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Resistance of cholestatic rats against epinephrine-induced arrhythmia: the role of nitric oxide and endogenous opioids

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Abstract

Short-term ligation of bile duct has been used as a model to study acute cholestasis and is associated with various cardiovascular abnormalities. We examined the role of nitric oxide (NO) and endogenous opioids on epinephrine-induced arrhythmia in 7-day bile duct-ligated (BDL) rats. Six groups of rats, each of which was subdivided into two subgroups (sham-operated and BDL), were examined. First group of animals were chronically treated with normal saline. In the second and third groups, single intraperitoneal administration of *N*(ω)-nitro-L-arginine methyl ester (L-NAME, 10 mg/kg) or naltrexone (20 mg/kg) was performed 30 min before evaluation of epinephrine-induced arrhythmia. Two groups received chronic administration of low dose (3 mg/kg/day) or high dose (10 mg/kg/day) L-NAME; and the last group was treated chronically with naltrexone (20 mg/kg/day). Chronic drug administration was performed subcutaneously for 6 consecutive days following BDL or sham operation. After induction of arrhythmia by intravenous injection of 10 μg/kg epinephrine, mean arterial pressure and electrocardiogram were recorded for 1 min. Heart rate and mean arterial pressure were significantly lower in BDL rats ($P<0.01$). Chronic injection of naltrexone increased heart rate and mean arterial pressure in BDL ($P<0.05$). Chronic low dose L-NAME administration had no effect on baseline hemodynamic parameters. High dose L-NAME injection corrected hypotension in BDL rats, but not bradycardia ($P<0.05$). Epinephrine induced less arrhythmia in BDL rats ($P<0.05$). Acute and chronic injection of naltrexone had no effect on the resistance of BDL rats against epinephrine-induced arrhythmia. Although acute L-NAME administration enhanced arrhythmias in sham-operated rats ($P<0.001$), it had no effect on BDL animals. Chronic injection of low dose or high dose L-NAME, without having any effect on sham-operated animals, increased arrhythmias in BDL rats ($P<0.01$). This study showed that BDL animals are resistant against epinephrine-induced arrhythmia and this resistance depends on long-term NO overproduction.

Keywords: Cholestasis; (NO) Nitric oxide; Endogenous opioids; Epinephrine-induced arrhythmia; (Rat)

1. Introduction

Short- and long-term ligation of bile duct has been used as a model to study acute cholestasis (Gaskari et al., 2002; Mani et al., 2002; Nahavandi et al., 2001) and biliary cirrhosis (Ma et al., 1999), respectively, and it has been associated with cardiovascular abnormalities such as bradycardia (Gaskari et al., 2002; Mani et al., 2002; Nahavandi et al., 2001), hypotension (Bomzon et al., 1990; Jacob et al., 1993) and attenuated response of cardiovascular system to adrenoceptor stimulation (Jacob et al., 1993; Ma et al., 1999; Namiranian et al., 2001). In addition to cardiodepressant effects of excess bile acids on cardiovascular system (Gazawi et al., 2000), accumulation of endogenous opioid peptides (Swain et al., 1992; Thornton and Lowosky, 1988) and overproduction of nitric oxide (NO) (Mani et al., 2002), which has been reported in cholestatic liver disease, may be involved in the development of these cardiovascular complications. NO by both direct and indirect (Massion et

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al., 2003) modulation of autonomic nervous system (Massion et al., 2003; Patel et al., 2001; Whalen et al., 1999) plays an important role in cardiovascular control. Decreased vascular responsiveness to vasoconstrictors, chronotropic and inotropic response to β-adrenoceptor agonists (Choate and Paterson, 1999; Massion et al., 2003), alteration of baroreflex tachycardia sensitivity (Souza et al., 2001; Spieker et al., 2000), and protection against ischemia–reperfusion (Sun and Wainwright, 1997; Bolli, 2001) and epinephrine-induced arrhythmia (Kawai et al., 2002; Murashev et al., 2003; Rajani et al., 1997) are among the known effects of NO on the cardiovascular system. There are some reports which suggest that NO overproduction has a causative role in cardiovascular abnormalities, including hyporesponsiveness of vascular beds to adrenoceptor agonists (Namiranian et al., 2001), and the induction of bradycardia (Mani et al., 2002; Nahavandi et al., 2001) in cholestatic animals.

In addition to overproduction of NO, accumulation of endogenous opioid peptides has been suggested to be involved in the pathophysiology of cardiovascular complications of cholestatic liver disease (Gaskari et al., 2002; Namiranian et al., 2001). It has been shown that opioids cause bradycardia, hypotension (Farias et al., 2001; Giuliani et al., 1997; Malinowska et al., 2002) and protection against ischemia reperfusion-induced arrhythmia (Schultz and Gross, 2001). In our in vitro studies, we have recently shown that endogenous opioids are involved in the generation of bradycardia (Gaskari et al., 2002), decreased chronotropic response of the heart (Gaskari et al., 2002) and hyporesponsiveness of vascular bed to adrenoceptor agents in a rat model of cholestasis (Namiranian et al., 2001).

The present study was carried out to determine the contribution of NO and endogenous opioids in development of bradycardia and hypotension in cholestatic rats. Based on the evidence of hyporesponsiveness of cholestatic animals to adrenoceptor stimulation and protective roles of NO and opioids against arrhythmias, we hypothesized that cholestatic animals are protected against epinephrine-induced arrhythmia; and we also examined the contribution of NO and endogenous opioids in this hypothesized protective state.

2. Materials and methods

2.1. Animal manipulation

The animals were handled in accordance with the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH US publication 86-23 revised 1985). Male Sprague–Dawley rats weighing 200–250 g were used. Animals were housed in groups of 3–4 in a room controlled at 22±1 °C and maintained in an alternating 12-h light/12-h dark cycles, and were allowed free access to food and water. Bile duct ligation was performed as described previously (Gaskari et al., 2002; Mani et al., 2002; Nahavandi et al., 2001). Laparotomy was performed under general anesthesia induced by an intraperitoneal (i.p.) injection of ketamine HCl (50 mg/kg; Gedoon Richter, Budapest, Hungary) and chlorpromazine HCl (10 mg/kg; Daroupakhsh, Tehran, Iran). In bile duct-ligated (BDL) rats, the bile duct was identified and doubly ligated. In the sham-operated rats, the bile duct was identified, manipulated and one untied loose tie was left in place. Because laparotomy distorts the intra-abdominal vasculature, the loose tie was left to mimic this effect of the bile duct ligation procedure. Then, the abdominal wall was closed in two layers. One day after laparatomy, BDL rats showed manifestations of cholestasis (jaundice, dark urine and steatorrhea).

2.2. Experimental groups

The animals were randomly divided into six groups; each of which was subdivided into two subgroups with seven to eight sham-operated or BDL rats.

1. Control: from the day after bile duct ligation or sham operation, chronic subcutaneous administration of isotonic sterile saline solution (normal saline 1 ml/kg/day, s.c.) was performed for 6 consecutive days, until the day before experimental protocol.
2. Acute *N*(ω)-nitro-L-arginine methyl ester (L-NAME): in this group, chronic normal saline injection was performed, as noted above. In order to evaluate the effects of acute inhibition of NO production, a single intraperitoneal injection of L-NAME (10 mg/kg; Sigma, St. Louis, MO, USA), non-selective NO synthase inhibitor, was administered 30 min before epinephrine injection on the day of experimental protocol.
3. Acute naltrexone: in this group, chronic normal saline injection was performed as noted above. In order to evaluate the effects of acute blockade of endogenous opioids, a single intraperitoneal injection of naltrexone HCl (20 mg/kg; Iran Darou, Tehran, Iran) was administered 30 min before epinephrine injection on the day of experimental protocol.
4. Chronic low dose L-NAME: from the day after bile duct ligation or sham operation, animals were treated with subcutaneous administration of low dose L-NAME (3 mg/kg/day, s.c.) for 6 consecutive days.
5. Chronic high dose L-NAME: animals were treated with subcutaneous administration of high dose L-NAME (10 mg/kg/day, s.c.) for 6 consecutive days as the previous group.
6. Chronic naltrexone: subcutaneous injection of naltrexone HCl (20 mg/kg/day, s.c.) was performed from the day after bile duct ligation or sham operation for 6 consecutive days.

As we have previously reported these treatment regimens can effectively reduce NO production, antagonize the effects

Table 1
Comparison of baseline heart rate (beats/min) in sham or bile duct-ligated rats chronically treated with saline, low dose L-NAME (3 mg/kg/day), high dose L-NAME (10 mg/kg/day) or naltrexone (20 mg/kg/day)

Chronic treatment	BDL	Sham	*P*-value
Saline	392±8	446±7	<0.001
Low dose L-NAME	385±7	432±9	<0.01
High dose L-NAME	350±4[a]	403±8[b]	<0.05
Naltrexone	431±12[a]	430±9	0.982

BDL=bile duct-ligated, L-NAME=*N*(ω)-nitro-L-arginine methyl ester.
[a] Significantly different compared to saline-treated BDL group ($P<0.05$).
[b] Significantly different compared to saline-treated sham group ($P<0.05$).

of accumulation of endogenous opioids, and reverse complications of short-term cholestasis (Gaskari et al., 2002; Mani et al., 2002; Nahavandi et al., 2001).

2.3. Experimental protocol

Seven days after BDL or sham operation, animals were anesthesized with sodium pentobarbital (50 mg/kg, i.p.; Merck, Darmstadt, Germany). Through a ventral midline cervical incision, trachea was exposed and was intubated with a cannula connected to a rodent ventilator. Rats were ventilated with room air. The right carotid artery was cannulated to measure arterial blood pressure using a pressure transducer (Pressure Transducer Model P-1000-A, Narco Biosystem, Houston, TX, USA). The left jugular vein was cannulated for drug injection. Lead II of electrocardiogram was recorded using subcutaneous needle electrodes and cardiac coupler connected to a DMP-4B physiograph (Narco Biosystems). After a steady state was achieved, two groups of animals received acute injection of L-NAME or naltrexone and other groups received sterile normal saline (1 ml/kg, i.p.). Thirty minutes later, arrhythmia was induced by intravenous injection of 10 μg/kg epinephrine (Fluka, Buchs, Switzerland).

2.4. Arrhythmia evaluation

As it has been reported previously (Rajani et al., 1997), the electrocardiogram showed first, second and third degree heart block, premature atrial contractions, premature ventricular contractions and runs of ventricular tachycardia defined as three or more consecutive premature ventricular contractions following epinephrine injection. The most frequent arrhythmias were premature ventricular contractions, runs of ventricular tachycardia, which were used for analysis.

2.5. Statistical analysis

Data are expressed as mean±S.E.M. In the case of three or more group, the results were analyzed by analysis of variance (ANOVA) followed by Tukey's HSD as post-hoc test to compare the means. For two groups, the differences between the means were assessed by Student's *t*-test. $P<0.05$ was considered as the significance level between groups.

3. Results

3.1. Baseline heart rate and mean arterial pressure

Baseline heart rate and mean arterial pressure are shown in Tables 1 and 2. Heart rate ($P<0.001$) and mean arterial pressure ($P<0.01$) were significantly lower in the BDL rats. Chronic injection of naltrexone significantly increased heart rate and mean arterial pressure in BDL rats ($P<0.05$) to the level of sham-operated rats, but had no significant effect on sham-operated rats. Chronic administration of low dose L-NAME had no significant effect on hemodynamic parameters in BDL and sham-operated animals. However, chronic high dose L-NAME administration caused bradycardia and hypertension in both BDL and sham-operated rats ($P<0.05$). Although chronic administration of high dose L-NAME abolished mean arterial pressure difference between BDL and sham-operated animals, there was still a significant difference in heart rate ($P<0.05$).

3.2. Effects of acute naltrexone and L-NAME administration on heart rate and mean arterial pressure

Acute administration of naltrexone had no significant effect on heart rate and mean arterial pressure in BDL or sham-operated rats (data are not shown, $P>0.05$). As it is demonstrated in Fig. 1, acute L-NAME administration increased mean arterial pressure and decreased heart rate in both BDL and sham-operated groups ($P<0.01$), and abolished baseline difference between BDL and sham-operated animals. No arrhythmia was produced by acute L-NAME or naltrexone injection.

3.3. Mean arterial pressure and arrhythmia after epinephrine injection

The intravenous administration of epinephrine elicited systemic hypertension ($P<0.001$). As it is shown in Fig. 2,

Table 2
Comparison of baseline mean arterial pressure (mm Hg) in sham or bile duct ligated rats chronically treated with saline, low dose L-NAME (3 mg/kg/day), high dose L-NAME (10 mg/kg/day) or naltrexone (20 mg/kg/day)

Chronic treatment	BDL	Sham	*P*-value
Saline	95±2	108±4	<0.01
Low dose L-NAME	101±5	115±6	0.651
High dose L-NAME	124±5[a]	130±5[b]	0.978
Naltrexone	109±4[a]	111±3	0.945

BDL=bile duct-ligated, L-NAME=*N*(ω)-nitro-L-arginine methyl ester.
[a] Significantly different compared to saline-treated BDL group ($P<0.05$).
[b] significantly different compared to saline-treated sham group ($P<0.05$).

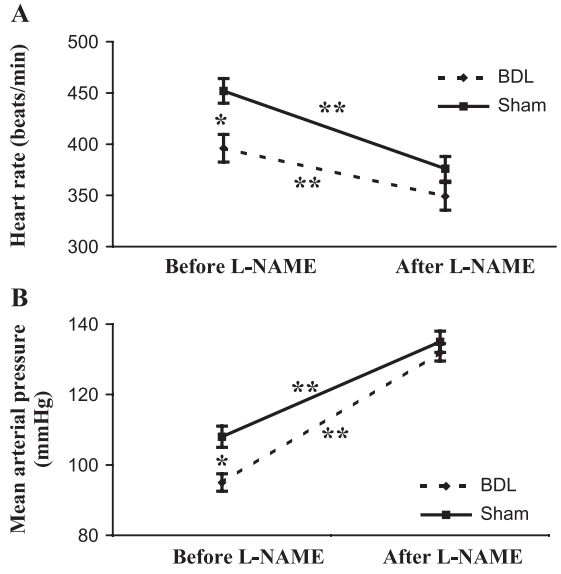

Fig. 1. Effect of acute injection of L-NAME on (A) heart rate and (B) mean arterial pressure in BDL and sham-operated (Sham) animals. *P<0.05, **P<0.01.

blood pressure began to rise within seconds after the administration of epinephrine and remained elevated for almost 1 min. As it has been reported previously (Rajani et al., 1997), practically all arrhythmias appeared simultaneously with the increase in blood pressure, during the period between 5 and 60 s after epinephrine injection. Peak mean arterial pressure was not different among groups (Table 3, P>0.05). Because of the irregular rhythm after injection of epinephrine, we did not compare heart rates. As it is shown in Fig. 3, premature ventricular contractions were significantly lower in BDL rats compared to sham-operated animals (P<0.05). While acute L-NAME administration accentuated arrhythmias, in the form of ventricular tachycardias, in sham-operated rats (P<0.001), it had no significant effect on BDL rats. On the other hand, chronic administration of either low or high dose of L-NAME significantly increased number of premature ventricular contractions in BDL rats (P<0.05) to the level of sham-operated animals. Acute or chronic naltrexone administration had no significant effect on epinephrine-induced arrhythmias in BDL or sham-operated subjects (P>0.05).

Table 3
Comparison of peak mean arterial pressure (mm Hg) and its increase compared to baseline pressure after intravenous injection of 10 μg/kg epinephrine

Experimental groups	BDL	Sham
Saline	163±5	167±6
Acute L-NAME	171±7	170±6
Chronic low dose L-NAME	165±6	170±5
Chronic high dose L-NAME	174±7	172±6
Acute naltrexone	164±6	166±5
Chronic naltrexone	169±5	170±6

BDL=bile duct-ligated, L-NAME=N(ω)-nitro-L-arginine methyl ester.

4. Discussion

In summary, our study on the 7-day BDL model of acute cholestasis showed that baseline heart rate and mean arterial pressure were lower in BDL rats, which is in accordance with previous reports (Bomzon et al., 1990; Gaskari et al., 2002; Jacob et al., 1993; Mani et al., 2002; Nahavandi et al., 2001). In addition, it showed for the first time that acute bile duct ligation is associated with protection against epinephrine-induced arrhythmia, which is related to chronic NO overproduction.

There is evidence that the cardiovascular system of cholestatic patients and animals is hyporesponsive to

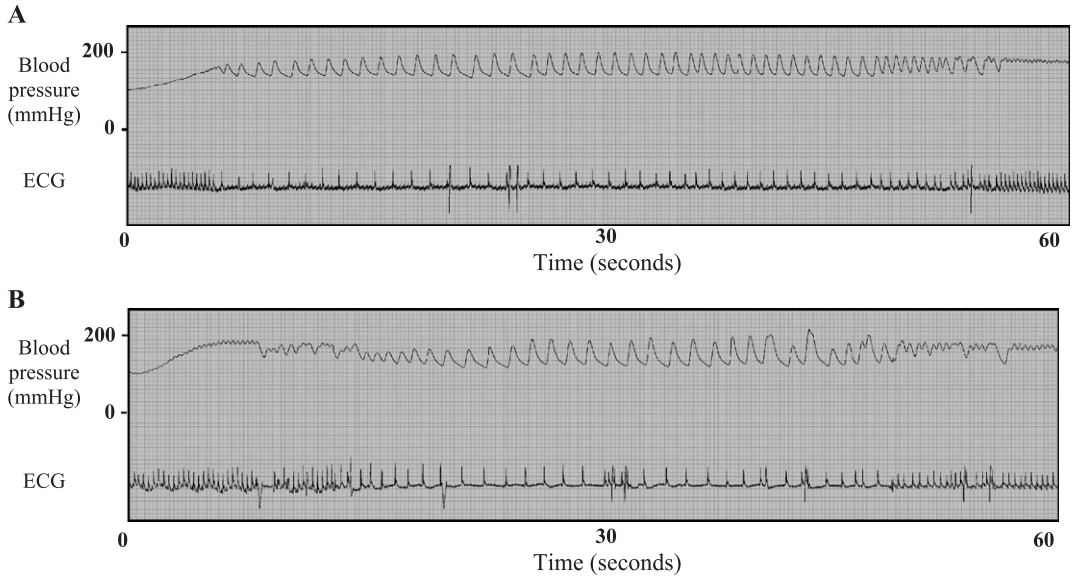

Fig. 2. Recording of lead II of the electrocardiogram and arterial blood pressure after the intravenous administration of 10 μg/kg epinephrine (time=0) in (A) bile duct-ligated and (B) sham-operated rats for 1 min.

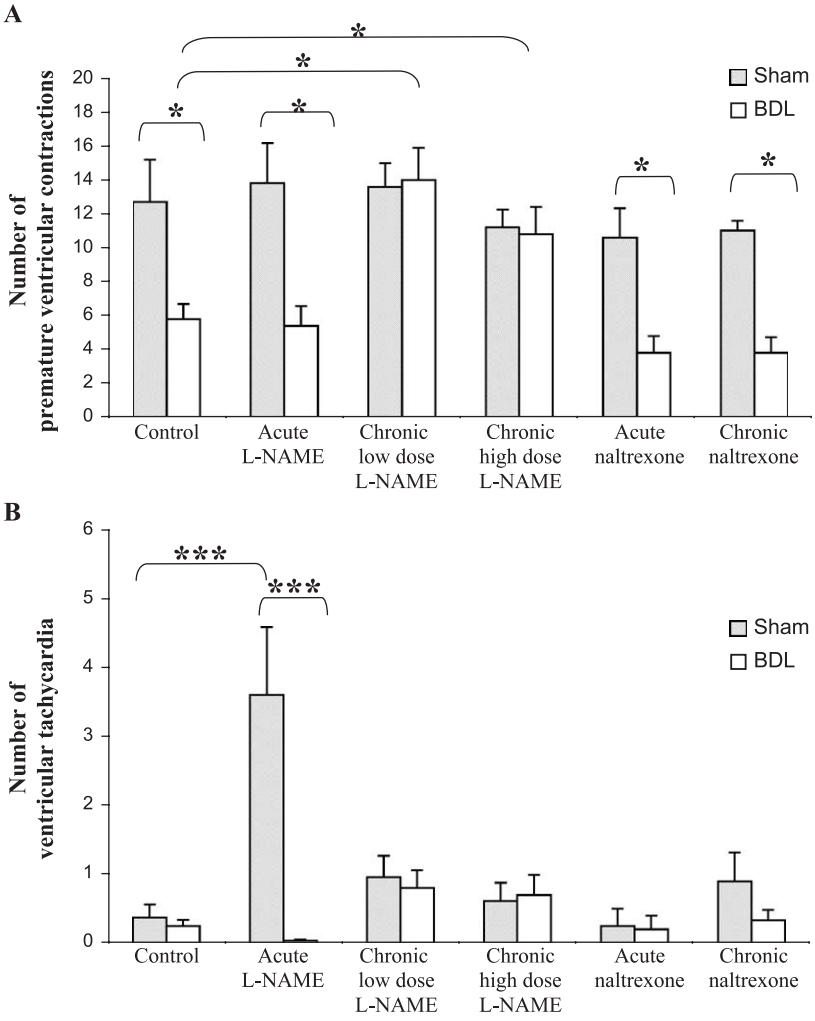

Fig. 3. Effect of acute or chronic injection of *N*(ω)-nitro-L-arginine methyl ester or naltrexone in comparison to chronic injection of normal saline (Control) on (A) the number of premature ventricular contractions and (B) ventricular tachycardia induced by intravenous injection of 10 μg/kg epinephrine in BDL and sham-operated (Sham) animals. **P*<0.05, ***P*<0.01, ****P*<0.001 after Tukey's HSD post-hoc test.

adrenoceptor stimulation (Jacob et al., 1993; Ma et al., 1999; Namiranian et al., 2001). For example, decreased chronotropic response of isolated atria (Nahavandi et al., 2001), inotropic response of papillary muscle (Ma et al., 1999) and pressor response of vascular beds (Namiranian et al., 2001) to adrenoceptor stimulation have been reported in BDL. Although some reports suggest the impaired responsiveness of the cardiovascular system to vasopressors and β-adrenoceptor agonists as the physiological basis of cardiovascular complications of cholestasis (Lumlertgul et al., 1991), others have reported that blunted responsiveness of the cardiovascular system is not an important physiological determinant of baseline cardiovascular abnormalities such as hypotension in cholestatic liver disease (Bomzon et al., 1985; Bomzon et al., 1990; Finberg et al., 1982).

NO plays a central role in the regulation of cardiovascular system, in large part through its interaction with the sympathetic nervous system (Khan et al., 2003). The involvement of overproduction of NO in the pathophysiology of cardiovascular abnormalities in cholestatic liver disease has been extensively investigated. Our in vitro studies found evidence that NO overproduction contributes to bradycardia and hyporesponsiveness of isolated atria derived from cholestatic animals to the chronotropic actions of epinephrine (Nahavandi et al., 2001). This study demonstrates that, while acute inhibition of NO production, using a single dose of L-NAME, exaggerates arrhythmias in sham-operated rats, it had no effect on the protective state of cholestatic animals against epinephrine-induced arrhythmia.

The protective role of endogenous NO against arrhythmias is controversial. While, in contrast to our results, a recent study showed that acute injection of L-NAME had no effect on epinephrine-induced arrhythmia (Kawai et al., 2002), in another study acute blockade of NO production by L-NAME ameliorated ischemic-induced arrhythmia (Sun and Wainwright, 1997). Although the causes of these discrepancies are not clear, methodological differences, such as different arrhythmogens, anesthetic drugs and using sham-operated instead of unoperated animals could be responsible. In this study, chronic injection of L-NAME

had quite opposite effects on epinephrine-induced arrhythmia, it exacerbated arrhythmia formation in cholestatic animals while exerting no effects on sham-operated animals. These findings suggest that the resistant state of cholestatic animals is, at least in part, the result of long-term overproduction of NO, which cannot be reversed by acute inhibition of further NO production. This difference suggests different mechanisms for NO-induced cardioprotection in these two groups of animals.

Endogenous opioid peptides have been shown to have cardiovascular effects such as a decrease in heart rate, cardiac output and total peripheral resistance (Champion and Kadowitz, 1998), which have been reported to be vagally mediated (Feldman et al., 1996; Kwok and Dun, 1998). In this study acute administration of naltrexone did not affect mean arterial pressure or epinephrine-induced arrhythmia formation. Although chronic injection of naltrexone in the cholestatic animals raised heart rate, mean arterial pressure up to the level of sham-operated animals, it had no effect on epinephrine-induced arrhythmia. There is some evidence that cholestatic animals are more responsive to the vagus nerve stimulation (Mani et al., 2002). The reason for this hyperresponsiveness is unknown, but it may be due to increased vagal tone or changes in end-organ responsiveness (Mani et al., 2002). The reason that chronic injection of naltrexone abolished baseline cardiovascular changes in cholestatic animals without effecting epinephrine-induced arrhythmias is not clear. Reversal of the increased parasympathetic tone without correction of sympathetic responsiveness, could be one possible explanation.

The elevation of arterial blood pressure has been suggested to facilitate the genesis of epinephrine-induced arrhythmias (Kawai et al., 2002). Thus, the hemodynamic abnormalities of cholestatic animals might be involved in their protection against epinephrine-induced arrhythmias. However, we did not observe significant difference in peak mean arterial pressure between BDL and sham-operated animals at the onset of arrhythmias (Table 3). In addition, this study provides evidence that neither acute nor chronic correction of baseline hemodynamic abnormalities in BDL rats could restore their susceptibility to epinephrine-induced arrhythmias. First, acute L-NAME injection, 30 min before induction of arrhythmia, increased mean arterial blood pressure in BDL rats to the level of sham-operated animals, but did not change the number of premature ventricular contraction in BDL rats. Second, chronic naltrexone administration corrected baseline blood pressure of the BDL rats, but we still observed significantly lower premature ventricular contractions in this group. On the other hand, hypertensive effect of long-term inhibition of NO production could not be considered as the only mechanism by which L-NAME restored the susceptibility of BDL animals against epinephrine-induced arrhythmias, since chronic low dose L-NAME administration abolished the resistance of BDL animals without a significant effect on baseline hemodynamic parameters.

In summary, this study confirms previous reports that cholestatic animals exhibited bradycardia and hypotension. We also found that cholestatic animals are resistant to epinephrine-induced arrhythmias and that this process depends, at least in part, on long-term NO overproduction.

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