CHAPTER V

Discussion

The results of this study demonstrated that the abnormalities of cardiovascular functions such as mean arterial pressure, aortic flow rate, coronary flow rate and left ventricular isotonic contraction were observed in streptozotocin treated rat for all three monitored time points. Besides, during the monitored time points the ventricular wall and arterial wall of STZ treated rats became thickening as compared to the controls. Interestingly, these thickening of ventricular and arterial walls were significantly less in the nicardipine treated STZ-rats and the nicardipine combined with cilazapril treated STZ-rats (Figures 4.15-4.34). Similarly, the decrease of cardiovascular functions such as cardiac output and coronary blood flow in STZ-rats were reported together with the observation of ventricular wall thickening by Penpargkul et. al. (1980).

Possible role of ACE-inhibitor on the diabetic cardiovascular complications.

We review the impact of diabetes on both microvascular and macrovascular defect are the major effects of cardiovascular disease. One of diabetic vascular disease is the thickening of capillary basement membrane in the myocardium (Fischer, 1979), which develops in relation to a duration of diabetes and a degree of glycemic control.Most of the effects of diabetes mellitus on the macrovasculature are the result of an acceleration of

atherosclerosis. The cardiovascular complications of diabetic mellitus were showned in our studies Figures 4.15-4.34 and Tables 4.1-4.14. Recently, many studies also showed the high incidence of abnormal renin - angiotensin system in associated with diabetes. Liberman, et al. (1980) reported that an increasing of serum angiotensin -converting-enzyme (ACE) was associated with diabetes mellitus. In their study, the mean value of ACE activity in diabetic group was significantly higher than those of the healthy and the hypertensive groups. Since the ACE is an enzyme that converts angiotensin I to angiotensin II , therefore, the increasing of serum ACE will cause the increase of serum angiotensin II synthesis. Angiotensin II is a potent vasoconstrictor and it's likely to promote hypertension in diabetic patients (Sowers, et al. 1995).

Leonardo., et al. (1994) showed the elevation of mRNA of myocardial angiotensin II receptor after streptozotocin induction in hyperglycemic diabetic rats. An increasing of mRNA level is important for the postulated intracardiac biosynthesis of these proteins. A physiological role of the cardiac angiotensin receptor is suggested by both positive inotropic and chronotropic effects of angiotensin II (Kobayashi. 1978). Angiotensin II also stimulates protein synthesis and cell growth in embryonic chick heart cells (Baker, 1990). Angiotensin II may induce cardiac hypertrophy by indirected mechanism such as the increase of after load .

Binding of receptor by angiotensin II will stimulate the phosphodiesterase activity in the phosphatidyl inositol system. Consequently, phosphodiesterase will breaks down the inositol phospholipids into I P_3 and diacylglycerol. The diacylglycerol then activates the proteink inase C which help to transfer a phosphate group from ATP to the target proteins. This mechanism is know as protein phosphorylation . (Morgan, 1990).

Since, angiotensin II has a variety of pathophysiological states these evidences suggested that the angiotensin II may play an important role in the development of smooth muscle hypertrophy. Angiotensin II stimulates the increase of intracellular calcium via activation of protein kinase C results in an increasing of new transcription of the early growth response gene (Naftilan, 1992). In addition, the role of angiotensin II on modulating the proliferative response was also confirmed by the model of vascular injury (Powell, 1989). Especially, in diabetic rat model it was suggested that a continue treatment of ACEI could decrease neointima formation.

After 24 hours of diabetic induction by using STZ, rats were treated with cilazapril 10 mg/kg BW for 16 weeks. Hypertension,myocardial hypertrophy and coronary arterial wall thickening which are usually observed in STZ - treated rats, could be protected by the oral treatment of cilazapril (Udaychalerm., et al. 1993). They suggest that the possible role of angiotensin II is likely seem to be a growth factor/modulator which relates to the development of cardiovascular hypertrophy. The

previous study also showed that angiotensin II acts through AT1 (angiotensin II subtype I) receptor to increase c-fos expression and phosphoinositide turnover in vascular smooth muscle cells (Lyall, 1992). Furthermore, angiotensin - II enhances the activation of the voltage-gate channel of calcium ion; that makes it easier for the channel to open in response to a wave of depolarization. This effect of angiotensin II is probably mediated by a GTP-binding protein (Brown, 1988).

In addition, calcium ion may involve in the regulation of muscle growth. This reasonable speculation would be factors in which temporarily act as vasoconstrictors in a short term, by increasing the level of cytosolic calcium during a long continued stimulation of vascular smooth muscle which lead to myointimal proliferation. Thus, calcium channel blocker and calcium channel blocker which combined with angiotensin converting enzyme inhibitor(ACEI) were used in this study to prevent cardiovascular complication in diabetic rats. In our study the result supported an observation that chronic diabetic hearts could cause an increasing of arterial wall thickening. Which caused the reduction of coronary flow rate and diminishing of ventricular contractility. In contrast, our results also showed that calcium channel blocker and calcium channel blocker which combined with angiotensin converting enzyme inhibitor can improve this defect.

Possible role of calcium-channel blocker on the diabetic cardiovascular complications.

Calcium movement from extracellular to intracellular can be regulated by a numbers of mechanisms, for example ; through plasma membrane via voltage or receptor operated channel. The previous studies demonstrated that the mechanism of dihydropyridine calcium channel blocker (nicardipine) help to reduce the accumulation of arterial cholesterol in dietary-induced atherosclerosis in animal model. They also found that calcium channel blocker enhanced lysosomal and cytoplasmic cholesterol ester hydrolytic activity. Moreover, the releasing of prostaglandin I_2 (PGI_2) was increased in response to nicardipine treatment. In addition to the implication of increase PGI_2 by nicardipine could block platelet depositon and activation, which became an early pro-atherosclerotic events in the genesis of vascular lessions.

Feron, O., and co-worker., (1996), demonstrated that dihydropyridine calcium antagonist exerted inhibition of ventricular hypertrophy and reduced cardiac pre-proendothelin - 1 mRNA expression in hypertensive rats. The effects of endothelin was involved in vascular hypertrophy (Schiffrin, 1995). Another studies showed that the heart weight/body weight ratio (represent to cardiomegaly) of diabetic rats were significantly larger than normal rats but reduced by calcium channel blocker treated.

In the present study, we found that the increase of heart weight/ body weight ratio, together with the decrease of the left ventricular isotonic contraction and coronary flow rate could be improved by using

nicardipine treated or nicardipine combined with cilazapril treated diabetic rats.

In other words, from this present study we propose that cardiovascular complications in diabetic rats could be party initiated by the increase of angiotensin II. Especially, angiotensin II could not only act as a growth promoting factor but also as an enhance for calcium ions which released from sarcoplasmic reticulum. And this cytosolic calcium ions as a mediator, could cause many physiological processes later as showed in Figure 5.1.

In conclusion, it is possible that angiotensin converting enzyme inhibitor and calcium channel blocker were the inhibitors for angiotensin II pathway on mitogenic effect showed in Figure 5.1.

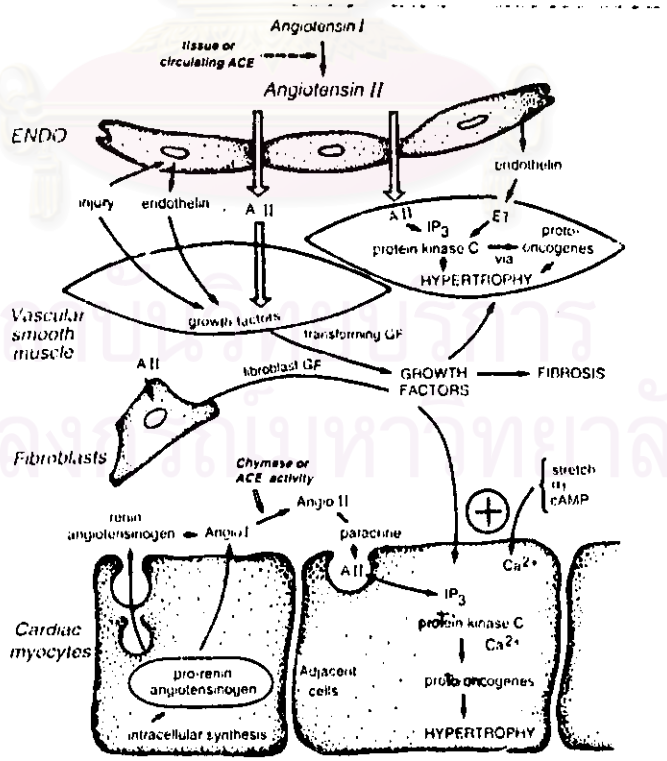

Figure 5.1 Effects of angiotensin II on cardiac myocytes (Baker, 1993.).