CHAPTER V

DISCUSSION

In these studies, the hearts of 8, 20 weeks STZ-induced diabetic rats exhibited the decreased cardiovascular functions which were characterized by low aortic flow rate (AFR), low coronary flow rate (CFR), increase mean arterial pressure (MAP), included diastolic pressure (DP)and systolic pressure (SP), and decrease 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, 20 weeks STZ-induced diabetic rats indicated that the left ventricular walls and coronary artery, arteriole and capillary walls were become thickening as compare to the age matched controls. These derangement of cardiovascular functions agreed with other results such as the previous studies done by Litwin et al., (1990) they found that in the STZ induced diabetic rat, a model of type I diabetes, abnormalities of cardiac function may be seen as early as 7 days after induction of diabetes. Moreover, Rosen et al., (1996) reported that in 4 month STZ-rats, cardiac performance was analyzed in the isolated heart perfused at constant volume, they found the increasing in end diastolic pressure (EDP), coronary perfusion pressure (CPP), and vascular resistance in diabetes. The intravascular volume strongly reduced in diabetes, and the epicardial perfusion rate was reduced in hearts of diabetic rats. Together with previously published morphological data reported by Shimizu et al., (1993) demonstrating the increasing of interstitial perivascular fibrosis and collagen type III in hearts of diabetic patients. In 1992, Grossmone et al. studied cardiac structure, systolic function and hemodynamics in diabetic hypertensive patients. The results showed that diabetes mellitus accelerates the development of arterial pressure and, therefore, may contribute to the increased

cardiovascular morbidity and mortality in patients with hypertension. Grossman et al., (1995) have emphasized that both in experimental animal models and in humans points to hypertension as of critical importance in the pathogenesis of severe diabetic heart disease. In diabetic hypertensive cardiomyopathy, coronary artery disease as well as structural and functional abnormalities are more pronounced than would be expected from either process alone.

Possible role of ACE-I on the diabetic cardiovascular complications

Diabetes is especially well documented in association with cardiovascular disorder including hypertension and congestive heart failure. The chronic cardiovascular complications of diabetes mellitus included hypertension atherosclerosis, myocardial dysfunction as shown in our studies. The renin angiotensin system, especially AngII, may potentially play a key role in these pathologic processes, and thus, contribute to the development of diabetic cardiovascular complication. Some of reports about the actions of ACE-I were preventing and slowing the progression of these complications, especially, the reduction of left ventricular hypertrophy and of vascular proliferation (Rosen et al., 1996). Diabetic patients have a lower basal plasma renin activity and less stimulation of plasma renin activity when compared with non-diabetic patients who are match for age, gender and blood pressure (Hsueh., 1992). Because of the low circulating renin activity, increased sensitivity to AngII and/ or enhanced activity of AngII production on the tissue has been suggested to account for the actions of ACE-I in diabetic vascular complications. The cellular effects of AngII are extensive and encompass hypertrophy, hyperplasia and the deposition of extracellular matrix (Rosen ., 1996). The action of AngII are mediated by AT1 and AT2 membrane receptor subtypes. Sung et al., (1994) reported that AT1 receptors mediate smooth muscle proliferation in rat vascular smooth muscle, thus, myocardial AngII receptor density is increased in diabetic rats in association with an increase in steady state

AT1 receptor mRNA levels (Leonado et al., 1994). Since AT1 receptors are prominent in cardiac fibroblasts (Iwami., 1993) and since AngII stimulates collagen production and firbonectin in the cardiac fibroblast (Colleaques., 1992).It seems that AngII may have a direct effect that may be important in fibroblast remodeling. AngII, reportly an angiogenic factor for endothelial cell (Okuda et al., 1996). They reported that AngII may paticipate in development of the diabetic angiopathy by significantly increase PDGF in human endothelial cells and the effect was accompanied by a transient increase in cytosolic calcium. Moreover, Bijlstra et al., (1995) reported that diabetes is associated with an impaired endothelium dependent assodilation and increase mean arterial pressure (MAP). AngII which is a potent vasoconstrictor would be a major cause of hypertension in diabetes through the mechanism showed in Fig. 2.1. And in our studies table 4.3-4.5 and Fig. 4.3- 4.5 the increasing on mean arterial pressure, including systolic pressure and diastolic pressure, interestingly lowering in aortic flow rate indicated for increasing systemic vascular resistance may be involved with AngII through the same mechanism.

Hypertension is also clearly demonstrated as a risk factor for the development of left ventricular hypertrophy. Since the increased work load was required by the heart in order to pump against the increasing of total resistance (Doba et al., 1996). Some believed that left ventricular hypertrophy does not usually occur in diabetes unless hypertension was present. Schenk et al., (1994) have emphasized that the complication of diabetes and hypertension may lead to more severe interstitial fibrosis and myocellular damage than in diabetes or hypertension alone. In our model of STZ-induced diabetic rats, ACE-I (cilazapril) 1 and 10 mg/kg.BW./day could prevent the development of left ventricular hypertrophy and coronary arterial wall thickening(table 4.11- 4.12 and Fig. 4.12, 4.16-4.18) when administrated at the onset of hypertension (STZ-C1). And these same doses could treat these stages after onset of ventricular hypertrophy (STZ-C8). These effects are

due, in part, to decrease the pressure overload on the heart. However, in the dose of non antihypertensive (0.01mg/kg.BW./day) of an ACE-I could prevent and treat the development of left ventricular hypertrophy. Suggesting that AngII has specific effects to increase heart size, independent of blood pressure. In our studies indicated that thickening of left ventricular wall were diminished in 20 weeks cilazapril treated STZ-rats. Our observations suggested that ACE-I by cilazapril is cardioprotective in diabetes through the mechanism that decrease structural collagen abnormalities, interstitial and perivascular fibrosis more than decrease hypertrophic of cardiomyocyte. These suggesting supported by LVIC increase in hearts of diabetic rats treated with cilazapril as compared to diabetic controls.

Speculation of action of ACE-I on coronary vascular changes in STZ-rats

The hearts of each age matched groups of controls, STZ-rats, and ACE-I treated STZ-rats were used in the pathological studies of intramural coronary arterial wall 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 artery, arteriole, and capillary walls were thicker than the controls as showed in Table 4.12 and Fig. 4.16- 4.18. The values of CFR assessed from STZ-rats at 8, 20 weeks after the STZ-injection were significantly decreased as compared to the controls Table 4.8 and Fig. 4.8. The decreasing of coronary flow rates observed in STZ-rats might be caused by the lesion of vascular wall that were observed in all three differences aged groups. From the point of views that the endothelium plays an important role in the transformation of some substances with a cardiovascular action and it secretes itself vasoactive substances. Vascular effections in diabetes and hypertension are characterized by impaired homeostasis of vasoactive substances of endothelial origin, raised levels of vasoconstricting factors and reduction of vasodilating factors. Vasoactive agents lead at the same time also to alteration of the growth and proliferation potential of smooth muscle cells of the

vascular wall and thus to remodeling of the vascular structure in diabetes. One of the vasoconstrictor is AngII. Veltmar et al.,(1991) reported that endothelium systhesis of AngI, possible, AngII and ACE in vascular smooth muscle cells (VSMCs), AngII is not only a potent vasoconstrictor, but also a hypertrophic factor. AngII significantly increased PDGF in human endothelial cells and the effect was accompanied by a transient increase in cytosolic calcium. The AngII induced intracellular calcium increase. AngII may participate in the development of the diabetic angiopathy (Okuda et al., 1996). In cultured adult rat aortic smooth muscle cells (ASMCs), AngII stimulates platelet-derived growth factor A-chain and transforming growth factor β1 gene expression and production (Gibbons.,1992).

The former substance stimulates migration and proliferation of VSMCs. Most of growth and vasoconstrictive effects of AngII in blood vessel are mediated by AT1 receptor. As the structure of arterial wall components became deformity, the elasticity of vessel walls could be changed concomitantly. Such that the blood flow resistance could be disturbed also.

Speculation of the major mechanism of ACE-I on morphologic changes of cardiovascular

From Table 4.11 and Fig. 4.12 , non-antihypertensive dose (0.01 mg/kg.BW./day) of an ACE-I could prevent and treat the development of left ventricular hypertrophy. Such results indicated that AngII has specific effects to increase heart size independent of blood pressure.As the result showed in Table 4.12 and Fig. 4.15-4.18. ACE-I seemed to prevent these morphological changes of intramural coronary arterial, arteriole, and capillary walls. Interestingly, non-antihypertensive dose of cilazapril in our studies (0.01 mg/kg.BW./day) could attenuate these morphologic changes of coronary arteries. Therefore, the hypothesis that can be purposed from our studies was that, the major mechanism of cilazapril that can prevent the vascular changes in diabetes is actually through the direct

inhibition of the hypertrophic effects of AngII. Hartman.,(1995, 1996) reported that such antitrophic effect of ACE-I on cardiovascular is mediated by inhibition of AngII and by also its action on the kinin- nitric oxide pathway. The potential bradykinin-sparing property of ACE-I may further promote the increase of bradykinin-stimulated nitric oxide production. As ACE-I was reported to increase bradykinin levels, while reducing angiotensin production. Moreover, bradykinin can exert its effect on the endothelium by activating the conversion of arachidonic acid to prostacyclin as well as by stimulating the release of endothelium derived relaxing factor (EDRF) or universally known as nitric oxide.

In summary, the present results of physiological and pathological studies indicated that the changes of cardiovascular functions assessed in STZ-rats could be prevented or attenuated by oral daily feeding of ACE-I that was administered at the beginning of the onset of diabetes or 1 day after the STZ injection) (STZ-C1). Moreover, our present studied also demonstrated that besides the prevention, ACE-I could also be used for curing the cardiovascular complication in diabetes (as the experimental data of STZ-C8) . Furthermore, our studies using different doses of ACE-I also showed that there were two major mechanisms worked for this preventing effects of ACE-I. Such those are the mechanism of a vasoconstrictor and a growth- promoting agent.