Zhi-Fuzi, a Cardiotonic Chinese Herb, a New Medical Treatment Choice for Portal Hypertension?

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Zhi-Fuzi (Radix Aconiti lateralis preparata) is prescribed fairly frequently in Chinese medicine clinical practice for treating the complications of cirrhosis. However, scientific evidence regarding its efficacy and safety has not been available until now; in addition, its treatment efficacy has not yet been evaluated in well-designed clinical trials. Hence, we investigated the hemodynamic effects of Zhi-Fuzi in conscious rats with portal vein ligation (PVL) and the safety in normal rats. Our study included 3 parts: (i) early administration during which the hemodynamic effects of low and high doses of Zhi-Fuzi (0.4 and 0.8 g/kg twice daily) and propranolol (15 and 30 mg/kg twice daily) administered for 14 days after PVL on male Sprague-Dawley rats were evaluated; (ii) late administration during which the other group of PVL rats received 2.4 g/kg of Zhi-Fuzi twice daily from the 15th to 28th postoperative day; hemodynamic effects were measured when the Zhi-Fuzi treatment was finished; and (iii) safety evaluation during which 2 groups of normal rats were administered Zhi-Fuzi (0.4 and 0.8 g/kg twice daily) for 14 days; biochemical and histopathologic studies were completed after hemodynamic measurement. In early administration the portal pressures in rats receiving low and high doses of Zhi-Fuzi, low and high doses of propranolol, and distilled water were 13.81 ± 0.11, 11.59 ± 0.07, 17.09 ± 0.06, 14.52 ± 0.29, and 20.11 ± 0.22 mm Hg, respectively. The high dose of Zhi-Fuzi exerted more portal hypotensive effects than propranolol and simultaneously ameliorated the systemic arterial hypotension in PVL rats. The late administration of Zhi-Fuzi also significantly reduced the elevated portal pressure (14.56 ± 0.19 vs. 19.50 ± 0.31 mm Hg in control, $P < 0.05$). There were no adverse effects seen in normal rats receiving Zhi-Fuzi. The results suggest that Zhi-Fuzi is a potential drug for the prophylaxis and treatment of portal hypertension. Exp Biol Med 232:557–564, 2007

Key words: portal hypertension; Chinese medicine; Zhi-Fuzi (Radix Aconiti lateralis preparata); portal vein ligation

Introduction

Portal hypertension, a consequence of cirrhosis, may lead to major complications including gastroesophageal varices, ascites, and hepatic encephalopathy (1). Ruptured esophageal varices cause 60%–70% of all upper gastrointestinal bleeding episodes in cirrhosis (2). After an index bleed, the risk of rebleeding is 30%–40% within the next 6 weeks and 70% within 1 year (3). Hence, how to prevent the development of variceal formation and bleeding through lowering the portal pressure becomes a very important issue in the treatment of cirrhosis.

Nonselective beta blockers, the accepted standard treatment for portal hypertension, were first proposed in the early 1980s by Lebrec *et al*. (4, 5) for the prevention of variceal bleeding; they have been hailed as a landmark in pharmacologic treatment of portal hypertension. In a portal hypertensive model, beta blockers lower the portal pressure through cardiac output reduction by blockade of beta-1 cardiac receptors and through splanchnic arteriolar vasoconstriction by blockade of beta-2 vascular receptors (6). However, only one-third of cirrhotic patients respond to beta blockers. In addition, the use of these drugs in cirrhotic patients is often limited by comorbidities such as hypotension and congestive heart failure (7, 8). Therefore, new approaches for the treatment of variceal bleeding were called for by Lebrec during the symposium held in Montreal, Canada, in April 2004 (9). Later Groszmann *et al*. (10) found that using nonselective beta blockers in patients with cirrhosis and portal hypertension does not

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prevent gastroesophageal varices and likely causes serious adverse events.

Fuzi (*Aconitum carmichaeli* Debx.) has been the main herb used in the treatment of massive gastrointestinal bleeding for nearly 2000 years in Chinese medicine (11, 12). For efficacy and safety concerns, Fuzi is usually processed into Zhi-Fuzi (Radix Aconiti lateralis preparata) when it is clinically prescribed. During this process the quantity of the toxic compound "aconitine alkaloid," which may cause arrhythmia or cardiac depression, diminishes and is not detectable in Zhi-Fuzi (13). Zhi-Fuzi is prescribed fairly frequently in clinical practice for other complications of cirrhosis such as lower leg edema and ascites. Unfortunately, scientific evidence regarding the efficacy and safety of Zhi-Fuzi in the treatment of cirrhotic complications has not been available until now. Well-designed clinical trials to establish an evidence base of clinical practice are necessary.

Zhi-Fuzi itself has been used in Chinese medicine as a cardiotonic herb for the treatment of congestive heart failure because of its positive inotropic and chronotropic effects (14). Thus, if Zhi-Fuzi is used in the treatment of portal hypertension, its role must be different than that of beta blockers. By considering the great difference in the cardiovascular effects of Zhi-Fuzi and beta blockers, whether Zhi-Fuzi improves or worsens portal hypertension becomes a very important question before the efficacy of Zhi-Fuzi is assessed in clinical trials. To evaluate the potential of Zhi-Fuzi as a potential drug for the prophylaxis and treatment of portal hypertension, we evaluated the hemodynamic effects of early and late administration of Zhi-Fuzi in conscious rats treated with portal vein ligation (PVL). We also evaluated the hemodynamic, biochemical, and histopathologic changes in normal rats for a safety assessment.

Materials and Methods

Drugs and Preparation. The Radix Aconiti lateralis preparata concentrated extract was purchased from a renowned GMP manufacturer of concentrated herbal extracts that conforms to international standards (Sun Ten Pharmaceutical Co., Taipei, Taiwan). Propranolol was purchased from Sigma-Aldrich (St. Louis, MO). For experiments each gram of Zhi-Fuzi was mixed with 5 ml of warm sterile distilled water (30°C), whereas each gram of propranolol was dissolved in 100 ml of sterile distilled water.

Animal Model. Eight-week-old male Sprague-Dawley rats weighing 220–260 g (Lasco, Charles River Technology, Taipei, Taiwan) were used for the experiments. The rats were kept at room temperature (25°C) under a 12:12-hr light:dark cycle and housed in individual stainless steel screened-flow cages. The rats were allowed free access to tap water and were fed laboratory rodent diet MF18 (Oriental Yeast, Tokyo, Japan) *ad libitum*.

The portal hypertensive model induced by PVL was previously described by Chojkier and Groszmann (15). The rats were anesthetized with ether after an overnight fast for 14–16 hrs. Then a ventral midline incision was made and the portal vein isolated. A calibrated constriction was gained by the following steps: (i) make a single ligature with 3-O silk around the portal vein and a 20-gauge blunt-tipped needle and (ii) remove the needle and let the portal vein reexpand partially. Rats in the control group received sham operation during which the portal vein was isolated, but no ligature was placed around the portal vein. The experiment protocols were approved by the Animal Experiment Committee of the China Medical University and conducted according to the American Physiological Society guiding principles for the care and use of laboratory animals.

Study Design. *Early Administration of Zhi-Fuzi in PVL Rats.* Thirty PVL rats were randomly assigned to 5 groups to receive low-dose Zhi-Fuzi (0.4 g/kg twice daily; LF group), high-dose Zhi-Fuzi (0.8 g/kg twice daily; HF group), low-dose propranolol (15 mg/kg twice daily; LP group), high-dose propranolol (30 mg/kg twice daily; HP group), or distilled water twice daily (DW-1 group) for 14 days.

Another 6 rats with the sham operation received distilled water twice daily (SO-1 group). The volume of treatment substance was kept at 3 ml each time, and the times of administration were 0900 and 1500 hrs. Hemodynamic effects were measured on the 14th day after PVL surgery.

Late Administration of Zhi-Fuzi in PVL Rats. Another 12 PVL rats were randomly assigned to received very high-dose Zhi-Fuzi (2.4 g/kg twice daily; VHF group) or distilled water twice daily (DW-2 group) from the 15th to 28th day after surgery. Six rats with the sham operation receiving distilled water twice daily during the same treatment period were regarded as the control group (SO-2 group). The volume of treatment substance and times of administration were the same as the early treatment. For rats with the late treatment, hemodynamic effects were measured on the 28th day after surgery.

Evaluation of Hemodynamic Effects and Safety of Zhi-Fuzi in Normal Rats. Eighteen normal rats were randomly assigned into 3 groups to receive low-dose Zhi-Fuzi (0.4 g/kg twice daily; LF-N group), high-dose Zhi-Fuzi (0.8 g/kg twice daily; HF-N group), or distilled water twice daily (DW-N group). The volume of treatment substance and times of administration were the same as the early treatment. The hemodynamic effects were measured after 14 days of treatment.

At the end of the hemodynamic measurement, specimens from the blood, heart, lungs, stomach, liver, spleen, and kidneys specimen were prepared for biochemical and histopathologic studies.

Hemodynamic Measurements. All rats, after being starved for 8–10 hrs, were anesthetized with ether. Mean arterial pressure and portal pressure were determined by direct cannulation with PE-50 tubing into the left femoral

artery and ileocolic vein, respectively (Clay Adams, Parsippany, NJ). To ensure that correct portal pressure was obtained, the following criteria were established: (i) the pressure tracing had to show a rapid rise followed by a stable plateau with slight respiratory variations and (ii) blood could be easily aspirated (16). All catheters were connected to highly sensitive pressure transducers that were calibrated before each study, with the zero reference point being the midportion of the rat. The pressure and heart rate were monitored and recorded by MP100 System (Biopac, Inc., Santa Barbara, CA).

Cardiac output was measured by thermodilution according to the method of Albillos *et al*. (17). Briefly, a thermistor was passed into the right carotid artery and advanced to the aortic arch. A thermal indicator (0.3 ml of normal saline at 22°C ± 0.5°C) was then injected rapidly by a Microlab autoinjector (Hamilton, Reno, NV) into the right atrium *via* a 25-cm length of PE-50 tubing placed in the jugular vein. The core temperature of the rat was maintained at 37°C ± 0.5°C. A typical thermodilution curve had a rapid upstroke and slow decay, and 3 thermodilution curves were obtained for each rat. Curves with unusual morphology were discarded. The aortic thermistor was connected to a cardiac output computer (Cardiotherm 400R; Columbus Instruments, Columbus, OH). The arithmetic mean of 3 thermodilution readings was taken as the cardiac output for each animal. The triplicate readings for each rat from the cardiac output computer were fairly consistent, with intraassay variability (coefficient of variation) generally less than 5%.

All the above catheters and injection routes were passed through the subcutaneous tunnel at the back of the neck. The abdominal incisions were closed with silk sutures. Then the rats were put in restrainers (model 81; IITC Life Science, Woodland Hills, CA). One hour after the rats recovered from ether anesthesia, when they were tranquil and the mean arterial pressures and heart rates were stable, we performed hemodynamic studies to take 20-min recordings and measure the cardiac output every 6 mins in this period.

Cardiac index was calculated as (ml/min/100 g) = cardiac output (ml/min) ÷ body weight (g) × 100; stroke volume was calculated as (ml/100 g/beat) = cardiac index (ml/min/100 g) ÷ heart rate (beats per min [bpm]); and systemic vascular resistance was calculated as (mm Hg·min·100 g/ml) = mean arterial pressure (mm Hg) ÷ cardiac index (ml/min/100 g).

Biochemical Studies. After the hemodynamic measurements, blood samples were drawn from the catheter and immediately centrifuged, and then the serum was kept at –80°C until the biochemical studies were performed. Aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and serum creatinine were measured by a clinical chemistry analyzer with integrated multisensor technology (Dimension RxL; Dabe Behring Inc., Deerfield, IL).

Histopathologic Analyses. The heart, lungs, stomach, liver, spleen, and kidneys were recovered after sacrifice from the group of normal rats that were used for biochemical studies. Small portions of these organs were fixed immediately in buffered para-formaldehyde (10%, pH 7.4) at room temperature. Representative fragments were washed in phosphate buffer and dehydrated in graded concentrations of ethanol; the fragments were embedded in Paraplast Plus (Oxford Labware, St. Louis, MO). For each specimen of heart, lungs, stomach, liver, spleen, and kidneys, 3-mm–thick sections were obtained and slides were stained with hematoxylin and eosin. Microscopy evaluation was performed by a nonaffiliated pathologist (Animal Technology Institute, Miaoli, Taiwan) who was blinded to the study.

Statistical Analysis. All data were expressed as mean ± SE and were analyzed with SPSS version 10.0 for Windows (SPSS Inc., Chicago, IL) by performing one-way analysis of variance and the Duncan Post Hoc test for multiple comparisons. Results were considered statistically significant at $P < 0.05$.

Results

Effects of Early Administration of Zhi-Fuzi in PVL Rats. In comparison with SO-1 control group, the DW-1 group successfully developed typical portal hypertension with hyperdynamic circulation, portal pressure, heart rate, stroke volume, and cardiac index significantly increased to 20.11 ± 0.22 mm Hg, 422 ± 7 bpm, 1.69 ± 0.04 ml/100 g/beat, and 713.76 ± 24.23 ml/min/100 g, respectively, whereas mean arterial pressure and systemic vascular resistance were decreased to 104.33 ± 0.89 mm Hg and 0.15 ± 0.01 mm Hg·min·100 g/ml, respectively (Fig. 1). The administration of both Zhi-Fuzi and propranolol lowered the portal pressure in PVL rats, but the total hemodynamic effects of these 2 drugs were fairly different in the following parameters (Fig. 1).

Portal Pressure. When compared with DW-1 group, the administration of both Zhi-Fuzi and propranolol significantly lowered the increased portal pressure in PVL rats in a dose-dependent manner. The portal pressure in HF (0.8 mg/kg of Zhi-Fuzi), LF (0.4 mg/kg of Zhi-Fuzi), HP (30 mg/kg of propranolol), and LP (15 mg/kg of propranolol) groups were lowered to 11.59 ± 0.07, 13.81 ± 0.11, 14.52 ± 0.29, and 17.09 ± 0.06 mm Hg, respectively. In addition, the portal pressure in HF group was significantly lower than that in HP group (11.59 ± 0.07 vs. 14.52 ± 0.29 mm Hg, $P < 0.05$) (Fig. 1A). The portal pressure in LF group was also significantly lower than that in LP group (13.81 ± 0.11 vs. 17.09 ± 0.06 mm Hg, $P < 0.05$) (Fig. 1A).

Mean Arterial Pressure. The hypotensive status in PVL rats was ameliorated in HF group, and there was no significant difference in mean arterial pressure between HF and SO-1 control groups. On the contrary, the administration of propranolol significantly lowered the mean arterial pressure in a dose-dependent manner. The mean arterial

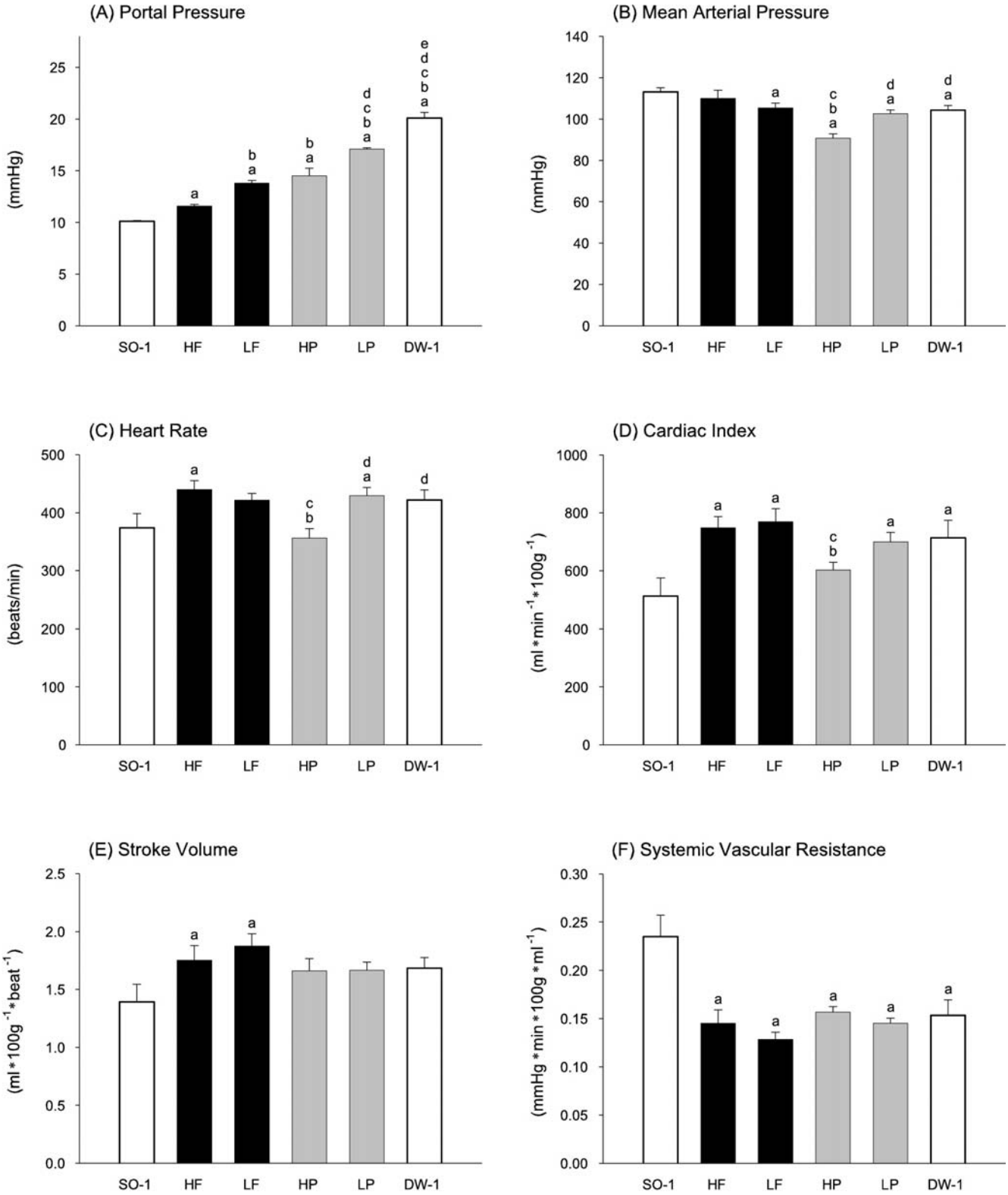

Figure 1. Hemodynamic effects of early administration of Zhi-Fuzi and propranolol. The SO-1 group received sham operations and administration of distilled water; the remaining groups received PVL. Treatment in PVL rats included: HF: Zhi-Fuzi 0.8 g/kg twice daily; LF: Zhi-Fuzi 0.4 g/kg twice daily; HP: propranolol 30 mg/kg twice daily; LP: propranolol 15 mg/kg twice daily; and DW-1: distilled water twice daily for 14 days. Notice that the portal pressure was the lowest in HF group (A). (B–F) Administration of Zhi-Fuzi increased mean arterial pressure, heart rate, cardiac index, and stroke volume and resulted in decreased systemic vascular resistance. Data are expressed as mean ± SE for 6 rats. $^{a}P < 0.05$ vs. SO-1 group, $^{b}P < 0.05$ vs. HF group, $^{c}P < 0.05$ vs. LF group, $^{d}P < 0.05$ vs. HP group, $^{e}P < 0.05$ vs. LP group by Duncan post hoc test.

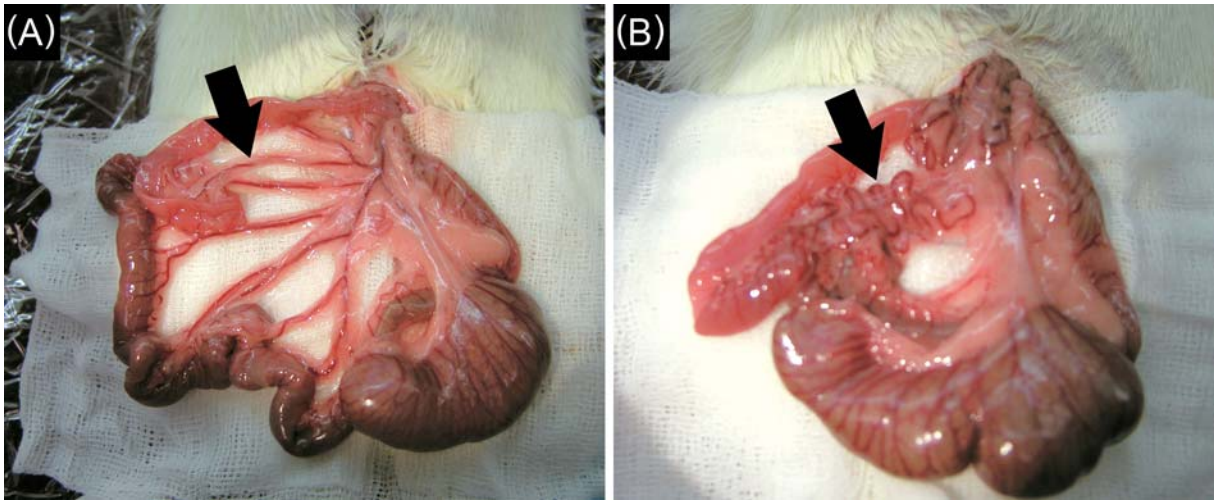

Figure 2. The gross appearance of the mesenteric veins in VHF and DW-2 groups. Notice that the mesenteric veins (indicated by arrows) in VHF group (A) was not as tortuous as those in DW-2 group (B). Color figure available in on-line version.

pressure in HP group was the lowest in all PVL groups (Fig. 1B).

Heart Rate. The administration of Zhi-Fuzi elevated the heart rate in a dose-dependent way. The heart rate was increased more prominently in HF group (440 ± 6 bpm) than in LF group (422 ± 5 bpm). The higher the dose of propranolol, the lower the heart rate (Fig. 1C).

Cardiac Index. As shown in Figure 1D, the cardiac index was increased in all groups of PVL rats, and there was no statistical significance among HF, LF, LP, and DW-1 groups. The cardiac index was the lowest in HP group; the cardiac index in SO-1, HF, LF, HP, LP, and DW-1 groups were 512.06 ± 25.80, 747.80 ± 16.06, 768.88 ± 18.30, 601.93 ± 11.05, 699.18 ± 13.46, and 713.76 ± 24.23 ml/min/100 g, respectively.

Stroke Volume. The stroke volume was also increased in all PVL groups. In comparison with SO-1 control group, the stroke volume only achieved statistical significance in HF (1.75 ± 0.05 vs. 1.39 ± 0.06 ml/100 g/beat, $P < 0.05$) and LF groups (1.88 ± 0.04 vs. 1.39 ± 0.06 ml/100 g/beat, $P < 0.05$) (Fig. 1E).

Systemic Vascular Resistance. The systemic vascular resistance was significantly decreased in all groups of PVL rats, and there was no significant difference among the PVL groups (Fig. 1F).

Effects of Late Administration of Zhi-Fuzi in PVL Rats. *Gross Appearance of the Mesenteric Veins in the PVL Rats Administered Zhi-Fuzi.* The mesenteric veins in VHF group were not as tortuous as those in DW-2 group (Fig. 2A and B).

Hemodynamic Changes. After the characteristic portal hypertension was fully developed within 14 days, the PVL rats were administered Zhi-Fuzi (VHF group) orally for 14 days; its hemodynamic effects are shown in Figure 3.

As shown in Figure 3A, the late administration of Zhi-Fuzi significantly reduced the increase of portal pressure in PVL rats. The portal pressure was 25% lower in VHF group than in DW-2 group (14.56 ± 0.19 vs. 19.50 ± 0.31 mm Hg, $P < 0.05$). When comparing the 2 groups of PVL rats, there was also no significant differences in mean arterial pressure, heart rate, cardiac index, stroke volume, and systemic vascular resistance between VHF and DW-2 groups (Fig. 3B–F).

Evaluation of Hemodynamic Effects and Safety of Zhi-Fuzi in Normal Rats. The hemodynamic, biochemical, and histopathologic analyses of the effects of Zhi-Fuzi in normal rats are listed in Table 1. There were no significant differences among the HF-N, LF-N, and DW-N groups in portal pressure, mean arterial pressure, and heart rate. The cardiac index and stroke volume were elevated significantly and the systemic vascular resistance was lowered in HF-N group compared with DW-N group.

According to the results of the biochemical and histopathologic studies, there were no adverse effects of Zhi-Fuzi found in normal rats.

Discussion

To our knowledge, this is the first study to evaluate the hemodynamic effects of Zhi-Fuzi in conscious PVL rats. We clarified the efficacy of Zhi-Fuzi in PVL rats and demonstrated its safety in normal rats. The early administration of Zhi-Fuzi lowered portal pressure and ameliorated systemic arterial hypotension, while the late administration of Zhi-Fuzi lowered the portal pressure without correcting the hyperdynamic circulation. Even in comparison with the hemodynamic effects of propranolol, Zhi-Fuzi exerted better portal-hypotensive effects. Furthermore, there were no adverse effects found in the normal rats administered Zhi-Fuzi.

Our experimental design, which included early and late administration of Zhi-Fuzi, attempted to clarify the effects

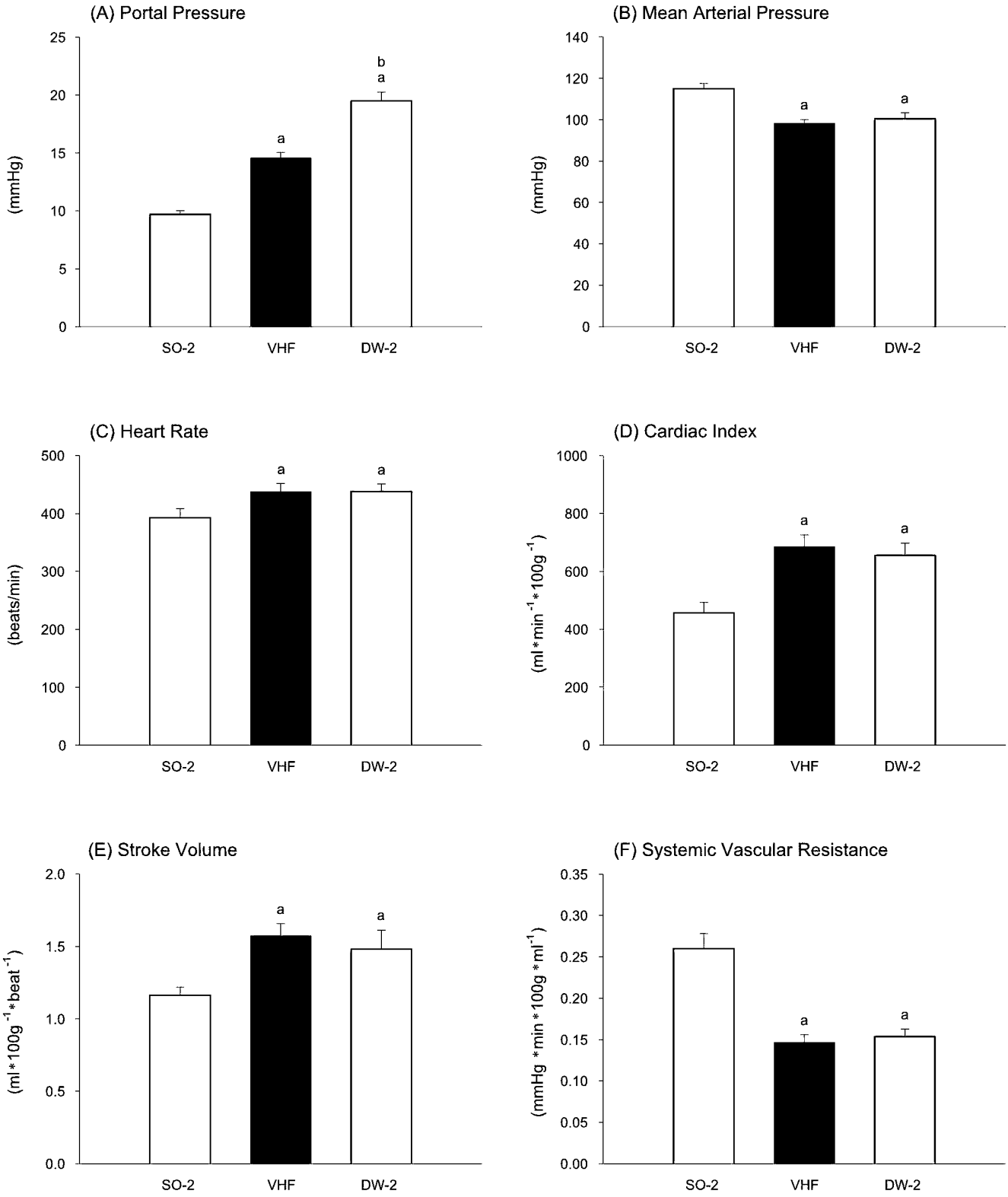

Figure 3. Hemodynamic effects of late administration of Zhi-Fuzi. SO-2 group received sham operations and administration of distilled water; the remaining 2 groups received PVL. The treatment, which started 2 weeks after PVL surgery, in PVL rats included: VHF: Zhi-Fuzi 2.4 g/kg twice daily and DW-2: distilled water twice daily for 14 days. Notice that the portal pressure was 25% lower in VHF group than DW-2 group (A). Data expressed as mean ± SE for 6 rats. $^{a}P < 0.05$ vs. SO-2 group, $^{b}P < 0.05$ vs. VHF group by Duncan post hoc test.

Table 1. Hemodynamic, Biochemical, and Histopathologic Analyses of the Effects of Zhi-Fuzi in Normal Rats[a]

Parameters	HF-N	LF-N	DW-N
Portal pressure (mm Hg)	8.21 ± 0.07	9.01 ± 0.14	8.95 ± 0.10
Mean arterial pressure (mm Hg)	107.58 ± 1.86	106.42 ± 1.46	95.77 ± 1.25
Heart rate (bpm)	460 ± 11	439 ± 5	417 ± 6
Cardiac index (ml/min/100 g)	613.72 ± 7.95*	580.46 ± 21.39	515.38 ± 9.36
Stroke volume (ml/100 g/beat)	1.29 ± 0.04*	1.26 ± 0.05	1.24 ± 0.02
Systemic vascular resistance (mm Hg·min·100 g/ml)	0.17 ± 0.01*	0.19 ± 0.01	0.19 ± 0.02
Aspartate aminotransferase (U/L)	72.50 ± 1.70	78.67 ± 2.62	69.83 ± 2.10
Alanine aminotransferase (U/L)	22.83 ± 0.88	23.50 ± 0.43	25.83 ± 1.05
Blood urea nitrogen (mg/dl)	12.17 ± 0.53	12.83 ± 0.29	12.00 ± 0.44
Serum creatinine (mg/dl)	0.82 ± 0.03	0.78 ± 0.04	0.58 ± 0.01
Heart	NSL[b]	NSL	NSL
Lungs	NSL	NSL	NSL
Stomach	NSL	NSL	NSL
Liver	NSL	NSL	NSL
Spleen	NSL	NSL	NSL
Kidneys	NSL	NSL	NSL

[a] Hemodynamic, biochemical, and histopathologic analyses were performed on 3 groups of normal rats; each was administered Zhi-Fuzi 0.8 g/kg twice daily (HF-N); Zhi-Fuzi 0.4 g/kg twice daily (LF-N); or distilled water twice daily for 14 days (DW-N). Data are expressed as mean ± SE for 6 rats.
[b] NSL, no significant lesions (in histopathologic analyses).
*$P < 0.05$ vs. DW-N group by Duncan post hoc test.

of Zhi-Fuzi in the prophylaxis and treatment of portal hypertension. In the early administration experiment, Zhi-Fuzi was given before the full development of portal-systemic shunts. The late administration of Zhi-Fuzi was started 14 days after the PVL surgery, when hyperdynamic circulation was fully achieved. This is more in line with clinical practice since 50% of cirrhotic patients are diagnosed with already-existing portal hypertension (18). Zhi-Fuzi was administered orally twice daily, which is compatible with clinical use in Chinese medicine. The dosage adopted in the early administration experiment was derived from the common dose range used in Chinese medicine for human adults and converted by the relationship of the body surface area between humans and rats. In the late administration experiment there was no obvious improvement in portal pressure of PVL rats receiving 0.8 g/kg twice daily (data not shown). After several tests, the dose adopted in the late administration experiment was 2.4 g/kg twice daily. However, this very high dose of Zhi-Fuzi (2.4 g/kg) converted into the dosage for human adults is extraordinary high and far beyond the common dose range of Zhi-Fuzi prescribed in clinical practice. Hence, we did not evaluate the effects of this dosage in normal rats.

Zhi-Fuzi is used in Chinese medicine to treat congestive heart failure and massive gastrointestinal bleeding. Chen *et al*. (19) evaluated the hemodynamic effects of Zhi-Fuzi in 35 patients with left ventricular failure and found that Zhi-Fuzi had positive inotropic, positive chronotropic, vasodilation, and diuretic effects, but they did not clarify whether the vasodilator effect was mediated through active or passive process. We revealed similar cardiovascular manifestations in the PVL rats receiving Zhi-Fuzi as elevated heart rate, cardiac index, and stroke volume associated with decreased systemic vascular resistance.

The mechanism of the action of Zhi-Fuzi against portal hypertension may be very different from that of propranolol. In previous studies it has been reported that the characteristics of some compounds in Zhi-Fuzi which show the chronotropic and inotropic effects are similar to alpha and beta agonists (13). Thus, Zhi-Fuzi may lower portal pressure by an increase of cardiac output resulting from the activation of alpha and beta agonists and the vasoconstriction in splanchnic and peripheral arterioles caused by activation of alpha agonists. Therefore, the blood volume in splanchnic circulation may be lowered through both of these effects, and this lowers portal pressure and ameliorates systemic arterial hypotension. In comparison with vasopressin (20), though, Zhi-Fuzi may also lower portal pressure through vasoconstriction, but the use of Zhi-Fuzi may not cause serious complications such as myocardial infarction.

Zhi-Fuzi has been reported to elevate blood pressure in previous studies which evaluated the effects of Zhi-Fuzi in an acute and short time manner by administering Zhi-Fuzi via an intravenous route. Anesthesia-induced hypotension in dogs and heart failure–associated hypotension in cats were corrected by administration of Zhi-Fuzi (13). In our study Zhi-Fuzi was administered *via* an oral route for 14 days. We aimed to evaluate its portal hypotensive effects and found that the systemic arterial hypotension in PVL rats was corrected in HF group by the cardiotonic and vasoconstriction effects of Zhi-Fuzi.

The portal hypotensive effects of propranolol in our study agreed with the results of Lin *et al*. (21). We found that portal pressure was lowered similarly in HP and LF groups (14.52 ± 0.29 vs. 13.81 ± 0.11 mmHg, $P > 0.05$),

but in LF group the mean arterial pressure, heart rate, cardiac index, and stroke volume were all increased, whereas all of these parameters were decreased in HP group. In clinical practice problems such as congestive heart failure, heart rates less than 50 bpm, and hypotension are contraindications and side effects of beta blockers in cirrhotic patients. On the contrary, these problems are indications for the clinical use of Zhi-Fuzi in Chinese medicine.

We did not use propranolol-treated rats as the control group in the late administration experiment for the following 2 reasons: (i) propranolol is only effective in early administration (21) and (ii) the portal hypotensive effects of propranolol was already weaker than Zhi-Fuzi in the early administration experiment.

In our study we chose the PVL model because of its excellent homogeneity and reliability of developing a large amount of portal-systemic shunts and hyperdynamic circulatory state (22). Since the integrity of liver cells is not changed in the PVL model, we did not observe the effects of Zhi-Fuzi on intrahepatic resistance, which may be another important issue for further investigation. We measured the hemodynamic variables in conscious rats so that the cardiovascular effects of Zhi-Fuzi and propranolol did not interfere with the anesthesia.

In conclusion, the results of our study provided evidence of the portal hypotensive effects of Zhi-Fuzi in PVL rats and demonstrated its safety in normal rats. Our investigation provided the scientific evidence of Zhi-Fuzi for conducting well-designed clinical trials in the future. Although Zhi-Fuzi has been already used in Chinese medicine for 2000 years, based on the results in our study Zhi-Fuzi may lower portal pressure by different mechanisms than that of propranolol. Thus, the use of Zhi-Fuzi, a cardiotonic Chinese herb, may provide a new medical treatment choice for portal hypertension.

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