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Department of **Pharmaceutical Sciences** (Faculty of)

The University of British Columbia
Vancouver, Canada

Date **April 23/91**
This investigation was concerned with measuring aspects of cardiac function in conscious control, diabetic, hypertensive control, and hypertensive diabetic rats.

Preliminary studies were conducted to determine catheter suitability and acute responses to atropine and angiotensin II in conscious animals. The catheter-manometer was tested using a square wave impact and was shown to accurately reproduce a left ventricular pressure pulse. Intravenous atropine caused both heart rate and left ventricular \(+\text{dP}/\text{dt}\) to rise. Intravenously administered angiotensin II caused systolic blood pressure to increase dramatically. In this case heart rate fell and \(+\text{dP}/\text{dt}\) was elevated.

Hypertension was induced with deoxycorticosterone acetate (DOCA) and saline drinking water. Rats were first made diabetic with streptozotocin (60 mg/kg; i.v.). One week following this, subcutaneous DOCA (25 mg/kg) was administered twice weekly and all animals received saline drinking water. Following 2 and 5 weeks of DOCA treatment rats were catheterized and resting cardiovascular function was measured.

DOCA treatment caused increased systolic and diastolic blood pressures to occur in control and diabetic rats at 2 and 5 weeks. Bradycardia was also observed in DOCA–diabetic and DOCA–control rats at 2 and 5 weeks of treatment. Two and 5 week hypertensive diabetic and control rats exhibited elevated \(-\text{dP}/\text{dt}\) and \(+\text{dP}/\text{dt}\). The rate of contraction was shown to be
proportional to the magnitude of systolic blood pressure in all treatment groups. It is concluded that diabetic rats and control rats did not differ in their response to hypertension after 5 weeks of DOCA treatment.
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1.0 INTRODUCTION

Diabetes mellitus and hypertension, as separate entities, both have deleterious effects on cardiovascular function. When hypertension occurs in conjunction with diabetes mellitus it would not be surprising to find that cardiovascular function is compromised to a further degree than either situation alone would produce. While several studies using an isolated heart preparation indicate that this is the case, it is not clear what effect the combination of diabetes and hypertension have on cardiac function in conscious animals.

It was the purpose of this investigation to study the combined effect of diabetes mellitus and hypertension on cardiac function in conscious freely moving rats. A brief introduction on the known effects of diabetes and hypertension in the context of cardiac function follows and will precede a description of the methods used and experimental results. The last chapters will consist of a results discussion and conclusion.

1.1 Cardiovascular Disease in Diabetes Mellitus

Diabetes mellitus has been shown to be an independent risk factor for cardiovascular disease (Kannel et al., 1974). Diabetic pathology leading to a deterioration of cardiovascular function includes alterations in cardiac vasculature, autonomic innervation, and direct qualitative changes of the myocardium. These changes result in abnormal hemodynamic responses and a possible reduction in the ability of the cardiovascular system to respond to an imposed stress.
An increased incidence of coronary artery disease has been associated with diabetes (Smith et al., 1982; Palumbo et al., 1976; Knowles et al., 1982; Garcia et al., 1974). Coronary heart disease occurs at a younger age in the diabetic population as compared to non-diabetics and is thought to be due to an accelerated atherosclerotic process (Rubler et al., 1977). Kannel and McGee (1979) estimate that relative to age-matched non-diabetic counterparts there is a two-fold increased risk of developing coronary heart disease. The increased incidence of coronary atherosclerosis with diabetes is likely due to risk factors such as hypertension, hypertriglyceridemia, and hypercholesterolemia (Rubler et al., 1977; Lau et al., 1989).

1.2 Autonomic Neuropathy

The diabetic population affected by autonomic neuropathy is subject to an increased mortality rate. Several reports of sudden death associated with myocardial infarction exist and are based on postmortem findings (Ewing et al., 1980; Watkins et al., 1980). Another study estimates that the mortality in this population is 50% within 2.5 years of the onset of cardiac autonomic neuropathy (Ewing et al., 1985).

Diabetic patients with cardiac autonomic neuropathy may suffer from exercise intolerance, postural hypotension, and cardiac denervation (Pfeifer, 1990). It is the last of these three syndromes that causes the increased mortality incidence associated with autonomic impairment. This could occur either by inducing a denervation supersensitivity to catecholamines resulting in ventricular
arhythmias or by decreasing anginal pain and delaying the diagnosis of coronary artery disease (Ewing et al., 1982).

1.3 Diabetic Cardiomyopathy

The existence of diabetic cardiomyopathy was proposed by Rubler in 1972. His proposal was based on the post mortem examination of 4 adults with diabetes mellitus who had died of congestive heart failure. The subjects lacked indications of coronary atherosclerosis, valvular or hypertensive heart disease. Diabetic cardiomyopathy is not a prevalent cardiac malady, however, there is now sufficient evidence to show that this is a specific pathogenic process (Fein and Sonnenblick, 1985).

Clinical investigations have demonstrated that abnormal left ventricular function occurs in some diabetic patients. These studies have been based on the use of noninvasive techniques such as measurement of systolic time intervals, echocardiography, and radionuclide ventriculography.

Ahmed et al. (1975) observed a shorter left ventricular ejection time (LVET) and a longer pre-ejection period (PEP). The ratio of these values (PEP:LVET) was higher in diabetic patients as compared to their controls. This abnormality was due to a decreased ejection fraction and/or decreased left ventricular filling subsequent to diastolic dysfunction.

Investigations using echocardiography have shown that isovolumic relaxation in some diabetic patients is prolonged (Shapiro et al., 1981).
Echocardiographic measurement has shown systolic function to be normal in many studies of diabetic patients with diabetes of a short duration (Lababidi et al., 1983; Fisher et al., 1989). Depressed systolic function has only been observed in patients with advanced diabetic complications (Friedman et al., 1982).

Radionuclide ventriculography studies indicate that diabetic subjects had a normal ejection fraction at rest which was significantly reduced during exercise stress testing when compared to controls (Zola et al., 1986). Similar investigations have shown that peak left ventricular filling rates were reduced in diabetic subjects (Kahn et al., 1986).

Noninvasive studies also indicate that hypertension aggravates cardiac dysfunction in diabetic subjects. Echocardiography conducted on normotensive and hypertensive diabetics showed both groups to possess prolonged relaxation times. Systolic dysfunction was exaggerated in the hypertensive diabetic group (Shapiro et al., 1981). Studies involving echocardiography have also shown that hypertensive diabetic patients had more severe diastolic impairment than controls (Venco et al., 1987).

Diabetic cardiomyopathy can be modelled in animals treated with the diabetogenic agent streptozotocin (STZ). These models are similar to clinical cases of cardiomyopathy because both systolic and diastolic function are impaired. Fein et al. (1980) observed that left ventricular papillary muscle obtained from 5 week STZ treated rats had a reduced shortening velocity and rate of relaxation compared to tissue obtained from control animals. Hearts
isolated from rats treated with STZ 8 weeks previously exhibited reduced left ventricular developed pressure and rate of pressure development and relaxation (Penpargkul et al., 1980). Myocardial oxygenation and the body/heart weight ratio were not different in diabetic and control groups. Other isolated heart studies have confirmed that there is a depression of left ventricular pressure development, slowed relaxation, and reduced cardiac output in STZ-diabetic rats (Vadlamudi et al., 1982). Abnormal cardiac function has been shown to be both prevented and reversed by insulin treatment and normalization of the diabetic state (Tahiliani et al., 1983; Rubinstein et al., 1984).

Cardiomyopathy associated with diabetes mellitus appears to be due to alterations that occur to several systems within the myocardium. This includes ultrastructural damage, myosin isoenzyme shifts, and a reduced ability of the sarcoplasmic reticulum to sequester calcium.

It is conceivable that ultrastructural damage could alter myocardial performance. A so called stiffening of the ventricle could interfere with contraction and especially with relaxation of the myocardium. Hearts obtained from rats given STZ 8 weeks previously exhibited mitochondrial swelling, myofibrillar change, lipid droplets and atherosclerotic plaque formation (Seager et al., 1984). Myocardial ultrastructural change has been observed within one week of STZ treatment (Reinila and Akerblom, 1984). STZ-diabetes of 3 months duration has been shown to cause focal edema and tissue vacuolization of rat myocardium (McGrath and McNeill, 1986). In addition, capillary basement membranes were thickened and lipid droplets were observed to be within mitochondria of individual myocytes. Insulin treatment
for the duration of the experiment was shown to prevent some of the cellular damage.

While ultrastructural deterioration could influence myocardial performance, studies showing that depressed ventricular function can occur prior to the manifestation of cellular damage (Jackson et al., 1985) indicate that other factors influence the development of cardiomyopathy. Such factors contributing to depressed cardiac function include myosin ATPase isoenzyme shifts and impaired calcium channeling by the sarcoplasmic reticulum.

Cardiac myosin ATPase activity has been shown to be proportional to the developed tension (Scheuer and Bhan, 1979) and contraction velocity (Schwartz et al., 1981) of the myocardium. These properties have prompted research into the role of myofibrillar ATPase activity in the development of diabetic cardiomyopathy, and it is clear that myosin ATPase in diabetic rats has reduced activity (Dillmann et al., 1982; Malhotra et al., 1981). The reduction in ATPase activity appears to be caused by a distribution shift in the predominant myosin isoenzyme type. Control rats possess myosin ATPase in its most active V1 form whereas diabetic rats express an increase in the less active V3 type (Pierce and Dhalla, 1985).

It has been speculated that the isoenzyme shift may be the result of a hypothyroid state that occurs in the untreated STZ-diabetic rat. Thyroidal hormone administration has been shown to reverse abnormal myosin ATPase in such rats (Dillmann et al., 1982; Malhotra et al., 1981; Pierce and Dhalla, 1985). However, the reversal is incomplete and the hormonal requirement is well in
excess of normal physiological levels. In another experiment physiological levels of triiodothyronine administered to STZ-diabetic rats did not reverse cardiac function to normal (Tahiliani and McNeill, 1985). This does not rule out the possibility that hypothyroidism adversely affects diabetic cardiac function as Peirce and Dhall (1981) have pointed out that thyroid hormone receptors may be reduced in diabetic animals. While the hypothyroid state associated with STZ diabetes may reduce cardiac function it is clear that there are other factors contributing to the pathology of diabetic cardiomyopathy.

Calcium transport within the myocyte is important in regulating systolic and diastolic function. The sarcoplasmic reticulum (SR) plays a major role in controlling intracellular calcium flux and has been shown to have a reduced ability to channel calcium in STZ-diabetic rats (Penpargkul et al., 1981). Reduced cardiac SR calcium transport activity has been confirmed in other studies (Lopaschuck et al., 1982; Lopaschuck et al., 1983; Ganguly et al., 1983).

1.4 Hypertension and Diabetes

Hypertension is a serious cardiovascular risk factor in the diabetic population. Diabetic hypertensive patients experience both accelerated microangiopathy (Mogensen et al., 1982; Parving et al., 1983) and atherosclerosis (Christlein et al., 1981; Jarret et al., 1984). Many studies have indicated that there is a high degree of association between diabetes and hypertension. Pell and D'Alonzo (1967) observed that hypertension occurred more often in diabetic patients than in an age, sex, and weight-matched control population. White diabetic patients over the age of 24 years were reported to have a higher prevalence of
hypertension than either the Framingham population or the population of the United States (Christleib et al., 1981). Elevated systolic blood pressure has also been observed in diabetic patients within the Framingham population (Garcia et al., 1974) and in a group of elderly women (Barret-Connor et al., 1981). A recent study has shown that hypertension also occurs in diabetic children and adolescents (Tarn and Drury, 1986).

1.5 Pathogenic Factors Contributing to Diabetic Hypertension

Hypertension may precede the onset of the diabetic state in the form of an essential hypertension. On the other hand metabolic abnormalities associated with diabetes may induce a pathologically distinct diabetic hypertension. Several factors contributing to diabetic hypertension include diabetic nephropathy, sodium (Na$^+$) retention, and abnormal cardiovascular reactivity.

Hyperglycemia in diabetes and a possible genetic predisposition for hypertension are likely to be risk factors that both increase the incidence of nephropathy (Krolewski et al., 1988). Glomerular capillary hypertension has been shown to injure the glomerular apparatus and is considered to be an important cause of nephropathy (Dunn et al., 1986). During the early stages of diabetic nephropathy blood pressure tends to rise (Feldt-Rasmussen et al., 1985). The likelihood of overt hypertension increases with the development of clinical nephropathy (Mogensen et al., 1985).

Diabetic hypertension may also be caused by abnormal electrolyte handling and altered cardiovascular responsiveness. Na$^+$ retention is a frequent
complication of diabetes and has been observed in numerous studies (Weidmann et al., 1985). Plasma and blood volumes were also low. It appears that in diabetes mellitus there is an abnormal accumulation of Na\(^+\) and fluid volume within the extravascular compartment. This condition has been observed in another study (Feldt-Rasmussen et al., 1987). There may also be a temporal association between Na\(^+\) retention and nephropathy.

The importance of Na\(^+\) retention in the pathogenesis of diabetic hypertension is underscored by other observed relationships. Systolic blood pressure can be correlated with plasma Na\(^+\) levels (Weidmann et al., 1985). Diuretic treatment that normalized plasma Na\(^+\) caused a further reduction in blood volume and normalized blood pressure (Weidmann et al., 1979).

Abnormal cardiovascular reactivity in response to vasoactive stimuli is reflected in blood pressure control. Diabetic patients often have an exaggerated blood pressure response to norepinephrine infusion. Weidmann et al. (1985) showed that in a sample of diabetic patients the dose of norepinephrine required to elevate mean blood pressure by 20 mmHg was 50% less than in control subjects. Norepinephrine hyperresponsiveness occurs in a broad spectrum of diabetic patients and appears to be an early complication of diabetes mellitus (Weidmann, et al., 1979; Barretta-Picolli and Weidmann, 1981). In a similar vein normotensive diabetic patients had an exaggerated response to Angiotensin II infusions (Drury et al., 1984).

This investigation deals with a model of type 1 diabetes in which hyperglycemia occurs due to pancreatic insufficiency. Diabetes may have
other causes such as insulin resistance. This is known as type 2 diabetes and is generally associated with a state of hyperinsulinemia. Recently it has become clear that insulin excess can be linked to abnormal cardiovascular performance.

Many conditions associated with insulin resistance and hyperinsulinemia exhibit a coexisting hypertension. These states include obesity (Christlieb et al., 1985), impaired glucose tolerance (Landsberg, 1986), and diabetes type 2 (The Working Group on Hypertension in Diabetes, 1987). Hyperinsulinemia and insulin resistance have also been shown to occur in essential hypertension (Ferrannini et al., 1990).

The relation between insulin resistance and hypertension has been the subject of several recent reviews (Reaven, 1988; Reaven, 1990). Insulin has many important metabolic effects which in a state of hyperinsulinemia will be exaggerated. The net effect of excess insulin may include sodium induced fluid retention caused by increased renal tubular sodium reabsorption, increased intracellular calcium content enhancing contractility of cardiac and vascular smooth muscle, increased sympathetic neural activity, and proliferation of vascular tissue (Ferrari and Weidmann, 1990). These processes singly or in combination could contribute to causing hypertension and associated sequelae.
1.6 Deoxycorticosterone Acetate–Sodium Chloride Hypertension

Deoxycorticosterone acetate (DOCA) administered subcutaneously in conjunction with a saline (NaCl) drinking solution will cause hypertension (Hebden et al., 1990). The mechanism behind the increased blood pressure is not entirely clear, however, DOCA appears to alter hormonal and neural pressor control. Relevant pre-hypertensive changes include altered neural angiotensin II (Itaya et al., 1986) and vasopressin activity (Zicha et al., 1989), elevated sympathetic drive (Sasaki and Bunag, 1982) and distorted baroreflex responses (Nakamura et al., 1988). In addition DOCA–NaCl hypertension induces characteristic changes in such as cardiac hypertrophy (Tomanek and Barlow, 1990) and coronary artery lesions (Anderson et al., 1988).

Unlike human diabetics, rats with experimental diabetes do not exhibit marked vascular disease (Chobanian et al., 1982). It is important to note that DOCA–NaCl treatment resulting in hypertension does cause coronary artery disease in STZ-diabetic rats (Hebden et al., 1990). This damage was manifest as a thickened smooth muscle layer and increased paracellular matrix. Adventitia adjacent to ventricular cardiocytes also had more numerous fibroblasts and increased collagen content.

1.7 Experimental Hypertension and Diabetic Cardiomyopathy

Human diabetics experiencing hypertension may be at an increased risk for developing cardiomyopathy (Factor et al., 1980; Shapiro et al., 1981). It is also interesting to note that Factor et al. (1981) were able to observe cardiac
ultrastructural damage only in those diabetic rats that had a coexisting renovascular hypertension. Further studies in rats with combined renovascular hypertension and diabetes suggested that these events compound the risk for cardiovascular dysfunction (Factor et al.,1984).

Morphological studies of myocardium obtained from renovascular hypertensive diabetic rats demonstrated myocyte necrosis, interstitial fibrosis, and possible microvascular spasm (Factor et al.,1981,1984). In particular hypertensive diabetic animals exhibited cardiac microvascular abnormalities (Factor et al.,1984). This was manifest as areas of focal constriction, segments of dilatation, and microaneurysms. The capillary basal lamina has been shown to be thickened in the hypertensive diabetic rat (Factor et al.,1983). Microvascular abnormalities would reduce myocardial perfusion and performance. Functional impairment was manifest as a reduction in the speed of contraction and relaxation, a prolonged duration of action potential, a high spontaneous mortality, and evidence of circulatory congestion among animals that had died.

These observations have been confirmed in a recent study on the function of papillary muscle isolated from renovascular hypertensive diabetic rats (Fein et al.,1990). In particular, the length tension relationship of these muscles was considerably blunted and the developed tension at maximum length was also lower than in either muscle obtained from diabetic or hypertensive rats. The peak rate of shortening and relaxation was reduced in hypertensive diabetic papillary tissue and the time to reach the peak rate of shortening was
decreased as compared to diabetic, hypertensive, and control muscle. It was shown that hypertensive diabetic animals experienced a complete conversion of myosin isoenzyme V1 to the V3 type. Left ventricular ultrastructural pathology was not notable in diabetic rats, however, in all hypertensive groups marked damage was present. Interestingly, the authors speculate that in this model biochemical abnormalities are due to diabetes and the structural changes are a consequence of hypertension.

The functional effects of combined hypertension and diabetes have also been observed in spontaneously hypertensive rats (SHR) made diabetic with streptozotocin (Rodrigues and McNeill, 1986; Rodgers et al., 1985). Isolated hearts obtained from SHR diabetic rats did not show marked reduction in performance as compared to diabetic normotensive controls at six weeks of diabetes. At 12 weeks of diabetes cardiac function was significantly impaired in hypertensive rats. Left ventricular developed pressure, rate of pressure development (+dP/dt) and relaxation (−dP/dt) were lower in the hypertensive diabetic group than any of the control groups over a range of filling pressures from 15.0 to 25.0 cm of H2O. In addition, SHR diabetic rats experienced an exceedingly high mortality rate in which nearly 50% of these animals died prior to completion of the experiment.
1.8 In vivo hemodynamic Measurements

Diabetes mellitus causes abnormal cardiac performance that can be observed in vivo. Paulson et al. (1986) have demonstrated depressed myocardial function in anaesthetized rats treated with streptozotocin (STZ) 8 weeks previously. The rates of pressure development (+dP/dt) and relaxation (−dP/dt) were significantly reduced in diabetic animals as compared to controls. Control +dP/dt was approximately 5800 mmHgs\(^{-1}\) versus 4000 mmHgs\(^{-1}\) in diabetic rats. Peak left ventricular developed pressure was not significantly different in the diabetic group. End diastolic pressure was also not different. Heart rate tended to be lower in diabetic rats as compared to control animals. Contrary to these results, a similar study was only able to show a reduced −dP/dt in diabetic rats (Heller et al., 1988).

Hemodynamic measurements have also been made in conscious diabetic animals. Various studies have indicated that rats made diabetic with STZ exhibit a systolic hypertension (Katayama et al., 1985; Kusaka et al., 1987). These measurements were obtained using a tail cuff method and have been shown to be an artifact. Apparently one consequence of STZ–diabetes is an increased collagen content in the tail of the rat which dampens the transmissions of the arterial pulse to the tail cuff. The cuff must be inflated to a higher pressure and this creates a false impression of hypertension (Kusaka et al., 1987).
Blood pressure measurements made using an intra-arterial catheter indicate that STZ-diabetic rats are generally normotensive or hypotensive (Kusaka et al., 1987; Dowell et al., 1986). These results have been confirmed recently in rats treated with STZ 6 weeks previously (Hebden et al., 1989; Hebden et al., 1990; Todd et al., 1990).

Conscious STZ-diabetic rats exhibit a reduced heart rate (Dowell et al., 1986; Carbonell et al., 1987; Hebden et al., 1989; Hebden et al., 1990; Todd et al., 1990). Dowell et al. (1986) were able to demonstrate bradycardia at 2 weeks following STZ treatment. At this time \( +dP/dt \), \( -dP/dt \) and cardiac output were normal. Cardiac output and contractility were both significantly depressed by 4 weeks into the study. The depression of cardiac output did not progress due to a compensatory increase in stroke volume that occurred later in the course of diabetes. Carbonell et al. (1987) observed similar results in rats 12 weeks after STZ administration. However, in this study cardiac output and stroke volume were elevated above control levels. This increase in cardiac output occurred despite a reduced \( +dP/dt \) and was likely a consequence of an increase in preload causing an enhanced stroke volume. Diabetic rats exhibited an increase in blood volume, a reduction in total peripheral resistance, and bradycardia. These factors could all increase preload. This situation taken to an extreme can also lead to congestive heart failure if the myocardium is further stressed and decompensates.

Blood pressure has been measured in conscious STZ-diabetic rats made hypertensive with deoxycorticosterone acetate (DOCA) and saline (NaCl) drinking water. Systolic and diastolic blood pressures have been observed to
increase progressively from 3 weeks following DOCA–NaCl administration in diabetic animals (Hebden et al., 1990). Atherosclerosis was also shown to occur in these animals.

Left ventricular performance has been investigated in DOCA–NaCl treated non-diabetic rats (Tomanek and Barlow, 1990). It should be noted, however, that all measurements were made in anaesthetized animals. DOCA–NaCl treated rats were hypertensive by the second week of treatment. Left ventricular mass was markedly elevated by 1 month of DOCA–NaCl administration. This hypertrophy translated into an enhanced cardiac output under resting conditions and during an acute increase in preload. Left ventricular developed pressure in response to aortic occlusion was also enhanced. Isolated papillary muscle obtained from DOCA–NaCl treated rats with left ventricular hypertrophy exhibited reduced shortening and relaxation velocities (Heller et al., 1978; Bing et al., 1971). While these features may be considered to represent impaired muscle mechanics, the work of Tomanek and Barlow (1990) suggests that myocardial hypertrophy may be a compensatory response allowing apparently normal heart function.

1.9 Experimental Rationale

Epidemiological data indicate that diabetes mellitus in humans is associated with an increased incidence of congestive heart failure due to a specific cardiomyopathy (Rubler et al., 1972; Kannel et al., 1974). The pathogenesis of diabetic cardiomyopathy has been studied in rats treated with the diabetogenic agent streptozotocin (STZ). Isolated perfused hearts from STZ–
treated hearts have been shown to have significantly reduced peak left ventricular pressures as well as a reduced rate of left ventricular pressure development (+dP/dt) and relaxation (−dP/dt) (Penpargkul et al., 1980; Tahiliani et al., 1983; Fein et al., 1980). Although these observations are indicative of cardiac abnormalities, they have been obtained under conditions of high filling pressures, the physiological relevance of which may be questioned. Surgical removal of the heart may also result in damage due to trauma and/or ischemia. In an attempt to improve upon these deficiencies, Paulson et al. (1987) examined in vivo cardiac function in anaesthetized diabetic rats. Since anaesthesia has been shown to alter cardiac function (Inoue and Kovig, 1988) this method is obviously also not physiological. Furthermore, these previous studies do not take into account the importance of cardiovascular autonomic innervation and the possible distortion of these responses in the diabetic state (Akiyama et al., 1989). To further characterize the nature of diabetic cardiomyopathy we have developed a cardiac intraventricular catheterization technique to measure both pressure and the rate of pressure change in the left ventricle of freely moving rats.

Hypertension is a frequent complication of diabetes mellitus in humans. The combination of hypertension and diabetes appears to increase the risk of developing cardiomyopathy in man (Factor et al., 1980; Shapiro et al., 1981). Renovascular (Factor et al., 1981) and genetic (Rodrigues and McNeill, 1986) forms of hypertension have been shown to potentiate existing cardiac dysfunction in diabetic rats. It must be emphasized that none of these studies addresses the effect of hypertension and diabetes on cardiovascular function in conscious animals.
Recently in our laboratory we have developed a new model of diabetic hypertension utilizing a deoxycorticosterone acetate treatment (Hebden et al., 1990). The cardiovascular consequences of establishing this form of hypertension in conscious unrestrained diabetic rats are unknown. Thus it would be of considerable interest to investigate the influence of this form of hypertension on the course of diabetic cardiomyopathy in conscious animals capable of eliciting a competent integrated cardiovascular response and adaptation.

1.10 Objectives

1. To investigate the affect of acute pharmacological interventions on the rate of left ventricular pressure development (+dP/dt) in conscious rats.

2. To examine the combined influence of hypertension and diabetes on cardiovascular function in conscious rats.

1.11 Research Plan

Cardiac function in conscious animals was assessed by measuring resting cardiovascular parameters. +DP/dt was used as an index of myocardial contractility. Measurements of +dP/dt were made using a cardiac intraventricular catheter. Other measurements made included left ventricular peak systolic pressure (LVSP), systolic and diastolic arterial pressure, −dP/dt and heart rate. Experiments were conducted in order to characterize the
response of some of these parameters to intravenous atropine and angiotensin II. In addition the catheter–manometer system was calibrated to ensure adequate signal fidelity.

Following completion of these experiments, resting cardiac function in conscious diabetic hypertensive rats was investigated after 2 and 5 weeks of deoxycorticosterone treatment. Control–normotensive, control–hypertensive, diabetic–normotensive, and diabetic–hypertensive rats were examined for the cumulative effects of diabetes and hypertension on cardiac function.
2.0 METHODS

2.1 Induction of Diabetes Mellitus and Hypertension

Diabetes was induced in male Sprague Dawley rats (200–250 g; Charles river, Montreal) by anesthetizing them with halothane (Fluothane; Ayerst labs, Vancouver) followed by an injection into the tail vein of 60 mg/kg streptococotocin (STZ; Sigma St. Louis, Mo.) dissolved in 0.9% saline. Control animals received a saline injection. The presence of glycosuria 48h after STZ administration was used to confirm whether the animals were diabetic. Blood samples were taken immediately prior to any experiments conducted in conscious animals for the determination of plasma glucose and plasma insulin. Seven days following administration of saline or STZ, animals to be made hypertensive were subcutaneously injected with 25 mg/ml Deoxycorticosterone acetate (DOCA; Sigma, St. Louis, Mo.) in vehicle. All other animals received vehicle (1.8 g sodium chloride, 1.8 g benzyl alcohol, 1.0 g carboxymethylcellulose, 0.8 g polysorbate 80; made up to 200 ml with distilled water). following the first injection of DOCA or vehicle all animals were given 0.9% saline to drink ad libitum. Animals continued to receive DOCA or vehicle twice weekly.

In order to avoid confusion these treatment groups will be referred to in the following manner. Animals injected with deoxycorticosterone acetate will receive the prefix DOCA. Animals injected with STZ will be called diabetic. As an example animals receiving STZ and DOCA will be grouped as DOCA–diabetic.
2.2 Measurement of Cardiac Function

Two and five weeks following the initiation of DOCA treatment, cardiac function was measured in conscious animals. All data are presented as a mean ± s.e.m. Data were analyzed by one way analysis of variance, followed by Neuman-Keul's test. Measurements of $+\frac{dP}{dt}$ and $-\frac{dP}{dt}$ were subject to a Bonferroni correction factor which changed the alpha value from 0.05 to 0.025.

2.3 Cardiac Function in Conscious Animals

Animals were anesthetized with sodium methohexital (60 mg/kg ;i.p.) (Brietal® Sodium, Eli Lilly, Toronto). A catheter was placed into the abdominal aorta via the caudal artery for the measurement of blood pressure. Another catheter was placed into the left ventricle via the right common carotid artery to measure intraventricular pressure. The pressure recording system was tested to show that it meets the minimum standard necessary to faithfully record blood pressure. The left ventricular pressure pulse was recorded on a Gould TA 2000 polygraph (Gould, Cleveland, Oh.) and differentiated by an on-line program developed in our laboratory. Using this system it was possible to record systolic and diastolic blood pressure, rate of pressure development ($+\frac{dP}{dt}$) and relaxation ($-\frac{dP}{dt}$), left ventricular end diastolic and systolic pressures, and heart rate.
2.4 Intravenous Atropine and Angiotensin II in Conscious Animals

Atropine: A 0.1 ml bolus of atropine sulphate (0.03 mg/kg) (Sigma, St. Louis, Mo.) was administered intravenously in less than 10 seconds and the change in heart rate and +dP/dt were measured.

Angiotensin II: A 0.1 ml bolus injection of intravenous angiotensin II (50–400 ng/kg) (Sigma, St. Louis, Mo.) was administered in under 10 seconds and changes in heart rate, blood pressure and +dP/dt were measured.

2.5 Plasma Glucose and Insulin

Plasma was obtained from all experimental animals 1 day in advance of surgery. All samples were frozen at −50 °C until analysed for glucose or insulin. Plasma glucose was determined using an enzymatic colorimetric assay kit (Boehringer Mannheim GmbH, Diagnostica). Plasma insulin was determined by means of a radio-immunoassay (Immunocorp).
3.0 RESULTS

3.1 Catheter Design

The recording system was tested by means of a square wave impact to ensure that it met standards required to faithfully record a pressure pulse (Hansen, 1949). This method made possible the determination of the relative damping and the undamped natural frequency of the catheter–manometer.

Figure 1 illustrates the inverse relationship between natural frequency and catheter length. Decreasing the fluid column length increases the catheter natural frequency. The catheters used to monitor blood pressure were constructed from 1 m of PE50 welded to 7 cm of PE10. These catheters have a relatively low undamped natural frequency of around 30 Hz and a damping factor which is approximately 0.8 (Table 1). The damping factor should eliminate any signal distortion due to the low natural frequency. Differences in catheter design were tested by comparing +dP/dt obtained from conscious rats using either 1 m of PE50 (n=10) or the PE50/PE10 combination catheter (n=11) (Figure 2). The PE50 catheter recorded a +dP/dt value of approximately 9400 ± 300 mmHg s$^{-1}$ and the PE50/PE10 catheter gave a value of 6400 ± 300 mmHg s$^{-1}$. The difference in the left ventricular pressure pulse recorded using these two catheters is apparent in Figure 3. Figure 3 also makes obvious the effect of damping and the lack thereof on the pressure pulse obtained using a catheter–manometer system with an inherently low natural frequency.
Figure 1. Natural frequency dependence on catheter length.

Polyethylene tubing was cut into 100, 50, 25, and 12.5 cm segments. The natural frequency of each section was determined by means of a square wave impact (Hansen et al., 1949). This figure illustrates that natural frequency and catheter length are inversely proportional. The technique used to characterize catheter performance, although simple, worked well as indicated by the high correlation coefficient (0.99) obtained in this experiment.
Table 1. Catheter natural frequency and relative damping as determined by a square wave impact.

<table>
<thead>
<tr>
<th>*Catheter</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damping</td>
<td>0.8</td>
<td>0.85</td>
<td>0.75</td>
<td>1.08</td>
</tr>
<tr>
<td>Natural Frequency (Hz)</td>
<td>28</td>
<td>28</td>
<td>33</td>
<td>48</td>
</tr>
</tbody>
</table>

Four catheters consisting of 1 m of PE50 and 7 cm PE10 were shown to possess a natural frequency of approximately 30 Hz and a relative damping in range of 0.8.

* Catheters consist of 1 m of PE50 and 7 cm of PE10.
Two different catheters were used to measure the rate of left ventricular pressure development (+dP/dt) in conscious rats. The PE50 catheter (n=10) consisted of 1 m of PE50 tubing and indicated that +dP/dt was . The same catheter with a serial addition of 7 cm of PE10 tubing (PE10/PE50) (n=10) gives a +dP/dt value of which is approximately 30% lower. The difference in obtained +dP/dt makes clear that catheter design is an important consideration in experiments measuring fluid pressures.
This figure graphically illustrates the effect of damping provided by the serial addition of 7 cm of PE10 tubing to the PE50 catheter. The PE50 catheter causes the pressure pulse to be amplified. This is made obvious by the pressure overshoot that occurs in the PE50 trace. The addition of 7 cm of PE10 tubing to the PE50 catheter provides a damping effect that reduces signal amplification caused by an inherently low natural frequency.
3.2 Intravenous Angiotensin II Administered to Conscious Rats

Angiotensin II (Ang II) was administered intravenously to conscious rats. The intent of this experiment was to document the effect of increasing afterload on $+\frac{dP}{dt}$ and heart rate. Figures 4 and 5 represent data obtained from one rat. Figure 4 indicates that when a bolus of Ang II (400 ng/kg) was introduced systolic blood pressure rose instantaneously from approximately 128 mmHg to well over 180 mmHg. The increase in systolic blood pressure was accompanied by a concommittant elevation in $+\frac{dP}{dt}$. The basal $+\frac{dP}{dt}$ was approximately 5200 ± 200 mmHg s$^{-1}$ and reached over 6700 ± 400 mmHg s$^{-1}$ at the same time point at which maximum blood pressure was obtained. Maximum blood pressure and $+\frac{dP}{dt}$ occurred within 1.5 minutes of Ang II administration. As blood pressure returned to basal levels so did $+\frac{dP}{dt}$.

Figure 5 shows the effect of intravenous Ang II on heart rate. As systolic blood pressure increased heart rate was reduced. Heart rate fell from approximately 360 to nearly 300 beats/min. This decrease in heart rate represents a baroreflex response. When blood pressure returned to normal heart rate rose but did not return to basal levels within the timeframe of measurement.

3.3 Intravenous Atropine Administered to Conscious Rats

The influence of parasympathetic cardiac innervation on heart rate and $+\frac{dP}{dt}$ in conscious rats was investigated using intravenous atropine (0.03 mg/kg). The reduction in vagal input resulted in an increase of both heart rate and $+\frac{dP}{dt}$. Table 2 shows that there is a positive correlation between $+\frac{dP}{dt}$ and
Figure 4. Angiotensin II effects on systolic blood pressure and +dP/dt in a conscious rat.

This figure is based on data obtained from one animal and represents observations made in 6 other rats. Intravenous angiotensin II caused an instantaneous rise in systolic blood pressure which was accompanied by an increase in +dP/dt. Both blood pressure and +dP/dt reach a maximum within one minute of drug injection. It appears that increasing afterload may result in an elevation of +dP/dt.
Figure 5. Angiotensin II increases systolic blood pressure and decreases heart rate in a conscious rat.

Data in this figure was obtained from the same set of observations used in figure 4. Immediately following injection of angiotensin II systolic blood pressure increased and heart rate fell. The decrease in heart rate likely represents a baroreflex mediated response.
Table 2. A positive correlation exists between heart rate and +dP/dt following i.v. atropine administration.

<table>
<thead>
<tr>
<th>dP/dt vs HR</th>
<th>r (mmHg/s/beat/min)</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=8)</td>
<td>X = 0.6±0.1</td>
<td>X = 3.9±0.9</td>
</tr>
</tbody>
</table>

Intravenous atropine (0.03 mg/kg) was administered to conscious rats. Both heart rate and +dP/dt were observed to increase in response to this intervention. B represents a slope obtained when +dP/dt was plotted against heart rate. R signifies the correlation coefficient of this relationship. These values are both the mean of data obtained from 8 animals.
heart rate with a slope of 3.9 ± 0.9 mmHg/s/beat/min. The values in Table 2 are the mean of data acquired from 8 animals.

3.4 Deoxycorticosterone Hypertension in Conscious Rats

3.4.1 Plasma Glucose and Insulin

Rats were considered to be diabetic when plasma glucose was in excess of 13 mmol/L. All animals injected with STZ met this requirement (Figure 6a and 7a). Two week DOCA–diabetic animals had a mean plasma glucose of 17.0 ± 1.0 mmol/L and diabetic animals had a mean plasma glucose of 19.0 ± 2.0 mmol/L (Figure 6a). The two week control and DOCA–control groups both had a mean plasma glucose of 7.0 ± 1.0. Plasma insulin levels were reduced in diabetic and DOCA–diabetic groups (Figure 6b). Diabetic animals exhibited a mean plasma insulin of 24.0 ± 5.0 μU/ml which was not significantly different than that of the DOCA–diabetic group (32.0 ± 4.0 μU/ml). Both control groups had plasma insulin levels above 45.0 ± 5.0 μU/ml.

At 5 weeks plasma glucose levels in all group were virtually identical to the levels in the 2 week experiment (Figure 7a). Plasma insulin in the control group was 47.0 ± 3.0 μU/ml which was significantly different than that of the DOCA–control group (33.0 ± 4.0 μU/ml. DOCA–diabetic and diabetic groups both had insulin levels of 20.0 ± 4.0 μU/ml (Figure 7b).
Figure 6a. Plasma glucose in control and diabetic rats treated with DOCA for 2 weeks.

All diabetic rats had elevated plasma glucose compared to their control counterparts. Data shown are mean ± s.e.m.
Figure 6b. Plasma insulin in control and diabetic rats treated with DOCA for 2 weeks.

All diabetic rats had reduced plasma insulin compared to their control counterparts. This is a clear indication of pancreatic insufficiency. Data shown are mean ± s.e.m.
Figure 7a. Plasma glucose in control and diabetic rats treated with DOCA for 5 weeks.

All diabetic rats had elevated plasma glucose compared to their control counterparts. Data shown are mean ± s.e.m.
Figure 7b. Plasma insulin in control and diabetic rats treated with DOCA for 5 weeks.

All diabetic rats had reduced plasma insulin compared to their control counterparts. Data shown are mean ± s.e.m.
3.4.2 Bodyweight

Diabetic rats were lighter than controls at 2 and 5 weeks (Table 3). The 2 week diabetic group had a mean bodyweight of 280 ± 22 g and the corresponding controls were 370 ± 6 g. Two week DOCA–diabetic animals were 280 ± 22 g as compared to the DOCA–control group with a mean bodyweight of 350 ± 15 g.

These trends persisted after 5 weeks of DOCA treatment. The control group had a mean body weight of 460 ± 17 g compared to the diabetic group mean of 360 ± 18 g. The DOCA–control group mean was 440 ± 7 g and the DOCA–diabetic mean body weight was 330 ± 13 g.

3.4.3 Systolic Blood Pressure

Two weeks of DOCA treatment caused systolic blood pressure to rise dramatically (Table 4). Control rats exhibited a mean systolic blood pressure of 128 ± 5 mmHg whereas the DOCA–control group had an extremely high reading of 162 ± 6 mmHg. DOCA–diabetic rats had moderately elevated systolic blood pressure (144 ± 8 mmHg) which was not significantly greater than that seen in the diabetic group (125 ± 5 mmHg).

A similar pattern existed at 5 weeks of DOCA treatment (Table 4). The DOCA–control group had a mean systolic blood pressure of 179 ± 5 mmHg compared to the control mean of 132 ± 5 mmHg. Systolic blood pressure in the DOCA–diabetic group had increased to 163 ± 7 mmHg which was
Table 3. Bodyweight of animals used in the DOCA–hypertension study.

<table>
<thead>
<tr>
<th>Week</th>
<th>Control (g)</th>
<th>Doca Con (g)</th>
<th>Diabetic (g)</th>
<th>Doca Dia (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>370±6</td>
<td>350±15</td>
<td>*280±22</td>
<td>*280±22</td>
</tr>
<tr>
<td>2</td>
<td>(n=9)</td>
<td>(n=8)</td>
<td>(n=9)</td>
<td>(n=8)</td>
</tr>
<tr>
<td></td>
<td>460±17</td>
<td>440±7</td>
<td>*360±18</td>
<td>*330±13</td>
</tr>
<tr>
<td>5</td>
<td>(n=11)</td>
<td>(n=9)</td>
<td>(n=7)</td>
<td>(n=7)</td>
</tr>
</tbody>
</table>

Diabetic animals exhibited markedly reduced bodymass compared to control groups. DOCA–treatment caused a consistent but insignificant reduction in bodyweight.

* Different from control
Table 4. Basal cardiovascular values observed in conscious animals.

<table>
<thead>
<tr>
<th>5-Week</th>
<th>2-Week</th>
<th>DOCA-treatment caused systolic and diastolic blood pressure to be increased. DOCA-treated animals were also bradycardic. Both (-dP/dt) and (+dP/dt) were elevated in DOCA-treated groups. All values are means ± s.e.m., (p &lt; 0.05).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(+dP/dt) (mmHg/s)</td>
<td>(-dP/dt) (mmHg/s)</td>
</tr>
<tr>
<td>DOCA Control (n=9)</td>
<td>(7190±290^{ab})</td>
<td>(6235±240^{ab})</td>
</tr>
<tr>
<td>DOCA Diabetic (n=7)</td>
<td>(6210±450)</td>
<td>(5180±370^{abc})</td>
</tr>
<tr>
<td>Control (n=11)</td>
<td>(5650±230)</td>
<td>(4790±200)</td>
</tr>
<tr>
<td>Diabetic (n=7)</td>
<td>(5740±210)</td>
<td>(4320±220)</td>
</tr>
<tr>
<td>DOCA Control (n=8)</td>
<td>(6690±490^{a})</td>
<td>(6060±380^{a})</td>
</tr>
<tr>
<td>DOCA Diabetic (n=8)</td>
<td>(6020±540)</td>
<td>(6220±380^{a})</td>
</tr>
<tr>
<td>Control (n=9)</td>
<td>(4650±310)</td>
<td>(4570±380)</td>
</tr>
<tr>
<td>Diabetic (n=9)</td>
<td>(5480±370)</td>
<td>(5310±380)</td>
</tr>
</tbody>
</table>

\(a\) different from control.
\(b\) different from diabetic.
\(c\) different from DOCA-control.
significantly less than in the DOCA–control group. The diabetic group was very similar to the control with a mean systolic blood pressure of $135 \pm 6$ mmHg.

3.4.4 Diastolic Blood Pressure

Diastolic blood pressure was elevated in all groups treated with DOCA (Table 4). At two weeks both the DOCA–control ($94 \pm 6$ mmHg) and DOCA–diabetic ($91 \pm 5$ mmHg) groups had increased diastolic blood pressure. The diastolic blood pressure in control rats was $86 \pm 2$ mmHg and $73 \pm 4$ mmHg in the diabetic group. No significant differences existed amongst these groups.

Five weeks of DOCA treatment caused a further increase in diastolic blood pressure (Table 4). DOCA–control and DOCA–diabetic groups had a mean diastolic blood pressure of $103 \pm 4$ mmHg. The control group exhibited a mean diastolic blood pressure of $87 \pm 3$ mmHg whereas in the diabetic group diastolic blood pressure was $84 \pm 4$ mmHg.

3.4.5 Left Ventricular Peak Systolic Pressure

Left ventricular peak systolic (LVSP) is related to systolic blood pressure. It is not surprising to see that in all groups the LVSP closely paralleled systolic blood pressure.
3.4.6 Heart Rate

Two weeks of DOCA treatment caused heart rate to decrease (Table 4). DOCA–control animals had a mean heart rate of 316 ± 9 beats/min as compared to the DOCA–diabetic group with a mean of 310 ± 14. Diabetic animals had a slightly depressed heart rate (331 ± 14 beats/min) compared to controls (350 ± 8).

At 5 weeks heart rate continued to be depressed in DOCA–treated groups (Table 4). DOCA–control animals had a mean heart rate of 293 ± 5 beats/min and the DOCA–diabetic mean was 300 ± 10 beats/min. Control heart rate was 343 ± 5 beats/min compared to a diabetic mean of 338 ± 10.

3.4.7 Rate of Relaxation

The rate of myocardial relaxation (−dP/dt) was not reduced in the diabetic rats observed in the 2 week experiment (Table 4). The control group had a mean −dP/dt of −4570 ± 380 mmHgs− compared to the diabetic mean of −5310 ± 380 mmHgs−. Two weeks of DOCA treatment caused the −dP/dt to be significantly increased in all treated animals. The DOCA–control mean was −6060 ± 380 mmHgs− which was very similar to the DOCA–diabetic mean of −6220 ± 380 mmHgs−.
3.4.8 Rate of Contraction

A substantial increase in the rate of contraction (+dP/dt) occurred at 2 and 5 weeks of DOCA treatment (Table 4). Two week DOCA-control animals had a mean +dP/dt of 6690 ± 490 mmHgs\(^{-1}\) which was significantly higher than the control value of 4650 ± 310 mmHgs\(^{-1}\). At two weeks of DOCA treatment the DOCA-diabetic group had a mean +dP/dt of 6020 ± 540 mmHgs\(^{-1}\) compared to a mean of 5480 ± 370 mmHgs\(^{-1}\) seen in the diabetic animals.

A similar pattern was observed after 5 weeks of DOCA treatment (Table 4). Five week DOCA-control animals had a mean +dP/dt of 7190 ± 290 mmHgs\(^{-1}\) compared to a control value of 5650 ± 230 mmHgs\(^{-1}\). The DOCA-diabetic group value was 6210 ± 450 mmHgs\(^{-1}\) whereas the diabetic mean +dP/dt was 5740 ± 210 mmHgs\(^{-1}\). The +dP/dt observed in the 4 treatment groups is also graphically illustrated in Figure 8. Systolic blood pressure values appear to have visually similar bar heights as can be seen in Figure 9. The ratios of +dP/dt divided by the systolic blood pressure for these groups are in Table 5. It is also apparent that +dP/dt is related to left ventricular peak systolic pressure (Figure 10).
Figure 8. The rate of left ventricular contraction in control and diabetic rats treated with DOCA for 5 weeks.

DOCA treatment appeared to increase +dP/dt in both control and diabetic rats. Measurements were made in conscious animals. This increase was only significant in control rats treated with DOCA. All values are means ± s.e.m., p < 0.05.
Figure 9. Systolic blood pressure in control and diabetic rats treated with DOCA for 5 weeks.

Systolic blood pressure was increased in control and diabetic rats treated with DOCA for 5 weeks. All measurements were made in conscious rats. The * indicates a significant difference from the control group. Values are means ± s.e.m., p < 0.05.
Table 5. The ratio of +dP/dt divided by systolic blood pressure.

<table>
<thead>
<tr>
<th>Week</th>
<th>Control</th>
<th>DocaCon</th>
<th>Diabetic</th>
<th>DocaDia</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>41.4±2.1</td>
<td>40.0±1.9</td>
<td>42.0±2.1</td>
<td>40.0±2.2</td>
</tr>
<tr>
<td>2</td>
<td>38.2±2.9</td>
<td>41.4±2.9</td>
<td>45.0±2.9</td>
<td>40.8±3.2</td>
</tr>
</tbody>
</table>

The ratios in this table are the means ± s.e.m. of ratios obtained from single animals within a group. Systolic blood pressure appeared to influence +dP/dt. It is likely that elevated blood pressure induced cardiac hypertrophy which was represented as an increased rate of contraction. Diabetic animals treated with DOCA responded equally compared to their control counterparts. No significant difference was observed between any of the groups.
Figure 10. Resting +dP/dt appears to increase in proportion to left ventricular peak systolic pressure in conscious animals.

Left ventricular peak systolic pressure (LVPSP) closely parallels systolic blood pressure. In light of this it is not surprising that an increasing +dP/dt can be associated with an elevated LVPSP. Each point in this figure represents a separate animal. 'b' represents the slope of +dP/dt plotted against the LVESP. The correlation coefficient of each relationship is described by 'r'. It is interesting to note that when all the animals are grouped together, the correlation coefficient (0.82) is very high.
4.0 DISCUSSION

4.1 Catheter Design

The conclusions drawn from this study are dependent on accurate and precise blood pressure recordings. The recording system was tested by means of a square wave impact to ensure that it met the standard required to represent blood pressure with an adequate degree of fidelity (Hansen, 1949). This method made possible the determination of the relative damping and the undamped natural frequency of the catheter–manometer.

The catheters used to monitor blood pressure were constructed from 1 m of PE50 welded to 7 cm of PE10. The experimental design dictated that all hemodynamic measurements be made in conscious freely moving rats. This required that the catheters be relatively long. Unfortunately such catheters have a low natural frequency. Figure 1 describes the relationship between natural frequency and length in a PE50 catheter. It is plain to see that as catheter length increases, natural frequency drops. The 100 cm long catheter had a natural frequency of approximately 30 Hz.

It is generally accepted that to accurately represent blood pressure the catheter–manometer must have a flat frequency response up to and over the fifth harmonic of the fundamental frequency (Geddes, 1974; Hansen, 1949; McDonald, 1974). If this criterion is not met the signal conveyed by the catheter will likely be amplified due to resonance originating from the catheter. Rats have a heart rate of approximately 360 beats/min. In this case the fundamental
frequency is 6 Hz and thus the catheter–manometer system should have a natural frequency of 30 Hz.

Table 1 shows that the natural frequency of the PE50/PE10 combination catheter is approximately 30 Hz. This is in agreement with the natural frequency obtained for 100 cm of PE50 seen in Figure 1. While the natural frequency of 30 Hz is theoretically adequate to reproduce a blood pressure trace, it became apparent that this was not the only property necessary for recording the left ventricular pressure pulse and $+dP/dt$.

Damping or internal impedance is inversely proportional to the catheter diameter and can correct signal amplification due to a low natural frequency. Figure 2 shows that $+dP/dt$ is 30% higher in the PE50 catheter compared to the PE50/PE10 combination catheter. The effect of damping is graphically represented in Figure 3. Here the increased $+dP/dt$ and the amplitude overshoot characteristic to a catheter with low natural frequency (PE50) has been corrected by the series addition of 7 cm of PE10 to the catheter. Table 1 indicates that the PE50/PE10 combination catheter has a relative damping in the range of 0.75 to 1.08. This is very close to the damping factor of 0.78–0.82 specified by Hansen (1949) for catheter–manometer systems with a low natural frequency.

The PE50/PE10 catheter is referred to as a low natural frequency overdamped system. It is by no means a hi–fidelity instrument. Its performance characteristics could easily be altered by shortening the length and choosing a larger diameter or stiffer catheter. The constraints of the experiments at hand
did not allow for such alternatives and therefore the catheter design represented an acceptable compromise of cost, utility and performance.

4.2 Hemodynamic Measurements in Conscious Rats

Hemodynamic measurements such as $+dP/dt$, heart rate, and blood pressure are interrelated and dependent on each other. Atropine and angiotensin II (Ang II) were administered to conscious rats to determine how $+dP/dt$ is affected by changes in blood pressure, heart rate and autonomic innervation.

4.2.1 Atropine in Conscious Rats

Intravenous atropine (0.03 mg/kg) was administered to rats. The intention of this experiment was to determine the effect of reduced cardiac parasympathetic tone on the myocardium of intact animals. The reduction in vagal input to the heart caused an instantaneous rise in both heart rate and $+dP/dt$. Table 2 shows that there is a positive correlation between $+dP/dt$ and heart rate ($r = 0.6 \pm 0.1; 3.9 \pm 0.9 \text{ mmHg/s/beat/min}$) that occurs following this intervention.

It is not clear if heart rate and $+dP/dt$ are related or if they are separate results of parasympathetic inhibition. Strictly speaking, the increase in $+dP/dt$ following atropine administration should be ascribed to the reduced tonic vagal input caused by atropine. Alternatively, the positive inotropic effect may be related to the increased heart rate. This effect has been observed in many species. Fein et al. (1980) have shown that rat papillary muscle possesses a
negative force–frequency relationship. In other words, as the frequency of the electrical stimulus was increased the papillary muscle developed less tension. While this is the case in isolated muscle, there is no evidence to suggest that the negative force–frequency relationship occurs in the intact myocardium of conscious rats. Data obtained from papillary muscle does not represent the left ventricle as a whole and an increase in heart rate could alter other cardiovascular factors that would increase +dP/dt.

It is likely that any inotropic effect related to heart rate would be masked by heightened ventricular sympathetic innervation concomitant to the blocked parasympathetic input. In this event the question of a positive or negative force–frequency relationship in the rat myocardium becomes irrelevant.

The effect of heart rate on +dP/dt in conscious rats has not been made clear by this experiment. However, it is apparent that atropine causes a simultaneous increase in heart rate and +dP/dt. This result may be useful in the interpretation of cardiovascular events inhibiting cardiac parasympathetic innervation. It is by no means clear if this observation can be extrapolated to a situation in which parasympathetic or sympathetic activity is increased. This result is, however, consistent with the observed effect of a β-adrenergic agonist such as isoproterenol on heart rate and +dP/dt in the isolated heart (Vadlamudi and McNeill, 1984) and intact anesthetized rats (Dowell et al., 1986).
4.2.2 Angiotensin II in Conscious Animals

To investigate the possibility that an increase in systemic resistance might effect $+\frac{dP}{dt}$, intravenous angiotensin II (Ang II) was administered to conscious rats. Ang II is a potent vasoconstrictor and caused blood pressure to be elevated (Figure 4 and 5). In addition, Ang II caused $+\frac{dP}{dt}$ to increase (Figure 4) and heart rate to fall (Figure 5).

The fall in heart rate can be assumed to be baroreflex mediated. Ang II has been shown to have a small positive chronotropic effect (Buckley, 1972). Such a response would be masked by the autonomic reflex response. The increase in $+\frac{dP}{dt}$ suggests that the baroreflex that depresses heart rate does not affect the left ventricle. Either this reflex does not control the left ventricle or its effect is countered by other mechanisms.

The increased $+\frac{dP}{dt}$ (Figure 4) observed following an Ang II injection could be the result of a direct effect of Ang II, sympathetic activation, changed heart rate, or an increase in afterload. Ang II has been shown to possess a negligible positive inotropic effect in isolated rat cardiac muscle (Freer et al., 1976). In an intact animal coronary vasoconstriction would impair cardiac performance. This could be countered by an increased coronary artery perfusion pressure. Sympathetic activation influencing left ventricular inotropy might be elevated by the stress of increasing blood pressure. The rate of contraction may also be influenced by the decreased heart rate caused by Ang II. Fein et al. (1980) have shown that rat papillary muscle exhibits a negative force–frequency relationship. This runs counter to the result obtained...
in the previous experiment in which atropine caused both heart rate and $+dP/dt$ to rise.

The increase in $+dP/dt$ observed following Ang II administration may be due to peripheral vasoconstriction. This would be achieved by means of the Frank–Starling mechanism. In this case the systemic resistance would decrease the volume of blood ejected from the heart during systole. Following diastole the left ventricle would have an increased volume. The myocardium of the expanded ventricle would in effect be stretched. The length–tension relationship would be optimized and the myocardium would develop more tension. This may be represented as an increased $+dP/dt$, however, strictly speaking this is not an increase in inotropy.

4.3 Deoxycorticosterone Acetate Hypertension in Conscious Rats

In this experiment the effect of hypertension on cardiac function in the diabetic state has been examined. Rats were first made diabetic with streptozotocin. Hypertension was induced by the administration of DOCA and saline drinking water.

The pathogenesis of DOCA–NaCl hypertension is not fully understood, however, a number of consistent features have been observed in many experiments allowing a generalized concept to be formed. It appears that administration of DOCA changes hormonal and neural pressor mechanisms. Relevant pre–hypertensive changes include altered angiotensin II and vasopressin activity, elevated sympathetic drive, and a distorted baroreflex
response. DOCA–NaCl hypertension also results in characteristic changes in vascular structure that contribute to the overall pathology of this hypertensive state.

Compared to other methods of inducing hypertension, the DOCA–NaCl model is relatively cheap and easy to institute. It has the advantage that it does not require surgical interventions such as nephrectomy or implantation of a renal artery clip. Unlike many genetic forms of hypertension, the control state is easy to define and unambiguous.

The cardiovascular effects of DOCA–hypertension have been extensively studied in normoglycemic rats (Tomanek et al., 1990; Yamamoto et al., 1985; Heller et al., 1978; Bing et al., 1971). This is not the case for diabetic animals. Only two other studies have looked at aspects of DOCA–hypertension in diabetic rats (Sasaki and Bunag, 1982; Hebden et al., 1990). Blood pressure and arterial lesions have been measured in conscious DOCA–diabetic rats (Hebden et al., 1990) but cardiac function has not been previously examined in this model.

Hypertension is the most obvious physiological change that occurred in DOCA–treated rats (Table 4). DOCA–control rats showed a significant increase in systolic blood pressure at two weeks which was further elevated at 5 weeks. Diastolic blood pressure was elevated at two weeks but this only became significant at 5 weeks. Similar results were obtained in DOCA–diabetic rats. Both systolic and diastolic blood pressures obtained are in good
agreement with previous experiments performed in our laboratory (Hebden et al., 1990).

Elevated systolic blood pressure may represent a combination of increased myocardial output, enhanced vasoconstriction, and vascular damage.

It is interesting to note that systolic blood pressure was higher in the DOCA-controls than in the DOCA-diabetics at both 2 and 5 weeks. This difference was only significant in the 5 week animals. Possibly the DOCA-diabetic animals have an enhanced ability to vasodilate. This would be in agreement with the observation that volume expansion always increased blood pressure to a greater extent in the DOCA-control group than in their diabetic counterparts (data not included in this report). DOCA-diabetic rats may not retain sodium to the same extent as DOCA-control rats. Since sodium is important to the development of this form of hypertension it could be expected that diabetic and normoglycemic rats would not experience the same degree of hypertension. On the other hand, the reduced systolic blood pressure observed in the DOCA-diabetic rats compared to DOCA-control rats may represent myocardial impairment. In this case the diabetic myocardium does not develop pressure to the same degree as in the control.

Diastolic blood pressure may be indicative of total peripheral resistance. Vascular damage in the form of atherosclerosis will reduce arterial compliance, decrease the arterial lumen, and increase systemic resistance to circulatory flow. DOCA-diabetic and DOCA-control groups exhibited similar diastolic blood pressures at both 2 and 5 weeks of treatment. This result is in
agreement with the observation of Hebden et al. (1990) that DOCA-hypertension caused an equivalent degree of atherosclerosis to occur throughout the vascular system of diabetic and control hypertensive groups. Reduced arterial compliance related to atherosclerosis may also contribute to the rise in systolic blood pressure by inhibiting the windkessel effect (Despopoulos, 1986).

The development of hypertension has important implications in terms of cardiovascular damage and adaptation. Coronary artery lesions have been observed to develop in 8 week DOCA-hypertensive rats and were shown to be the result of increased blood pressure (Anderson et al., 1988). In addition, coronary atherosclerosis developed following 6 weeks of DOCA-treatment in STZ-diabetic rats (Hebden et al., 1990). Cardiac hypertrophy is another characteristic of DOCA-induced hypertension and has been shown to occur in as little as 1 month following the initiation of DOCA treatment (Tomanek et al., 1990).

Any cardiovascular adaptation arising from an elevated blood pressure is likely to be proportional to the magnitude and duration of hypertension. Coronary atherosclerosis and cardiac hypertrophy may both be consequences of hypertension. In turn they will influence cardiovascular performance. While coronary lesions and increased myocardial mass were not examined factors in the present investigation, there is no reason to believe that these abnormalities did not occur in the DOCA-treated study groups. Our laboratory has shown that DOCA-diabetic animals do experience cardiac hypertrophy and reduced
coronary artery performance (Vadlamudi, isolated heart preparation, unpublished data).

Bradycardia observed in the DOCA treated groups may reflect an electrolyte imbalance, baroreflex response, or autonomic abnormality. Heart rate was greatly reduced in all DOCA–treated groups. Bradycardia was already present at two weeks in both DOCA–control and DOCA–diabetic rats. Heart rate depression continues to occur at 5 weeks of DOCA–treatment. Baroreflex responses have been shown to be abnormal or absent in DOCA–hypertension and it is not likely that they have an effect at this stage of DOCA–treatment (Nakamura et al., 1988). A reduction in heart rate is at odds with the concept of enhanced sympathetic activity in the early stages of DOCA–hypertension (Lamprecht, 1977). In this case tachycardia would be the expected observation. Bradycardia could also be the result of an electrolyte imbalance. DOCA–treated rats have been shown to be hypokalemic (Haack et al., 1972). Reduced plasma potassium levels would hyperpolarize pacemaker tissues reducing the resting membrane potential and increasing the time to reach a given threshold potential.

Bradycardia might influence cardiac performance. A reduction in heart rate could increase diastolic filling thus augmenting stroke volume. This mechanism could compensate myocardial performance for any contractile deficit incurred by diabetes or hypertension.

The rate of relaxation (–dP/dt) was significantly enhanced in both DOCA–control and DOCA–diabetic groups at 2 weeks of treatment. At 5 weeks of
treatment $-\frac{dP}{dt}$ remained high in the DOCA–control group. The relaxation rate in the DOCA–diabetic group was greater than that observed in diabetic rats but reduced compared to the DOCA–control animals. A reduced rate of relaxation may be indicative of ultrastructural damage or impaired calcium sequestration within the sarcoplasmic reticulum. This observation is consistent with the hypothesis that diabetes and hypertension cause impairment of myocardial relaxation.

The enhanced $-\frac{dP}{dt}$ associated with DOCA treatment may be due to altered metabolism or increased sympathetic tone. DOCA has been shown to cause cardiac hypertrophy despite the prevention of hypertension using hydralazine (Anderson et al., 1988). It is possible that DOCA could affect other metabolic processes within the myocyte altering relaxation characteristics. Calcium metabolism or sarcoplasmic reticular function may be influenced. Alternatively, the increased sympathetic activity associated with the initial phases of DOCA–hypertension (Lamprecht et al., 1977) may cause the increased $-\frac{dP}{dt}$. This mechanism would be consistent with the observation that $-\frac{dP}{dt}$ in the 5 week DOCA–diabetic group was significantly less than that of the DOCA–control animals. Left ventricular $-\frac{dP}{dt}$ can be influenced by $\beta$-receptor stimulation. The number of cardiac $\beta$–adrenoceptors has been shown to be reduced in the STZ–diabetic rat (Savarese and Berkowitz, 1979) decreasing left ventricular responsiveness to norepinephrine stimulation (Paulson et al., 1986). In this case elevated plasma catecholamines or increased sympathetic activity would not effect the rate of relaxation in DOCA–diabetic rats to the same degree as in DOCA–control rats. It is interesting to note that $-\frac{dP}{dt}$ was the same in both the 2 and 5 week diabetic and control groups not treated with DOCA.
The most striking observation of this experiment is that the rate of left ventricular pressure development (+dP/dt) in DOCA–diabetic group was increased compared to the diabetic group at 2 weeks of treatment and remained so at 5 weeks (Table 4). This is in direct opposition to the results of other studies using SHR or renovascular hypertensive diabetic rats (Rodrigues and McNeill, 1986; Factor et al., 1981; Fein et al., 1984; Fein et al., 1990). All of these studies indicate that the rate of pressure or tension development suffers the greatest impairment by the combined influence of diabetes and hypertension.

Similar to –dP/dt, elevated +dP/dt may be explained by increased circulating catecholamines, enhanced sympathetic activity, or altered calcium metabolism. These hypothesis are mere speculation as none of the markers indicative of such changes were investigated.

The increased rate of left ventricular pressure development observed in the DOCA–treated groups may also be an adaptive response to a hypertension related stress. The nature of such a stimulus is not entirely clear and could be related to metabolic, anatomical, or physiological abnormalities caused by DOCA–treatment. The +dP/dt in the DOCA–diabetic rats was less than that observed in DOCA–control rats at both 2 and 5 weeks of treatment. While this difference was not statistically significant after 5 weeks of DOCA treatment, it may be indicative of a trend in which the hypertensive diabetic myocardium is unable to respond to hypertension in a manner similar to that of its control counterpart.
An alternative hypothesis to explain the reduced increase of +dP/dt in the DOCA–diabetic group is that the hypertensive stress is greater in the DOCA–control rats compared to their diabetic counterparts. This theory is particularly attractive when systolic blood pressure is taken to be a measure of hypertensive stress.

It is interesting to observe that the 5 week +dP/dt (Figure 8) and systolic blood pressure (Figure 9) values represented in the form of bar graphs are visually identical. The bar heights from group to group are similar for both variables. Indeed, the ratio of +dP/dt divided by systolic blood pressure is virtually identical for each treatment group (Table 5). This suggests that the diabetic myocardium responds to hypertension in a manner similar to that of the control. This result also indicates that +dP/dt can be related to blood pressure. Reinforcing this concept is the data in Figure 10 in which 5 week +dP/dt values observed in each treatment group are plotted against the corresponding left ventricular peak systolic pressure.

The increased rate of left ventricular pressure development does not necessarily represent enhanced contractility. Rather, this may be an apparent increase in contractility due to cardiac hypertrophy resulting from hypertension. A myocardium of increased mass may simply overcome systemic resistance more rapidly.

Enhanced myocardial performance in DOCA–treated rats has been previously observed. Heller et al. (1978) have indicated that contractile function in
papillary muscle isolated from DOCA-hypertensive rats was unaltered. Normal cardiac index and acceleration of flow in response to increased preload have also been observed in such rats (Yamamoto et al., 1985). Tomanek et al. (1990) have shown that in DOCA-treated rats ventricular function is normal at rest. Hypertensive groups exhibited increased peak stroke and cardiac index values during volume expansion experiments. Of particular interest was the observation that peak stroke volume divided by left ventricular weight was the same in DOCA-treated and control groups.

Hypertension was induced in diabetic and control animals. The rate of left ventricular pressure development appears to respond to increased blood pressure. This response occurs to the same degree in both hypertensive diabetic and control groups. It can be concluded that at this stage of diabetes and hypertension diabetic animals possess an adaptive plasticity similar to that of controls.
5.0 CONCLUSIONS

1. Catheter design affects the reproduction of a cardiac left ventricular pressure pulse. A catheter consisting of 1 m of PE 50 attached in serial fashion to 7 cm of PE 10 has an adequate frequency response for purposes of measuring blood pressure in rats.

2. Intravenous atropine administered to conscious rats caused heart rate and $+dP/dt$ to rise. It is not clear if this change was the result of a positive force–frequency relationship or if it was an effect of reduced cardiac vagal input.

3. Intravenous angiotensin II administered to conscious rats caused both systolic blood pressure and $+dP/dt$ to rise. It appears that an increased afterload was responsible for causing an increase in $+dP/dt$.

4a. DOCA–control and DOCA–diabetic rats exhibited increased $+dP/dt$ and $-dP/dt$ compared to control and diabetic groups.

4b. The rate of left ventricular pressure development was consistently shown to be related to systolic blood pressure in all treatment groups including 5 week DOCA–diabetics.

4c. The combination of 5 weeks of DOCA–hypertension and diabetes did not impair cardiac performance in conscious rats according to the indices of cardiac function used in this investigation.
6.0 REFERENCES


