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BARORECEPTOR AND CHEMORECEPTOR CONTRIBUTIONS TO THE ASPHYXIA AND ASPHYXIA ALONG WITH NICOTINE (DRIP) INDUCED BLOOD PRESSURE AND URINE FLOW IN CONSCIOUS CAT

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ABSTRACT ■ **Background:** It has been evidenced in the literature that exposure to cigarette smoke causes cardio-renal changes. Baro- and chemo-receptors are the most important sensory receptors that participate in the maintenance of cardio-renal homeostasis. Any respiratory distress like asphyxia, emphysema and bronchitis also causes the same results. However, it has not been demonstrated how baro and chemoreflex functions are responsible for the alterations of cardio-renal homeostasis during cigarette smoking (nicotine) along with respiratory distress (asphyxia).

Objective: The objective of the study was to evaluate the cardio-renal changes of cigarette smoking (nicotine exposure) along with respiratory distress (asphyxia) on baro- and chemo-reflex functions in cat.

Methods: Experiments were carried out in 10 normal adult cats of either sex, weighing about 2 to 3 kg. Experimental asphyxia was induced by clamping the free end of the tracheal tube, through which the animal respired. Mean arterial blood pressure (MABP) and urine flow were evaluated through cannulation of the femoral artery and urethra during asphyxia (40 to 90 second) and nicotinic (20 μg/Kg. body weight/ min) condition. To observe the role of baro- and chemo-receptors, bilateral common carotid occlusion and sino-aortic denervation was made.

Results: In case of both sino-aortic denervated and bilateral carotid artery occluded animals, asphyxia and asphyxia with nicotine causes significantly increase of blood pressure (hypertension), which is modified by baro and chemoreceptors. Nicotine might excite the receptors further. Urine flow (antidiuresis and dieresis) is also modified partially at the same experimental condition but insignificant.

Conclusions: Our data suggest that exposure to smoking (nicotine) along with respiratory distress (asphyxia) are enough to significantly aggravate the cardiovascular responses through baro and chemoreceptors sensitivity in cat. But renal parameter are partially modified through these receptors though it insignificant.

Key Words: Baroreceptors, Chemoreceptors, Asphyxia, Nicotine, Hypertension, Urine flow

INTRODUCTION

Hypertension is the most common modifiable risk factor for cardio-renal disease and death. Cigarette smoking is a leading preventable risk factor for the development and progression of cardiovascular disease. It is well established that respiratory distress like asphyxia also produces hypertensive as well as renal dysfunctions. Maziak and their group (2011) reported that the effects of water

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pipe tobacco smoking on the autonomic nervous system can be assumed to be virtually the same as those with cigarette smoking and emerging evidence supports this assumption. It has been evidenced in the literature that exposure to cigarette smoke increases arterial pressure in rats also (Castardeli et al., 2005). Nicotine exerts its deleterious cardiovascular effects through multiple mechanisms. Inadequate regulation of mean arterial pressure has important pathophysiological implications including syncope, end organ damage, and stroke. Such regulation requires appropriate central integration of barosensory afferents and autonomic reflex control of the heart and blood vessels (Derek, 2017). In cardiovascular physiology, the baro and chemoreceptor reflex is one of the body's homeostatic mechanisms to maintain blood pressure (Valenti et al., 2009).) Smoking one cigarette acts significantly on vascular regulation by increasing resistance, impairing baroreflex (Mancia et al., 1997; Arosio et al., 2006) function and increasing carotid wall tension in mild smokers. All these changes may take part in the atherosclerotic damage and could explain the higher rate of cardiovascular events affecting smokers. Eva et al. (2016) suggested that the two arterial baroreceptors, aortic and carotid baroreceptors, have different pressure sensitivities and the aortic baroreceptors have a higher pressure sensitivity than carotid baroreceptors. Acute activation of peripheral arterial chemoreceptors, located on carotid and aortic bodies, leads to acute increases in sympathetic nerve activity (SNA), as well as rate and volume of breathing; chronic arterial chemoreflex sensitization in smokers could lead to sustained sympathetic activation. Arterial chemoreceptors are activated by hypoxia, to which habitual smokers are susceptible due to underlying lung damage and exposure to carbon monoxide in tobacco smoke (Park and Middlekauff, 2009; Zevin et al., 2001). The carotid sinus nerve contains efferent fibers as well as chemoreceptors and baroreceptors afferents (Biscoe and Sampson, 1967). Baroreceptors are stretch receptors located in the carotid sinus and on the wall of the aortic arch and also on the wall of the common carotid artery (Heymans and Neil, 1958).The baroreceptors are very sensitive to stretch and excited when the systemic pressure is increased. Main functions of these baroreceptors are to depress the blood pressure through involvement of medullary vasomotor centre and vagal efferent activity. So the net function is to maintain the normal blood pressure by reflexly activating the vagus and depressing the sympathetic. Chemoreceptors on the other hand are most important in controlling the blood pressure when the blood pressure is depressed. Both chronic and acute activation (by smoking and any respiratory distress) of afferent inputs from peripheral and central chemoreceptors increases sympathetic drive in animal models and humans (Fatouleh et al. 2014; Xing et al. 2014). Enfeeble circulation results local accumulation of metabolites that stimulate chemoreceptors. Glomus cells are the sensory chemoreceptors, which are very sensitive to CO2, other metabolites and also low oxygen tension. So many investigators reported that arterial chemoreceptors are relatively slowly adapting and their firing rate is influenced by changes in the arterial PO2, PCO2 and pH, by certain abnormal constituents such as CO and by changes in chemoreceptor blood flow (Paintal and Riley, 1966). It is also established that stimulation of the hypothalamus or medulla oblongata leads to a greater pressor effect during anoxia than during a state of normal oxygenation of the blood. So during

enfeeble circulation chemoreceptors are stimulated and afferent sensation is transmitted to the medulla and there by blood pressure is increased by depressing the vagus and activating the sympathetic system.

Joseph (1964) reported that urine flow increases when renal arterial pressure is increased in- dependent of a change in the activity of the renal vasoconstrictor nerves and independent of a change in renal blood flow. Consequently, the rise in arterial pressure associated with carotid occlusion can contribute directly to the response of the kidney to carotid occlusion. The variability of the changes in water and electrolyte excretion by the kidney during carotid occlusion may represent a varying contribution of direct and reflex mechanisms to the total response. Renal function will also be considered as because baroreceptors have got influence on the release of ADH (Thrasher, 1994), which promotes water reabsorption in the renal tubules. In the conscious rabbit, maximal renal sympathetic nerve activity (RSNA) is produced by activation of trigeminal pathways by smoke (the nasopharyngeal reflex). The relationship between resting and maximal RSNA is stable with time and is independent of baroreceptor input (Burke & Head, 2003). Activation of efferent sympathetic nerves to the kidney stimulates renin release, enhances tubular reabsorption of sodium and water and decreases renal blood flow. In addition, activation of afferent sensory nerves, for example, stimulated by stretch, renal ischemia, hypoxia, or other injury, increases central nervous system sympathetic outflow (DiBona and Kopp 1997). Renal denervation is also being evaluated for treatment of various comorbidities, like chronic heart failure, cardiac arrhythmias and chronic renal failure (Suzanne and Roland, 2015).

In the 20th century, the role of the carotid baroreflex was demonstrated for short-term blood pressure (BP) regulation, but it was assumed to play no role in long-term BP control. However, based on several important studies in animals, interest in the role of the carotid sinus baroreceptor on long-term BP control has returned (Lohmeieret al., 2007) and a surgical implantable device has been developed to administer baroreflex activation therapy via electrical stimulation of the carotid baroreceptors (Scheffers et al., 2010). CB hypersensitivity has been shown to precede the development of hypertension in spontaneously hypertensive rat (Tan et al., 2010). Surgical removal of the CB has been performed in humans for reasons other than hypertension (eg, bronchial asthma and chronic obstructive pulmonary disease) (Winter and Whipp, 2004).

There is a lack of information regarding how the physiological responses on cardio-renal effects due to smoking with respiratory distress like asphyxia. The aim of the current study, therefore, was to use directly recorded cardio-renal parameter through baro and chemoreceptor reflex during severe asphyxia in cat to examine first whether the blood pressure and renal flow increase more or not and second, whether there is any extra effort behind this response to asphyxia. So it is worthwhile to investigate whether baroreceptors and chemoreceptors have got any specific role in altering the cardiovascular function as well as renal function.

METHODS AND MATERIALS

1. Experimental design:

Experiments were carried out in 10 normal adult cats of either sex, weighing about 2 to 3 kg. All the animals were classified in to two groups with five numbers per group. Group-

I represented the asphyxiated animals without nicotine drip. Group-II represented asphyxiated animals along with nicotine drip. The experimental protocols were according to the guidelines of International Ethical Committee (Registration No. 506/01/a/ CPCSEA).

➢ **Animal preparation:**

The investigation was carried out on normal adult cats of either sex weighing between 2-3 Kg and maintained with nutritious food and water. The day before the experiment the cats were given water *ad libitum* and no solid food was given. The rectal temperature was noted by using a thermometer (Zeal, UK) and the temperature (37°± 0.5°C) was maintained throughout the experiment using the heating pad placed below the operating table. The cats were anaesthetized by injecting á-chloralose (60-70 mg / Kg. body weight; i. v.) through femoral vein after an initial induction with anaesthetic ether and the á-chloralose was maintained throughout the experiment with a maintenance dose of 10 mg / Kg. body weight (i.v) when required. Dose of nicotine (drip) was used 20 μg/Kg body weight/min. Asphyxia was induced by clamping the free end of the tracheal tube, through which the animal respired. Clamping was done during the inspiratory phase and continued for 40 to 90 seconds, if the condition of the animal permitted.

General surgical preparation before the experiment:

A portion of the skin was cut off over the femoral vein at the junction of body and right hind leg. Then the femoral vein was cleared off from the surrounding tissues. An incision was made over the femoral vein and a polyethylene tube, filled with normal saline, fitted to a three-way stopcock (Pharmaseal, U.S.A.) at one end and other end was introduced to the femoral vein for administration of drugs and saline. In the same way femoral artery of the same side was cleared off from the surrounding tissues and cannulated with another polyethylene tube, also filled with normal saline and fitted with stopcock for recording of blood pressure. Right femoral artery was cannulated for recording of blood pressure through INCO pressure transducer coupled with INCO Polyrite (Koley et al., 1987).

Artificial ventilation and asphyxia was achieved *via* tracheal intubation. For this intubation an incision was made carefully over the skin and then with the blunt scissor trachea was exposed after cutting the smooth muscle around the trachea. After giving a lateral small incision one end of a 'T' shaped glass tube was inserted in the trachea and tied with a cotton thread firmly.

Left ureter was approached by retroperitonial incision over the left side of lower abdomen. The ureter was cleared off carefully from the surrounding tissues. A very fine soft polyethylene tube was introduced through the ureter after giving an inclined incision. The catheter was pushed upward until the tip was at the opening of the pelvis and fixed by tying with a silk thread. After catheterization, the skin and the smooth muscle over the incision were stitched by sewing, keeping the opened end of the catheter outside the body.The left ureter was cannulated for recording of urine flow as one spike per drop through a drop recorder connected with the INCO Polyrite. The urine flow was calculated as drops/min.

(Koley et al., 2001).

Urethra was exposed ventrally by a small incision over the skin just above the pelvic girdle. Then the urethra was pulled up and one end of a wide polyethylene tube was introduced through the urethra and another end of the catheter was fixed to a three-way stopcock (Pharmaseal, U.S.A.) so that the bladder could be evacuated time to time.

2. METHODS OF EXPERIMENTAL ASPHYXIA AND ARTIFICIAL RESPIRATION:

Asphyxia was induced experimentally by clamping the free end of the tracheal tube, through which the animal was allowed to respire. Clamping was done during the inspiratory phase and continued for 40 to 90 seconds, if the condition of the animal permitted (Ghosh and Koley, 1977). In case of animals, which were artificially ventilated (through artificial ventilator machine), asphyxiation was done only by withdrawal of the ventilation (Koley and Mukherjee, 1964).

3. CAROTID ARTERY OCCLUSION AND DENERVATION OF ANIMALS:

To observe the role of baro and chemoreceptors, bilateral common carotid occlusion and sino-aortic denervation was performed at the cervical level.

a) Preparation of Sino-aortic denervated animals:

Denervation of the carotid sinus region was performed by extirpating the carotid sinus nerve, stripping the adventitia of the external, internal, and common carotid arteries for 1 to 2 cm on both sides of the sinus. Then the aortic nerve was separated from the vago-sympathoaortic trunk in the neck region and denervated when required. (Floyd et al.,1977).

b) Preparation of temporary bilateral carotid artery occluted animals:

Particular care was taken in isolating the common carotid arteries from its pre-adventitial tissues, up to its bifurcation, without damaging the nervous connection. The occlusion (reversible) of each artery (when needed) was accomplished by putting arterial clamp on either side of the sinus, first in the proximal side (towards the heart) and then to the distal, to keep the sinus empty. The techniques of bilateral occlusion, instead of denervation were followed only to avoid respiratory complication (occasional) as reported by Mukherjee et al., 1958.

4. ADMINISTRATION OF DRUGS:

All the drugs were dissolved or diluted in the normal saline solution (0.9 gm% NaCl) freshly before the experiments. Desired quantities of tested drugs were introduced through the three-way stopcock attached with the femoral vein catheter in all cases. The infusion of each drug was followed by 0.5 ml of normal saline. In all the experiments, the animals were given 5% dextrose saline by drip fed for the maintenance of normal body fluid and electrolyte balance. Femoral arterial blood pH was checked and maintained at normal range either by alteration of ventilation or by infusion of $NaHCO_3$ (8.4%) intravenously.In the present experimental study nicotine (drip, 8-10 drop/min.) also used intravenously through the right femoral vein in a dose ranging from 20-60 çgm/ Kg., since in cats on administration of 10-20 ìgm / Kg body weight / min intravenously, plasma level of nicotine as measured (Zapata et al 1976) is about 40-70 çgm/ml which was approximately similar to smoker's nicotine level in blood.

5. DRUGS USED:

Anaesthetic ether (Kabra Drugs Ltd., India), Alpha-chloralose (Koch-Light Lab. Ltd. England), Sodium Chloride (E. Merck Ltd., India), Dextrose anhydrous GR (LobaChemie, India), Heparin (Biological E Ltd. India), Nicotine (Technical, BDH Chemicals Ltd. Pool, England).

6. DATA ANALYSIS:

The formula is used to calculate the mean arterial blood pressure is MABP = DP + 1/3 (SP-DP), where DP is diastolic pressure, SP is systolic pressure. At the same time urine flow is measured by drops / min. One spike indicate one drop of urine.All data are presented as means ± standard error of mean (SEM). Percentage changes in parameters in response to asphyxia and asphyxia with nicotine were calculated using the following formula: (Response value – Control value) / (Control value) × 100%. Changes in all data were analyzed using Student's *t*-tests.

7. RESULTS

➢ **Effects of asphyxia on blood pressure and urine flow in both normal and nicotinized animals.**

The animals were initially allowed to breathe spontaneously. For practical purposes the start of asphyxia has been taken for 40-90 seconds as the condition of the animal is permitted. Initially for a short period, there was no alteration of mean arterial blood pressure (MABP) and urine flow (UF) with asphyxia. Post-asphyxial rise in blood pressure, as observed by the present author, due, probably to sympathetic and sympathoadrenal discharge, not only during asphyxia but also in post-asphyxial stage, consequent upon re-admission of air. Blood pressure returned back to initial level slowly over a period of 5-10 minutes and simultaneously urine flow also returned to its initial level (Fig. 1A). During asphyxia resting MABP (85.85 ± 1.93 mmHg) was increased (107± 2.54 mmHg, $P < 0.001$) up to 24.63 % and changes in urine flow as antidiuresis was 39.16 % (from 2.86 ± 0.14 to 1.74 ± 0.10 drops / min, $P < 0.01$) and diuresis was 66.78% (from 2.86 ± 0.14 to 4.77 ± 0.33 drops / min, $P < 0.05$) (Table -1). In this study it was also observed that the asphyxia induced percentage change in MABP and UF during antidiuresis (AD) and diuresis (D) were 20.81 ± 1.33 mmHg, -39.57 ± 1.42drops / min and 35.38 ± 2.43drops / min respectively (Table -2, Fig. 1A).

After the intravenous application of nicotine drip (10-20 μgm/kg/min) blood pressure began to rise slowly and stabilized at a constant level after 20-30 min. When the pressure began to rise, urine flow also decreases considerably

Table-1: Shows the mean blood pressure (mmHg) and urine flow (AD and D) (drops / min.) during resting and asphyxia (without and with nicotine drip) condition.

Experimental Condition	Mean Arterial Blood Pressure(mmHg)		Mean Urine flow (drops / min.)		
	Resting	During Asphyxia	Resting	Antidiuresis (AD)	Diuresis (D)
Group I: Asphyxia.	85.85 ±1.93 (n=36)	107.87±2.5* (n=37)	2.86±0.14 (n=28)	1.74±0.10** (n=29)	4.77±0.33*** (n=24)
Group II: Asphyxia with nicotine (drip)	104±2.37 (n=25)	134±2.67* (n=37)	3.01±0.14 (n=24)	1.00±0.06* (n=25)	4.83±0.31* (n=27)

All data are presented as means ± standard error of mean (SEM) at the level of *P<0.001, **P<0.01, ***P<0.05

Table-2: Shows the percentage changes in mean blood pressure (mmHg) and urine flow (AD and D) (drops / min.) in control and asphyxia (without and wit nicotine drip) with Sino-aortic denervation (SAD), Bilateral Carotid Artery Occlusion (BLCO) condition.

Experimental Condition	**Blood Pressure (mmHg)**	**Urine flow (drops / min.)**	
	Percentage changes in Mean Arterial Blood Pressure (MABP)	**Percentage changes in Antidiuresis (AD)**	**Percentage changes in Diuresis (D)**
Asphyxic Control	20.81±1.33 (n=19)	-39.57±1.42 (n=15)	35.38±2.43 (n=15)
Asp+ Sino-aortic denervation (SAD)	25.14±0.39* (n= 07)	-35.00±0.65# (n=07)	33.21±1.11# (n=07)
Asp+ Bilateral Carotid Artery Occlusion (BLCO)	27.66±2.10** (n= 10)	-36.81±1.90# (n= 07)	32.89±1.35# (n= 07)
Asphyxia with Nicotinized(drip) Control	30.60±1.85 (n= 13)	-62.36±1.60 (n= 18)	36.66±3.87 (n= 07)
Asp+ Nic.+ Sino-aortic denervation (SAD)	34.95±0.61*** (n= 07)	-57.58±0.97# (n= 07)	32.78±0.92# (n= 07)
Asp+ Nic.+ Bilateral Carotid Artery Occlusion (BLCO)	38.79±1.37* (n= 07)	-58.19±1.03# (n= 07)	34.39±0.98# (n= 07)

All data are presented as means ± standard error of mean (SEM) at the level of *P<0.001, **P<0.01, ***P<0.05 and # indicate insignificant results.

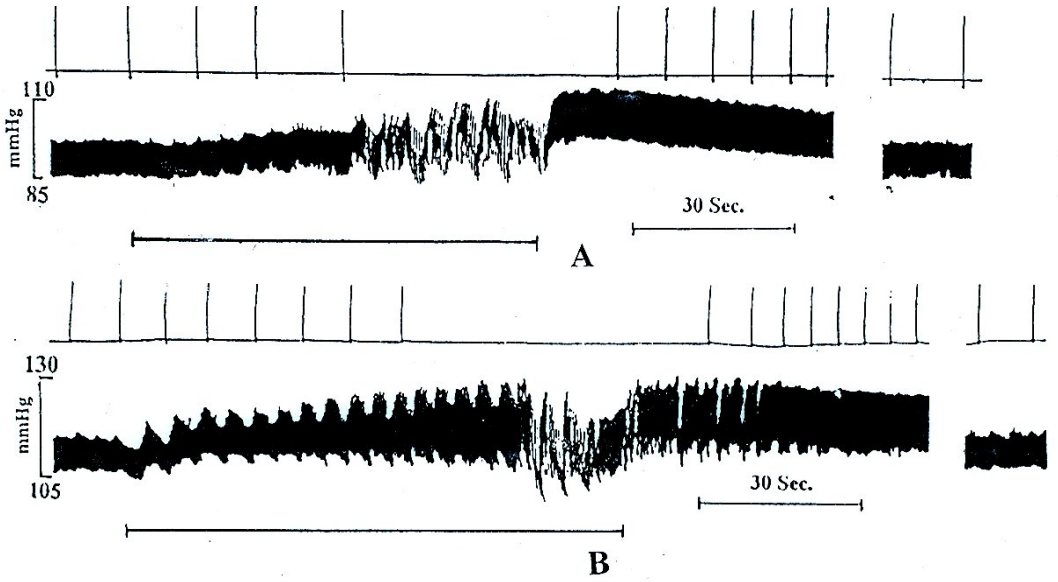

Fig.1: Typical response pattern of blood pressure and urine flow to **asphyxia (A)** and **asphyxia with nicotine (drip) (B).** The upper tracing shows the urine flow and lower tracing shows the blood pressure pattern. Each upward spike indicates one drop of urine. The horizontal bar indicates duration of asphyxia. To accommodate the tracing a break for 5 min. is made for each panel.

(Fig.1B). Due to asphyxia (40-90 seconds) resting pressure was further increased 28.84 % (from 104 ±2.37 to 134 ±2.67, *P <0.001*) along with more AD (from 3.01 ±0.14 to 1.00 ±0.06, drops / min, *P <0.001*). After withdrawal of asphyxiation as usual post asphyxial rise of pressure observed, UF remained in decreased state. But when the BP began to fall UF began to rise (from 3.01 ±0.14 to 4.83 ± 0.31 drops / min, *P <0.001*) (Table -1). These changes in BP and urine flow are more pronounced during asphyxia only.

On the other hand the percentage change in MABP during asphyxia along with nicotine (drip) is 30.60 ± 1.85 mmHg and antidiuresis and diuresis was –62.36 ± 1.6 and 36.66 3.87drops / min respectively (Table-2, Fig. 1B). Thus it is clear that in nicotinized condition asphyxic effects on hypertension and urine flow are more profound and intensive (Fig.1B). However there was no significant percentage change in diuresis in nicotinized state in comparison with the results of asphyxia without nicotine.

➢ **Effect of asphyxia and asphyxia along with nicotine induced blood pressure and urine flow in sino-aortic denervated animals.**

To check the role of baro and chemoreceptors in asphyxia and asphyxia along with nicotine (drip) induced alterations in the blood pressure and urine flow, sino-aortic nerves are denervated in such animals. In control animals (before sino-aortic denervation), the percentage change in MABP was 20.81 ± 1.33 and in urine flow during AD was –39.57 ± 1.42 and during D was 35.38 ± 2.43 (Table-2, Fig.2 and 3). In sino-aortic denervated animals, asphyxia induced percentage change in mean arterial blood pressure was higher than control animals and attained the mean value 25.14 ± 2.35 (P<0.001). Urine flow was also modified though partially but insignificant, during antidiuresis was – 35.00 ± 0.65 and during diuresis was 33.21 ± 1.11. It indicates that asphyxia-induced hypertension might be mediated through chemoreceptors only but the urine flow is partially mediated through these chemoreceptors but insignificant ((Table-2, Fig.2 and 3).

In case of control nicotinzed animals, before sino-aortic denervation the asphyxia induced percentage change in MABP, AD and D were 30.60 ±1.85, -62.36 ± 1.60 and 36.66 ± 3.87 respectively ((Table-2, Fig.3A).). After denervation, in nicotinized animals asphyxia causes change of MABP to 34.95 ± 1.62 (P<0.05) and urine flow 57.58 ± 2.57 (AD) and 32.78 ± 0.92(D) in compare to control animal ((Table-2, Fig.2 and 3). It indicates that in nicotinized animals, asphyxia causes increase of blood pressure which is further modified by chemoreceptors only. Nicotine might excite the receptors further. Urine flow is also modified though partially but insignificant.

➢ **Effect of asphyxia and asphyxia along with nicotine (drip) induced blood pressure and urine flow before and after bilateral carotid artery occlusion (BLCO).**

By another way to check the role of baro and chemoreceptors, in asphyxia and asphyxia with nicotine drip induced alterations in the blood pressure and urine flow, common carotid artery was occulted bilaterally in such animals. In control animals (before common carotid occlusion), the percentage change in MABP was 20.81 ± 1.33 and in urine flow during AD was –39.57 ± 1.42 and during D was 35.38 ± 2.43 (Table-2, Fig.2 and 3). The vasopressor response to asphyxia was more or less unaltered. When the carotid arteries

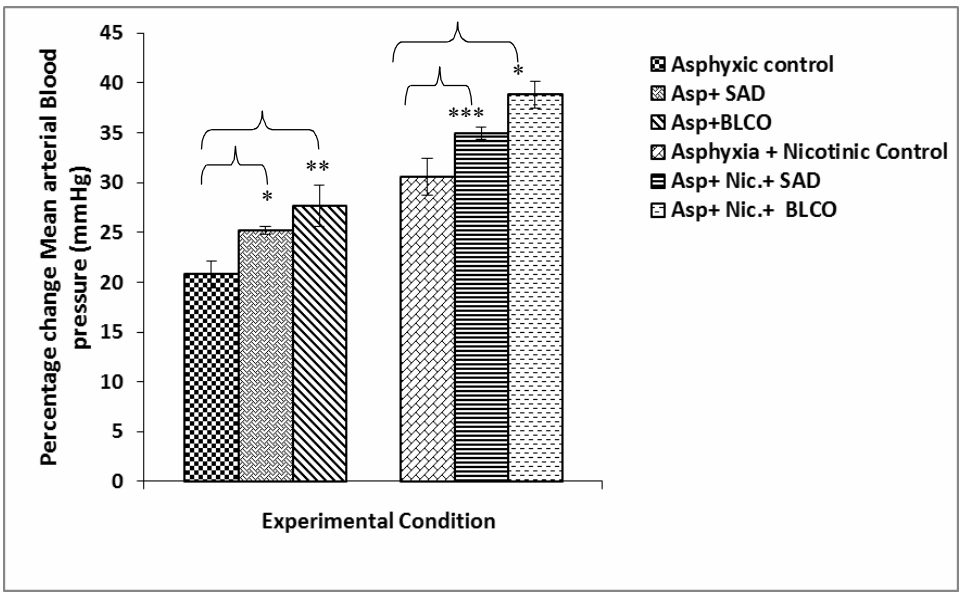

Fig.2: Shows the percentage changes in Mean Arterial Blood Pressure (mmHg) in control and asphyxia (without and with nicotine) with Sino-aortic denervation (SAD), Bilateral Carotid Artery Occlusion (BLCO) condition. All data are presented as Means ± Standard Error of Mean (SEM) at the level of *P<0.001, **P<0.01, ***P<0.05

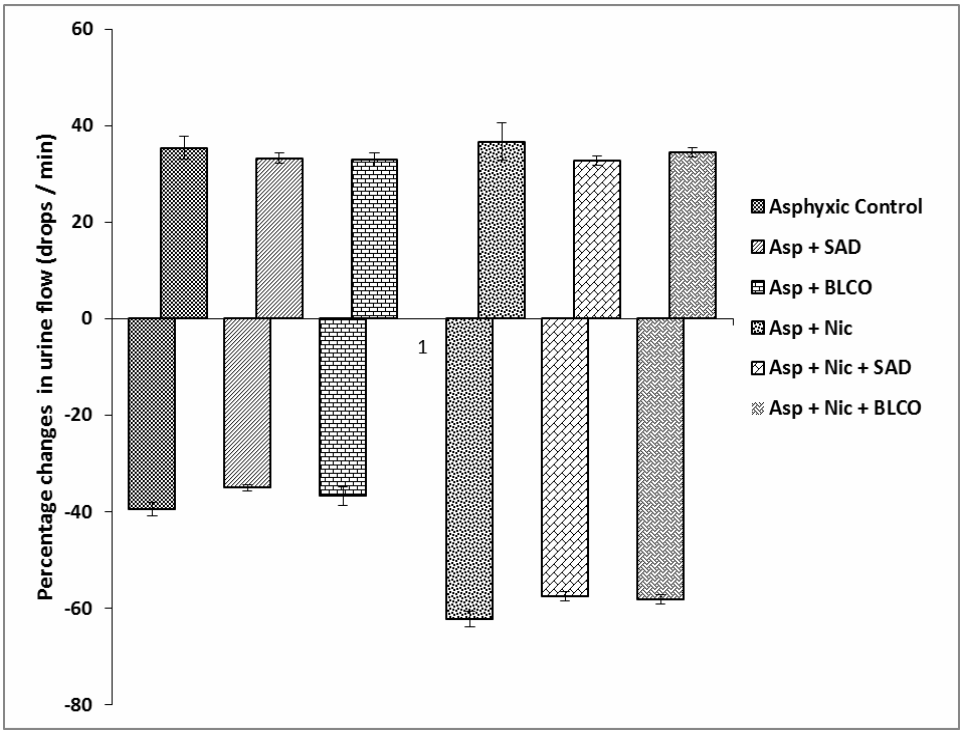

Fig.3: Shows the percentage changes in urine flow (drops / min) in control and asphyxia (without and with nicotine) with Sino-aortic denervation (SAD), Bilateral Carotid Artery Occlusion (BLCO) condition. All data are presented as Means ± Standard Error of Mean (SEM). **NS**: Non-significant compare to normal.

were occluded below the level of their bifurcation, the blood pressure and heart rate increased significantly during the period of asphyxiation. During this period the rise (34%) of blood pressure was greater (20.81 ± 1.33 to 27.66 ± 6.31, P<0.01) when compared with the rise of blood pressure in intact animals. Urine flow (AD was –36.81 ± 1.90; D was 32.89 ± 1.35) is also partially modified though significant (Table-2, Fig.2 and 3). It indicates that asphyxia-induced hypertension is mediated through the baro and chemoreceptors but the urine flows is partially mediated through these receptors but not significant.

In case of control nicotinized animals, before carotid occlusion the asphyxia induced percentage change in mean arterial blood pressure, antidiuresis and diuresis were 30.60 ±1.85, -62.36 ± 1.60 and 36.66 ± 3.87 respectively (Table-2, Fig.2 and 3). After carotid occlusion in nicotinized animals, asphyxia induced hypertension was slightly greater than control and both antidiuresis and diuresis are partially counteracted though not significant. In such case, asphyxia induced percentage change in mean arterial blood pressure, antidiuresis and diuresis were 38.79 ± 1.37 (P<0.001), -58.19 ± 1.03 and 34.39 ± 0.98 respectively (Table-2, Fig.2 and 3), indicating that in such nicotinized animal asphyxia induced urine flow is partially mediated through these baro and chemoreceptors though insignificant but there is a direct role of these receptors in such asphyxia induced hypertension.

8. DISCUSSION

Cigarette smoking an as endemic habit that traverses across the world population is associated with various diseases ranging from cardiovascular and respiratory system. Cigarette smoking increases the risk for atrial and ventricular arrhythmias (Sandhu et al., 2012). In view of the harmful effects of cigarette smoking and respiratory distress like hypoxia on cardio-renal system previously presented in the literature (Zornoff et al., 2007; Janssen et al., 2018). The baroreflex, which suppresses sympathetic activation, is attenuated in habitual smokers and plays a permissive role in this sustained sympathetic activation (Holly et al., 2014). Previously Robertson et al. (1988) suggested that nicotine may interact with aortic baroreceptor system in producing its sustained presser response, an effect which had received very little attention. Here it is aimed to evaluate the baro and chemoreflex functions in cats exposed to nicotine during short term respiratory distress (asphyxia). Also examine whether the relationship between pressor response and renal urine flow was causative, bilateral sino-aortic denervation and bilateral carotid artery occlusion was performed in a cat. According to Gellhorn (1957) Asphyxia elicits at first a rise of the blood pressure; later however the blood pressure falls and the pulse rate decreases. Since such variations in the blood pressure cause corresponding changes in the discharges from the sinoaortic baroreceptors, asphyxia enables one to investigate the modifying action of baroreceptor discharges on autonomic function when these functions are also altered by changes in the internal environment. First, the modifying action of the increased blood pressure may be considered. Hypothalamic stimulation during asphyxia produced a greatly increased pressor response but at the same time, Gellhorn (1957) showed a smaller contraction of the nictitating membrane than in the control. The former effect is owing to the state of sympathetic tuning in asphyxia

whereas the latter is caused by baroreceptor reflexes that are due to the greatly increased blood pressure. From the present observations, it may be suggested that the rise of blood pressure in intact animals during asphyxiation for 1 minute is probably due to stimulation of vasomotor centre and hypothalamus directly. In such case direct effect on the above centres is mostly predominant as because sino-aortic denervation does not affect such vasopressor response, instead pressor response is always slightly higher. Smoking shifts the relation between baroreceptor input and vagal output to operate at higher than normal arterial pressure. Smoking increases sympathetic nerve activity to the skin, heart and adrenal glands, and it reduces sympathetic nerve activity to the muscle; these effects are elicited by increased baroreceptor activity triggered by arterial pressure elevation addressed. Besides this, nicotine might be responsible for the further overstimulation of the higher centres during pressor response. In 1986, Walker reported that addition of CO2 to a hypoxic mixture causes graded vasoconstriction in the barodenervated conscious rat relative to the response to hypocapnic hypoxia which caused marked fall in blood pressure and total peripheral resistance. Similar responses have been noted in the dog and attributed to increasing chemoreceptor stimulation by Koehler *et al.* (1980). But in 1990, Benjimen *et al.* reported that the arterial baroreflex is an important component of the overall cardiovascular responses to both hypercapnic and hypoxic stimuli in the conscious rat.

Under such condition effect of asphyxia and asphyxia with nicotine were studied. In such animals, there was greater increase of blood pressure with asphyxia and even asphyxia with nicotine, as compared with control value. This indicates that pressure response due to asphyxia is comparatively higher with that of the control animals (Table-2, Fig.4 & 5). Thus in intact animals, baroreceptors modify the pressor response induced by asphyxia and asphyxia with nicotine. Koley and Mukherjee (1964) reported that after a short period of rise, blood pressure begins to fall, which is due to direct baroreceptor effect-influenced by increased blood pressure and direct stimulation of CO2 (excess) to the sino-aortic chemoreceptors.

In sino-aortic denervated condition, same experiment was repeated. In this experiment vago-aortic nerves and sinus nerve were sectioned bilaterally. In such animal's asphyxia and asphyxia with nicotine drip causes initial rise of pressure which is comparatively higher than that was observed in intact animals (Table-2, Fig.2 &3). This higher response is presumably due to absence of baroreceptors influence on systemic pressure. A decline in baroreflex function is due to two major possibilities. First, pathological arterial changes that reduce the distensibility of the vessel wall with miss match increases in compensatory receptor sensitivity (Anderson and Brown, 1980) and secondly, due to the functional derangements in autonomic nervous tone (Volpe et al., 1982). The acute nature of this experiment makes the reduction of baroreflex sensitivity entirely accountable for by increased sympathetic activity (beta adrenergic increase in heart rate) and or reduced parasympathetic tone (Adigun and Fentem, 1984 and Adigun and Akinjuola, 1991). It is also an indication that nicotine do interact with baroreflex pathway to inhibit baroreflex response either centrally: to increase sympathetic activity, similar to stimulation of hypothalamic or peripherally, by interacting with the receptors to reduces afferent information to the centre,

as has been observed in afferent traffic oblation experiment in animals (Nathan and Reis, 1977). Thus acute nicotine-induced in baroreflex sensitivity, indicating reduced baroreflex buffering of arterial blood pressure might lend an important contribution to the sustained blood pressure response it produces. Giussani et al. (1996) interestingly reported that, the intense peripheral vasoconstriction during acute hypoxemia in the llama fetus is unaltered by section of the carotid sinus nerve. At the same time occlusion of the common carotid artery, causes withdrawal of baroreceptors effect and also partly stimulation of carotid chemoreceptors (Heymans and Neil, 1958). In 1994, Marshall pointed out that peripheral chemoreceptor activation is an excitatory input that results in increased sympathetic outflow and blood pressure. It was also suggested that carotid chemoreceptors were stimulated by injection of nicotine in to the common carotid artery of anesthetized dogs (Heistad et al., 1975).

Guyton and their group (1975) state that cardiovascular baroreceptors are sensitive to vascular pressures and their input to the central nervous system is essential for the regulation of arterial blood pressure. They also contribute to the regulation of extracellular fluid volume, because their reflex effects upon arterial pressure and renal blood flow have marked consequences for urine flow. Daly et al. (1993) reported that distension of the bladder modified the relationship between the pressure in the isolated perfused carotid sinus regions and the hind limb vascular response. Antidiuretic and diuretic effects of asphyxia and asphyxia with nicotine drip were also modified in carotid occulted animals but it is insignificant. These effects probably due to release of ADH form the posterior pituitary as the baroreceptors role was withdrawn. So during rising phase of blood pressure in carotid occluted animals there was decreased of antidiuresis. This effect is probably due to release of ADH (Thrasher, 1994). So, the present experiment showed that the increased sympathetic responsiveness is retained in asphyxia in spite of the removal of the chemoreceptors and baroreceptors. Also indicate that sino-aortic baro and chemoreceptors act as a counteracting mechanism against alterations of internal environment.

9. CONCLUSION:

So from the above study it was summarized that in sino-aortic denervated (SAD) and bilateral carotid artery occluded (BLCO) animals, asphyxia and asphyxia with nicotine drip caused an initial rise of pressure which was comparatively higher than that was observed in intact animals. This higher response was presumably due to absence of baroreceptors influence on systemic pressure and chemoreceptors might play the main role for higher pressor response. Thus in intact animals, baroreceptors further modify the pressor response induced by asphyxia and asphyxia with nicotine supplementation. Antidiuretic and diuretic effects of asphyxia and asphyxia with nicotine drip were also changed in carotid occluded animals though it was insignificant. These effects (AD and D) probably due to release of ADH form the posterior pituitary as the baroreceptors role was withdrawn. So during rising phase of blood pressure in carotid occluded animals there was decreased of antidiuresis. So baroreceptors modulate the asphyxia and asphyxia with nicotine (drip) induced hypertension as well as urine flow alterations. Chemoreceptors play an important role in the manifestation of cardio-renal changes, induced by asphyxia and asphyxia with nicotine (drip).

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