Chapter 9

GENERAL DISCUSSION
It has long been known that cardiopulmonary reflexogenic areas when excited may lead to dramatic changes in different visceral functions. The receptors attached to vagal and sympathetic afferents transduce mechanical and chemical stimulations into electrical signals and produce different cardiovascular and visceral responses. Activation of left ventricular sensory receptors triggers an inhibitory cardiovascular reflex including bradycardia and hypotension often referred to as Bezold-Jarisch reflex. The clinical counterpart of the reflex can be seen after acute myocardial infarction.

Application of different algesic agent like nicotine, lactic acid, bradykinin etc. over the left ventricular wall excites the nociceptors and cause nausea and vomiting (Abrahamsson and Thoren, 1972; Koley et al., 1992), defecation (Koley et al., 1997a) pseudoaffective response (Koley et al., 1988); vesicular and renal responses (Koley et al. 1995b, 1977b). It was demonstrated that transient occlusion of the left anterior descending coronary artery evokes a painlike or pseudoaffective response (Sherrington, 1906 and Brown, 1967). Several authors have attempted to study the cardiac pain and associated visceral responses with endogenous putative nociceptive mediators like 5HT (Guzman et al., 1962), adenosine (Sylven, 1989), prostaglandins (Wennmalm et al., 1974), potassium (Webb et al., 1987), histamin (Guzman et al., 1962) etc. and also algesic agents nicotine (Sleight and Widdicombe, 1965; Muers and Sleight, 1972; Koley et al., 1985; 1987; 1988; 1992; 1995a,b; 1997a,b) and bradykinin (Koley et al., 1985). It seems likely that one or more of these chemicals either released during myocardial ischaemia or applied from outside act in concert to excite the cardiac afferents and induce cardiac pain and associated visceral symptoms.

Thus, attempts have been made to study in anaesthetised, open chested cats the role of myocardial ischaemia and chemical stimulation of ventricular receptors by nicotine in modulation of renal function and vesicular motility under different experimental conditions. Myocardial ischaemia was produced in cats by occluding the main branch of the left anterior descending coronary artery (LAD) for 3-4 minutes. The ventricular epicardial receptors were stimulated by application of nicotine (100-200 µg/ml) over the epicardial surface for 30 seconds. LAD occlusion resulted initial increase followed by decrease of vesicular motility (intravesicular
pressure). Epicardial application of nicotine also resulted similar initial increase followed by decrease of vesicular motility. LAD occlusion resulted initial antidiuresis followed by transient diuresis. Epicardial nicotine also showed similar initial antidiuresis followed by transient diuresis.

LAD occlusion also induced fall of blood pressure. Epicardial nicotine application induced fall of blood pressure followed by increase of blood pressure. Thorough investigations have been made to find out the causative factors in the manifestation of reflex modulation of renal function as well as vesicular function. Attempts have also been made to find out whether cardiovascular status and its modulation has got any relation with the reflex changes of kidney function.

Ventricular receptor stimulation evoked a biphasic vesicular response having an initial large contraction followed by inhibition of bladder contractions. Muscarinic cholinergic receptors are not involved as atropine has failed to counteract such effects. Such effects (both contraction and inhibition) were abolished by sympathetic blocker guanethidine sulphate. However, the same reflexes (contraction and inhibition) was unaffected by phentolamine but completely counteracted by propranolol indicating the involvement of ß-adrenoceptors. Further works in atenolol and salbutamol treated animals have clarified that the vesicular inhibition induced by LAD occlusion or application of nicotine are due to the involvement of ß1 adrenoceptors which are blocked by atenolol. While the contraction of the bladder induced by LAD occlusion or by epicardial application of nicotine are abolished by salbutamol indicating ß2 adrenoceptor involvement in the initiation of vesicular contraction.

deGroat (1975) while describing the mechanism underlying sympathetic inhibition in the urinary bladder has reported that catecholamines either administered intraarterially or released endogenously may elicit two distinct inhibitory responses in the urinary bladder (deGroat and Saum, 1972; Saum and deGroat, 1972a,b). He described that one type of inhibition which was practically a depression of spontaneous bladder contractions were antagonised by ß adrenergic blocking agents and must have been mediated by direct action on the vesical smooth muscle cells. Second type of inhibition was unaffected by ß-blocking agent but was completely antagonised by ß-adrenergic blocking agents and such inhibition occurred in the parasympathetic ganglia on the surface of the urinary bladder.
In the present investigations, vesicular inhibition induced by coronary occlusion or by epicardial application of nicotine may not be of two types as suggested by deGroat (1975) though such inhibition was abolished by application of propranolol and also by application of ganglionic blocker hexamethonium. Hexamethonium can block both sympathetic and parasympathetic ganglia. At this stage, it is difficult to comment whether parasympathetic ganglionic influence is involved in the manifestation of inhibition of second type suggested by deGroat (1975). The inhibition is probably of type I which was blocked by propranolol. Such inhibition was not blocked by phentolamine and atropine. Probably propranolol blocks directly acting on the vesicular smooth muscle cells.

Afferent and efferent pathways for initiating the above cardiovesicular reflexes have also been investigated after sectioning the cardiac vagi and cardiac sympathetic. Cardiac sympathectomy abolished the inhibition of vesicular motility induced by both LAD occlusion and epicardial nicotine application. This observation indicates that cardiac nociception may cause reflex inhibition of bladder motility and afferent pathways are lying in the cardiac sympathetic. Bilateral cervical vagotomy did not abolish the biphasic reflex response completely. The initial vesicular contraction induced by LAD occlusion or epicardial application of nicotine was reduced significantly. These observations indicate that vagal afferents probably play important role in the initiation of contraction of the bladder. The involvement of vagus in causing bladder contraction was confirmed by stimulating the central cut end of the cervical vagus which produced a sustained large contraction of the bladder. Stimulation of the central cut end of the LICN induced sustained inhibition. So, these observations clearly indicate that initial large contraction is due to involvement of vagal afferents, whereas, sustained inhibition is presumably due to cardiac sympathetic afferents.

The efferent pathways in the manifestation of the cardiovesicular reflex have been studied. To study the role played by the pelvic efferents in mediating cardiovesicular reflexes, ventral rhyzotomy was done at the level of S2-S4. Ventral rhyzotomy resulted replacement of spontaneous rhythmic bladder contractions with short amplitude high frequency bladder contractions. In such animals ventricular stimulations failed to induce any reflex modulation of the vesicular motility. Stimulation of the cut ventral roots at the S2-S4 level produced large contractions of the bladder
though some fibers failed to show any effect and some fibers also showed inhibition of the vesicular motility. In propranolol pretreated cats ventral root stimulation failed to produce inhibition or contraction.

Sectioning of the hypogastric nerve to the bladder did not show any alteration of the cardiovesicular reflexes induced by LAD occlusion or application of nicotine. However, electrical stimulation of the peripheral cut end of the hypogastric nerve resulted inhibition of bladder contraction. This indicates that hypogastric nerves carry some inhibitory fibers to the bladder.

In spinal animals, transected at the level of C₇-C₈ disrupted the connection in between the supraspinal centres and the sacral spinal micturition centre and abolished the spontaneous rhythmic bladder movement as well as the cardiovesicular reflex. In midcollicular decerebration, the initial large contraction of the bladder which was often observed after LAD occlusion or on epicardial application of nicotine, is abolished. The inhibitory effect on vesicular movement following LAD occlusion was generally prolonged in decerebrated animals. Koyama et al. (1962) have stated that there are two separate areas located in the superiorcollicular and the inferiorcollicular levels. They have reported that vesicoconstrictor area was located at the superior and intercollicular levels whereas the vesicorelaxer area was located at the inferiorcollicular and intercollicular levels. Decerebration at the midcollicular level has probably dissociated the two areas resulting potentiation and prolongation of the vesicular inhibition by the vesicorelaxer areas due to LAD occlusion. So, the absence of initial large contraction following LAD occlusion or on epicardial nicotine application is probably due to lack of connection in between the vesicoconstrictor area to the rest of the centres probably the pontine centres for the micturition reflex.

Cardiorenal reflexes, such as effect of excitation of the cardiac receptors on urine formation was also investigated in order to find out relation, if any, with cardiovesicular reflexes. It has been observed that LAD occlusion or epicardial application of nicotine caused initial decrease followed by rise of urine formation. Apart from this effect it was observed that on epicardial application of nicotine for 30 seconds, there was a biphasic change of blood pressure with initial
hypotension followed by hypertension. Occlusion of the coronary artery (LAD occlusion) also induced fall of blood pressure and antidiuresis. This haemodynamic alteration as a result of excitation of the cardiac receptors due to LAD occlusion or epicardial nicotine application indicates the possibility of interrelation in between the urine formation and intrarenal hemodynamics. In many cases relationships have been observed in between the systemic blood pressure and urine flow. When the blood pressure has been decreased urine flow has also decreased and vice-versa (Fig.6.1) indicating the partial dependence of renal response on the demodynamic patterns. As regards neurotransmitters involved it is presumed that cholinergic mechanisms as well as adrenergic mechanisms are also involved in the elicitation of renal responses induced by LAD occlusion and application of nicotine on the epicardial surface. It has been demonstrated that atropinisation partially counteracted the antidiuresis induced by coronary occlusion whereas the same induced by nicotine was completely counteracted. Pickford (1947), Abrahams and Pickford (1956), Bhargava et al. (1972) and Kuhn (1974) reported that acetylcholine could probably act centrally to stimulate the secretion of vasopressin. So, it may be opined that cholinergic mechanisms are involved in the mediation of this renal response. Occlusion of the coronary artery resulted systemic hypotension along with antidiuresis. Both the effects are counteracted by atropine. These observations may suggest at least partial interdependence of renal responses on hemodynamic status of the systemic bed. There are adrenergic projections to the supraoptic and paraventricular nuclei and these adrenergic projections may have got influence on vasopressin release. Bhargava et al. (1972) have reported that in hydrated animals intracerebroventricular (i.c.v.) administration of adrenaline resulted inhibition of vasopressin release at low doses whereas at high doses vasopressin release is increased. In the present experiment, diuresis has not been observed in chemically sympathectomised cats indicating the involvement of adrenergic pathway. In phentolamine treated cats diuresis was also counteracted partially. Propranolol - the β adrenergic antagonist also blocked the diuretic response partially. Similar observations were also obtained after treatment with β, adrenoceptor blocker atenolol. From these observations it is apparent that ventricular receptors induced diuretic response is mediated through both α and β adrenoceptors.

To study whether renin-angiotensin system is also involved in the development of renal responses following LAD occlusion or application of nicotine, captopril, an angiotensin converting
enzyme inhibitor was also taken into consideration. In captopril pretreated animals reflex antidiuresis was blocked. It has been reported that renin-angiotensin system may take part in the release of ADH by acting centrally from the hypothalamic peptidergic neurones secreting vasopressin (Nicoll and Barker, 1971; Siret et al., 1977). Captopril inhibits the synthesis of angiotensin II and probably in absence of which ADH release has been blocked resulting absence of antidiuresis.

In the present study, antidiuresis followed by diuresis is observed on epicardial application of nicotine and on LAD occlusion. Antidiuresis is always associated with hypotension. The nicotine induced diuresis was accompanied by hypertension. However, such effect was not observed consistently in coronary occluded animals. The antidiuretic response was abolished by sectioning of ICN while the diuretic response was abolished by vagotomy in both the cases. So, the observations indicate that for diuresis afferent limb of the reflex is lying in the cardiac vagus, whereas, for antidiuresis afferent limb of the reflex is lying in the cardiac sympathetic. Haemodynamic correlation with the diuresis and antidiuresis is lacking.

Bilateral renal sympathectomy abolished the urine flow responses induced by ventricular receptor stimulation without any alteration in the blood pressure responses. Karim et al. (1989) have already clearly shown that efferent renal sympathetic nerve primarily mediate the renal responses due to excitation of atrial receptors. It is presumed that renal sympathetic nerve is involved mediating the cardiorenal response.

In order to find out the relationship between vesicular movement and urine flow induced by excitation of cardiac nociceptors either by epicardial application of nicotine or by coronary occlusion, detailed studies were made under different experimental conditions and preparation of the animals (Chapter 8). It has been demonstrated clearly that although in the intact control cats the biphasic changes of the vesicular motility and rate of urine formation (urine flow rate) are superimposed, these are not interdependent. Experimental results clearly indicate that initial antidiuresis can take place even in absence of increase of intravesicular pressure. So, increased IVP probably plays no significant role in inhibiting the urine formation by the kidney. Similarly, decrease of IVP probably has got no effect on the rate of urine formation. It may be opined that
changes in intravesicular pressure and changes in urine formation are not interdependent, and probably these are two separate reflexes being elicited in response to stimulation of the ventricular receptors.