INTRODUCTION

The relationship between disturbance of the function of autonomic nervous system (ANS) and cardiovascular system (CVS) morbidity as well as mortality has been the subject of many studies in the last two decades ***(Bigger, 1998)***. The ANS is of critical importance in the moment to moment regulation of heart rate, myocardial contractility and resistance of the vascular bed, thereby it is important in controlling cardiac output, blood flow distribution and arterial blood pressure ***(Crick et al., 2000)***. Cardiac autonomic function could be easily evaluated clinically by several non-invasive cardiovascular reflex autonomic function tests (AFTs) based on measuring the reflex changes in heart rate in response to standardized stimuli ***(Scott, 2001).***

Cardivascular autonomic neuropathy (CAN) has been reported in chronic rheumatic diseases as systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis (JRA) ***(Maule et al., 1997)***. It may result in sudden death possibly from arrhythmia and myocardial infarction due to its frequent association with microvascular disease resulting in myocardial hypoperfusion ***(Lagana et al., 1999)***. Thus, assessment of autonomic function in these patients is required ***(Hogarth et al., 2002)***.

The autonomic neural control of cardiovascular function involves a number of autonomic neuropeptides as neuropeptide Y (NPY) and vasoactive intestinal peptide (VIP) ***(Pedrazzinin et al., 2003).*** The disturbance in the interaction between the autonomic nervous system and the immune system may contribute to the initiation and perpetuation of rheumatic diseases. It is quite obvious that autonomic neuropeptides play

a part in the orchestraction of the various molecules (e.g., cytokines) exerting modulatory effects on immune cells ***(Pozo and Delgado, 2004)***.

Sympathetic regulation of immunity is not only mediated by catecholamines but also involves NPY which modulates immunological functions ***(Bedoui et al., 2004)***. NPY is a 36 sympathetic amino acid neuropeptide ***(Bettio et al., 2003)*** expressed in the central and peripheral neurons and regulates a variety of physiological activities including food intake, energy expenditure, vasoconstriction, anxiolysis and nociception ***(Mullins et al., 2002).*** In sympathetic nervous system, NPY is co-localized and co-released with norepinephrine (NE) and it augments the vasoconstrictor action of NE and angiotension II ***(Renshaw and Hinson, 2001)***. It has a positive chronotropic ***(Ullman et al., 2002)***, a negative inotropic and a coronary vasoconstrictor effects ***(Cerda-Reverier et al., 2000)***. In addition, NPY receptor 4 (N4) is responsible for the control of autonomic balance within CVS ***(Smith-While et al., 2002)***.

VIP, a 28 amino aicd parasympathetic neuropeptide, is found in the neurons of the gastrointestinal tract, brain and many autonomic nerves. It often occurs in the same neuron with acetyl choline as it facilitates its post-synaptic actions. It causes vasodilatation, bronchodilatation and it is the main mediator of vagally induced tachycardia. It has a positive inotropic effect ***(Opgaard et al., 2001)*** and it also increases coronary blood flow ***(Henning and Sawmiler, 2001)***. VIP is an anti-inflammatory immunomodulator neuropeptide which may be beneficial in treatment of Th1-type autoimmune disease as JRA ***(Delgado et al., 2004)***.

AIM OF THE WORK

This study aimed at assessment of cardiac autonomic function in lupus and JRA patients by standard clinical tests and measurement of serum autonomic neuropeptides (NPY and VIP as indicators of sympathetic and parasympathetic functions, respectively). In addition, the relationship between cardiac autonomic function and important disease characteristics was studied in order to address the possible etiopathogenic role of CAN in these diseases.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) is the part of nervous system (NS) concerned with the innervation of unstriated muscles and many of the secretory glands. It also helps to maintain the constancy of the internal environment of the body. Physiologically, it is divided into two parts, sympathetic and parasympathetic. They are integrative in functions and have anatomically separate pathways ***(Gyton, 2006).***

General organization of the autonomic nervous system:

The ANS is activated mainly by centers located in the spinal cord, brain stem and hypothalamus. Also portions of the cerebral cortex and, especially the limbic system, can transmit impulses to the lower centers and in this way they influence the autonomic control. Often, the ANS operates by means of visceral reflex. The visceral reflex is a sensory signal that enters the centers of autonomic ganglia, cord, brainstem and hypothalamus and these in turn send appropriate reflex responses back to the visceral organs through the efferent pathways to control their activities ***(Walton, 1993).***

The autonomic signals are transmitted to the body through two major subdivisions called the sympathetic and parasympathetic systems.

1- Parasympathetic Nervous System:

It consists of parasympathetic fibres that leave the central nervous system through several nerves, the cranial nerves (vagus, occulomtor, facial and glossopharyngeal), the second and third sacral spinal nerves and occasionally the first and fourth sacral spinal nerves. About 75% of all parasympathetic nerve fibers are in the vagus nerve. The vagus nerves supply parasympathetic fibers to the heart, lungs, esophagus, stomach, small intestine, the proximal half of the colon, liver, gall bladder, pancreas and upper portions of uterus ***(Walton, 1993).***

2- Sympathetic nervous System:

The sympathetic nerves originate in the spinal cord between the first thoracic and second lumbar segments and pass to the sympathetic chain, then to the target tissues and organs. The distribution of sympathetic nerves to each organ is determined partly by the embryologic site at which the organ originates, for instance, the heart receives many sympathetic fibers form the cervical portion of the sympathetic chain via the superior cardiac nerves ***(Gang and Malik, 2003).***

The sympathetic nerves supplying adrenal medulla have special nature as they pass without synapsing from the intermediolateral horn cells of the spinal cord through sympathetic chain to splanchnic nerves and finally into the adrenal medulla where they end directly on special cells. These cells secrete epinephrine and norepinephrine hormones directly into the blood. These secretory cells are embryologically derived from nervous tissue and are analogous to sympathetic ganglia cells ***(Walton, 1993).***

Functional organization of the autonomic nervous system:

Whereas the somatic portion of the NS operates to preserve integrity of the organism with reference to the external environment, the ANS acts to maintain a state within the internal environment ***(Gang and Malik, 2003).***

The ANS is largely concerned with the control of visceral activity. It affects the cardiac rhythm, cardiac output, respiration, blood vessel tone, the behavior of visceral smooth muscles, ducted and ductless glands ***(Crick et al., 2000).***

The many functions governed by ANS include the distribution of blood flow and maintenance of tissue perfusion, the regulation of blood pressure, the regulation of the volume and composition of extracellular fluid, the expenditure of metabolic energy and the control of visceral smooth muscle and glands ***(Landesberg and Young, 1996).***

Activation of the sympathetic system results in dilatation of the pupil and slight protrusion of the eye, increased cardiac output with tachycardia, bronchial dilation, cutaneous vasoconstriction but dilation of coronary and intramuscular arteries, sweating, inhibition of intestinal movement and closure of vesical and rectal sphincters. It may also raise the blood sugar by liberating glucose from the liver ***(Crick et al., 2000).***

Most terminal sympathetic fibers are adrenergic i.e. secreting noradrenaline at their nerve endings and their effects can be largely reproduced by an increase in the amount of

circulating adrenaline or noradrenaline in the blood. Exceptions to this rule are those innervating the sweat glands (secretomotor fibers) which are cholinergic i.e. secreting acetylcholine at the effector organ ***(Ganong, 1999).***

Activity of parasympathetic system is merely concerned with anabolic, excretory and reproductive activities. Parasympathetic stimulation results in constriction of pupils, slowing of the heart rate, diminution of cardiac output, bronchial constriction, increased intestinal peristalsis, evacuation of bladder and bowel and increase secretory activity of salivary and lacrimal glands. Also, its activation results in lowering of blood sugar by stimulating insulin secretion. The parasympathetic fibers are mainly cholinergic secreting acetylcholine at their terminals ***(Gang and Malik, 2003).***

Autonomic Innervations of the Heart:

Histological study of the distribution of autonomic nerves in the human heart:

To investigate the distribution of autonomic nerves in the human heart, six autopsied hearts without cardiovascular disease were studied by a photochemical method for acetylcholinesterase (AChE) as a test for parasympathetic fibers and by an immunohistochemical method for tyrosine hydroxylase (TH) as a test for sympathetic function. The density of nerve distribution was microscopically calculated by the point counting method to evaluate regional distribution of the autonomic nerves. There were more AChE-positive nerves in the subendocardial area than in the subepicardial area of the myocardium. In the atrium, AChE-positive nerves were more numerous than TH-positive nerves. On the other hand, there were more TH-positive nerves than AChE-positive nerves in the ventricle. Predominance of the distribution density at the anterior than the posterior wall of the ventricle was observed for TH-positive nerves. The different distribution patterns of sympathetic and parasympathetic nerves could modify cardiac performance under both physiologic and pathologic conditions ***(Kawano, 2003).***

The autonomic nerve supply to the heart consists of many mixed fibers, containing both vagal and sympathetic nerves, which cross over the aorta, pulmonary artery and vena cava to reach the cardiac chambers, conduction system and coronary arteries ***(Crick et al., 2000).*** *They include:*

I- Sympathetic Fibers:

Fibers from the central nervous system traverse the spinal cord and synapse in the sympathetic chain. Efferent fibers from the sympathetic chain provide a rich network of postaganglionic nerve endings, whose neurotransmitter is norepinephrine to the atria, ventricles, sino-atrial (SA) node, and atriovenricular (AV) node ***(Gyton, 2006).***

II- Vagal (parasympathetic) fibers:

The vagal control of heart is mediated by fibers, which synapse in ganglia in the heart. It provides a network of fibers that contain acetylcholine and supply the atria, SAN and AVN; a few fibers also supply the ventricular muscles ***(Gyton, 2006).***

Autonomic Influence on the Cardiac Function:

Although cardiac automaticity is intrinsic, heart rate and rhythm are largely under control of ANS ***(Watanabe and Kadoma, 2002).***

The ANS is of critical importance in the moment to moment regulation of HR, myocardial contractility and of the capacitance and resistance of the vascular bed, thereby it is important in controlling cardiac output, blood flow distribution and arterial blood pressure ***(Crick et al., 2000).*** The sympathetic influence on the heart is mediated by release of epinephrine and norepinephrine which act locally on beta receptors to stimulate G protein as signal transducer to activate adenylcyclase, which in turn catalyses the conversion of ATP to cAMP that activates protein kinases which phosphorylate the slow calcium channels, increasing myocellular Ca^{++} entry and myocardial contractility (positive inotropic effect). At the same time, protein kinase phosphorylates a protein, which causes a sarcoplasmic reticulum to take up Ca^{++} more enhancing, myocardial relaxation (lusitropic effect). Once nerve stimulation stops, the same nerve endings take up and store NE for reutilization. A small amount of the NE is also metabolized locally. Sympathetic nerve fibers reach the entire atria and ventricles as well as the SAN and AVN ***(Ganong, 1999)***.

Sympathetic stimulation increases atrial and ventricular contractility, and HR ***(Hainsworth, 1995).*** The parasympathetic

influence on heart is mediated via local release of acetylcholine by the vagus nerve. Vagal fibers influence predominantly the atrial musculature, SA and AV nodes. Some vagal innervation, however, has also been shown to reach the ventricles, and its stimulation can decrease ventricular contractility modestly. In general, vagal stimulation exerts effects opposite to those of sympathetic stimulation on the SAN of the atrium. At any given instant, the effect of the ANS on the heart is the net balance of these two opposing controls, which usually vary reciprocally ***(Crick et al., 2000).***

Autonomic Nervous System Dysfunction:

Autonomic dysfunction is defined as impaired function of the peripheral ANS and it can be divided into two categories:

1- Autonomic Neuropathy (AN) in which there is a structural lesion of the peripheral autonomic neuron.

2- Functional autonomic dysfunction in which no known structural lesions occurs.

Autonomic neuropathy is not simply an "all or none" phenomenon and ranges from minor to severe which may have an adverse effect on survival ***(Cechetto, 2000).*** Functional changes associated with autonomic dysfunction are shown in table (1).

Table (1): Functional changes associated with autonomic dysfunction.

System involved	Manifestation
Cardiovascular	Resting tachycardia, impaired exercise-induced cardiovascular response, cardiac denervation, orthostatic hypotension, impaired venoarteriolar reflex (dependent edema), painless myocardial infarction, sudden death due to prolonged QT interval.
Eye	Decreased diameter of dark adapted pupil, miosis, Argyl Robertson like pupil.
Gastrointestinal	Oesophageal motor in coordination, gastric dysrhythmia, hypomotility, pylorospasm, uncoordinated intestinal motility (diarrhea, spasm), intestinal hypomotility (constipation), cholecystopathy, fecal incontinence.
Genitourinary	Cystopathy (impaired bladder sensation, postmicturition drippling, detrusal hyperreflexia), male impotence, ejaculatory disorders, reduced vaginal lubrication, dysparonia.
Respiratory	Impaired breathing control, sleep apnea, decreased bronchial response to cold air.
Thermoregulatory	Sudomotor (diminished, excessive or gustatory sweating). Vasomotor (vasoconstriction, vasodilatation neuropathic edema.
Neuroendocinal	Reduced release of pancreatic polypeptide, somatostation, motilin gastric inhibitory peptide, gastric, norepinephrine with elevated immunoreactive atrial natriuetic hormone.

(Harati, 1996)

AN can be divided into primary, secondary and drug induced neuropathy. Primary autonomic failure includes pure autonomic failure, autonomic failure with multisystem atrophy, familial autonomic neuropathy and autonomic failure with Parkinson's disease. Secondary autonomic failure may be the result of central cerebral lesions involving the hypothalamus, midbrain and spinal cord lesions. It may be also a complication of renal failure, various autoimmune or collagen disease,

diabetes mellitus, alcoholism, amylodiosis, acute intermittent porphyria and paraneoplastic autonomic neuropathy. Also, autonomic dysfunction was well recognized to occur in some cases of Guillain Barre syndrome ***(Flachenecker et al., 1999).***

Many drugs have been known to produce autonomic dysfunction as an occasional complication such as tranquillizers, especially phenothiazines, tricyclic anti-depressants, monoamine oxidase inhibitors, centrally and peripherally acting hypotensive agents, alpha and beta adrenergic blockers and ganglion blockers ***(Gang and Malik, 2003).***

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Cardiac autonomic neuropathy is easily evaluated and has a major impact on survival due to sudden death possibly from arrhythmias. It may be associated with changes in the following parameters:

1. Heart Rate (HR):

Some subjects with autonomic dysfunction have resting HR> 95 beats/min ***(Pumpurla, 2002).***

With varying degrees of cardiovascular autonomic involvement, the slowest HR was found in patients with normal reflexes, the fastest HR was elicited in patients with cardiac parasympathetic involvement and intermediate HR was found in patients with additional sympathetic abnormalities ***(Scott, 2001).***

In cardiac autonomic neuropathy, both sympathetic and parasympathetic activity of the heart begin to decline. However, the parasympathetic nervous system activity declines more rapidly resulting in imbalance between the two arms of ANS. The relative increase in sympathetic tone would result in an increase in the HR. The subsequent progressive impairment of sympathetic nervous system gradually slows the HR. Finally, when both sympathetic and parasympathetic nervous system are maximally impaired, syndrome exists which is characterized by fixed HR response to cardiovascular reflex testing which is