Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression

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Grippo, Angela J., Claudia M. Santos, Ralph F. Johnson, Terry G. Beltz, James B. Martins, Robert B. Felder, and Alan Kim Johnson. Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression. Am J Physiol Heart Circ Physiol 286: H619–H626, 2004;10.1152/ajpheart.00450.2003.—Depression is an important public health problem and is considered to be an independent risk factor for coronary artery disease. The pathophysiological mechanisms that link depression with adverse cardiovascular events (e.g., myocardial ischemia, myocardial infarction, and sudden death) are not well established. It is possible that an increased susceptibility to life-threatening cardiac arrhythmias in depressed patients influences the risk of morbidity and mortality in coronary artery disease. This idea was tested with the use of an experimental model of depression that was developed to induce anhedonia, the reduced responsiveness to pleasurable stimuli observed in human depressed patients. Rats exposed to 4 wk of chronic mild stress (e.g., paired housing, strobe light, and white noise) displayed anhedonia, which was operationally defined by the reduced intake of a palatable sucrose solution relative to an established baseline and to control animals. Furthermore, compared with control rats, the anhedonic rats showed increased basal heart rate and decreased heart rate variability. In response to an intravenously infused chemical challenge, aconitine, anhedonic rats exhibited an increased vulnerability to ventricular arrhythmias, as indicated by a reduced threshold for premature ventricular complexes, salvos, and ventricular tachycardia. These findings suggest that the presence of depressive symptoms is associated with a lower threshold for ventricular arrhythmias, which may contribute to the increased risk for adverse cardiovascular events in patients with depression.

A conitine; animal models; chronic mild stress; coronary artery disease; electrocardiogram; heart rate variability; rats

Psychological depression is a common mood disorder that affects 2–3% of males and 5–9% of females at any single point in time (1). This condition is considered the leading cause of disability worldwide (quantified by years lived with a disease) and is exceeded only by coronary artery disease as the leading cause of disability in the United States (25). In addition to the impact that depression has on the population, this mood disorder is also considered a risk factor for coronary artery disease (8). The prevalence of depression in patients with coronary artery disease (e.g., myocardial infarction and heart failure) is ~5 times that of the general population (37). Major depression is a significant predictor of mortality after myocardial infarction (8, 9). Its predictive ability on subsequent cardiovascular events, for example, myocardial infarction, arrhythmias, isch-
argued that the CMS model of depression has a high degree of predictive, face, and construct validity (46). Previously, we have shown elevated resting HR, reduced HR variability, exaggerated pressor and HR responses to a novel environmental stressor, and elevated sympathetic tone in rats exposed to 4 wk of CMS (11, 14). This animal model has also been used to study behavioral and physiological changes associated with depression (6, 10, 48), central nervous system mechanisms (27), and treatments for depressive disorders (17, 26).

In the present study, we have used the CMS model to examine a potential link between experimental anhedonia and the susceptibility to ventricular arrhythmias in rats. The current protocol employed a chemical challenge, aconitine, in rats exposed to CMS. Aconitine is arrhythmogenic in cardiac myocytes due to enhanced sodium influx into myocardial cells on both depolarization and repolarization and as a result of an increase in active Na⁺ current during depolarization (32). The utility of aconitine for the study of electrocardiographic activity is well documented. This drug has been used experimentally in anesthetized rats to investigate the vulnerability to ventricular arrhythmias as well as the efficacy of antiarrhythmic drugs (2, 18, 30, 40).

Previous work by Verrier and colleagues (7, 19, 21) and Skinner et al. (38, 39) has investigated the cardiac vulnerability in large animals, such as dogs and pigs, and has evaluated the effects of acute stressors that evoked short-lived emotional changes (e.g., akin to anger or fear). The study of ventricular function in the rat allows for testing hypotheses relating to behavioral changes associated with mood and physiological mechanisms of depression and cardiovascular function.

METHODS

Animals

Twenty-five male Sprague-Dawley rats (Harlan; Indianapolis, IN), weighing 300–400 g, were used for the experimental procedures. Rats were allowed 1 wk to acclimate to the surroundings before any experimentation began. Animals were housed in individual plastic cages with bedding. Food (Purina Rat Chow 5012) and tap water were available ad libitum for the duration of the experiments unless otherwise noted. Sucrose solution (1.0% w/v) was available ad libitum for 1 wk before the experimental procedures to allow for adaptation to the taste of the sucrose. Sucrose was monitored daily to verify that all rats were sampling the solution. The temperature in the rat colony was maintained at 22 ± 2°C. The light cycle was held at 12:12 h, with lights on at 6 AM, unless otherwise noted. All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the American Physiological Society’s “Guiding Principles for Research Involving Animals and Human Subjects” and were approved by the University of Iowa Institutional Animal Care and Use Committee.

General Experimental Paradigm

The details for each procedure are described in Specific Experimental Procedures. After adaptation to the animal colony, 13 of the rats were exposed to 4 wk of CMS and 12 of the rats were assigned to a control group. To operationally define anhedonia, sucrose preference tests were conducted before the onset of CMS and immediately after its termination. Three days after the CMS period, all rats were instrumented with a femoral vein catheter and two intramuscular recording electrodes. While under an Equithesin-like anesthetic, the rats were connected to a data-acquisition system for the electrocardiogram (ECG) recording. The anesthetized rats were tested for vulnerability to ventricular arrhythmias produced by an intravenous infusion of the arrhythmogenic drug aconitine.

Specific Experimental Procedures

CMS. In the CMS group, anhedonia was produced by the CMS protocol using a slight variation of methods described previously (11, 14). Briefly, the CMS group was exposed to the following mild stressors each week in random order: 1) continuous overnight illumination (two 12-h periods), 40° cage tilt along the vertical axis (one 7-h period); 2) paired housing (one 7-h period and one 48-h period); 3) soiled cage (300 mL of water spilled on bedding for one 12-h period); 4) exposure to an empty water bottle immediately after a period of acute water deprivation (17-h period of water deprivation and 1-h period of empty water bottle); 5) strobescopic illumination (300 flashes/min; one 4-h period and one 6-h period); and 6) white noise (one 5-h period). The CMS procedure was carried out for a total of 4 wk. Control animals were left undisturbed in their home cages with the exception of routine handling (i.e., regular cage cleaning and measuring of body weight), which was matched to that of the CMS group.

Sucrose preference tests. Sucrose preference tests were employed to operationally define anhedonia. Anhedonia was specifically defined as a reduction in absolute sucrose intake and sucrose preference relative to a control group and preestablished baseline values. A sucrose preference test consisted of first removing the food and water (at 2 PM) from each rat’s cage for a period of 20 h. At 10 AM the next day, water and 1.0% sucrose were placed on the cages in preweighed glass bottles, and animals were allowed to consume the fluids for 1 h. The bottles were then removed and weighed. One preference test was conducted before beginning CMS (baseline) and one preference test was conducted after 4 wk of CMS.

Catheter and electrode preparation. Surgical procedures were conducted under an Equithesin-like anesthetic (composed of 0.97 g pentobarbital sodium and 4.25 g chloral hydrate/100 mL distilled water; 0.35 mL/100 g body wt; University of Iowa Hospital Pharmacy, Iowa City, IA) with the use of aseptic techniques. A polyethylene (PE-10 fused to PE-50) catheter was inserted into the abdominal vena cava via the left femoral vein. The catheter was filled with heparinized saline (200 U/mL). In a subset of rats, a second catheter was inserted into the aorta via the left femoral artery for the purpose of arterial pressure measurements. Immediately after this preparation, animals were implanted with two insulated wires (20 cm length, 2.03 mm internal diameter; lead II) for the recording of ECG. The skin was incised above the muscle in the right foreleg and the left hindleg. The wires were attached to the muscles with a nonabsorbable suture.

ECG testing and aconitine administration. ECG testing was performed while the rat was anesthetized immediately after the surgical preparation. Aconitine suppresses respiration and is toxic to cardiac myocytes (20, 35, 40); therefore, the animals were anesthetized rather than conscious. The rat was placed inside a grounded Faraday cage to shield electrical noise. The electrodes were connected to an ECG amplifier (Grass-Telefactor; W. Warwick, RI), which was attached to a PowerLab data-acquisition system (ADInstruments; Mountain View, CA). The analog input was acquired at a rate of 200 samples/s. Care was taken to ensure that each rat was anesthetized with a standardized dosage of an Equithesin-like anesthetic so that the level of respiration was similar across all animals. A measure of resting (baseline) ECG was recorded for 2–5 min.

All rats that participated in the behavioral tests were tested for arrhythmias in response to aconitine but were separated into two subgroups for the ECG tests. In one subset of rats (n = 5 CMS and 4 control), aconitine (Sigma Chemical Co; St. Louis, MO) was administered via constant intravenous infusion at a dose of 5 μg·kg⁻¹·min⁻¹ for 7–9 min. ECG activity was recorded continuously during drug infusion and for 2–5 min after discontinuation of the drug. The drug dosage...
was chosen for its capacity to produce experimental ventricular arrhythmias in rats according to previously reported results (40). This first subgroup was used to determine a sufficient amount of aconitine to produce PVCs, and therefore only PVCs were recorded in these rats.

On the basis of the data recorded from the first subgroup of rats, the remaining rats in each group \((n = 8\) CMS and 8 control) were exposed to exactly 35 \(\mu g/kg\) of intravenous aconitine delivered at 5 \(\mu g/kg\) \(\text{min}^{-1}\). ECG activity was recorded continuously during drug infusion and for 10–20 min after discontinuation of the drug. Because aconitine appears to be nonreversibly toxic without further intervention, anesthetized animals were euthanized with an overdose of pentobarbital sodium (50 mg/rat iv; Abbott Laboratories; Chicago, IL) at the end of the protocol.

**Arterial pressure recordings.** Arterial pressure was monitored in a subset of rats from each group \((n = 3\) CMS and 3 control rats). Catheters were connected to a pressure transducer (Maxxim Medical; Athens, TX) coupled to a multichannel recorder through a custom-designed amplifier for the recording of arterial pressure. The analog input was converted into a digital signal using a PowerLab data-acquisition system. This program permits sampling of hemodynamic data with a computer. Mean arterial pressure (MAP) was derived electronically using a low-pass filter, set at 100 Hz, and was calculated online using the cyclic mean. The sampling rate was 200 samples/s.

**Data Analysis**

Values are presented as means \(\pm SE\) for the indicated analyses and figures. For all statistical tests reported herein, a probability value of \(P < 0.05\) was considered to be statistically significant. Water and sucrose bottles from the 1-h sucrose preference tests were weighed to determine the amount of fluid consumed (in grams). Data from the preference tests were analyzed using mixed-design ANOVA (one factor for independent groups and one repeated-measures factor) and Student’s \(t\)-tests where appropriate. Body weight was statistically analyzed with a mixed-design ANOVA and Student’s \(t\)-tests.

Baseline electrocardiographic parameters were calculated from the data recorded before aconitine administration (baseline). HR was calculated from the raw data recording by measuring the number of heartbeats triggered from the ECG waveform using PowerLab data-analysis device. Mean values were statistically compared in CMS and control rats using Student’s \(t\)-test. An index of HR variability was calculated by taking the standard deviation of all R-R intervals (in ms) from the raw ECG waveform during a 2- to 5-min segment for each rat [SDNN index, as described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (42)]. These segments of data were scored with a custom-designed macro. A mean SDNN index was calculated from these individual values and compared with the use of Student’s \(t\)-test. MAP was calculated from the arterial pressure waveform and compared with the use of Student’s \(t\)-tests. For blood pressure calculations, care was taken not to include any data during a period of changing or unstable blood pressure. For HR and HR variability calculations, care was taken not to include data during periods of unstable HR.

Classification of arrhythmias was based on the Lambeth Conventions (45; see Table 1). Six classes of arrhythmias were determined for each rat: none (normal rhythmic activity with a P wave), PVC (a nonrecurring QRS complex that is not associated with a P wave), a series of PVC sequences with alternating P waves, with a minimum sequence of P, PVC, P, PVC, PVC, and PVC, bigeminy (a series of at least two PVC sequences with corresponding QRS complexes, with a minimum sequence of P, QRS, PVC, P, PVC, PVC, and PVC), salvo (a series of two or three PVCs for each P wave corresponding QRS complex, with a minimum sequence of P, QRS, PVC, P, PVC, and PVC), ventricular tachycardia (VT; a run of four or more premature QRS complexes not to be distinguished from one another and for which a rate can no longer be measured).

| PVC, premature ventricular complex. See Ref. 45 for details about Lambeth conventions. |

<table>
<thead>
<tr>
<th>Convention</th>
<th>Definition</th>
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<tr>
<td>Isolated ventricular</td>
<td>A discrete and identifiable premature QRS complex (premature with respect to the P wave).</td>
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<tr>
<td>premature beat/PVC</td>
<td>A variant of ventricular premature beats characterized by the following minimum sequence: P, QRS, PVC, P, QRS. PVC.</td>
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<tr>
<td>Bigeminy</td>
<td>A run of four or more premature QRS complexes: not to be defined in terms of its rate or the prevailing sinus rate.</td>
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<tr>
<td>Salvo</td>
<td>A signal for which individual QRS deflections can no longer be distinguished from one another and for which a rate can no longer be measured.</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>A run of four or more premature QRS complexes; not to be defined in terms of its rate or the prevailing sinus rate.</td>
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<tr>
<td>Ventricular fibrillation</td>
<td>A signal for which individual QRS deflections can no longer be distinguished from one another and for which a rate can no longer be measured.</td>
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**RESULTS**

**Sucrose Preference Tests and Body Weight**

Figure 1 displays the fluid intake during the sucrose preference tests used to define anhedonia in the CMS and control groups at baseline and after 4 wk of CMS. Figure 1A presents absolute water and sucrose intake in the two groups. Mixed-design ANOVAs were performed separately for water and sucrose intake. No significant differences in water intake were found. An ANOVA performed on sucrose intake yielded a main effect of time, main effect of group, and a group by time interaction. There was no difference in sucrose intake between the two groups at baseline. After 4 wk of CMS, the CMS group consumed significantly less sucrose than the control group and its respective baseline value.

Figure 1B displays the percent preference for sucrose in CMS and control groups at baseline and after 4 wk of CMS. The percent preference for sucrose was calculated according to the following formula: \%preference = (sucrose intake/total fluid intake) \times 100. An ANOVA yielded a main effect of group. The baseline preference for sucrose did not differ between CMS and control animals. However, after 4 wk of CMS, the preference for sucrose was reduced in the CMS group compared with its respective baseline value and that of the control group.

Body weight was statistically compared in CMS and control rats with an ANOVA. As expected, there was a main effect of time, but there was no main effect of group and no group by time interaction. Body weight during the baseline period was 322.7 ± 4.1 g in CMS rats and 323.5 ± 3.7 g in control rats, and after 4 wk of CMS, body weight was 396.4 ± 5.6 g in CMS rats and 395.6 ± 5.0 g in control rats. The two groups did not statistically differ in body weight at either of these time points.
Baseline Electrocardiographic Parameters

Data recorded before aconitine administration (baseline) were analyzed for HR and HR variability. The CMS group demonstrated significantly elevated HR compared with the control group (Fig. 2A). HR variability (SDNN index) was significantly reduced in the CMS group relative to the control group (i.e., the CMS group displayed a reduced threshold for isolated PVCs). Isolated PVCs were typically the only arrhythmic event present during 7 min of aconitine infusion; therefore, a subset of rats was exposed to 35 μg/kg of aconitine at 5 μg·kg⁻¹·min⁻¹ for the purpose of observing more complex arrhythmias that take place after discontinuation of the drug. Figure 5 presents the time required for onset of bigeminy, salvo, VT, and VF in this subset of rats. Rats exposed to CMS displayed a reduced threshold for salvo and VT in response to aconitine administration. The time required for the onset of salvo (n = 6 CMS and 6 control) and VT (n = 8 CMS and 5 control) was significantly reduced in the CMS group relative to control rats. The time required for the onset of bigeminy (n = 7 CMS and 7 control) was not significantly different between the two groups.

Aconitine Administration

Experimental ventricular arrhythmias were classified into the following categories: isolated PVC, bigeminy (bigeminal PVCs), salvo, VT, and VF. Figure 3 displays the raw data recording from a representative rat showing each category of arrhythmia. Not all rats demonstrated a stepwise progression through these stages and some rats did not display certain types of arrhythmic events during the ECG recording period. Therefore, statistical analyses were performed on those rats that displayed similar types of ventricular arrhythmias. Atrial events were not used in the statistical comparisons. Sample sizes are noted for all statistical tests.

Figure 4 presents the PVC data for 11 CMS and 11 control rats, showing the time required for aconitine to produce the onset of isolated PVCs. The mean latency for the onset of PVCs, and hence the total drug dosage administered (10.6 ± 1.2 μg in CMS vs. 13.0 ± 1.1 μg), was significantly reduced in the CMS group relative to the control group (i.e., the CMS group displayed a reduced threshold for isolated PVCs). Isolated PVCs were typically the only arrhythmic event present during 7 min of aconitine infusion; therefore, a subset of rats was exposed to 35 μg/kg of aconitine at 5 μg·kg⁻¹·min⁻¹ for the purpose of observing more complex arrhythmias that take place after discontinuation of the drug. Figure 5 presents the time required for onset of bigeminy, salvo, VT, and VF in this subset of rats. Rats exposed to CMS displayed a reduced threshold for salvo and VT in response to aconitine administration. The time required for the onset of salvo (n = 6 CMS and 6 control) and VT (n = 8 CMS and 5 control) was significantly reduced in the CMS group relative to control rats. The time required for the onset of bigeminy (n = 7 CMS and 7 control) was not significantly different between the two groups.

**Fig. 1.** A: mean ± SE water and sucrose intake in chronic mild stress (CMS) and control groups at baseline and after 4 wk of CMS. The main effects of time [F(1,23) = 22.91] and group [F(1,23) = 4.68] and a group by time interaction [F(1,23) = 7.69] were found. The groups did not differ in the amount of baseline water or sucrose consumed. After 4 wk of CMS, the CMS group consumed significantly less sucrose than control rats [t(23) = 3.88] and baseline values [t(12) = 4.67]. B: mean percent preference for sucrose in CMS and control groups at baseline and after 4 wk of CMS. The ANOVA yielded a main effect of group [F(1,23) = 6.91]. The groups did not differ in sucrose preference at baseline. After 4 wk of CMS, the preference for sucrose was reduced in the CMS group relative to its respective baseline values [t(11) = 6.69] and compared with control [t(23) = 2.27] values. *P < 0.05 vs. respective control value; #P < 0.05 vs. respective baseline value.

**Fig. 2.** A: mean baseline (preaconitine) heart rate (in beats/min, bpm) in CMS and control groups after 4 wk of CMS. The CMS group displayed a significantly elevated heart rate compared with the control group [t(16) = 2.05]. B: mean baseline (preaconitine) standard deviation of R-R intervals (SDNN index) in CMS and control groups after 4 wk of CMS. This index of heart rate variability was significantly reduced in the CMS group relative to the control group [t(17) = 1.85]. *P < 0.05 vs. control value.

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groups, nor was the time required for the onset of VF (n = 4 CMS and 4 control).

**Arterial Pressure Recordings**

In a subset of rats, arterial pressure was recorded via a catheter in the left femoral artery. These measurements were taken concurrently with the ECG recordings. Baseline (pre-aconitine) MAP was 80.4 ± 3.5 mmHg in the CMS group and 79.0 ± 2.6 mmHg in the control group; these values were not significantly different. Administration of aconitine reduced MAP in all rats (CMS and control groups). Figure 6 presents MAP in CMS and control groups at baseline and at significant time points during aconitine infusion. During aconitine infusion but before the onset of the first arrhythmic event, MAP was significantly higher in the CMS group than the control group. However, there was no significant difference in MAP between CMS and control groups immediately preceding the onset of VF (data not shown).

**DISCUSSION**

The current study was undertaken to determine whether rats with CMS-induced anhedonia (i.e., experimental depression) were more susceptible than control rats to experimentally induced cardiac arrhythmias. Both behavioral and cardiovascular changes were observed in rats exposed to CMS. CMS appears to produce a reduced threshold for ventricular arrhythmias that may signal an increased risk of detrimental cardiovascular outcomes (e.g., myocardial infarction, heart failure, and sudden cardiac death).

Similar to previous investigations (14, 50), sucrose intake was significantly reduced in rats exposed to 4 wk of CMS in

![Fig. 3. Raw data recordings from a representative rat showing the following: baseline ECG (A); an isolated premature ventricular complex (PVC) (B); bigeminy (C); salvo (D); ventricular tachycardia (VT) (E); and ventricular fibrillation (VF) (F). Arrhythmic events in B–F are marked with dashed lines.](image)

![Fig. 4. Means ± SE amount of time required for onset of isolated PVCs during intravenous infusion of aconitine (5 μg·kg⁻¹·min⁻¹) in CMS and control groups after 4 wk of CMS. Significantly less time was required for the onset of PVCs in the CMS group relative to the control group (t(20) = 2.88). *P < 0.05 vs. control.](image)

before VT, MAP was significantly higher in the control group versus the CMS group, but there was no significant difference in MAP during the time that immediately preceded the first arrhythmic event. Furthermore, MAP was not different between the two groups either during VT or during VF (data not shown).

![Fig. 5. Means ± SE amount of time required for the onset of bigeminy, salvo, VT, and VF during/after 35 μg/kg of intravenous aconitine administered at 5 μg·kg⁻¹·min⁻¹ in CMS and control groups after 4 wk of CMS. Relative to the control group, significantly less time was required for the onset of salvo (t(10) = 1.98) and VT (t(11) = 3.20) in the CMS group. *P < 0.05 vs. respective control value.](image)
the present study. The reduced sucrose intake and sucrose preference in the CMS group is a specific indication of decreased responsiveness to a pleasurable stimulus. This group did not alter its water intake after CMS, nor did it differ in body weight from the control group, which reduces the likelihood that CMS produced nonspecific changes in ingestive behavior. Whereas body weight alterations have been observed in some studies of CMS (24, 33), these changes have not been consistently observed across all studies (10, 14). Furthermore, Willner and colleagues (47) have suggested that anhedonia due to CMS is a specific hedonic deficit, which is not secondary to a loss in body weight.

The present investigation also showed that anhedonic rats displayed elevated HR and reduced HR variability. These alterations in CMS rats are similar to changes found in human depressed patients (4, 5) as well as results from our laboratory, which describe cardiovascular and behavioral effects associated with CMS in conscious rats (14). Because blood pressure and HR are reduced in anesthetized animals due to the chloral hydrate content in the Equithesin-like anesthetic, the possibility exists that the absolute measurements of these parameters are not scientifically relevant. However, it is interesting to note that the relative differences in HR and HR variability between the CMS and control groups in the present study are consistent with those found in our previous studies with unanesthetized CMS rats (11, 14). Thus, to the extent that CMS and control rats were tested at the same dosing regimen of anesthesia, the HR and HR variability changes observed in the present study provide useful information regarding the robustness of these consequences due to CMS. Future studies might focus on the relative differences of blood pressure, HR, and HR variability in anesthetized versus awake CMS and control rats.

Aside from changes in baseline cardiovascular parameters, rats that displayed anhedonia in the current study also showed a reduced threshold for specific ventricular arrhythmias after the fourth week of CMS exposure. Isolated PVCs appeared significantly earlier (and therefore with less aconitine) in CMS rats compared with control rats. Likewise, the time required for onset of salvos and VT was significantly reduced in the CMS group. The reduced threshold for arrhythmic events associated with CMS appears to have not only statistical significance but also clinical relevance. The onset of PVCs occurred 20% earlier, whereas salvos and VT occurred 17% and 23% earlier, respectively, in CMS rats compared with control rats suggesting that CMS is associated with important ventricular disturbances. However, it is possible that ventricular function is differentially altered in CMS and control animals under anesthesia, and thus it would also be beneficial to investigate ECG activity in conscious rats.

Aconitine may also affect blood pressure, thereby indirectly influencing cardiac rhythm via stress on the left ventricle. In the present study, baseline blood pressure was similar in the CMS and control groups. During aconitine infusion (before the first arrhythmic event), MAP was lower in the control group than in the CMS group. However, when MAP was calculated immediately preceding the first isolated PVC, it was not significantly different in CMS and control groups. MAP was also similar in the two groups immediately preceding VF, during VT, and during VF. The similarities of blood pressure in CMS and control groups both at baseline and during arrhythmic events suggest that changes in arterial pressure do not modulate changes in ECG. On a related note, Lown and colleagues (22) have suggested that changes in HR and blood pressure are not necessary for changes in cardiac excitability.

The present study provides an important step in the mechanistic analysis of the nature of cardiovascular disease that accompanies a key component of psychological depression, anhedonia. Rats exposed to CMS show an increased vulnerability to ventricular arrhythmias in an experimental paradigm, which supports the hypothesis that the association between depression and heart disease involves an arrhythmic mechanism (9). The cardiac arrhythmias observed in the present study were of several varieties, including isolated PVCs as well as more complex tachycardia. It is possible that the generation of these abnormalities in CMS rats is a result of inappropriate impulse formation from the sinus node or a problem with impulse conduction due to reentrant mechanisms (16, 51). The data from the present investigation complement our previous finding that rats exposed to CMS display elevated sympathetic cardiac tone, which mediates HR and HR variability in these animals (14). Increased sympathetic activity predisposes the heart to ventricular arrhythmias, and may influence the ectopic activity that precedes VF (22, 43). Thus it is possible that altered autonomic tone, in particular elevated sympathetic tone, plays a role in the susceptibility to arrhythmic events observed in the present study. Furthermore, the central nervous system pathways that affect sympathetic outflow to the cardiovascular system may also be altered in CMS, in turn increasing the risk of cardiac arrhythmias (41).

Further investigations should focus on determining the central nervous system mechanisms that are driving the changes in sympathetic tone and susceptibility to cardiac arrhythmias in the CMS model. It might be interesting to also examine the susceptibility to arrhythmias in CMS rats that were allowed to recover from the anhedonic effects of CMS. Given a recent
study from our laboratory (11), which showed elevated resting HR and reduced resting HR variability in CMS rats that were tested 4 wk after discontinuation of the CMS procedure, one might predict that the susceptibility to cardiac rhythm disturbances would similarly persist beyond the recovery of behavioral alterations.

The current study extends the findings from previous investigations of stress and cardiac function by providing additional insight regarding the nature of cardiovascular function in a rodent model of psychological depression as defined by the presence of anhedonia. Furthermore, these data complement a previous study from our laboratory showing that experimental heart disease (congestive heart failure) induces anhedonia in rats (12). Whereas previous work (7, 19, 21, 23, 38, 39) has focused on cardiovascular vulnerability during or after acute stressors, the present investigation examined the susceptibility to ventricular arrhythmias in the presence of anhedonia after a prolonged period of exposure to mild stressors. In addition, these methods were conducted in the rat, providing a foundation for systematically evaluating behavioral and physiological influences on cardiovascular regulation and the role that the nervous system plays in these associations. The use of controlled experimental methods, such as those employed here, may shed light on the mechanisms that underlie the increased risk for coronary artery disease in individuals with mood disorders, and may aid in the development of beneficial treatments for these patients.

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