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Full Length Research Paper

Effect of sodium tanshinon IIA silate on heart function of children with myocarditis

Huang Weizhe[1], Zhang Dongtao[2], Zhang Ge[3] and Li Tong[4]*

[1]Department of Cardiac Pulmonary Surgery, The First Affiliated Hospital of Shantou University Medical College, Shantou, PR China.
[2]Department of Cardiovascular Medicine, The First Affiliated Hospital of Shantou University Medical College, Shantou, PR China.
[3]Departments of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, PR China.
[4]Department of Paediatrics, The First Affiliated Hospital of Shantou University Medical College, Shantou, PR China.

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This study intends to evaluate the effects of sodium tanshinon IIA silate on cardiac function of children with myocarditis. 69 children were randomly divided into myocarditis untreatment and sodium tanshinon IIA silate treatment groups. Another 24 healthy children served as normal control. Our experimental results demonstrated that the sodium tanshinon IIA silate treatment can significantly improve heart function in children with myocarditis.

Key words: Sodium tanshinon IIA silate, myocarditis, children, troponin I.

INTRODUCTION

The topic of myocarditis is fraught with controversy, ranging from the mode of diagnosis to the optimal means of therapy. There is a broad range of presentation, ranging from virtually no symptoms to sudden cardiac death. So far, however, investigators have mostly focused on assessing either acute (Friedrich et al., 1998) or chronic (De Cobelli et al., 2006) myocarditis or have attempted to monitor only 1 of these injuries, for example, tissue necrosis (Mahrholdt et al., 2004). Danshen, the dry root and rhizome of *Salvia miltiorrhiza* Bge (Labiatae), was widely used in therapeutic remedies in China and other countries (Wu et al., 2004). Many clinical studies indicated that Danshen and its preparations could treat coronary artery diseases, myocardial infarction, liver malfunction, etc (Wu et al., 2004; Bi et al., 2008; Oh et al., 2006; Lee et al., 2008). Tanshinon IIA is isolated from *S. miltiorrhiza* and one of the main ingredients of Danshen for cardioprotective effects (Zhou et al, 2005). Tanshinone IIA was shown to exert beneficial effects on cardio-vascular system with minimal reported side effects (Wu et al., 1993; Lin et al., 2006; Fu et al., 2007; Yang et al., 2009; Shan et al., 2009). This study is designed to evaluate the effect of sodium tanshinon IIA silate on heart function of children with myocarditis.

*Corresponding author. E-mail: shantfygz@yahoo.com.cn.

Abbreviations: HRV, Heart rate variability; **LVEF,** left ventricular ejection fraction; **LVFS,** left ventricular fraction shortening; **VU-AMS,** vrije universiteit ambulatory monitoring system; **ECG,** electrocardiogram; **SDNN,** standard deviations of all normal-to-normal intervals; **RMSSD,** root mean squares of the successive differences; **CKMB,** creatine kinase MB**; SPSS,** statistically package for social sciences; **LF,** low frequency; **HF,** high frequency; **cTnI,** cardiac troponin I; **LVED,** left ventricle end-diastolic diameter; **WSC,** water-soluble compounds; **LDQ,** lipophilic diterpenoid quinines; **CK,** Creatine kinase; **FS,** fractional shortening; **EDD,** end-diastolic dimension; **ESD,** end-systolic dimension; **LVES,** left ventricle end-systolic diameter.

MATERIALS AND METHODS

Subject and experiment design

A retrospective study of 69 patients (age 9 and 14 years) with myocarditis was carried out in the Department of our hospital between 2010 and 2011. Myocarditis was diagnosed by attending cardiologists clinical symptoms compatible with myocarditis were observed along with at least one of the following: elevated troponin I (>0.1 ng/ml); cardiomegaly (cardiothoracic ratio, >0.5) on the chest radiograph, or impaired heart contractility on echocardiography (ejection fraction <55%). The exclusion criterion

Table 1. Effect of sodium tanshinon IIA silate treatment on HRV time domain index's in myocarditis children patients.

Group	SDNN (*t*/ms)	SDANN (*t*/ms)	SDNN index (*t*/ms)	rMSSD (*t*/ms)	PNN50 (%)
I	148.4±17.8	131.6±11.9	74.5±12.6	53.7±10.8	27.1±4.7
II	109.6±13.7 **	117.8±12.8 *	40.2±5.8 **	42.1±15.2 *	17.6±4.8 *
III	145.6±19.7 ##	128.6±11.5 #	69.8±13.6 ##	50.4±7.3 #	25.2±7.8 #

* *P<0.05*, ** *P<0.01*, compared with group I; # *P<0.05*, ## *P<0.01*, compared with group II.

Table 2. Effect of sodium tanshinon IIA silate treatment on HRV frequency domain indexs in myocarditis children patients.

Group	TP (ln[ms^2])	LF (ln[ms^2])	HF (ln[ms^2])	LF/HF
I	7.12±0.98	7.08±0.83	4.81±0.95	1.81±0.37
II	6.81±0.84 *	6.79±0.93 *	4.46±0.72 **	1.98±0.28 *
III	7.11±0.83 #	7.05±0.99 #	4.76±0.71 ##	1.92±0.31

* *P<0.05*, ** *P<0.01*, compared with group I; # *P<0.05*, ## *P<0.01*, compared with group II.

was children with congenital heart disease or enterovirus 71 infections with central nervous system involvement proved by brain magnetic resonance imaging. 24 healthy children (aged 9 and 14 years) served as normal control (group I). In these 69 patients, 31 patients (group II, 17 males and 14 females) served as myocarditis control and were not treated with sodium tanshinon IIA silate. 38 patients (group III, 23 males and 15 females) were treated with the sodium tanshinon IIA silate (20 mg) once every day using intramuscular injection method for 6 weeks. All patients had several examinations (for example, cards cardiac enzymes, troponin I, heart function (LAED, Left ventricular ejection fraction (LVEF), left ventricular fraction shortening (LVFS) and heart rate variability (HRV).

Creatine kinase MB (CKMB)

CKMB was measured by using test kits (CK activated, Boehringer and Mannheim) at 25°C. The normal upper limit is 50 U/1. Creatine kinase isoenzymes were separated electrophoretically in agarose gel and determined by a fluorescence technique (Somer and Konttinen, 1972). The method does not allow detection of serum CKMB activities lower than 3 U/1.

Heart rate variability time domain index

The Vrije Universiteit Ambulatory Monitoring System (VU-AMS) device continuously recorded the electrocardiogram (ECG) from a 6-electrode configuration. Two HRV measures were extracted from the interbeat interval time series: the standard deviations of all normal-to-normal intervals (SDNN) and the root mean squares of the successive differences between adjacent normal-to-normal intervals (RMSSD). In addition to cardiac measures, the device also recorded vertical acceleration as a proxy for gross body movement. The vertical accelerometer information was combined with the diary information to divide the entire recording into smaller fragments that were stationary with regard to physical activity and posture for example, within each fragment no shifts in activity/posture occurred. The fragments were not <5 min or >1 h. They were coded for posture (lying, sitting, standing, walking and bicycling), activity (for example, desk work, housekeeping, watching television) and location (at home, at work and at a public place). SDNN was computed across 5 min periods that fitted in the coded fragment, effectively yielding the SDNN index. SDNN index and RMSSD were averaged over the entire fragment. On the basis of the reported times of dinner and lunch, awakening and bedtime, mean RMSSD and SDNN index were computed across all fragments in the morning, afternoon, evening and nighttime sleep periods. SDNN, ADANN: Standard deviations of all mean 5 min R-R intervals, SDNN index: for all 5 min segments of 24 h, RMSSD: Square root of the mean of the squares of differences between adjacent NN intervals. PNN50: Percentage of differences between adjacent NN intervals that are greater than 50 ms; a member of the larger pNNx family.

Statistical analysis

All data are presented as mean ± SD. Comparison of nonparametric data between groups was performed with the Wilcoxon rank sum test and the Mann-Whitney U test. Nonparametric correlation was calculated by the Spearman correlation. Statistical significance was assumed at a value of $p < 0.05$. All statistical analyses were performed with statistically package for social sciences (SPSS) for windows (version 15, SPSS, Chicago, Illinois).

RESULTS

In the present study, HRV time domain indexs were measured for all groups of patients. HRV time domain index (SDNN, SDANN, SDNN index, rMSSD and PNN50) were significantly decreased in the myocarditis untreated group (II) compared with the normal control group (I) (Table 1). This indicated that HRV time domain indexs abnormality was found in myocarditis children. Following 6 weeks of medicine treatment, HRV time domain index (SDNN, SDANN, SDNN index, rMSSD and PNN50) were significantly higher in the sodium tanshinon IIA silate treated group (III) compared with the myocarditis untreated group (II), the effect of which was ablated by treatment. As shown in Table 2, HRV frequency domain index (TP, low frequency (LF), high frequency (HF),

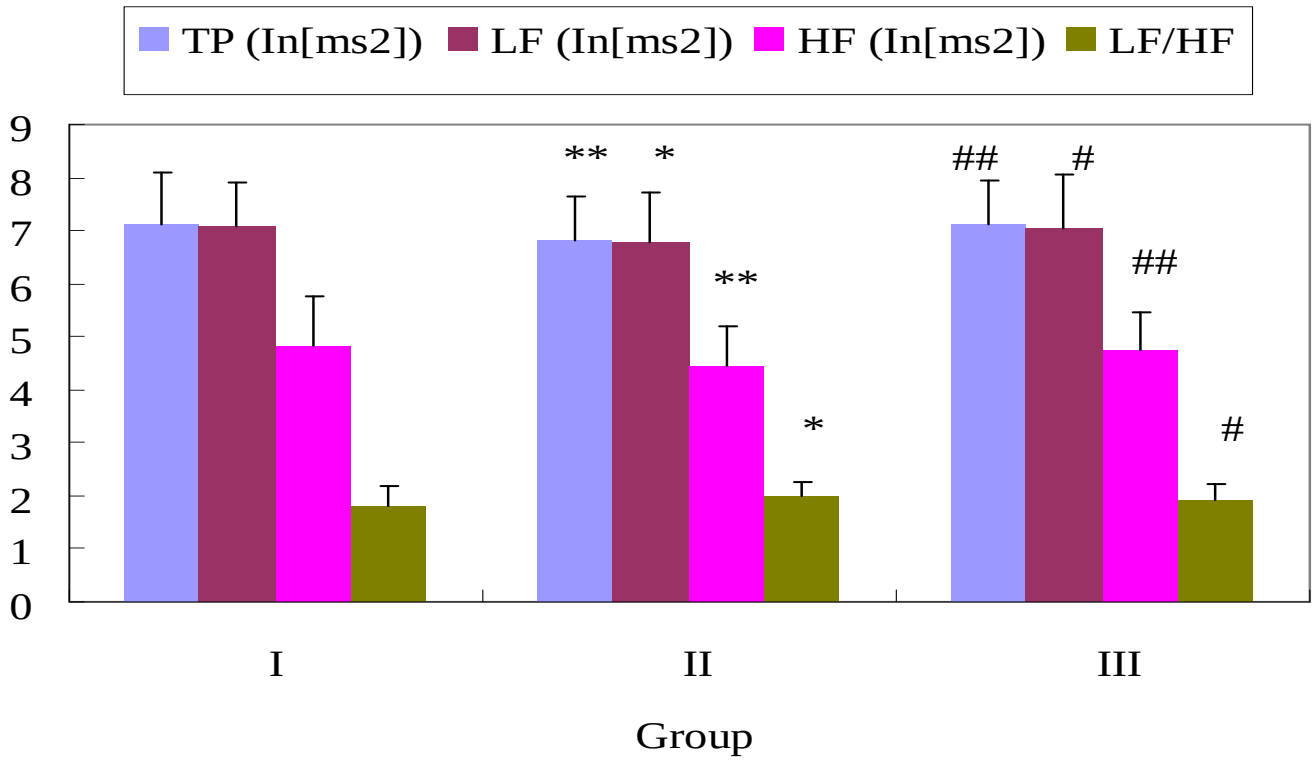

Figure 1. Effect of sodium tanshinon IIA silate treatment on HRV frequency domain indexs in myocarditis children patients; * *P<0.05*, ** *P<0.01*, compared with group I; # *P<0.05*, ## *P<0.01*, compared with group II.

Table 3. Effect of sodium tanshinon IIA silate treatment on CKMB and cTnI in myocarditis children patients.

Group	CKMB (IU/L)	cTnI (ρ/ng·ml^{-1})
I	14.82±1.93	0.091±0.009
II	33.19±5.76 **	0.114±0.018 *
III	16.52±4.92 ##	0.106±0.009

* *P<0.05*, ** *P<0.01*, compared with group I; ## *P<0.01*, compared with group II.

LF/HF) in group II were significantly lower or higher than those in group I (Table 2 and Figure 1). Comparing with patients in the myocarditis untreated group, sodium tanshinon II asilate treatment significantly increased the myocarditis children's TP, LF and HF enhanced the LF HF ratio, as shown in Table 2. Although the LF/HF ratio in sodium tanshinon IIA silate treatment group was lower than that of the myocarditis untreated group, the result was not statistically significant. Children with the myocarditis showed a marked increase in CKMB and cTnI activities as compared to the normal control group (Table 3). However, children fed with the Sodium tanshinon IIA silate significantly decreased CKMB activities when compared with the myocarditis untreated group (II). No significant change in cardiac troponin I (cTnI) between the group III and II. In this study, echocardiography was performed to assess heart function in all the groups. And there was no significant difference in LVFS and left ventricle end-diastolic diameter (LVED) among the groups, the myocarditis significantly enhanced LVED, LAED and LVEF while decreased LVFS, indicating severely altered cardiac structure and contractile function under myocarditis. Sodium tanshinon IIA silate treatment significantly attenuated myocarditis-induced myocardial contractile dysfunction and left ventricular remodeling (Table 4 and Figure 2).

DISCUSSION

Myocarditis is a clinical syndrome characterized by inflammation of myocytes resulting from infectious, toxic and autoimmune etiologies. Ongoing viral infection,

Table 4. Effect of sodium tanshinon IIA silate treatment on heart size and function in myocarditis children patients.

Group	LVED (*l*/mm)	LAED (*l*/mm)	LVEF (%)	LVFS (%)
I	37.95±3.99	22.57±1.87	71.43±9.07	42.06±6.06
II	38.99±4.37	33.63±2.47 **	60.74±10.76 *	38.13±4.38
III	38.73±4.91	21.06±4.05 ##	70.53±8.68 #	41.96±5.52

* *P<0.05*, ** *P<0.01*, compared with group I; # *P<0.05*, ## *P<0.01*, compared with group II.

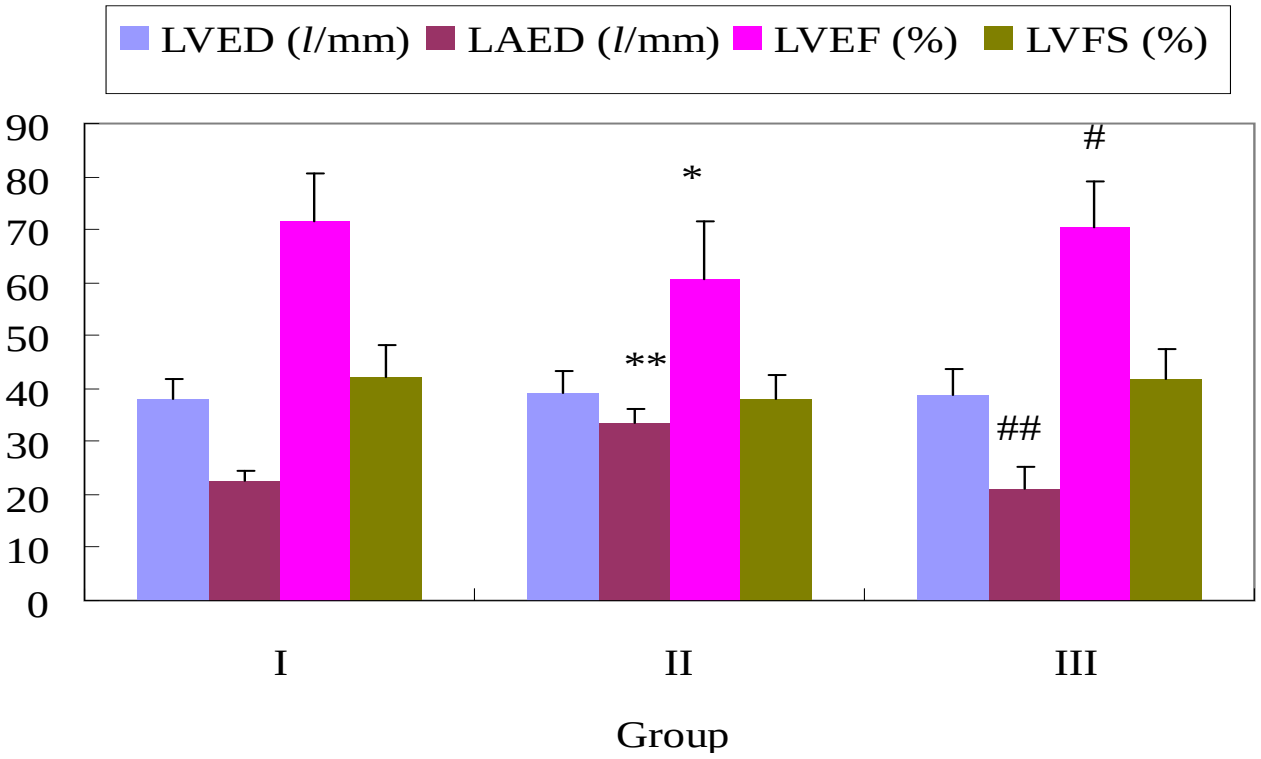

Figure 2. Effect of sodium tanshinon IIA silate treatment on heart size and function in myocarditis children patients; * *P<0.05*, ** *P<0.01*, compared with group I; # *P<0.05*, ## *P<0.01*, compared with group II.

myocardial destruction and adverse remodeling can lead to persistent ventricular dysfunction and dilated cardiomyopathy. Myocarditis is an elusive illness to study and must be treat because the clinical presentation may range from nearly asymptomatic to over heart failure requiring transplantation; a myriad of causes exist and it is occasionally the unrecognized culprit in cases of sudden death (Foerster and Canter, 2011; Durani et al., 2010). *S. miltiorrhiza* (Danshen) is an annual sage plant which grows in China, Mongolia, Korea and Japan. Chemical constituents from *S. miltiorrhiza* root extract are classified into 2 major categories: water-soluble compounds (WSC) and lipophilic diterpenoid quinines (LDQ), the compounds of both have been mostly identified and purified (Han et al., 2008). Among the major diterpenes isolated, including cryptotanshinone, tanshinone I, sodium tanshinon II asilate and dihydrotanshinone, sodium tanshinon II asilate had been shown to posses various pharmacological activities. Li et al. (2009) reported 23 clinical case study of sodium tanshinon II asilate on viral myocarditis.

In this study, we investigated the effect of sodium tanshinon II asilate on children with myocarditis. Result showed that sodium tanshinon II asilate can enhance HRV time domain index. Creatine kinase (CK) is an enzyme protein that helps cells perform their normal function found in the heart, brain, muscle and blood of healthy people. Blood levels of CK rise when your muscle or heart cells are injured. CKMB is a form of the enzyme that is found mainly in heart muscle. While a high level of total CK can indicate damage to muscle, a high CKMB level suggests that there is disease or damage to the heart muscle specifically. CK-MB is usually ordered along with total CK in persons with chest pain to determine

whether the pain is due to a heart attack. It may also be ordered in a person with a high CK to determine whether damage is to the heart or other muscles. Increased CK-MB can usually be detected in heart attack patients about 3 to 4 h after onset of chest pain (Kanemitsu and Okigaki, 1994; Kanemitsu and Okigaki, 1992). Cardiac troponin is the standard for diagnosis or exclusion of acute myocardial infarction. Recent guidelines recommend a cutoff value at the upper 99th percentile (99^{th}%) of values for a reference population of healthy individuals and assay imprecision 10% at this cutoff (Leonardi et al., 2008).

Measurements of cTnI are used in the diagnosis and treatment of myocardial infarction and as an aid in the risk stratification of patients with acute coronary syndromes with respect to their relative risk of mortality (Song et al., 2011). Our present work showed that sodium tanshinon II asilate can increase CKMB and cTnI in myocarditis children patients. Fractional shortening (FS) is the fraction of any diastolic dimension that is lost in systole. When referring to endocardial luminal distances, it is End-diastolic dimension (EDD) minus End-systolic dimension (ESD) divided by EDD (times 100 when measured in percentage) (Costa et al., 2003). LVED is the most important measurement. It is measured at end diastole, on the frame after mitral closure (Haasler et al., 1984). It normally corresponds to the largest cardiac dimension. Left ventricle end-systolic diameter (LVES) is measured at end systole, on the frame preceding mitral valve opening. It corresponds to the smallest cardiac dimension (Sambola et al., 2008). In our present study, LAED is reduced and LVEF and LVFS are increased in medicine-treated children group.

Conclusion

Our work suggests that sodium tanshinon II asilate is useful for therapy of myocarditis children patients.

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