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RESEARCH ARTICLE

EFFECT OF *TERMINALIA ARJUNA* ON HEART RATE VARIABILITY IN DIABETIC RATS

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Abstract

In the present study the possible role of *T. arjuna* treatment on heart rate variability (HRV) in diabetic rats was examined. HRV was assessed from each 5 minute ECG recording using HRV software. Heart rate variability parameters i.e. standard deviation of normal R-R intervals (SDNN), square root of mean- squared difference of successive R-R intervals (RMSSD), power in low frequency range (LF), high frequency range (HF), LF:HF ratio and total power were significantly decreased in diabetic rats as compared to normal rats which was improved after *T. arjuna* treatment. The results of the present study suggest that *T. arjuna* can serve as a therapeutic agent for improving autonomic control in diabetes.
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Keywords: *T. arjuna,* heart rate variability, diabetes.

Introduction

Cardiovascular autonomic neuropathy (CAN), a common form of autonomic dysfunction found in patients with diabetes mellitus, causes abnormalities in heart rate control, as well as altered central and peripheral vascular dynamics. Autonomic nervous system abnormalities may occurquite early in the course of diabetes, followed by a continued gradual decline (Maser & Lenhard, 2005; Vinik & Ziegler, 2007). Early detection of subclinical autonomic dysfunction in diabetic individuals is important for risk stratification and subsequent management (Vinik & Ziegler, 2007). Heart rate variability (HRV) can detect cardiac autonomic impairment in diabetic individuals before traditional cardiovascular autonomic function tests (Malpas & Maling, 1990). HRV analysis is the ability to assess over all cardiac health and the state of the autonomic nervous system (ANS) responsible for regulating cardiac activity. It reflects the heart's ability to adapt to changing circumstances by detecting and quickly responding to unpredictable stimuli (Acharya et al., 2006).

Many traditional treatments have been recommended in the alternative system of medicine for treatment of diabetes and its complications. The stem bark of *Terminalia arjuna* (*T. arjuna*) is used for the treatment of various cardiovascular diseases (Dwivedi et al., 1997; Parveen et al., 2012). Both experimental and clinical studies demonstrated cardioprotective propertiesof *T. arjuna*, ranging from positive inotropic, hypolipidemic, coronary vasodilatory and antioxidant effects to induction of stress protein in heart (Maulik & Katiyar, 2010). In the present study we investigated the possible effect of *T. arjuna* treatment on HRV in diabetic rats.

Material and Methods

Healthy male Wistar albino rats, weighing between 250 and 300 g, were obtained from the animal house of University College of Medical Sciences (UCMS), Delhi. They were housed in polyethylene cages and kept in room temperature maintained at 25 ± 2^{o} C with a 12-h light/dark cycle, given food

and water ad libitum. Experiments were performed according to the guidelines of the Committee for the purpose of control and supervision of experiments on animals (CPCSEA), India, after approval by Institutional Animal Ethical Committee, UCMS, Delhi, India.

Terminalia arjuna Bark Extract was procured from Jamia Hamdard, Delhi, India. *T. arjuna* bark was used in the form of 50 % aqueous ethanol extract. The shade dried bark was coarsely powdered and extracted with ethanol (50 %) using soxhlet apparatus. The extract was then filtered and concentrated to obtain the solid residue. The yield of the total aqueous ethanolic extract was 28.76 %. Primary phytochemical screening of the ethanolic extract of *T. arjuna* barkrevealed the presence of glycosides, triterpenoids, phenols, flavonoids, tannins and saponins.

Diabetes was induced by a single intraperitoneal injection of STZ (65 mg/kg, SIGMA) dissolved in citrate buffer (Szkudelski, 2001). This dose induced type I diabetes mellitus in animals. The control animals were injected with equal volume of vehicle. After 7 days of STZ administration, blood was collected and serum samples were analyzed for blood glucose with Accu-chek glucometer. Animals showing blood glucose higher than 250 mg/dl were considered as diabetic rats and were used for the study.

Grouping of Animals

Animals were randomly divided into 3 groups each having 7 rats.

Group 1: Normal control rats injected with vehicle (citrate buffer) and fed normal pellet diet (control group). Group 2: Rats were injected STZ intraperitoneally and kept for 8 weeks (diabetic group). Group 3: STZ-diabetic rats treated with extract of *T. arjuna* bark (500 mg/kg body weight) by gavage for 30 days. Treatment was started after 8 weeks of STZ administration.

Experimental protocol

On the day of the experiment, rat was anesthetized with urethane dissolved in distilled water and injected intraperitoneally (i.p.) at a dose of 1 gm/kg body weight. Disappearance of pedal reflexes indicated adequate anesthesia. Bipolar limb lead II was used for recording the electrocardiogram (ECG). Electrodes were connected through a bioamplifier (AD Instruments) to the power lab data acquisition system.

Estimation of heart rate variability

HRV was assessed from each 5 minute ECG recording using HRV software (AD Instruments) as previously described (Chaswal et al., 2011). From the surface ECG the programme computed the individual R-R intervals and stored them in the memory as techogram. In the time domain, we determined the standard deviation of normal R-R intervals (SDNN) and square root of mean- squared difference of successive R-R intervals (RMSSD). Spectral power in different frequency bands was computed using Fourier transformation (FFT). Specific frequency bands for the determination of power of the HRV spectrum included, total spectral power (0-3 Hz), power in low frequency range (LF, 0.25-1 Hz), high frequency range (HF, 1-3 Hz). The LF:HF determined the sympathovagal balance.

Statistical Analysis

Analysis was done on SPSS 20.0 statistical package. The data are presented as mean ± SEM. The groups were compared by one-way ANOVA with Tukey's test at 5 %level of significance. P value of less than 0.05 was considered to be significant.

Results and Discussion

All rats given streptozotocin developed severe hyperglycemia (550.57 ± 23.65 versus 83.8 ± 7.85 mg% in control group) associated with a decrease in body weight (185.71 ± 5.91 versus 253.57 ± 4.52 g in control group). Rats on *T. arjuna* therapy did not show any improvement in the bodyweight and blood glucose levels. Basal heart rate was significantly low in diabetic group as compared to controls and did not improve with *T. arjuna* therapy (Table 1). For the time domain analysis of HRV, SDNN and RMSSD, were significantly decreased in diabetic rats as compared to controls but improved with *T. arjuna* therapy. For the frequency domain analysis LF power (0.25-1Hz) and HF power (1-3Hz) of the HRV spectrum showed a significant decline in diabetic rats as compared to controls but improved after *T. arjuna* therapy (Table 1). LF:HF ratio taken as an index of sympathovagal balance was significant decreased in diabetic rats as compared to controls but improved after *T. arjuna* therapy. Similarly total power (0-3Hz) was significant decreased in diabetic rats as compared to controls but improved after *T. arjuna* therapy (Table 1).

Table 1. Heart rate variability parameters: standard deviation of normal R-R intervals (SDNN), square root of mean- squared difference of successive R-R intervals (RMSSD), power in low frequency range (LF), high frequency range (HF), LF:HF ratio and total power in control (group 1), diabetic (group 2) and therapeutic *T. arjuna* group (group 3).

	Group 1 Normal control	Group 2 Diabetic	Group 3 Diabetic on *T. arjuna* therapy
Time domain			
Heart rate (HR)	345.43± 12.57	292± 13.31*	296.14± 11.18*
SDNN	5.73± 0.49	2.78± 0.50†	5.62± 0.74
RMSSD	5.48± 0.41	2.39± 0.50†	5.22± 0.51
Frequency domain			
LF	1.89± 0.32	0.27± 0.05†	1.97± 0.16
HF	5.19± 1.35	1.69± 0.26†	5.05± 0.49
LF/HF	0.43± 0.07	0.15± 0.02†	0.42± 0.07
Total power	11.95± 2.65	3.43± 0.29†	11.05± 1.34

Values are expressed as mean ± SEM (n = 7)
* P< 0.05 compared to group 1, † P< 0.05 compared to group 1 and 3

The high levels of blood glucose confirmed the efficacy of streptozotocin in producing an experimental chronic (8 weeks) diabetes in rats. In the present study there was a significant decline in all the parameters of HRV in diabetic rats. The lower HRV is an indication of cardiac parasympathetic nerve function impairment and is consistent with clinical observations showing decreased HRV in long-term diabetic patients exhibiting autonomic neuropathy (Fazan et al., 1997). Studies comparing cardiac autonomic function tests and HRV indices (based on 5-minute or 24-hourelectrocardiographic recordings) demonstrated that HRV is also decreased in patients without abnormal function tests (Malpas & Maling, 1990), indicating that cardiac parasympathetic nerves are affected early in the development of autonomic neuropathy associated with chronic diabetes. The relative bradycardia observed in our chronic diabetic rats is consistent with earlier observation by Fazan et al (1997). It could be related to a decrease in cardiac ß-adrenergic receptors or to cardiac sympathetic nerve impairment, since it has been shown that a sympathetic nerve dysfunction as severe as the parasympathetic one can occur in chronic diabetic patients (Savarese & Berkowitz, 1979; Weise et al., 1990).

In the present study the time domain analysis of HRV i.e. SDNN and RMSSD, were significantly decreased in diabetic rats as compared to controls but improved with *T. arjuna* therapy. SD provides an evaluation of overall HRV. Reduction in SDNN indicating decreased parasympathetic activity is reported earlier in diabetic patients without the usual cardiovascular signs of autonomic neuropathy (Malliani et al., 1994). As observed by our results, *T. arjuna* improved the impaired parasympathetic activity in diabetic rats.

An understanding of the modulatory effects of neural mechanisms on the sinus node has been enhanced by spectral analysis of HRV (Malliani et al., 1994). Vagal activity is the major contributor to the HF component. Disagreement exists in respect of the LF component. Some studies suggest that LF, when expressed in normalized units, is a quantitative marker for sympathetic modulations, other studies view LF as reflecting both sympathetic and vagal activity. The frequency domain analysis of the HRV spectrum in the present study showed a significant decline in diabetic rats as compared to controls but improved after *T. arjuna* therapy. LF:HF ratio taken as an index of sympathovagal balance was significant decreased in diabetic rats as compared to controls but improved after *T. arjuna* therapy. In diabetic patients without evidence of autonomic neuropathy, reduction of the absolute power of LF and HF during controlled conditions is reported earlier (Acharya et al., 2006).

T. arjuna bark extract contains triterpenoid saponins (arjunic acid, arjunolic acid, arjungenin, arjunglycosides), tannins, flavonoids (arjunone,arjunolone), gallic acid, minerals and phytosterol (b-sitosterol). Flavonoids have been reported to exert antioxidant, anti inflammatory, antiproliferative, anti-platelet and lipid lowering effects, while glycosides have cardiotonic property (Dwivedi et al., 1997; Manna et al., 2010). Thus, combined or independent action of several constituents like flavonoids, tannins and glycosides might be responsible for the beneficial effects of *T. arjuna* in improving autonomic control in diabetes.

A number of different therapeutic agents are emerging for the treatment of diabetic neuropathy. Not all investigational drugs have been studied with regard to the effect on autonomic nerve-fiber function. Given the multifactorial process involved in the pathogenesis of diabetic neuropathy, it is likely that combination therapies directed at various components of the pathogenic pathway may be required. Since the pathogenesis of neuropathy is affected by more than just glycemic control, *T. arjuna* can serve as a therapeutic agent for improving autonomic control in diabetes.

References

Acharya, U.R., Joseph, K.P., Kannathal, N., Lim, C.M., Suri, J.S. 2006. Heart rate variability: a review. Med. Bio. Eng. Comput. 44:1031–1051.

Chaswal, M., Das, S., Prasad, J., Katyal, A., Fahim, M. 2011. Cardiac autonomic function in acutely nitric oxide deficient hypertensive rats: role of sympathetic nervous system and oxidative stress. Can. J. Physiol. Pharmacol. 89(12): 865-874.

Dwivedi, S., Jauhari, R., Varshney, A. 1997. *Terminalia arjuna* the cardiovascular friendly plant. Atherosclerosis. 134: 47.

Fazan, R. J., Ballejo, G., Salgado, M.C., Moraes, M.F., Salgado, H.C. 1997. Heart rate variability and baroreceptor function in chronic diabetic rats. Hypertension. 30: 632-5.

Malliani, A., Lombardi, F., Pagani, M. 1994. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. Br Heart J. 71(1): 1–2.

Malpas, S.C., and Maling, T.J.B. 1990. Heart-Rate Variability and Cardiac Autonomic Function in Diabetes. Diabetes. 39:1177-81.

Manna, P., Ghosh, J., Das, J., Sil, P.C. 2010. Streptozotocin induced activation of oxidative stress responsive splenic cell signalling pathways: Protective role of arjunolic acid. Toxicol. Appl. Pharmacol. 244: 114–129.

Maser, R.E., Lenhard, M.J. 2005. Cardiovascular autonomic neuropathy due to diabetes mellitus: Clinical manifestations, consequences, and treatment. J. Clin. Endocrinol. Metabol. 90: 5896–5903.

Maulik, S.K. and Katiyar, C.K. 2010. *Terminalia arjuna* in Cardiovascular Diseases: Making the Transition from Traditional to Modern Medicine in India. Curr. Pharm. Biotechnol. 11: 855-860.

Parveen, A., Babbar, R., Agarwal, S., Kotwani, A., Fahim, M. 2012. *Terminalia arjuna* enhances baroreflex sensitivity and myocardial function in Isoproterenol-induced chronic heart failure rats. J. Cardiovasc. Pharmacol. Ther. 17: 199-207.

Savarese, J.J., Berkowitz, B.A. 1979. ß-Adrenergic receptor decrease in diabetic rat hearts. Life. Sci. 25: 2075-2078.

Szkudelski , T. 2001. The mechanism of Alloxan and Streptozotocin action in B Cells of the rat pancreas. Physiol. Res. 50: 536-546.

Vinik, A.I., Ziegler, D. 2007. Diabetic cardiovascular autonomic neuropathy. Circulation. 115: 387-397.

Weise, F., Heydenreich, F., Gehrig, W., Runge, U. 1990. Heart rate variability in diabetic patients during orthostatic load: a spectral analytic approach. Klin Wochenschr. 68: 26-32.

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