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Effects of ACE inhibitor on diabetic cardiovascularcomplications : cardiovascular functional changes

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Using streptozotocin induced diabetic rats, the effects of angiotensin converting enzyme inhibitor (ACEI) on cardiovascular complications were studied. Animals were separated into three groups of controls (CON), streptozotocin induced diabetic rats (STZ-rats), and STZ-rats treated with ACEI (STZ-C; 10mg/kg. bw. /day). At 8, 12, and 16 weeks after STZ injection, cardiovascular parameters consisting of heart rate, mean arterial pressure, aortic flow rate, coronary flow rate, and left ventricular isotonic contraction assessed from STZ-rats were significantly different from their CON (p<0. 05). Also, the parameters determined from STZ-C rats were significantly different from those of STZ-rats. It is concluded that the diabetic cardiovascular complications could be prevented by ACEI. Additionally, angiotensin II might play a key role in diabetic cardiovascular complications through its hypertension and growth-promoting actions.

Key words : *Diabetes, Cardiovascular functional changes, ACE inhibitor.*

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การศึกษาครั้งนี้เป็นการศึกษาผลของตัวยับยั้งแองจิโอเทนซินคอนเวอร์ติ้งเอนไซม์ (ACEI) ต่อภาวะแทรกซ้อนของหัวใจและหลอดเลือด โดยใช้หนูที่ทำให้เป็นเบาหวานด้วย streptozotocin สัตว์ทดลองที่นำมาศึกษาในครั้งนี้แบ่งเป็น 3 กลุ่มของหนูควบคุม (CON) หนูเบาหวาน (STZ) และหนูเบาหวานที่ได้รับ ACEI (STZ-C) ในปริมาณ 10 mg/kg bw/day โดยนำมาทำการศึกษาที่ 8,12. และ 16 สัปดาห์ หลังการฉีด STZ พบว่าค่าพารามิเตอร์คือ อัตราการเต้นของหัวใจ ค่าเฉลี่ยความดันเลือด ค่าอัตราการไหลเวียนของเลือดในเอออร์ตาและโคโรนารีย์ ตลอดจนค่าแรงการหดตัวของหัวใจห้องล่างข้างซ้ายแบบไอโซโทนิค ที่วัดได้จากหนูเบาหวานแตกต่างจากหนูควบคุมอย่างมีนัยสำคัญทางสถิติ ($p<0.05$) และค่าพารามิเตอร์เหล่านี้ซึ่งประเมินได้จากกลุ่ม STZ-C แตกต่างจากกลุ่ม STZ อย่างมีนัยสำคัญทางสถิติ ($p<0.05$) โดยอาจสรุปได้ว่า ACEI สามารถป้องกันการเกิดภาวะแทรกซ้อนของหัวใจและหลอดเลือดในเบาหวานได้ รวมทั้งอาจกล่าวได้ว่า แองจิโอเทนซินทู อาจมีบทบาทสำคัญที่ทำให้เกิดภาวะแทรกซ้อนของหัวใจและหลอดเลือดได้ โดยผ่านทางกลไกการเพิ่มความดันเลือดและการกระตุ้นการเจริญ ภายในเซลล์

The elevation of serum angiotensin II (Ang II) reported in diabetic patients may play a key role in the pathogenesis of cardiovascular complications including hypertension, atherosclerosis, myocardial hypertension, and myocardial dysfunction. Recently, several studies have provided evidence of the actions of angiotensin converting enzyme (ACE) inhibitor and some renin inhibitors on the reduction of left ventricular hypertrophy and on vascular proliferation.[1] However, the effects of ACE inhibitor on diabetic cardiovascular complications have not yet been determined. Therefore, the major objective of our investigation was to study the effect of ACE inhibitor on cardiovascular functional changes in diabetes mellitus.

Materials and Methods

Male Wistar-Furth rats (n=45) weighing 100-150 g with ages of 4-5 weeks were used in this study. All rats were fasted overnight, then 30 rats received intraperitoneal injections of streptozotocin (STZ) 65 mg/kg bw. Control animals (CON, n=15) received sham injections of normal saline. On the following day, fifteen of the STZ-injected rats received cilazapril with the dose of 10 mg/kg bw, and these rats were referred as the STZ-C group. The STZ-C rats were received daily feedings of cilazapril every day until the day of the experiment. Those animals that did not meet the criteria of blood glucose concentrations of >400 mg/dl were omitted from the investigation. The blood glucose concentrations were determined by hemoglucostrip and glucometer (Reflolux S).

The cardiovascular parameters of heart rate (HR), common carotid arterial pressure (CAP), aortic flow rate (AF), coronary flow rate (CF), and left ventricular isotonic contraction (LVIC) were determined at 8,12, and 16 weeks after the STZ injections. Totally, there were 5 rats in each of the three different age groups.

In each experiment, each rat was weighed and anesthetized by sodium pentobarbitol (i.p., 30 mg/kg bw.). After tracheotomy, the animals were ventilated with small animal respirators (Haward Rodent Model 683). The chest was opened to expose the heart and three major vessels: the right subclavian artery, the innominate artery, and the ascending aorta. AF was measured by a flow probe (Nikhon model FE-020T) placed on the ascending aorta. Blood pressures were monitored via a catheter (PE-180) cannulated to the common carotid artery connected to a pressure transducer (Nikhon model TP-300T) coupled to a polygraph (Nikhon RM 6000). The hearts were then carefully isolated by the modified Langendroff's method.[2] Fifteen minutes after the hearts were isolated the left ventricular contraction values were measured via a wire hooked at the apex of the left ventricle connected to an isotonic transducer and to a polygraph recorder. The preload was equal to 5 grams.

Statistics

An unpaired Student's t-test was used to analyse the difference of each parameter between the STZ-rats and their age-matched CON, and between the STZ-and STZ-C rats ($p<0.05$).

Results

The injections of 65 mg/kg bw. STZ into the 100-150g Wistar-Furth rats resulted in polydipsia, polyuria, polyphagia, and stable

hyperglycemia within 24-48 hours. The concentrations of plasma glucose are summarized in table 1. The results indicated that the plasma glucose levels of STZ-rats were significantly elevated as compared to their age-matched CON group. Also there was no significant difference in plasma glucose between STZ-rats and the STZ-C groups for all three monitored time points (8, 12,16 wks).

Table 1. Plasma glucose (mg/dl) of controls (CON), streptozotocin-induced diabetic rats (STZ-rats), and cilazapril-treated STZ-rats (STZ-C) at 8, 12, 16 weeks of experiment.

	plasma glucose (mg/dl)		
	8-wk	12-wk	16-wk
CON (n=5)	106.28±8.67	109.37±9.27	109.20±14.32
STZ-rats (n=5)	430.00±43.79*	476.00±25.09*	451.00±41.67*
STZ-C (n=5)	417.20±12.85^{ns}	412.60±14.95^{ns}	420.00±13.76^{ns}

*Statistical difference compared to controls ($p<0.05$).
NS = non significant difference compared to STZ-rats ($p<0.05$)

In table 2, the body weights of all CON, STZ-rats, and STZ-C rats are shown. The results indicated that the weights of STZ-rats were significantly decreased as compared to their age-matched CON. There was no significant difference between the weights of STZ-rats and STZ-C.

Table 2. Body weight (g) of controls (CON), streptozotocin-induced diabetic rats (STZ-rats), and cilazapril-treated STZ-rats (STZ-C) at 8, 12, and 16 weeks of experiment.

	Body weight (g)		
	8-wk	12-wk	16-wk
CON (n=5)	349.71±22.60	413.60±18.36	456.25±9.65
STZ-rats (n=5)	280.00±17.26*	280.60±22.82*	281.40±12.83*
STZ-C (n=5)	280.80±19.58^{ns}	275.20±9.65^{ns}	293.40±20.44^{ns}

*Statistical difference compared to controls ($p<0.05$).
NS = non significant difference compared to STZ-rats ($p<0.05$)

In table 3, ratios of heart weight per 100 g body weight were calculated and summarized as means and SD for each group of each monitored time point. AT 8 weeks the ratio of heart weight per 100 g body weight was significantly increased as compared to their age-matched CON. This elevation trend persisted throughout the remainder of the study period (16 wks). These ratios indicated that STZ hearts tended to increase their size referred as myocardial hypertrophy. However, the ratio of heart weight per 100 g body weight of the STZ-C groups were not significantly different as compared to the STZ groups during 8-12 wks. Interestingly, at 16 wks the ratio of heart weight per 100 g body weight of the STZ-C group become significantly less than for the STZ group.

Table 3. Ratio of heart weight per 100g body weight of control (CON), streptozotocin-induced diabetic rats (STZ-rats), and cilazapril-treated STZ-rats (STZ-C) at 8, 12, and 16 weeks of experiment.

	Ratio of heart weight per 100g body weight		
	8-wk	12-wk	16-wk
Con (n=5)	0.35±0.01	0.34±0.03	0.33±0.06
STZ-rats (n=5)	0.41±0.04*	0.42±0.05*	0.44±0.02*
STZ-C (n=5)	0.36±0.05^{ns}	0.37±0.43^{ns}	0.37±0.03**

*Statistical difference compared to controls ($p<0.05$).

**Statistical difference compared to STZ-rats ($p<0.05$).

As shown in table 4, the HR values of the STZ groups were significantly decreased as compared to those of the CON groups. Interestingly, the HR values of the STZ-C groups were significantly higher than those of the STZ groups for all three time points.

Table 4. Heart rates (beats per min) of control (CON), streptozotocin-induced diabetic rats (STZ-rats), and cilazapril-treated STZ-rats (STZ-C) at 8, 12, and 16 weeks of experiment.

	Heart rate (beats/min)		
	8-wk	12-wk	16-wk
CON (n=5)	185.71±0.61	179.20±21.05	182.50±28.66
STZ-rats (n=5)	147.20±9.23*	128.80±18.42*	136.00±18.11*
STZ-C (n=5)	184.00±12.33*	198.00±23.82**	192.00±14.97**

*Statistical difference compared to controls ($p<0.05$).

**Statistical difference compared to STZ-rats ($p<0.05$)

In Fig 1, the CAP values of the STZ-rats are shown to be significantly increased as compared to the CON groups for every monitored time point (8, 12, 16 wks). However, the CAP values of the STZ-C group were significantly different from the STZ-rats. At three mornitored time points the CAP values of the STZ-C group were significantly less than those of the STZ-rats as shown in Fig. 1.

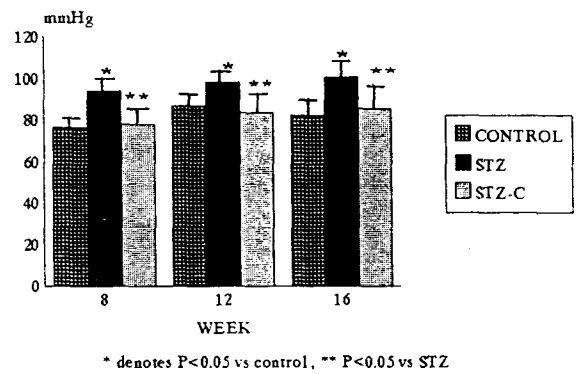

Figure 1. Means ± SD of carotid arterial pressure (CAP; mmHg) determined from controls (CON), streptozotocin-induced diabetic rats (STZ-rats), and STZ-rats treated with ACEI (STZ-C) at 8, 12, 16 weeks after the streptozotocin injections.

In Fig. 2 and 3, the AF and CF values of the STZ groups are shown to be significantly decreased as compared to the CON groups. However, the AF and CF values of the STZ-C groups were significantly higher than those of the STZ-rats at all three time points, as shown in Fig. 2 and 3.

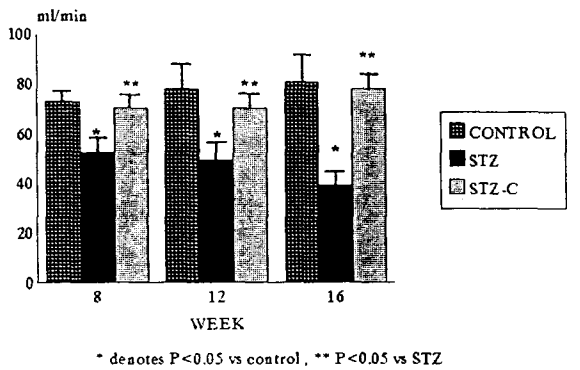

Figure 2. Means ± SD of aortic flow rate (ml/min) determined from controls (CON), streptozotocin-induced diabetic rats (STZ-rats), and STZ-rats treated with ACEI (STZ-C) at 8, 12, 16 weeks after the streptozotocin injections.

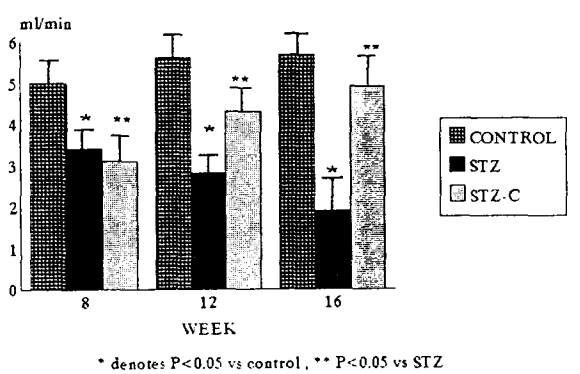

Figure 3. Means ± SD of coronary flow rate (ml/min) determined from controls (CON), streptozotocin-induced diabetic rats (STZ-rats), and STZ-rats treated with ACEI (STZ-C) at 8, 12, 16 weeks after the streptozotocin injections.

In Fig. 4, the LVIC values of the STZ-rats are shown to be significantly decreased as compared to those of CON groups during 12-16 wks after STZ injection. Interestingly, the LVIC values of the STZ-C group were significantly higher than those of the STZ groups for all three time points as shown in Fig. 4.

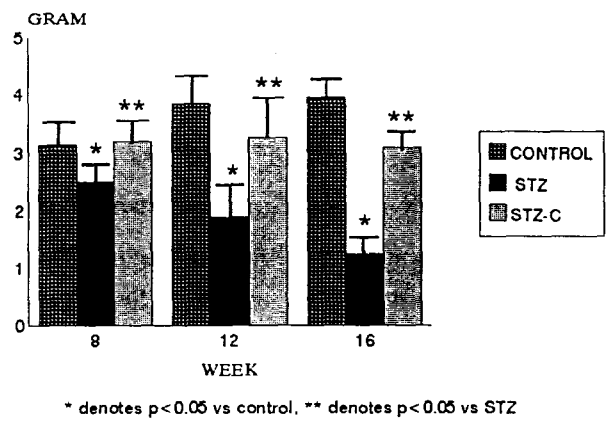

Figure 4. Means±SD of left ventricular isotonic contraction (gram) determined from controls (CON), streptozotocin-induced diabetic rats (STZ-rats), and STZ-rats treated with ACEI (STZ-C) at 8, 12, 16 weeks after the streptozotocin injections.

Discussion

In our study, we found that the hearts of 8-16 wk STZ-rats exhibited abnormalities of cardiovascular functions. These included decrease of HR, AF, CF, and LVIC; and the increase of CAP. These functional derangements were concomitant with the hyperglycemic state and myocardial hypertrophy as compared to their age-matched controls.

Recently, many studies have shown that there is a high incidence of abnormal renin-angiotensin system (RAS) in association with diabetes. The increase of serum ACE has been reported in both human and animal diabetic models.[3-5] Even though in our study we did not evaluate the level of serum ACE in STZ-rats, we did find that cilazapril, one of ACE inhibitors, could attenuate diabetic cardiovascular complications. As the results show in Fig. 2, 3, and 4, the AF, CF, and LVIC values obtained from STZ-rats were significantly less than those of the STZ-C groups. Moreover, in the STZ-C groups both hypertension (data from Fig. 1) and myocardial hypertrophy (data from Table 3) were significantly decelerated as compared to the STZ-groups for all three monitored time points. According to the effects of cilazapril, we believe that Ang II should have some relation to diabetic cardiovascular complications. Ang II, which is well known as a vasoconstrictor, could therefore, be involved as a major cause of hypertension and myocardial hypertrophy. Recently, it has been reported that Ang II had some action as a mediator of hypertrophy in both myocardial cells and vascular smooth muscle cells.[6-7] Therefore, it might be speculated that Ang II could accelerate diabetic cardiovascular complications through both the mechanisms of hypertension and growth-promotion. However, in order to confirm these speculated effects of Ang II, in other words the actions of ACE inhibitors, further pathological studies of myocardial and vascular wall structure need to be conducted.

In summary, our study showed that cardiovascular complications in STZ-rats could

be attenuated by daily oral feeding of 10 mg/kg bw cilazapril. And the effects of cilazapril were observed as the progression of a diabetic state for up to 16 weeks without insulin or any other sugar-lowering drug treatments. However, for benefit to diabetic patients, further investigations are needed in order to explain the mechanisms of this agent.

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