240  | 1.60     | 150  | 240  | 1.60     | 0.00                |
| 1300*         | 150  | 220  | 1.47     | 160  | 220  | 1.38     | 0.09                |

* Measurements at different times/days.
† Measurements taken prior to infection and QT values are in milliseconds.
‡ Measurements taken postinfection and QT values are in milliseconds.

postinfection (mean R-wave voltage = 0.28 ± .09 mV, P < .001 vs baseline) (Figs. 2, 3). T-wave voltages were reduced throughout the acute phase in 45% of the rabbits, with the lowest mean voltage (0.11 ± 0.12 mV) recorded on day 5 postinfection, (P < .001 vs baseline). Other abnormalities observed during the acute phase included: QTc prolongation (32 to 42%), low-grade Mobitz type II 2° AV block (13%), ventricular premature complexes (10%), electrical alternans (10%), right bundle branch block (7%), supraventricular premature complexes (7%), and 1° AV block (3%) (Table 4, Fig. 4). Occasional ventricular premature complexes were observed in two animals with borderline QTc prolongation.

Among those animals that died in the acute phase of infection (n = 10), ECG abnormalities also included sinus tachycardia (70%) and decreased voltage of T waves (40%). Right bundle branch block and ventricular premature complexes were detected in two animals each prior to death (20%). ST-segment depression, QRS prolongation, and QTc prolongation were detected in one animal each (10%) prior to death during the acute phase. There were no significant differences identified between ECG parameters measured in animals dying in the acute phase and those animals surviving into the subacute and chronic phases.

Fig. 2. Baseline (day 0) and serial electrocardiograms of a rabbit infected with rabbit coronavirus between days 0 and 49. All recordings shown are in lead II. 50 mm/sec. 1 mV = 10 mm.
ECG Findings in the Subacute Phase

The subacute phase (n = 21) was marked by persistent sinus tachycardia in 90% of the animals, with the highest mean heart rate recorded on day 6 after infection (271 ± 24 beats/min vs baseline, P < .001). During the subacute phase, the mean heart rate decreased slowly in animals that survived, returning to baseline by day 13 (232 ± 53 beats/min) for most animals. Mean R-wave voltage decreased significantly during the subacute phase (62%) with the mean low voltage (0.23 ± 0.1 mV, P < .001 vs baseline) occurring on day 8 postinfection. After day 8, the mean voltage began to rise, and by day 13 had returned to near normal (0.32 ± 0.13 mV) for most animals (Figs. 2, 3). T-wave voltages were also reduced in 95% of the animals and generally paralleled the R-wave voltage changes during the subacute phase. The lowest T-wave mean voltage occurred on day 7 after infection (0.08 ± 0.07 mV vs baseline, P < .001). Many animals in the subacute phase of infection had prolongation of the QTc interval (43% to 89%), QRS duration (29%), and PR interval (29%). Occasional supraventricular tachyarrhythmias (10%) were seen and 2° AV block (19%) persisted in two animals and developed in two others, while one animal displayed isolated ventricular depolarizations (5%) (Table 4, Fig. 4).

Among animals that died in the subacute phase of infection (n = 7), ECG changes consisted of sinus tachycardia (71%), decreased voltage of T waves (86%), 1° AV block (29%), 2° AV block (29%), decreased voltage of R waves (29%), and electrical alternans (14%). There were no significant differences between ECG parameters measured in animals that died in the subacute phase and those animals that survived.

ECG Findings in the Chronic Phase

The chronic phase (n = 14) was characterized by the return of the sinus rate to near-baseline values
Table 4. Electrocardiographic Changes in 31 Rabbits After Infection With Rabbit Coronavirus

| Electrocardiographic Changes | Acute (2–5 days) | Subacute (6–12 days) | Chronic (13–200 days) |
|------------------------------|------------------|----------------------|-----------------------|
| Interval/segment abnormalities|                  |                      |                       |
| QRS prolongation†            | 4 (13%)          | 6 (29%)              | 2 (14%)               |
| QTc prolongation‡            | 10 (32%)         | 9 (43%)              | 4 (29%)               |
| QTc prolongation§            | 15 (42%)         | 17 (78%)             | 11 (80%)              |
| ST segment                   |                  |                      |                       |
| Depression                   | 1 (3%)           | 0 (0%)               | 3 (21%)               |
| T wave depression            | 14 (45%)         | 20 (95%)             | 8 (57%)               |
| R wave depression            | 5 (16%)          | 13 (62%)             | 7 (50%)               |
| Electrical alternans         | 3 (10%)          | 3 (14%)              | 0 (0%)                |
| Rhythm disturbances          |                  |                      |                       |
| Ventricular premature complexes| 3 (10%)         | 3 (15%)              | 1 (7%)                |
| Supraventricular premature complexes | 2 (7%) | 2 (10%)              | 2 (14%)               |
| Sinus arrhythmia             | 0 (0%)           | 0 (0%)               | 4 (29%)               |
| Sinus tachycardia            | 23 (74%)         | 19 (90%)             | 7 (50%)               |
| Conduction defects           |                  |                      |                       |
| 1° AV block‡                 | 1 (3%)           | 6 (29%)              | 5 (36%)               |
| 2° AV block (Mobitz type II) | 4 (13%)          | 4 (19%)              | 1 (7%)                |
| Right bundle branch block    | 2 (7%)           | 0 (0%)               | 0 (0%)                |

* Number of animals at beginning of each phase.
† Interval is increased above each animal's baseline measurement; typically 0.036 sec.
‡ Interval is >0.32 s as calculated by Bazett's formula [QTc = QT/√RR].
§ PR interval is >0.08 s.
‡ Two SD above the baseline QTc interval as calculated proposed by Van de Water et al. [QTc = QT – 87 (60/HR – 1) (23)].
AV, atrioventricular.

Discussion

ECG Findings in the Acute Phase

ECG observations (sinus tachycardia, QRS and decreased voltage of T waves, ST-segment changes, and ventricular and occasional supraventricular ec-
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ECG Findings in the Subacute Phase

The most frequent ECG findings in the subacute phase of RbCV infection (T waves, QTc prolongation, and sinus tachycardia with low-voltage QRS complexes) were compatible with the findings of...
myocarditis and pleural effusion. These ECG findings are comparable to the variety and type of changes seen in humans with myocarditis and heart failure as well as those observed in other animal models of myocarditis and CHF (14,15,18, 40,46–48). Taken together, the ECG and pathologic findings suggest that the primary cause of death in the subacute phase of RbCV infection was heart failure.

First and low-grade 2° AV block were also commonly seen in the subacute phase. In some animals with AV block, edema and inflammatory infiltration of the AV node and surrounding myocardium were observed. In humans, inflammatory infiltration of the conduction system is believed to be the cause of death in some cases of fatal myocarditis (43,45). It has also been suggested that electrical instability of the ventricular myocardium due to damage to the cardiac sympathetic nerves may lead to prolongation of the QTc interval, which can result in potentially fatal ventricular arrhythmias (36,38).

**ECG Findings in the Chronic Phase**

In most survivors of the acute and subacute phases of infection, the heart rate and QRS voltages returned to normal for most animals by day 30 after infection. This was probably due to the resolution of both the acute viral myocarditis and the resultant clinical signs of heart failure. The chronic phase of infection was characterized histopathologically by hypertrophy of the remaining cardiac myocytes and resolution of the myocardial edema, findings similar to those reported following encephalomyocarditis infection (15). Some ECG abnormalities seen during the chronic phase (decreased voltage of T waves, 1° AV block and QTc prolongation, QRS prolongation, ST-segment elevation, and supraventricular ectopy) probably reflect the ongoing, presumably chronic myocarditis observed histologically.

In the chronic group judged morphometrically to have moderate myocyte hypertrophy, the dilatation and eccentric hypertrophy of the left and right ventricle in the absence of valvular or vascular lesions suggests the development of dilated cardiomyopathy (15,39,49–51). Fibrosis, myocyte hypertrophy, and persistent myocarditis are associated with ventricular conduction delays in dilated cardiomyopathy (50), producing ECG changes similar to those observed in the chronic phase of RbCV infection. Both PR interval (1° AV block) and QRS prolongation were accompanied by microscopic myocardial fibrosis as well as the presence of persistent myocarditis and myocyte hypertrophy. Despite the ECG and histopathologic abnormalities, rabbits in the chronic phase did not have clinical or gross pathologic signs of heart failure, possibly reminiscent of asymptomatic human patients with cardiomegaly and nonspecific ECG abnormalities in whom the possibility of previous acute viral myocarditis has been raised (38).

**Conclusions**

The ECG and pathologic findings associated with RbCV infection are consistent with changes seen in humans and are similar in many respects to other animal models of viral myocarditis. Not surprisingly, the resting ECG was a relatively insensitive and nonspecific indicator of the presence and severity of RbCV-induced myocarditis, although the ECG and pathologic findings suggest that RbCV infection may increase ventricular vulnerability. RbCV infection may provide a rare opportunity to study a reproducible model of sudden cardiac death associated with viral infection in a species large enough to easily monitor the heart rate, rhythm, and function. Continuous telemetered or ambulatory ECG monitoring will be needed to completely disclose the ECG changes associated with RbCV-induced sudden cardiac death, myocarditis, and dilated cardiomyopathy.

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