10.1515/chilat-2016-0012

PROBLEM-SOLVING ARTICLE

Apoptosis, ANUP, Chromogranin A, PGP 9.5, Endothelins and VEGF in Acquired Heart Diseases: Review of Literature

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SUMMARY
According to the Centre for Disease Prevention and Control of Latvia data, in 2014 16076 latvians died from cardiovascular diseases and it is 57,03% of all deaths. Changes in myocardium of the diseased hearts are complex and pathogenesis is still not fully clear. Morphopathogenesis of cardiovascular diseases are complex molecular cell changes which include apoptosis, homeostasis regulating factors, and innervation and ischemia markers.
In this article we wanted to provide an overview about apoptosis, atrial natriuretic peptide, chromogranin A, neuropeptide-containing innervation, endothelins and vascular endothelial growth factor in pathomorphology of acquired heart diseases and their clinical implications.
Key words: apoptosis, ANUP, chromogranin A, PGP 9.5, endothelins, VEGF, heart

INTRODUCTION

More than 4 million Europeans die of cardiovascular diseases every year despite recent decreases in mortality rates in many countries including Latvia where in 2012 10 year change in mortality rate from cardiovascular diseases was -19% for males and -24% for females (65). Notwithstanding the fact, according to the Centre for Disease Prevention and Control of Latvia data, in 2014 16,076 thousands latvians died from cardiovascular diseases and it was 57,03% of all deaths (90).

Changes in myocardium of the diseased hearts are complex and pathogenesis is still not fully clear. Morphopathogenesis of cardiovascular diseases is complex molecular cell changes which include apoptosis, homeostasis regulating factors, and innervation and ischemia markers. Understanding the pathomorphology and its clinical implications of the cardiovascular diseases are important for every physician including cardiac surgeons, because the choice of treatment, surgical timing, pre and postoperative therapy depends on pathogenesis of the disease.

Programmed cell death (apoptosis) is a regulated mode of cell death in multicellular organisms (42). Apoptosis of cardiac muscle cells has been identified as an essential process in the pathogenesis and progression of heart failure which is a complication of other heart diseases (27).

Atrial natriuretic peptide (ANUP) is a cardiac hormone secreted mainly from atria in response to acute or chronic atrial stretch and is involved in fluid, electrolyte and vascular homeostasis (95).

Chromogranin A (ChgA) is a glycoprotein that is stored and released in the extracellular environment together with neurotransmitters and hormones in the nervous, endocrine and diffuse neuroendocrine systems (36). ChgA measurement has gained interest in cardiovascular disease, because increased plasma concentrations are associated with risk of clinical deterioration and death with acute coronary syndromes or chronic heart failure (37).

Protein gene product 9.5 (PGP 9.5) is a cytoplasmic neuron and neuroendocrine cell-specific protein used as general marker to visualize diffuse neuropeptide-containing innervation (74, 97). PGP 9.5 has been proposed as reliable marker for visualisation of the cardiovascular system innervation (5).

Endothelin 1 (ET-1) is a potent vasoconstrictor and pro-inflammatory peptide (9). Endocardial endothelial cells and intramyocardial capillary endothelial cells are major source of ET-1 in the normal heart and cardiomyocytes are its primary target (67). Endothelins play an important role in cardiac and vascular pathology associated with heart failure (109).

Vascular endothelial growth factor (VEGF) is glycoprotein which is produced by a variety of adult tissues and vascular and inflammatory cells and it controlls vascular growth and function, vascular homeostasis, permeability, and vasodilatation (25, 47).

Apoptosis

Programmed cell death (apoptosis) is a regulated mode of cell death in multicellular organisms (42). Apoptosis plays a key role in maintenance of steady state in continously renewing tissues under both physiological and pathological conditions (33, 49). It is genetically driven and is characterized by chromatin condensation, nuclear shrinkage and eventual loss of nuclear membrane, membrane blebbing that produces apoptotic bodies containing cellular organelles and chromatin, DNA degradation into distinct nucleosomal units and

energy and protein synthesis requirement (41). The controlled degradation of nuclear DNA is a hallmark of apoptosis (41).
Programmed cell death in heart can be induced by several stimuli, such as hypoxia, reperfusion injury, tumor necrosis factor alpha, aldosterone, sodium nitroprusside, mechanical stretching of ventricular cardiomyocytes (12, 39, 50, 54, 78). Chlolesterol accumulation in macrophages leads to apoptosis and favors the formation of the necrotic core in complex atherosclerotic plaques (34). Cardiomyocyte apoptosis can be reduced by beta-adrenoreceptor blockers and inhibition of angiotensin converting enzyme (45, 48).
Apoptosis is not detected in normal adult human heart (101).
Apoptotic cell death is a component of myocardial infarction in acute myocardial infarction patients (77). Apoptosis is the first and predominant form of myocyte cell death in recently infarcted human myocardium before the ischemic myocyte cell death with typical coagulative necrosis (101). Acute myocardial infarction in humans is characterized also by activation of programmed cell death in the surviving portion of the left ventricular wall (69). Apoptosis affects 5.1 - 12% of the myocyte population of the region bordering on the infarct (69, 83). Inflammatory cells that invade the infarct also undergo apoptosis (77). The higher rates of cardiomyocyte apoptosis are associated with more severe complications after myocardial infarction - earlyer clinical manifestation of heart failure, left ventricular systolic and diastolic dysfunction, ventricular dilatation and death (2,13,88). Apoptosis certainly is important in chronic ischemic conditions such as hibernating myocardium (84). Experimentally, apoptosis is particularly prominent during the transition from chronically stunned to hibernating myocardium, at which time there is a loss of approximetaly 30% of the regional myocytes (14).
Apoptosis of cardiac muscle cells has been identified as an essential process in the pathogenesis and progression to heart failure (27). Apoptotic index in end stage dilated cardiomyopathy ranges from 5.0 - 35.5 (64). And predominantly it is observed in subendocardium or subepicardium (64).

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANUP) is a cardiac hormone secreted mainly from atria and is involved in fluid, electrolyte and vascular homeostasis - the maintenance of arterial blood pressure and intravascular volume (51, 95). ANUP is produced primarily by atrial cardiomyocyte and also in little amount by ventricular tissue in normal and failing (with either systolic or diastolic dysfunction) hearts and in hypertrophied ventricles (10, 11, 15, 76). For the first time ANUP was described by Bold et al. in 1980, when they observed decrease in blood pressure and greatly increased fractional excretion of sodium and chloride during the infusion of atrial extract in rats (10). Human ANUP precursor peptide gene reside on chromosome 1p36.2 and it`s mRNA encodes a high molecular wight precursor peptide proANUP which is proteolytically cleaved by corin, a cardiac serin protease, into the biologically active ANUP (15, 76).
The natriuretic peptide family comprises five principal peptides: atrial natriuretic peptide (ANUP), brain natriuretic peptide (BNP), C-type natriuretic peptide, urodilatin and dendroaspis natriuretic peptide (15). B-type natriuretic peptide is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload (57). C-type natriuretic peptide has more widespread distrubution, mainly in human vascular endothelial cells, lungs, kidneys, CNS and reproductive organs (15,68). It is potent endothelium-independent vasodilator, including coronary arteries (15, 19). Urodilatin is synthesized in the kidney distal tubules and interacts in a paracrine function with the tubular cells, and is mainly responsible for sodium-water homeostasis (31). Dendroaspis natriuretic peptide is one of the recent discovered ntriuretic peptides (85). It is present in healthy human plasma and is significantly increased in chronic heart failure patients (85). Similarly to ANUP and BNP, dendroaspis natriuretic peptide is widely distributed in the peripheral cytoplasm of atrial myocites and also in the perinuclear region (85).
ANUP is secreted from atrial granules into the circulation in response to acute or chronic atrial stretch to physiologically act as antihypertensive and antihypervolaemic factor (51). In adult human heart, chronic overload induces an increment in both ANUP and BNP, although it is grater in the latter, while a short term stimulus induces a greater increase in ANUP than in BNP (15, 100). ANUP is able to stimulate the production of cyclic guanosine monophosphate (GMP) (15). The physiologic actions include reducing both cardiac preload and afterload (decrement in peripheral vascular resistance) by their natriuretic, diuretic, and vasodilatory actions including selective renal vasodilation and inhibition of renin and aldosterone (63, 15, 11). Reduction of cardiac pre-load is mediated by shifting of intravascular fluid into extravascular compartment, increment in venous capacitance and inducing of natriuresis (15).
ANUP synthesis is increased in various pathologic conditions, causing hemodynamic overload (95). The natriuretic peptides, including ANUP and BNP, are one of the most important counterregulatory systems that become activated in heart failure (58). Secretion of ANUP in the heart are increased in patients with congestive heart failure in relation to its severity (62). Plasma levels of ANUP are elevated also in patients with chronic kidney disease, mainly because of hypertension and hypervolemia and in hyperthyroid patients because of stimulating by thyroxin (43, 92). In the ventricles of heart with hypertrophic cardiomyopathy and hypertensive hypertophy, the expression of ANUP is augmented despite the absence of heart failure (94, 95). ANUP is found to be overexpressed in the myocytes surrounding myocardial lesions, such as myocardial infarction and myocarditis (95). In patients with cardiac

amyloidosis biopsy specimens from right and left ventricles show slightly higher immunoreactivity for ANUP than in the control group (95). But endocardium, connective tissue, vasculature and amyloid fibers are not immunoreactive to ANUP in cardiac amyloidosis patients (95).

Chromogranin A

Chromogranin A (ChgA) is an acid, Ca^{2+} binding glycoprotein that is stored and released in the extracellular environment by exocytosis together with neurotransmitters and hormones in the nervous, endocrine and diffuse neuroendocrine systems (36,73,16). ChgA is a member of the granin family, witch includes chromogranin B and secretogranin II (99). The gene encoding for ChgA is located in chromosome 14 (66). Originally chromogranin was discovered in the chromaffin granules of the adrenal medulla (16).

The serum concentration of ChgA is elevated in patients with various neuroendocrine tumours. Elevated levels are strongly correlated with tumour volume and the highest levels are recorded in subjects with metastatic neuroendocrine tumours (66). Increased levels of circulating ChgA also have been detected in postmenopausal women, heart failure, renal failure, hypertension, rheumatoid arthritis, sepsis, atrophic gastritis and in subjects treated with proton pump inhibitors (24, 66). This protein has long been known as a marker for neuroendocrine tumors, but it`s role in cardiovascular disease has only recently been recognized (8).

Heart failure is a syndrome comprising cardiac dysfunction and neurohumoral activation (38). In 2007, Pieroni et al. for the first time demonstrated that human ventricular myocardium produces and releases Chg A, they showed that in the presence of dilated and hypertrophic cardiomyopathy, the peptide is also immunologically detectable on tissue sections (73, 99). In atrial myocytes it is co-stored with atrial natriuretic peptide and in the ventricle it co-localizes with brain natriuretic peptide (99, 104). ChgA measurement has gained interest in cardiovascular disease, because increased plasma concentrations are associated with risk of clinical deterioration and death in patients with acute coronary syndromes or chronic heart failure, even more - Jansson et al. demonstrated that circulating levels of ChgA provide prognostic information (long term mortality and heart failure hospitalization) independent of conventional risk markers in acute coronary syndromes (37, 99). ChgA levels have been found to reflect sympathetic activity, indicating that circulating ChgA levels may represent overall neuroendocrine activity. Increased activity in the sympathetic nervous system is a recognized risk factor for poor outcome in heart failure (82). ChgA is significantly increased in chronic heart failure patients due to tensile stretch during cardiac dilatation compared to healthy controls. After mechanical ventricular support ChgA decreases only in the heart, but not in the blood (6).

ChgA acts as a prohormone giving rise several biologically active peptides by proteolytic cleavage operated by several proteases and prohormone convertases in secretory cells such as vasostatin (a vasodilator), chromacin (an anti-microbial agent), pancreastatin (a dsyglycemic hormone), parastatin (blocks parathyroid hormone release) and catestatin (a potent inhibitor of catecholamine release from chromaffin cells and adrenergic neurons and an antimicrobial agent)(8, 24, 52, 99). The first of these peptides reported was pancreastatin, which inhibits glucose - stimulated insulin release from pancreatic beta cells and secretion of parathyroid hormone from the parathyroid gland (52).

Vasostatin is a peptide, derived from the N-terminal part of ChgA by serine protease (24, 66). It has been shown to inhibit vasoconstriction of human veins by antagonizing the endothelin mediated contraction of smooth muscle, it also can inhibit endothelial cell proliferation, migration and invasion induced by vascular endothelial growth factor (22, 52, 66).

Catestatin is a catecholine release inhibitory peptide that can inhibit endothelin-1 induced positive inotropism and coronary constriction and can induce secretion of potent proangiogenic factor - basic fibroblast growth factor (24, 99). Catestatin is preventing hypertension by vasodilatation, decreasing peripheral and central symphathetic activity and reducing cardiac contractility (55). Mutations in the catestatin domain of the ChgA gene are associated with hypertension in humans (55).

C-terminal ChgA- derived serpinin peptides are present in the rat heart and influence myocardial contractility (concentration dependent positive inotropic effect) and enhanced relaxation (positive lusitropy) in β-agonist-like manner, without affecting heart rate, providing innovative insight into the ChgA- elicited regulation of cardiac function (55). Serpenin peptides may contribute to cardiac homeostasis by counterbalancing the vasostatin 1 and catestatin induced cardiosupressive and antiadrenergic effects (55).

Protein Gene Product 9.5

Protein gene product 9.5 (PGP 9.5) is a cytoplasmic neuron and neuroendocrine cell-specific protein used as a general marker to visualize diffuse neuropeptide-containing innervation (74, 97). PGP 9.5 was originally detected as a brain specific protein (97). PGP 9.5 has been proposed as reliable marker for visualisation of the cardiovascular system innervation (5).

In adult human heart there are abundant network of PGP 9.5 immunoreactive nerves in the walls of the atria, but in the ventricules relatively fewer (21, 59). Also in human newborns very numerous PGP 9.5 immunoreactive nerve fascicles and fibers are found in both - right and left atrial tissue and slightly less, but also numerous, in the walls of the ventricles (21). Within the atrial and ventricular myocardium PGP 9.5 pozitive nerve fibers are forming perivascular plexi along the walls of the major cardiac vessels and occasionally some separate nerve fibers are running in close relationship

with myocardial cells (21, 40, 81). Nerve fiber terminals are identified in the atrial endocardium, epicardium and coronary sinus (18).

PGP 9.5 immunoreactive varicose nerve fibers, nerve fascicles, and nerve trunks are observed throughout conduction system (sinus node, atrioventricular node, atrioventricular bundle and ventricular branches) of the human heart (23). The nerve density in conduction system is significantly higher than in the adjacent atrial or ventricular myocardium (23). And the most densely innervated region of conduction system is sinus node, where PGP 9.5 immunoreactive nerve fibers and fascicles are distributed between nodal cells in the fibrous tissue matrix (23). Abundant PGP 9.5 immunoreactive nerve fascicles and fibers are present in the sinus node of human newborns and the same as in adults - positively staining nerve fascicles and fibers are also seen among the cells of the atrioventricular node, bundle of His, and the branching bundle, the density of fibers being slightly less than in sinus node (22).

There are rich neworks of nerves immunoreactive to PGP 9.5 in cusps of atrioventricular – mitral and tricuspid valves and in chordae tendineae (5). The nerve fibres ramifies from the ventricles through the papillary muscles into the chordae tendineae and than passe up through the chordae to terminate in the valve cusp (5). The nerves of the terminal innervation network of the atrioventricular valves are part of a complex neural mechanism that is involved in the reflex control of the heart valves, chordae tendineae and papillary muscle during each cardiac cycle (5). In 1989. Kawano et al. described neuropeptide Y and calcitonin gene related peptide containing nerve fibre degeneration in a prolapsed mitral valve cusp (5).

Sympathetic overactivity, usually accompanied by reduced parasympathetic activity and heart rate variability, is increasingly recognized as a feature in the pathogenesis of a number of cardiovascular pathologies (40). Cardiac neuronal remodeling accompanies hypertension, post-myocardial infarct remodeling and heart failure (40). There is association between local nerve density and a clinical history of ventricular arrhythmia in patients with severe heart failure, and it is hypothesed that in some patients myocardial injury (myocardial infarction) results in nerve injury, followed by nerve sprouting and regional myocardial hyperinnervation (18). In patients with end stage heart failure due to severe coronary heart disease and miocardial infarctions there are found thicker and more numerous irregularly distributed nerve fibers in the scar tissue than in adjacent normal myocardium (103).

After cardiac transplantation human cardiac allografts remain functionally extrinsically denervated, but they still appear to contain viable intrinsic nerves (105). The relative number of PGP 9.5 immunostained nerves in transplanted hearts is less than in innervated (105). In patients after cardiac transplantation, reinnervation is associated with significantly improved exercise performace (18).

Endothelin

In 1988, a 21-amino-acid vasoconstricting factor termed endothelin was isolated from cultured porcine aortic endothelial cells (46, 106). Endothelins are family of peptides, which comprises endotheli-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3) (4). ET-1 is primarily secreted by endothelial cells, but it can also be synthesized and released by a variety of cell types, such as cardiac myocytes, endocardial endothelial cells, intramyocardial capillary endothelial cells, kidney, central nervous system (CNS) and posterior pituitary (58, 67, 75). Endocardial endothelial cells and intramyocardial capillary endothelial cells are major source of ET-1 in the normal heart and cardiomyocytes are its primary target (67). ET-2 is produced in endothelial cells, heart and kidney. ET-3 is expressed in endocrine, gastrointestinal and CNS, but not in endothelial cells (4, 58, 75). Neonatal rat cardiac myocytes express preproET-1 mRNA and synthesize and secrete mature ET-1 (109). ET-1 is the predominant isoform expressed in the vasculature (4). Intracellular ET-1 is produced from inactive big ET-1 via specific cleavage by endothelin converting enzyme-1a that is expressed in endothelin producing cells (including endocardium and myocardium) and extracellular big ET-1 is cleaved by endothelin converting enzyme-1b at the plasma membrane (4, 109). ET-1 generation is increased by many stimuli, including vasoactive hormones, growth factors, hypoxia, stress, lipoproteins, free radicals, endotoxin and cyclosporin (4). Production of ET-1 is inhibited by endothelium derived NO, nitrovasodilatators, natriuretic peptides, heparin and prostaglandins (4). Cultured endothelial cells secrete substantially more ET-1 toward the adjacent vascular smooth muscle than into the lumen, therefore endothelin is thought to be a locally acting paracrine substance rather than a circulating endocrine hormone (4).

Endothelins play an important role in cardiac and vascular pathology associated with heart failure (109). Plasma concentrations of endothelin-1 (ET-1) are increased two to three hold in patients with heart failure irrespective to aetiology (109). Plasma endothelin levels increase significantly (more than fivehold) in few hours after uncomplicated myocardial infarction in humans (46, 91). Increased levels of ET-1 in patients with heart failure correlate with patient outcomes and plasma endothelin concentrations correlate directly with pulmonary artery pressure and pulmonary vascular resistance (58). Increased production and biological activity of the potent vasoconstrictor and pro-inflammatory peptide endothelin is a hallmark of endothelial dysfunction (9), while the endothelial dysfunction is associated with accelerated progression of heart failure (30). Significant amounts of tissue ET-1 is found also in active coronary aterosclerotic plaques (107). ET-1 immunostaining localizes predominantly to areas with extensive macrophage infiltration and hypercellular regions with evidence for neovascularization - that suggests a role of local inflammatory processes in the

production of ET-1 within aterosclerotic lessions (107). Endothelin is a potent vasoconstrictor, has inotropic and chemotactic properties, and has mitogenic effects on smooth muscle cells and fibroblasts, and it stimulates synthesis of inflammatory mediators in macrophages and fibronectin in smooth muscle cells (32, 46, 56, 58). Endothelin has other important effects in the heart, including stimulation of myocyte hypertrophy and atrial natriuretic peptide secretion from myocytes (61, 87). The overall action of endothelin is to increase blood pressure and vascular tone (4).

Biological activities of ET-1 are mediated mainly through two distinct receptor subtypes – ET_A and ET_B and they both are expressed in human atrial and myocardial myocytes, atrioventricular conducting system, endocardial cells, coronary and pulmonary arteries (26, 60, 61, 109). ET_A-receptors are located in vascular smooth muscle, but not in endothelial cells (4). ET_B- receptors are located on endothelial cells (4). ET_A-receptor stimulation by ET-1 cause vascular smooth muscle constriction, but ET_B- receptor activation by ET-1 leads to vasodilation via production of NO and prostaglandins (4). Some ET_B- receptors are located in vascular smooth muscle where thay may mediate vasoconstriction (14). Systemic administration of ET-1 leads to shortlived decrease (up to few minutes) in vascular resistance, followed by the longterm (≥1 hour) increase and secondary, probably through increased afterload, decrease cardiac output (4, 46). The initial increase in perfusion is caused via nitric oxid and prostacyclin release by ET_B stimulated endothelial cells (46). The decrease in perfusion is primarly mediated by ET_A on smooth muscle cells. Activation of ET receptors lead to an induction of markers of cardiac remodeling, including mRNA for troponin I, myosin light chain 2 and skeletal alpha actin (87).

Endothelin receptor antagonists were developed for the treatment of patients with heart failure, but the effect in clinical heart failure trials has not been beneficial and has led to worsening outcomes in some setting (58, 96). Endothelin receptor antagonists have been shown to be beneficial in the setting of pulmonary hypertension and are currently approved for the treatment of pulmonary artery hypertension in patients with moderate disability (58).

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is basic, heparin-binding, hemodinamic glycoprotein and is also known as a vascular permeability factor (29, 28). It is produced by a variety of adult tissues and vascular and inflammatory cells (25). VEGF in both physiologic and pathologic conditions induces endothelial cell migration, proliferation, and sprouting and results in angiogenesis and it is essential for embryonic vascular dvelopment (25). The location of the VEGF gene is in the chromosome 6p21.3 (102). VEGF proteins become available to endothelial cells by at least two different mechanisms: as freely diffusable proteins and following protease activation and cleavage of the longer isoforms (28). There are three VEGF related factors - placental growth factor (PGF), vascular endothelial growth factor B (VEGF-B), Vascular endothelial growth factor C (VEGF-C). PGF can potentiate the bioactivity of low contentrations of VEGF on endothelial cell growth and it has minimal mitogenic activity on endothelial cells (71). PGF promotes cardiac hypertrophy (3, 25). VEGF-C is found in several human tissues including adult heart, it stimulates the growth of human lung endothelial cells and induces lymphangiogenesis (25, 29, 53). VEGF-B distributes primarily in the sceletal muscle and myocardium, and is coexpressed with VEGF (70). VEGF-B stimulates the growth of human vascular endothelial cells and may participate in the regulation of angiogenesis, particularly in muscle (29, 70). Lack of VEGF-B leads to characteristic defect (increase in the PQ interval in the ECG) in the atrial conduction system in mice and may yield to reduced functional recovery after myocardial ischemia (1, 7).

Biological activities of VEGF are mediated mainly through two receptors: VEGFR-1 (flt-1) and VEGFR-2 (flk-1). VEGFR-1 is expressed in a variety of cells including endothelial cells, smooth muscle cells, monocytes and macrophages, and hematopoietic stem cells (25). It may regulate arteriogenesis, pathological angiogenesis, myelomonocyte cell recruitment and lipid metabolism (25, 86). VEGFR-2 is mainly expressed on vascular endotheliel cells. In adults VEGFR-2 expression presents only at sites of active angiogenesis such as wound healing, tumors, and after myocardial inferction (25, 86). In myocardial infarction and sepsis VEGFR-2 is a major regulator of vascular permeability and cardiac dysfunction (25, 86). VEGFR-2 stimulates not only angiogenic signals, but also the secretion of various proteins such as the von Willebrand factor from endothelial cells (86).

VEGF are major molecules controlling vascular growth and function, vascular homeostasis, permeability, and vasodilatation (47). It is a potent mitogen for micro and macrovascular endohelial cells from arteriae, veins, and lyphatics, but it lacks significant mitogenic activity for other cell types (29, 28). VEGF is preventing apoptosis in vascular endothelial cells by inducing expression of the antiapoptotic proteins Bcl-2 and A1 (35).

Myocardial neovascularization is important not only for heart development, but also during hypertrophy, ischemia and after myocardial infarction (98). VEGF mRNA expression in heart is induced by ischemia and cyclic stretch of cardiac myocytes and cardiac microvascular endothelial cells (28, 108). VEGF is critical for angiogenesis in the healing area after myocardial infarction - it is promptly expressed in the living cardiomyocytes around the infarcted loci and in the early stage also in infarcted cardiomyocytes (25, 44). Angiogenesis in the lesion begins at 4-5 hours and continues up to 90 days (25). VEGF has a role of enhancing the development of small coronary arteries that supply the ischemic myocardium, as well as a protective role against myocardial ischemia - reperfusion injury (44). VEGF has been shown to be

important for neovascularization of the chronically ischemic adult heart, it can stimulate collateral vessel development in the ischemic myocardium (47, 72).

There is also evidence of VEGF role in rheumatic and degenerative heart valve diseases. In contrast to healthy avascular aortic valves, stenotic valves show marked neovascularization - small microvessels, medium microvessels and organized arterioles (93). Neovascularization in the thickened aortic valves can suppress disease progression by providing oxygen and nutrients to deeper parts of hypertrophied valve leaflet, but on the other hand, provoke disease by facilitating the transport of inflammatory cells and lipids into the leaflets, neovascularization can accelerate valvular thickening and calcification (93). Calcification of rheumatic cardiac valve tissue and non-rheumatic degenerative valve tissue is similar to skeletal bone formation and is associated with neoangiogenesis which is stimulated by an active inflammatory process and the release of VEGF (79, 80). VEGF and it`s receptors VEGFR-1 and VEGFR-2 are locally expressed in aortic valves and upregulated in stenotic valves (93, 17). VEGF and its receptors in stenotic valves are seen preferentially in endothelial cells and also to some extent in stromal myofibroblasts and histiocytic cells (89, 93). Must cell derived tumor necrosis factor α, hypoxic conditions and tobacco smoke induces significant increase in VEGF secretion by cultured aortic valve myofibroblasts (93).

CONCLUSIONS

Cardiomyocyte apoptosis is an essential process in the pathogenesis and progression of heart failure irrespective to aetiology, but it can be reduced by appropriate timing of surgical intervention and precise choice of pre and postoperative medication. ANUP, ChgA, VEGF and ET-1 secretion is a protective response to heart failure accordingly it allows to evaluate the preoperative condition, effectiveness of treatment and further prognosis as well as it may be a therapeutic target.

Conflict of interest: None

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