CHAPTER V

DISCUSSION

In this study, the hearts of 8-16 week STZ-induced diabetic rats exhibited the decreased cardiovascular functions which were characterized by low aortic flow rate (AFR), low coronary flow rate (CFR), increased common carotic arterial pressure (CAP), and decreased left ventricular isotonic contraction (LVIC). Moreover, results of pathological studies of ventricular wall and intramural coronary arteries in left ventricle of hearts obtained from 8-16 week STZ-induced diabetic rats indicated that the ventricular wall and coronary arteries wall were become thickening as compared to the age-matched control hearts. These derangement of cardiovascular functions agreed with other results such as the previous studies done by Regan and Ettinger et al., (1974),and by Regan and Wu et al., (1981). They reported that in chronic diebetic dogs, the decreased deposition of myocardial glycoprotein and collagen was in association with the diminished left ventricular compliance. In chronic diabetic model of STZ-treated rats, the declining of left ventricular contractility was also reported (Fein et al., 1980; Modrak, 1980). These abnormalities of myocardial compositions and functions were concomitant with the changes in their metabolism as reported by Penpargkul and co-workers (1980). Using isolated hearts of 8 - week STZ-treated rats, Penpargkul and co-workers indicated that myocardial glycogen stores, calculated glycogen utilization and

pyruvate production were increased with the same myocardial oxygen consumption rate. They also demonstrated that insulin did not correct these metabolic abnormalities.

Possible roles of ACE-inhibitor on the diabetic cardiovascular complications

Diabetes is especially well documented in association with cardiovascular disorder including hypertension and congestive heart failure (Kessler, 1971). Recently, many studies also showed the high incidence of abnormal renin-angiotensin system (RAS) in associated with diabetes. Funakawa et al., (1983) and Schernthaner et al., (1984) showed that serum ACE in diabetic rats and humans were significantly increased, respectively. Further study done by Valentovic et al., (1987) confirmed that there was increased serum ACE in STZ diabetic rats. In their study, ACE activity measured 12 days after STZ injection was significantly increased by 58 % as compared ($p<0.05$) to controls. As the basic is that angiotensin I will be converted to angiotensin II by this ACE-catalytic activity. Therefore the increasing of serum ACE activity will cause more serum angiotensin II (Ang II) synthesis. The increasing of serum Ang II which is generally known as a vasoconstrictor would be a major cause of hypertension in diabetes through the mechanism showed before in Figure 2.2.

Hypertension is well-known as a possible cause of left ventricular hypertrophy. Since the increase workload was required by the heart in order to pump against the increase of total resistance (Levy et al., 1980). Some

believed that left ventricular hypertrophy does not usually occur in diabetes unless hypertension was present. However, with the presence of diabetes, damage of the myocardium caused by hypertension appeared to be accelerated (Valentovic et al., 1987). In our study the result supported such observation that chronic diabetic hearts with hypertension could cause the left ventricular hypertrophy and diminished ventricular contractility. Moreover, our results also showed that ACE-inhibitor could attenuate this effect of hypertension. Since all three age groups of ACE-inhibitor treated STZ-rats had less CAP, no hypertrophy of both RV and LV walls, and ventricular contractility was significantly higher than the STZ-rats. The mechanism of this effect of ACE-inhibitor might be purposed simply that ACE-inhibitor could prevent further cardiovascular complications in STZ- rats because ACE-inhibitor directly regulate CAP through inhibiting Angiotensin II synthesis that is oftenly increased in diabetic models.

Besides this mechanism of ACE-inhibitor on hypertension, the ability of ACE-inhibitor in preventing diabetic cardiovascular complications that we have showed in our studies might be resided on the newly described action of Ang II as a growth-promoting agent (as described and showed the mechanism previously in Figure 2.2). Such that the increase of serum ACE activity that resulted to the increase of serum Ang II might have a direct effect on cardiac muscle cell growth (Baker and Aceto, 1990). Recently, many studies have shown that Ang II is a potent, direct

stimulus of protein synthesis in chick-heart cell culture (Baker and Campanile, 1984; Allen et al., 1988; Baker and Singer, 1988), suggesting that binding of Ang II to its cell-membrane receptor in cardiac tissue could stimulate the processes of inositol phosphate release, intracellular Ca^{2+} mobilization and activation of voltage-sensitive Ca^{2+} channels (Baker and Campanile, 1984; Allen et al., 1988 ; Baker and Singer, 1988). According to these postulated mechanisms, renin-angotensin system (RAS) may effect on cardiac functions specially through the modulation of myocardial cell growth directly.

Speculation of actions of ACE-inhibitor on coronary vascular changes in STZ-rats.

Three hearts of each aged-groups of control, STZ-rats and ACE-inhibitor treated STZ-rats were used in the pathological studies of intramural coronary arterial walls by performing the fixation methods as described before in chapter III. Our results of this part of the study indicated that the vascular walls of intramural coronary arteries in STZ-rat hearts were thicker than the controls as showed in Figure 4.19 - 4.27.

In each experiment before isolation of the hearts the aortic flow rate (AFR) were measured by flow probe as described before in chapter III. Means and SD of these AFR of 5 controls, 5 STZ-rats, and 5 cilazapril-treated STZ-rats were summarized and showed in Table 4.6 and Figure 4.3. As compare to the controls, the results indicated that AFR of STZ-rats were significantly decreased in all three

aged-groups. The same as these results, the values of CFR assessed from STZ-rats at 8, 12, 16 weeks after the STZ injections were significantly decreased as compared to the controls (Table 4.7 and Figure 4.4).

The decreasing of both aortic and coronary flow rates observed in STZ-rats might be caused by the lesion of vascular wall that were observed in all three different aged groups. As the structure of arterial wall components became deformity, the elasticity of the vessel wall could be changed concomitantly. Such that the blood flow resistance could be disturbed also. However, the results of this study concerning with the thickening of intramural coronary arterial wall, and the low flow occured in both aorta and coronary still need further more investigations in order to explain the correlation of these changes.

As the result showed in Figure 4.19 - 4.27, ACE-inhibitor seemed to prevent these morphological changes of intramural coronary arterial walls.

In summary, the results of these physiological and pathological studies indicated that the changes of cardio-vascular functions assessed in STZ-rats could be prevented by oral feeding of ACE-inhibitor (10 mg/kg body weight/day) The mechanisms of angiotensin II as a vasoconstrictor and a growth-promoting agent might be explained this preventing effects of ACE-inhibitor. However, the levels of serum angiotensin II, the ultrastructures of myocardial cells and vascular smooth muscle cells were not determined in this investigation. Therefore, more informaiton is needed to confirm this hypothesis.