Chapter

Thrombotic Tendencies in Excess Catecholamine States

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Abstract

Catecholamines are neurotransmitters distributed throughout the body including adrenal glands, chromaffin tissues and other tissues innervated by post ganglionic adrenergic neurons. The rate of release of medullary hormones is responsible for the control of serum catecholamines. Thrombogenicity of catecholamines are due various mechanisms including hypercoagulable states, endothelial damage, blood stasis and platelet aggregation. Oxidative stress generated by catecholamine excess causes coronary spasm, ultrastructural cell damage and arrhythmias. Elevated plasminogen activator inhibitor-1 during catecholamine excess causes hypercoagulability by hypofibrinosis. During stress, Catecholamines released in procoagulant environment causes vasoconstriction in adrenal veins resulting in venous thrombosis. Catecholamines generate moderately elevated levels of platelet count which enhances the risk of thrombosis. Hypercoagulability results in formation of coronary thrombus, rupture of atherosclerotic plaque and plaque progression due to gradual fibrinogen accumulation in the vessel walls. High levels of circulating catecholamines produce elevated levels thrombomodulin, the biomarkers of endothelial cell damage. In patients with hypertension in catecholamine excess, resistance to blood flow and damage to the integrity of blood vessels lead to atherosclerosis. A case report has been discussed which suggests an association of thrombotic tendency and catecholamine excess.

Keywords: catecholamines, thrombotic tendencies, atherosclerosis, hypercoagulation, platelet aggregation, endothelial damage, blood stasis

1. Introduction

Catecholamines are the class of neurotransmitters and hormones produced by the adrenergic nervous system, with a core structure of catechol and an amine group, regulating physiological processes [1]. Catechol refers to *ortho-dihydroxybenzene* and epinephrine and norepinephrine are the two major ethanolamine derivatives [2] occurring in the blood [3]. About 80% of epinephrine and 20% of norepinephrine are produced and released by the human adrenal medulla with a small amount of dopamine along with it [2].

1.1 Catecholamine biosynthesis

Catecholamines are synthesised and secreted from the chromaffin cells in adrenal medulla and sympathetic paraganglia [4]. Chromaffin granules produce catecholamines and fairly high concentration of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) for active transport mechanism [2].

Syntheses of catecholamines occur at two levels [5]:

1. Sympathetic nervous fibre extremities for norepinephrine.

2. Chromaffin cells of adrenal medulla for both epinephrine and norepinephrine.

Tyrosine hydroxylase is the rate limiting enzyme of catecholamine synthesis. Tyrosine from dietary proteins is transported to the brain and tyrosine hydroxylase (in the dopaminergic and noradrenergic neurons of CNS and in the non-neuronal cells of gastrointestinal tract and kidneys) converts it to 3,4-dihydroxyphenylalanine (DOPA). In the presence of aromatic L-amino acid decarboxylase, DOPA is converted to dopamine (DA) which is transported to vesicular storage granules. It may be released in the dopaminergic neurons or converted to norepinephrine in the noradrenergic neurons by dopamine beta-hydroxylase [6]. Norepinephrine is converted to epinephrine by phenyl ethanolamine-N-methyltransferase (PNMT) [4].

Medullary hormones synthesised and stored in the chromaffin granules are a pool of ready to release hormones upon stimulation [7].

1.2 Catecholamine functions and receptors

Norepinephrine and epinephrine together contribute to an increase in cardiac output, heart-rate, respiration, blood pressure, blood flow to muscles, alertness and decrease in splanchnic and renal blood flow [2]. Norepinephrine alone causes a decrease in heart-rate indirectly as a result of reflex bradycardia because of vasoconstriction effects [2].

Functions of catecholamines are mediated and regulated by alpha, beta adrenoreceptors and dopamine receptors. Each receptor located at distinct locations serves different functions and actions.

Alpha-1 receptors mediate adrenergic vasoconstriction [8]. Alpha-2 receptor stimulation causes inhibition of norepinephrine secretion [6]. Three subtypes of α_2 receptors are α_{2A}, α_{2B}, and α_{2C}. Alpha-2A in the peripheral postsynaptic region contributes to vasoconstriction in different vascular beds [8]. Beta-1 receptor stimulation causes positive inotropic and chronotropic action [6]. Beta-2 receptors stimulate vasodilation [9]. Beta 3 causes lipolysis in fatty cells and increase renin secretion [9].

Two types of dopamine receptors are D1 and D2.Stimulation of D1 receptors in coronary, renal, mesenteric and cerebrovascular beds causes vasodilation, diuresis and natriuresis. D2 receptor stimulation in presynaptic nerve endings causes inhibition of norepinephrine release [6].

1.3 Catecholamine metabolism

Neuronal catecholamines get metabolised intraneuronally after leakage from its stores [1]. Catecholamine metabolism mainly occurs in the liver [2]. There are two major catecholamine metabolites (i) metanephrines (constitutes 15% of urinary catecholamine) and (ii) vanillylmandelic acid, VMA (major end-point of norepinephrine and epinephrine metabolism [1] and constitutes 85% of excreted catecholamine) [2].

1.4 Catecholamine inactivation

Two major enzymes involved in the inactivation of catecholamines are catechol-o-methyl transferase (COMT) and monoamine oxidase (MAO).COMT adds methyl

group to hydroxyl at 3-position of catechol ring and MAO catalyses oxidative deamination reaction [2].

Norepinephrine is inactivated by two processes (i) reuptake into the nerve terminals by the active carrier mechanism associated with Na^+-K^+-ATPase of which some part is stored to granular vesicles and the rest is metabolised and (ii) extra-neuronal accumulation to vascular smooth muscles [10].

1.5 Catecholamine excess

The three distinct peripheral catecholamine systems are [11].

1. Sympathetic nervous system (SNS)

2. Adrenomedullary hormone system (AHS)

3. Dopamine autocrine/paracrine system (DOPA)

Sympathetic nervous system: the measure of norepinephrine release in the specific regions allows the clinical assessment of organ-specific sympathetic nervous tone and penetrating analysis of SNS in the pathophysiology of a disease state [12].

Adrenomedullary hormone system: the catecholamines stored in the chromaffin cells get released by innervations of preganglionic sympathetic fibres of splanchnic nerves and get dispersed after its entry to medulla [2].

Dopamine derived from plasma DOPA acts as an autocrine/paracrine substance. Human urine contains higher concentration of dopamine and its metabolites rather than norepinephrine and its metabolites as dopamine is generated in the non-noradrenergic and non-adrenergic cells [13].

Catecholamines are distributed throughout the body including adrenal glands, chromaffin tissues and other tissues innervated by post ganglionic adrenergic neurons [3]. The rate of release of medullary hormones is responsible for the control of serum catecholamines [2].

The cellular uptake and metabolism of catecholamines in the extraneuronal tissues and the exogenous administration of catecholamines together contribute to 25% of total metabolism of catecholamines produced in the SNS and adrenergic chromaffin cells [1].

During stressful conditions, the level of enzymes catalysing biosynthesis of catecholamines increase and enzymes degrading the catecholamines decrease [14]. Stress-induced changes in the adrenergic receptors occur due to the combination of neuronal and extraneuronal catecholamine uptake system, level of cAMP, density of adrenoceptor subtypes and coupling of agonist receptor complex with different G-proteins [14].

During chronic stress, increased levels of catecholamines produce aminolutins and oxyradicals. Oxidative stress thus generated causes coronary spasm, ultrastructural cell damage and arrhythmias [14]. They also cause Ca^{2+}overload and cardiac dysfunction by acting on beta-1-adrenoceptor signal transduction pathway [14].

1.6 Catecholamine excess in pheochromocytoma

Catecholamine excess is seen in certain types of tumour such as pheochromocytomas that are functional tumours of the chromaffin cells [15]. Norepinephrine secreting tumours are known to cause hypertension (in 80–90% of these patients [4]) and hypertensive crisis and their abrupt release may cause arrhythmias [6]. Of this nearly 40% of the patients suffer from sustained hypertension

(norepinephrine secreting tumours), 45% from paroxysmal hypertension (epinephrine secreting tumours) and 5–15% from normotension (dopamine secreting tumours) [4].

Other vasoactive substances like neuropeptide Y, adrenomedullin and atrial natriuretic peptide contribute to hypertension in these patients [6]. Neuropeptide Y increase coronary and peripheral vascular resistance and potentiate norepinephrine-induced vasoconstriction [7].

Pheochromocytoma produces enormous amounts of catecholamines due to mutation of succinate dehydrogenase by oxidative phosphorylation deficit [6].Two major mechanisms in pheochromocytoma that leads to catecholamine excess are translocation of dopamine into storage granules and the presence of dopamine beta hydroxylase enzyme [1].

In extra-adrenal tumours, norepinephrine levels are high, in adrenal tumours both norepinephrine and epinephrine are in excess and in multiple endocrine neoplasia type 2 and neurofibromatosis type 1, epinephrine levels are high [6].

In non-functional/silent pheochromocytoma, metanephrine levels are elevated instead of catecholamines [6].

Complication of pheochromocytoma in hypertensive crisis are sustained hypertension by continuous elevated levels of catecholamine causing vasoconstriction and orthostatic hypertension due to reduced blood volume that resulting in vasoconstriction, postural tachycardia and postural hypotension [4].

Neurological complications are hypertensive encephalopathy, haemorrhage (due to paroxysmal hypertension) and acute ischemic stroke (due to postural hypertension) [4].

In 78% of pheochromocytoma patients, thrombus exists at the time of their tumour discovery and 75% of the secondary thrombi are located in inferior vena cava or heart or both [16]. Venous thromboembolism and acute arterial thrombi are well described in such patients [17] but evidence of stroke, aortic thrombi and myocardial infarction are fewer [18].

Several mechanisms explain thrombotic tendencies in pheochromocytomas by elevated catecholamines:

- Catecholamines generate moderately elevated levels of platelet count which enhance the risk of thrombosis [19].

- Platelet aggregation is increased in pheochromocytoma [18] and produce thrombi in low-flow areas causing coronary events [19].

- Contributing factors to thrombus formation are erythropoietin, pro-coagulation and serotonin [6].

- Catecholamine excess in other tumours like paragangliomas may cause ADP-mediated platelet aggregation leading to thrombotic events [20].

- During stress, catecholamine release in procoagulant environment causes vasoconstriction in adrenal veins resulting in venous thrombosis [21].

- Loss of antithrombin III in glomerular diseases associated with hypertension may increase thrombotic risk [22].

- Pheochromocytoma causes thrombosis of caudal vena cava and aortic thromboembolism through Virchow's triad list [20, 22]:

(i) Endothelial damage

(ii) Blood stasis

(iii) Hypercoagulability state

Mortality of pheochromocytoma patients occur due to either acute intramyocardial necrosis or diffuse patchy myocardial fibrosis [23].

2. Mechanisms associated with thrombus formation in catecholamine excess

Thrombus formation and dissolution are physiological processes with dynamic balance between procoagulation and anticoagulation mechanism [24]. Catecholamine excess contributes to long-term development of atherosclerosis and cardiovascular risk [25] due to their effect on carbohydrate and lipid metabolism [23].

3. Cascade of thrombus formation

Thrombotic process occurs by the activation of coagulation cascade in different phases [26].

1. Initiation phase—the extrinsic pathway of coagulation in which low amounts of active pro-coagulant factors are produced.

2. Amplification phase—level of coagulation factors increase.

3. Propagation phase—active coagulation factors are generated like thrombin which binds to phospholipid at the surface of activated platelets.

4. Stabilization phase—thrombin provides strength and stability to growing clot and thrombin activatable fibrinolysis inhibitor.

Injury to the vessel walls due to resistance, in catecholamine excess states, causes exposure of glycoprotein tissue factor (TF) to the blood. After exposure, TF bind to Factor VII/VIIa and forms tertiary complex in the presence of calcium to activate factor X to Xa, factor IX to IXa and factor VIIa. At the site of injury, platelet activation, conversion of fibrinogen to fibrin and thrombus formation occurs. Platelets are able to regulate their gene and protein expression for binding to sub endothelium [26].

Diseases affecting Virchow's triad can induce clot formation [27].

4. Hypercoagulability

Hypercoagulability is the tendency to produce thrombosis by inherited or acquired molecular defects. Thrombus is formed based on the number of predisposing factors and environmental stress [13].

Cancer is the second major cause of hypercoagulation with clinical thrombosis in 15% and thrombosis on autopsy in 50% patients [28].

Catecholamines increase plasminogen activator inhibitor-1 (PAI-1) mRNA by expression of PAI-1 genes in the cardiovascular system by neurological and neuroendocrine mechanisms via beta-adrenoreceptors [29]. PAI-1, a member of serine-protease inhibitor, inhibits both tissue type and urinary-type plasminogen activator. Elevated PAI-1 during catecholamine excess causes hypercoagulability by hypofibrinosis. High levels of PAI-1 act on adipokines in the atherogenic process and cause atherosclerotic lesions and atheromas [30]. Epinephrine regulates Beta-mediated tissue-type plasminogen activator to produce an increase in fibrinolytic capacity [25].

Antithrombin III (AT-III) inhibits the protein-splitting reaction, characteristic of haemostasis, by interfering with the activity of four of the serine proteases and antagonising thrombin [31]. Hypertension associated glomerular diseases in catecholamine excess may cause loss of AT-III by protein loss in the urine. Hypoalbuminemia and hypercholesterolemia in Proteinuria causes platelet hyperaggregability and aggravate hypercoagulability. Increased levels of fibrinogen and thromboxane in protein-losing nephropathy contribute to thrombosis [27].

Hypercoagulability result in formation of coronary thrombus, rupture of atherosclerotic plaque and plaque progression due to gradual fibrinogen accumulation in the vessel walls [24].

In patients with borderline hypertension, coagulation activation occurs before clinical manifestations of vascular damage appear [32].

5. Platelet aggregation

In thrombus formation, a high proportion of platelets translocates from their initial point of attachment to the injured vessel wall and forms a firm adhesion contact [31]. Catecholamine infusion induces platelet aggregation in ex-vivo and animal models [16]. They activate platelets by interacting with platelet α2-adrenoreceptor in in-vitro studies. Stimulation of α1-adrenoreceptor inhibits platelet aggregation by inactivating platelet response to epinephrine [25]. In-vivo adrenergic infusion causes platelet activation and an increase in platelet size, aggregation and releasing factors [24]. Elevated factor V: C, factor VIII: C, v Willebrand Factor: Ag, tissue-plasminogen activator (t-PA): Ag, contribute to risk of atherothrombotic events [25]. Redistribution of cardiac blood flow in catecholamine infusion causes regional slowing of blood flow and enhanced tendency for intravascular platelet aggregation [23].

The anticoagulative effect of epinephrine is explained by a 50% decrease in the ratio of maximal coagulation activation and maximal fibrinolytic activation by decreased tumour necrosis factor (TNF) and interleukin (IL) 10 [33]. Epinephrine induce fibrinogen receptor exposure and fibrinogen binding to potentiate platelet aggregation. Epinephrine infusion causes short-term recruitment of platelets and functionally active Factor VIII from the spleen for thrombus formation. They discharge high molecular von Willebrand Factor (vWF) which increase the activity of platelet adhesion from its storage compartments. Elevated epinephrine levels increase platelet deposition on the atherosclerotic vessels with high local shear rate [25].

Norepinephrine activates platelet aggregation in-vivo by stimulating α2-adrenoreceptor [24].

It causes platelet aggregation in two phases [16]:

- Initial reversible aggregation.
- Simulated release of adenosine diphosphate.

Norepinephrine initiates platelet thrombosis by directly damaging the endothelial walls of vessels and breaking its integrity [24]. In acute mental stress, 60% of variation in thrombin formation depends on amount of norepinephrine secreted and sensitivity of β2-adrenergic receptor [19].

6. Clotting time

Adrenergic activation by epinephrine injection increases factor VIII: C and cause a decrease in clotting time. In-vivo adrenergic infusion stimulate β-2 adrenergic vascular receptors to release clotting factors like FVIII, v WF, and t-PA from endothelium to the circulation [24] resulting in thrombotic risk in both coronary artery disease and hypertension [25].

7. Endothelial damage

Endothelium maintains balance between prothrombotic and atherothrombotic tendencies [27]. Endothelial cells provide a non-thrombogenic surface that inhibits platelets and blood cells from adhering and activating coagulation cascade [34]. Antithrombotics like thrombomodulin, heparin sulfate, tissue factor pathway inhibitor and protein S are involved in reducing the activation of AT III and protein c to elevate antithrombotic tendencies. Synthesis and induction of prothrombotic mediators such as tissue factor and antifibrinolytic factors like PAI-1 take part in prothrombotic tendencies [27].

Disproportion in the tendencies causes endothelial damage where subendothelial proteins are exposed and favour platelet adhesion [27]. According to Gando et al. [35], endothelial damage can occur due to both exogenous and endogenous release of catecholamines. High levels of circulating catecholamines produce elevated levels thrombomodulin, the biomarkers of endothelial cell damage [36]. Due to loss of endothelial cell protection and expression of procoagulant and prothrombotic molecules, platelets adhere to the subendothelial surface and release ADP and thromboxane A2 causing imbalance in haemostasis and thrombosis [37].

8. Blood stasis

Blood stasis plays an important role in the formation of thrombus. Thrombus forms in regions of blood stasis like narrow artery due to atheromatous plaque, mechanical vasoconstriction, prolonged immobilisation and varicose vein. From the injured tissue, tissue thromboplastin produced causes initial thrombus formation followed by platelet activation by thrombin. Thrombin transforms fibrinogen to insoluble fibrin and release to stagnant blood [36].

In patients with hypertension in catecholamine excess, resistance to blood flow and damage to the integrity of blood vessels lead to atherosclerosis [27, 32]. Three mechanisms explain the overall increased vascular resistance [37]:

(i) Rarefaction of arterioles and capillaries.

(ii) Reduced internal diameter of arterioles.

(iii) Increase in arterial and arteriolar wall mass.

S. No.	Mechanism of thrombosis	Factors involved in thrombosis
1.	Hypercoagulability	1. Tissue plasminogen activator inhibitor-1 (t-PAI-1) 2. Antithrombin-III (AT-III) 3. Fibrinogen 4. Thromboxane
2.	Platelet aggregation	1. Factor V: C 2. Factor VIII: C 3. v Willebrand factor (v WF) 4. t-PAI-1 5. Tumour necrosis factor (TNF) 6. Interleukin 10 (IL-10)
3.	Clotting time	1. Factor VIII:C 2. (v WF) 3. t-PAI-1
4.	Endothelial damage	1. t-PAI-1 2. Thrombomodulin 3. Thromboxane A2
5.	Blood stasis	1. Thromboplastin 2. Thrombin

Table 1.
Summary of factors associated with thrombosis.

The significant role of sympathetic nervous system in elevated haemostatic activity in atherosclerosis and thrombus formation explains the role of catecholamines in cardiovascular diseases and associated arterial thrombus formation [25]. The factors associated with thrombosis in different mechanisms are summarised in **Table 1**.

9. Management of thrombosis

Hypertension associated with catecholamine excess plays an important role in the thrombus formation by mechanisms explained above. So treatment for hypertension is the primary objective in treatment and prevention of thrombotic tendencies. The most preferred antihypertensive is phenoxybenzamine which is an alpha and beta receptor antagonist given at 10 mg once a day with gradual dose titration to 30 mg three times a day. Appropriate anti-coagulation with heparin is vital for patients with risk of thrombosis to prevent devastating outcomes [19].

Removal of tumours producing excess catecholamines play a crucial role in alleviating symptoms associated with hypertension and thus thrombus formation. Due exaggerated fall in blood pressure after surgical removal of these tumours, adequate vascular volume replacement with oral fluids and salt is recommended [38].

Here in a case report has been discussed which suggests an association of thrombotic tendency and catecholamine excess.

10. Case report

A Case report on cerebral venous thrombosis due to pheochromocytoma in a patient with Von Hippel Lindau (VHL) mutation [39] explains an unusual connection between thrombosis and pheochromocytoma in a 15 year old boy with pheochromocytoma and associated hypertension. The patient was primarily presented with cerebral venous thrombosis and seizures. Initial examination revealed left

frontoparietal hematoma and superior sagittal and transverse sinus thrombus for which he was treated with heparin and antiepileptics. Follow-up showed elevated blood pressure and high urine catecholamine levels. The diagnosis of abdominal mass after evaluation for consistent elevated blood pressure turned out to be pheochromocytoma. He underwent para-aortic dissection and right adrenalectomy.

VHL disease is an autosomal, dominant inherited tumour syndrome which occurs as a result of a germline mutation in the VHL gene. Even though its association with pheochromocytoma is under-studied, VHL proteins are found to cause tumorigenesis in pheochromocytoma by induction of either gain of function, dominant negative effect or gene dosage effect in chromaffin cells [40].

Some mechanisms are established to explain the association of Catecholamine excess in pheochromocytoma and thrombus formation:

1. Tumours produce different chemicals with prothrombotic nature that cause hypercoagulability as a paraneoplastic feature [41]. The release of procoagulants, fibrinolytics and proteolytic factors induce thrombosis. Neoplastic vascular invasion damages the thromboresistant properties of vessel wall and tumour cell attachment to the endothelial surface leading to endothelial retraction and exposure of basement membrane. The damaged endothelial cells and matrix cause platelet adhesion and aggregation by release of procoagulatory and antagonistic substances [42].

2. Adrenal tumours release excess catecholamines and cause thrombophilia and clot formation [16].

3. In the case of VHL mutation, certain changes are produced in the Hypoxia inducible factor (HIF) resulting in polycythaemia and increased venous thrombosis [43]. HIF regulates both oxygen hemostasis and erythropoietin receptor expression [44, 45].

To associate hereditary disorders with thrombosis in excess catecholamine state is restricted because of unavailability of literatures explaining the same. Excess catecholamines themselves produce thrombosis even though an inherent mutation of VHL was found in the above patient as a cause of thrombosis. Hypertension associated with high catecholamine levels make a patient more prone to thrombosis than others with normal blood pressure. In patients with tumours such as pheochromocytoma and paraganglioma, there is high catecholamine levels which increase the risk of thrombotic tendencies compared to other patients with catecholamine excess alone.

11. Conclusion

Though there have been evidences of thrombus formation after infusion of catecholamines in animals and humans, available evidence of the exact mechanism of thrombotic tendencies is scanty. Catecholamine excess states are a diagnostic challenge due to heterogenous clinical presentation like fluctuating hypertension in young which may not attract enough clinical and laboratory attention. Thrombogenicity of catecholamines are due various mechanisms including hypercoagulable states, endothelial damage, blood stasis and platelet aggregation. Surgical removal of tumours associated with catecholamine excess provide a clinical approach in treating abnormalities of thrombus formation.

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Conflict of interest

There are no conflicts of interest.

Abbreviations

ADP	adenosine diphosphate
ATP	adenosine triphosphate
DOPA	3,4-dihydroxyphenylalanine
DA	dopamine
PNMT	phenyl ethanolamine-N-methyl transferase
COMT	catechol-O-methyl transferase
MAO	monoamine oxidase
SNS	sympathetic nervous system
ANS	autonomic nervous system
DOPA	dopamine autocrine/paracrine system
PAI-1	plasminogen activator inhibitor-1
AT-III	antithrombin III
t-PA	tissue plasminogen activator
TNF	tumour necrosis factor
IL	interleukin
v WF	von Willebrand factor
VHL	Von Hippel Lindau
HIF	hypoxia inducible factor

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References

[1] Eisenhofer G, Kopin IJ, Goldstein DS. Catecholamine metabolism: A contemporary view with implications for physiology and medicine. Pharmacological Reviews. 2004;**56**:331-349

[2] Brandt M. Chapter 4: The Adrenal Medulla. In: Endocrine. Rose-Hulman Institute of Technology; pp. 49-54. Avaiable from: https://www.rosehulman.edu/~brandt/Chem330/EndocrineNotes/Chapter_4_Adrenal_Medulla.pdf

[3] Fluck DC. Catecholamines. British Heart Journal. 1972;**34**:869-873

[4] Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: Characteristics and treatment. Endocrinology and Metabolism Clinics of North America. 2011;**40**(2):295-311

[5] Zouhal H, Jacob C, Delamarche P, Cratas A. Delamarche. Sports Medicine. 2008;**38**(5):401-423

[6] Pacak K. Pheochromocytoma: A catecholamine and oxidative stress disorder. Endocrine Regulations. 2011;**45**(2):65-90

[7] Bravo EL, Tagle R. Pheochromocytoma: State-of-the-art and future prospects. Endocrine Reviews. 2003;**24**(4):539-553

[8] Duka I, Gavras I, Johns C, Handy DE, Gavras H. Role of the postsynaptic α_2 adrenergic receptor subtypes in catecholamine induced vasoconstriction. General Pharmacology. 2000;**34**:101-106

[9] Giovannitti JA Jr, Thomas SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: A review of current clinical applications. Anesthesia Progress. 2015;**62**(1):31-38

[10] Nedergaard OA. Catecholamines: Regulation, release and inactivation. Pharmacology and Toxicology. 1998;**1**:5-8

[11] Goldstein DS. Catecholamines and stress. Endocrine Regulations. 2003;**37**:69-80

[12] Esler MD, Hasking GJ, Willett IR, Leonard PW, Jennings GL. Noradrenaline release and SNS activity. Journal of Hypertension. 1985;**3**(2):117-129

[13] Goldstein DS, Mezey E, Yamamoto T, Aneman A, Friberg P, Eisenhofer G. Is there a third peripheral catecholaminergic system? Endogenous dopamine as an autocrine/paracrine substance derived from plasma DOPA and inactivated by conjugation. Hypertension Research. 1995;**18**:s93-s99

[14] Adameova A, Abdellaftif Y, Dhalla NS. Role of the excessive amounts of circulating catecholamines and glucocorticoids in stress-induced heart disease. Canadian Journal of Physiology and Pharmacology. 2009;**87**:493-514

[15] Wheeler MH, Chare MJB, Austin TR, Lazarus JH. The management of the patient with catecholamine excess. World Journal of Surgery. 1982;**6**:735-747

[16] Kaiser S, Chronakos J, Dietzek AM. Acute upper extremity arterial thrombosis and stroke in an unresected pheochromocytoma. Journal of Vascular Surgery. 2013;**58**(4):1069-1072

[17] Raghavan R, Ince PG, Walls TJ, Gholkar A, Dark JH, Foster JB. Malignant cerebrovascular thromboembolisation by pheochromocytoma. Clinical Neuropathology. 1995;**14**:69-71

[18] Garg SK, Garg P, Urumdas M. An interesting presentation of pheochromocytoma. Indian Journal of Critical Care Medicine. 2018;**22**(1):48-50

[19] Hou R, Leathersich AM, Rudd BT. Pheochromocytoma presenting with arterial and intracardiac thrombus in a 47-year-old woman: A case report. Journal of Medical Case Reports. 2011;**5**:310

[20] Shafiq A, Nguyen P, Hudson MP, Rabbani B. Paraganglioma as a rare cause of left ventricular thrombus in the setting of preserved ejection fraction: Discussing the literature. BML Case Reports. 2013;**2013**:1-4

[21] Wordsworth S, Thomas B, Agarwal N, Hoddell K, Davies S. Elevated urinary catecholamines and adrenal haemorrhage mimicking phaeochromocytoma. BML Case Reports. 2010;**2010**:1-3

[22] Marcasso RA, Bahr Arias MV, Gianini L, Headly SA, Bracarense APFRL. Pheochromocytoma in a dog as a cause of aortic thomboembolism. Brazilian Journal of Veterinary Pathology. 2011;**4**(2):145-149

[23] Haft JI, Kranz PD, Albert FJ, Fani K. Intravascular platelet affregation in the heart induced by norepinephrine. Circulation. 1972;**46**(4):698-708

[24] Preckel D, von Kanel R. Regulation of hemostasis by sympathetic nervous system: Any contribution to CAD? Heart. 2004;**4**(2):123-130

[25] von Kanel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusion on hemostasis in vivo. European Journal of Haematology. 2000;**65**:357-369

[26] Cimmino G, Salvatore F, Paolo G. The two faces of thrombosis: Coagulation cascade and platelet aggregation. Are platelets the main therapeutic target? Journal of Thrombosis and Circulation: Open Access. 2017;**3**(1):117- 122

[27] Good LI, Manning AM. Thrombotic disease: Predisposition and clinical management. Compendium. 2003;**25**(9):660-675

[28] Thomas RH. Hypercoagulability syndromes. Archives of Internal Medicine. 2001;**161**:2433-2439

[29] Venugopal B, Sharon R, Abramovitz R, Khasen A, Miskin R. Plasminogen activator inhibitor-1 in cardiovascular cells: Rapid induction after injecting mice with kainath or adrenergic agents. Cardiovascular Research. 2001;**49**:476-483

[30] Cesari M, Pahor M, Incalzi RA. Plasminogen activator inhibitor-1 (PAI-1): A key factor linking fibrinolysis and age-related subclinical and clinical conditions. Cardiovascular Therapeutics. 2010;**28**(5):72-91

[31] Pickering NJ, Brody JI, Fink GB, Finnegan JO, Ablaza S. The behavior of antithombin III, alpha 2 macroglobulin and alpha 1 antitrypsin during cardiopulmonary bypass. American Journal of Clinical Pathology. 1983;**80**(4):459-464

[32] van Wersch JWJ, Rompelberg-Lahaye J, Lustermans FAT. Plasma concentration of coagulation and fibrinolysis factors and platelet function in hypertension. European Journal of Clinical Chemistry and Clinical Biochemistry. 1991;**29**:375-379

[33] van der Poll T, Levi M, Dentener M, Jansen PM, Coyle SM, Braxton CC, et al. Epinephrine exerts anticoagulant effects during human endotoxemia. The Journal of Experimental Medicine. 1997;**185**(6):1143-1148

[34] Wu KK, Thiagarajan P. Role of endothelium in thrombosis and

haemostasis. Annual Review of Medicine. 1996;**47**:315-331

[35] Gando S, Nanzaki S, Morimoto Y, Kobayashi S, Kemmotsu O. Out-of-hospital cardiac arrest increases soluble vascular endothelial adhesion molecules and neutrophil elastase associated with endothelial injury. Intensive Care Medicine. 2000;**26**:38-44

[36] Hassouna HI. Editorial comment: Blood stasis, thrombosis and fibrinolysis. Hematology/Oncology Clinics of North America. 2000;**14**(2):17-22

[37] Struyker Boudier HAJ, van Bortel LMAB, De Mey JGR. Remodelling of the vascular trace in hypertension; drug effects. Tips. 1990;**11**:240-245

[38] Ramachandran R, Rewari V. Current perioperative management of pheochromocytomas. Indian Journal of Urology. 2017;**33**(1):19

[39] Vivek K, Nambiar SS, Viswanath N, Praveen VP, Bindhu MR. Cerebral venous thrombosis due to pheochromocytoma in a patient with Von Hippel Lindau mutation. Neurology India. 2017;**65**(3):643-645

[40] Hes FJ, Hoppener JWM, Lips CJM. Pheochromocytoma in Von Hippel-Lindau disease. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**(3):969-974

[41] Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis. Stroke. 2011;**42**:1158-1192

[42] Hiller E. Hemostatic paraneoplastic syndrome. Contributions to Oncology. 1998;**52**:122-137

[43] Semenza GL. Hydroxylation of HIF-1: Oxygen sensing at the molecular level. Physiology. 2004;**19**:176-182

[44] Semenza GL. Involvement of oxygen-sensing pathways in physiologic and pathologic erythropoiesis. Blood. 2009;**114**(10):2015-2019

[45] Jackson SP. The growing complexity of platelet aggregation. Blood. 2007;**109**(12):5087-5095. DOI: 10.1182/blood-2006-12-027698