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The Role of Adrenomedullin in Cardiovascular Response to Exercise – A Review

by
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Adrenomedullin (ADM), the product of the vascular endothelial and smooth muscle cells, and cardiomyocytes, is considered to be a local factor controlling vascular tone, cardiac contractility and renal sodium excretion. The aim of this article was to review the existing data on the effect of different types of exercise on plasma ADM concentration in healthy men. The results of studies on the effect of dynamic exercise on the plasma ADM are contradictory. Some authors reported an increase in plasma ADM, while others showed a slight decrease or did not observe any changes. The inverse relationship between plasma ADM and mean blood pressure observed during maximal exercise support the concept that ADM might blunt the exercise-induced systemic blood pressure increase. Positive relationships between increases in plasma ADM and those in noradrenaline, atrial natriuretic peptide (ANP) or interleukin-6 observed during prolonged exercise suggest that the sympathetic nervous system and cytokine induction may be involved in ADM release. Increased secretion of ADM and ANP during this type of exercise may be a compensatory mechanism attenuating elevation of blood pressure and preventing deterioration of cardiac function. Studies performed during static exercise have showed an increase in plasma ADM only in older healthy men. Positive correlations between increases in plasma ADM and those in noradrenaline and endothelin-1 may indicate the interaction of these hormones in shaping the cardiovascular response to static exercise. Inverse relationships between exercise-induced changes in plasma ADM and those in cardiovascular indices may be at least partly associated with inotropic action of ADM on the heart. Interactions of ADM with vasoactive peptides, catecholamines and hemodynamic factors demonstrate the potential involvement of this peptide in the regulation of blood pressure and myocardial contractility during exercise.

Key words: *vasoactive peptides, catecholamines, effort, cardiovascular indices.*

Introduction

There are two types of exercise, dynamic (isotonic) and static (isometric), depending on the kind of muscle contraction. Both dynamic and static exercise cause an increase in heart rate and cardiac output. During dynamic exercise the increase in cardiac output results mostly from an accelerated heart rate. Stroke volume also increases, due to a larger preload and myocardial contractility. Systolic blood pressure increases linearly with the workload and diastolic blood pressure shows only minor changes or tends to decrease in the normotensives. Total peripheral resistance decreases as a result of vasodilatation induced mainly by local metabolic factors in the working muscles.

Static exercise in healthy people is characterized by a large increase in systolic and diastolic arterial blood pressure resulting from the combination of increased cardiac output and sympathetically mediated vasoconstriction in both visceral organs and inactive skeletal muscles (Victor et al., 1989a; Middlekauff et al., 1997; Momen et al., 2003). The increase in cardiac output results primarily from an accelerated heart

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rate. Stroke volume during static hand grips at loads greater than 20% of the maximal voluntary contraction (MVC) can be significantly reduced due to the increased left ventricular afterload (Bezucha et al., 1982; Chapman and Elliot, 1988).

Neural mechanisms of cardiovascular regulation during exercise

The hemodynamic responses to exercise are regulated by central and peripheral mechanisms. The central mechanism, termed as "central command", involves parallel activation of motor and cardiovascular centers (Goodwin et al., 1972). The neural signals from the motor cortex irradiate to autonomic neurons in the brainstem, leading to sympathetic activation and parasympathetic withdrawal (Dipla et al., 2012; Iellamo, 2001; Nobrega et al., 2014; Williamson 2010, 2015). The peripheral neural mechanism involves signals arising from contracting skeletal muscle receptors (mechanoreflex and metaboreflex), arterial baroreceptors (baroreflex) and arterial chemoreceptors (arterial chemoreflex). Reflex input from the exercising skeletal muscle to cardiovascular regulatory centers within the medulla oblongata has been termed as the "exercise pressor reflex" (Kaufman et al., 1984; McCloskey and Mitchell, 1972; Megan et al., 2011; Mitchell et al., 1983). The exercise pressor reflex is especially prominent during static exercise, where increases in intramuscular pressure limit the blood flow to active skeletal muscle. Both central command and the exercise pressor reflex stimulate cardiac sympathetic nerve activity and are involved in the resetting of the carotid baroreflex during exercise (Iellamo et al., 1997; Gallagher et al., 2006; Tsuchimochi et al., 2009).

The exercise pressor reflex is triggered by stimulation of sensory receptors located on unencapsulated endings of group III (thinly myelinated fibers) and group IV (unmyelinated fibers) afferent nerve fibers. The endings of group III afferents terminate in the skeletal muscle collagenous connective tissue and respond mainly to mechanical stimuli (mechanoreflex), while the endings of group IV afferents terminate within the walls of small capillaries, venules and lymphatic vessels of skeletal muscle, and respond mainly to metabolic changes in the contracting muscles (metaboreflex). It has been shown that the group IV afferents release vasodilator peptides such as substance P and calcitonin gene-related peptide (CGRP) (Kruger et al., 1989; von During and Andres, 1990). Metabolic by-products following muscle contraction such as hydrogen ions, lactic acid, adenosine monophosphate (AMP), adenosine-5'-diphosphate (ADP), inosine monophosphate (IMP), diprotonated inorganic phosphate and reactive oxygen species have the ability to stimulate both metabo- and mechano-receptors and therefore, play an important role in evoking the exercise pressor reflex (Green, 1997; Hanna and Kaufman, 2004; Kaufman et al., 1983; Kaufman and Rybicki, 1987; Rotto et al., 1990; Zając et al., 2015). It is considered that intramuscular acidosis is one of the most important factors that triggers metaboreflex-mediated increases in muscle sympathetic nerve activity (Pryor et al., 1990; Rotto et al., 1989; Victor et al. 1988). It has been demonstrated that mechanical stimulation of muscle afferents contributes to the initial blood pressure response during contraction, while metabolic stimuli are necessary to maintain this response (Baum et al., 1995). Endo et al. (2013) suggested that the muscle mechanoreflex also played an important role in mediating vasoconstriction within inactive limbs.

The exercise pressure reflex has been shown to increase sympathetic nerve activity to the non-exercising muscle, heart and kidneys (Hill et al., 1996; Mark et al., 1985; McCloskey et al., 1972; Momen et al., 2003; Saito, 1995; Saito et al., 1990). In the heart, sympathetic stimulation increases heart rate and heart muscle contractility as well as accelerates atrioventricular conduction (Kaufman and Forster, 1996; Matsukawa et al., 1994; Mitchell, 1983). Kaufman et al. (1984, 1996) showed that the magnitude of the cardiovascular reflex response to muscle contraction was dependent on active muscle mass and magnitude of force or tension production. Stebbins et al. (2002) found that increases in heart rate and mean arterial pressure as well as activation of central command and muscle metabolite-induced stimulation of the exercise pressor reflex during static and dynamic contraction in humans seemed to be similar when peak tension and tension-time index were equal. In the kidneys, enhanced sympathetic nerve activity causes arteriolar renal vasoconstriction, reduces the renal blood flow and glomerular filtration rate, increases renin release

with activation of the renin-angiotensin-aldosterone system, increases tubular sodium and water reabsorption (Matsukawa et al., 1990; Middlekauff et al., 2001; Momen et al., 2003; Victor et al., 1989b). This results in increased peripheral vascular resistance and thus arterial blood pressure. The sympathetic efferent nerves to the adrenal medulla and hypothalamus control the secretion of adrenal catecholamines and vasopressin, which contribute to adjustments in vascular resistance.

Activation of neurohormonal systems as well as shear stress enhance production and release of endothelin-1 (ET-1) by vascular endothelial cells (Wang et al., 2002). Endothelin-1 causes vasoconstriction, increases sympathetic activity, potentiates the vasoconstrictor action of noradrenaline and stimulates the renin-angiotensin-aldosterone system (Bruno et al., 2011; Miller et al., 1989). Endothelin-1, catecholamines as well as hemodynamic shear stress stimulate production and secretion of adrenomedullin (ADM) and nitric oxide (NO) by vascular endothelial and smooth muscle cells to oppose vasoconstriction (Cardillo et al., 2000; Cardillo et al., 2009; Haynes and Webb 1998). Production and secretion of ADM are linked to the endothelin-B receptors subtype (ETB-R) (Jougasaki et al., 1998). Adrenomedullin reduces the activity of the sympathetic nervous system as well as secretion of endothelin-1 and catecholamines (Andreis et al., 1997; Del Bene et al., 2000; Khan et al., 1999; Kohno et al., 1995a; Tschakovsky et al., 2002; Yűksel et al., 2002).

The aim of this article was to review the existing data on the effect of different types of exercise on plasma ADM concentration and to describe the relations between exercise-induced changes in plasma ADM and those in both humoral and hemodynamic factors.

Structure of adrenomedullin

Human ADM is a 52-amino acid peptide with one intramolecular disulfide bridge and with an amidated tyrosine at the carboxy terminus (Kitamura et al., 2012). Adrenomedullin gene is located on chromosome 11 and its expression can be regulated by substances acting through protein kinase A, protein kinase C and cytokine receptor gp130 (Ishimitsu et al., 2003). This peptide was first identified in pheochromocytoma of the human adrenal gland and belongs to the calcitonin gene-related peptide family. Synthesis of adrenomedullin starts with the precursor molecules, termed preproadrenomedullin and proadrenomedullin, mainly in endothelial and vascular smooth muscle cells in response to shear stress, ischemia, hypoxia, acidosis and under the influence of catecholamines, angiotensin II, vasopressin and cytokines (Hasbak et al., 2002; Kitamura et al., 2002; Krzeminski et al., 2006a, 2006b; Nagata et al., 1999; Niebauer and Cooke, 1996; Sugo et al., 1994, 1995a, 1995b). Its presence has also been shown in the adrenal medulla, heart, lung, gastrointestinal organs, kidneys and the central nervous system. Hirayama et al. (1999) found that the ADM and ET-1 could be synthesized and secreted from human cardiac myocytes and that the expression and function of ADM receptors were modulated by humoral and mechanical factors in myocardium. Immunohistochemical staining showed the presence of ADM in atria, ventricles and muscular layer of the aorta in the dog heart (Jougasaki et al., 1995b). Some vasoactive substances, such as angiotensin II and ET-1 have been shown to stimulate the production and secretion of ADM from both vascular smooth muscle cells and cardiomyocytes (Mishima et al., 2001; Sugo et al., 1995b; Tsuruda et al., 1998). Nishikimi et al. (2003) suggested that both mechanical stress and cytokines were important stimuli for ADM production in the heart. Tsuruda et al. (2000) reported enhanced gene expression and production of ADM in cultured cardiomyocytes in response to static stretching.

Mechanisms of adrenomedullin action

Adrenomedullin acts through calcitonin receptor-like receptor (CRLR) associated with one of the three receptor-activity-modifying proteins: RAMP1, RAMP2 or RAMP3 (Nikitenko et al., 2006; Sexton et al., 2001). Co-expression of RAMP1 with CRLR produces a CGRP receptor, whereas co-expression of RAMP2 or RAMP3 with CRLR produces an ADM receptor (Eguchi et al., 1994b; Kamitani et al., 1999; McLatchie et al., 1998). However, Nagoshi et al. (2002) found that ADM could also bind with the CRLR/RAMP1 complex. Some authors believe that ADM acts on the heart by specific membrane receptor AM-R cDNA located on the surface of rat

cardiomyocytes (Kapas et al., 1995; Miller et al., 1996). This receptor appears to be a relatively unique member of a family of membrane receptors associated with G protein. The vasodilator action of ADM is mainly mediated by endothelium-derived NO (Feng et al., 1994; Hirata et al., 1995; Miura et al., 1995; Yukihito et al., 2004). ADM increases endothelial NO synthase (eNOS) activity by elevating intracellular free calcium concentration (Boussery et al., 2004; Shimekake et al., 1995) or by activating phosphatidylinositol 3-kinase and protein kinase B/Akt (Nishimatsu et al., 2001). It has also been shown that ADM increases interleukin-1 (IL-1) - induced NO synthesis by enhancing the expression of inducible NO synthase (iNOS) in vascular smooth muscle cells (Hattori et al., 1999; Ikeda et al., 1996a).

Adrenomedullin increases intracellular cyclic adenosine monophosphate (cAMP) by stimulation of adenylyl cyclase and activation of protein kinase A (cAMP/PKA signaling pathway) as well as increases cyclic guanosine 3′5′-monophosphate (cGMP) by stimulation of NO-activated guanylyl cyclases and activation of cGMP-dependent protein kinase (PKG) (NO/cGMP/PKG signaling pathway) (Chini et al., 1995; Coppock et al., 1996; Kohno et al., 1995b; Sato et al., 1997). Zhang and Hintze (2001) suggested that cAMP increased NO through activation of protein kinase A and subsequent phosphorylation of endothelial NOS by protein kinase B through a phosphatidylinositol 3-kinase–mediated effect. It has been shown that ADM-induced increases in NO are mediated by activation of protein kinase A and phosphatidylinositol 3-kinase (Boo, 2006; Nishimatsu et al., 2001).

Adrenomedullin has also been shown to activate other signal transduction mechanisms including potassium-ATP channels (Sakai et al., 1998) and c-fos expression (Moody et al., 1997; Sato and Autelitano, 1995). Furthermore, in an isolated perfused rat heart ADM induced both Ca^{2+} release from Ca^{2+} stores and activation of protein kinase C (PKC) via cAMP-independent mechanisms (Szokodi et al., 1998). Lamping (2001) suggested that relaxation of vascular smooth muscle to selected endothelium-independent agents was mediated by an interaction between cGMP and cAMP pathways.

Physiological action of adrenomedullin

Many studies have revealed a wide range of biological actions of ADM on cardiovascular, renal and endocrine systems, the central nervous system as well as cellular growth and differentiation (Hinson et al., 2000; Jougasaki et al., 1995a, 1995c; Lainchbury et al., 1997; Nicholls, 2004; Parkes and May, 1997; Samson et al., 1999). Adrenomedullin is a potent vasodilator that reduces systemic and pulmonary vascular resistance, induces renal vasodilation, increases the glomerular blood flow and filtration rate, sodium excretion and myocardial contractility, as well as inhibits renin release, decreases plasma aldosterone and vasopressin levels (He et al., 1995; Hinson, 2000).

The vasodilatory action of ADM may be mediated by endothelium-derived NO and/or vasoactive prostanoids (endothelium-dependent vasodilation) as well as by an increase in intracellular cAMP (endothelium-independent vasodilation) (Eguchi et al., 1994a; Ishizaka et al., 1994).

The effect of ADM on myocardial contractility is controversial. Some authors believe that ADM has a positive inotropic effect (Ihara et al., 2000; Szokodi et al., 1996, 1998), while others that it has a negative inotropic effect mediated by the NO-cGMP pathway (Ikenouchi et al., 1997) or has no effect on myocardial contractility (Lainchbury et al., 2000). It has been shown that ADM inotropic action is mediated via CRLR/RAMP2 or CRLR/RAMP3 complexes and involves the activation of adenylyl cyclase and cyclic AMP production in cardiomyocytes (Bell and McDermott, 1994; Ihara et al., 2000; McLatchie et al., 1998; Sato et al., 1997; Szokodi et al., 1998). It has also been shown that ADM has an ability to rapidly facilitate intracellular Ca^{2+} release and enhance cardiac contractility via mechanisms involving Ca^{2+} release from intracellular ryanodine- and thapsigargin-sensitive Ca^{2+} stores, activation of protein kinase C and protein kinase A, as well as Ca^{2+} influx through L-type Ca^{2+} channels (Huang et al., 1999; Szokodi et al., 1998). In addition, ADM dilates the coronary artery and attenuates myocardial remodeling (Lainchbury et al., 1997; Nicholls, 2004; Rademaker et al., 2003).

Some authors reported a strong link between plasma ADM and the renin-angiotensin-

aldosterone system (Charles et al., 2000, 2003; Krzeminski et al., 2012**)**. Angiotensin II increases the expression of ADM-mRNA and inotropic action of ADM onthe heart (Mishima et al., 2003; Onitsuka et al., 2005; Romppanen et al., 1997).

Hypotensive, diuretic and inotropic properties of ADM and its interactions with vasoactive substances demonstrate the potential involvement of this peptide in the regulation of blood pressure and cardiac contractility as well as in maintenance of water and electrolyte homeostasis during exercise.

Adrenomedullin and dynamic exercise

Studies on the effect of dynamic exercise on plasma ADM concentration have yielded contradictory results. Tanaka et al. (1995) reported an increase of plasma ADM during three 4-min steps of submaximal cycle exercise (workloads: 25, 50 and 75 Watts) in healthy subjects and in patients with various diseases. The increase of adrenomedullin was inversely related to systolic blood pressure. Similarly, Piquard et al. (2000) found a significant increase in plasma ADM during maximal bicycle exercise both in normal subjects and in the heart transplant recipients. Tanaka et al. (1995) suggested that the exercise-induced quantity of ADM released to the circulation was too small to directly affect the blood pressure so it may rather reflect the increased activity as an autocrine or a paracrine factor. The paracrine mechanism was also suggested by Meeran et al. (1997). On the other hand, Nishikimi et al. (1997) and Morimoto et al. (1997) did not find any changes in plasma ADM during two 4-min steps of submaximal exercise (workloads: 40 and 80 Watts) in normotensive healthy subjects. Similarly, Poveda et al. (1998) and Dursun et al. (2012) did not observe any changes in plasma levels of ADM in response to a treadmill stress test or a cycle exercise test until volitional exhaustion in both young and old healthy volunteers. Nishikimi et al. (1997) suggested that ADM secretion did not respond to short-lasting stimuli since it was regulated by gene expression.

The results of the study performed during graded bicycle ergometer exercise until exhaustion in healthy young men (Krzeminski et al., 2003) showed a slight decrease in plasma ADM concentration at the end of exercise. This was accompanied by significant increases in plasma noradrenaline (NA), adrenaline (A), growth hormone and lactate. Plasma ADM at the end of exercise correlated negatively with systolic blood pressure, mean blood pressure and blood lactate. A positive correlation was found between the exercise-induced decrements of plasma ADM and diastolic blood pressure. The authors concluded that the decrease in peripheral resistance and metabolic acidosis might be involved in the inhibition of ADM secretion during exhausting exercise in healthy young men. It seems to be very likely that a decrease in plasma ADM results from increased bounding of the peptide to the receptors on the endothelium and vascular smooth muscle cells or other tissues (Eguchi et al., 1994b; Ishiyama et al., 1993; Meeran et al., 1997; Nandha et al., 1996; Shimekake et al., 1995). Meeran et al. (1997) suggested that the proximity of vascular smooth muscle cells to endothelial cells resulted in a much higher concentration of ADM around these cells than in the plasma. The authors concluded that ADM prevented the excessive blood pressure increase during exhausting exercise in healthy men.

The results of the study performed during prolonged submaximal dynamic exercise (90 min at 70% of maximal oxygen uptake (VO_{2max})) in healthy young men (Krzeminski et al., 2006a) revealed a significant increases in plasma ADM and interleukin-6 (IL-6) concentrations at the 90th min of exercise. The plasma NA, A, atrial natriuretic peptide (ANP), lactate as well as plasma renin activity (PRA) were elevated already at the 30th min of exercise. Positive correlations were found between plasma ADM and NA, ANP or IL-6. The exercise-induced increases in plasma ADM correlated positively with those in plasma NA and inversely with changes in diastolic blood pressure. Plasma renin activity correlated positively with plasma NA and ANP. A significant positive correlation between plasma NA and PRA indicates the existence of a link between the increased activity of the sympathetic nervous system and stimulation of the renin-angiotensin-aldosterone system during prolonged exercise in healthy men. A negative correlation between the exercise-induced changes in plasma ADM and diastolic blood pressure indicates a participation of ADM in the regulation of blood pressure during prolonged dynamic exercise. The

authors suggested that an increase in sympathetic nervous activity and cytokine induction may be involved in plasma ADM release during prolonged submaximal exercise and that the increase in plasma ADM and ANP secretion may be a compensatory mechanism against further elevation of blood pressure. In view of reports indicating that the ADM gene expression in vascular smooth muscle and adrenal cells is stimulated by protein kinase C and/or protein kinase A and submitted to feedback from cAMP level (DaPrada et al., 1979; Ishimitsu et al., 1994), it is possible that noradrenaline stimulates the expression of mRNA-ADM in vascular smooth muscle cells and cardiac myocytes through α-1 (activation of protein kinase C) and β (activation of protein kinase A and cAMP) adrenergic receptors (Isumi et al., 1998). A positive correlation between plasma ADM and ANP suggests the possibility of direct stimulation of ADM secretion in the heart by hemodynamic changes. The results of experiments using cultured cardiomyocytes imply that mechanical stress and cytokines are important stimuli for ADM production in the heart (Dawson et al., 2005; Middleton et al., 2006). Horio et al. (1999) demonstrated that ADM augmented endothelin-1-stimulated ANP secretion from cardiac myocytes at least partly via the cAMP-independent mechanism. Some studies showed that ADM inhibited both ANP gene expression in cultured cardiac myocytes and ANP secretion from isolated atrium (Kaufman and Deng, 1998; Sato et al., 1995, 1997).

Adrenomedullin and ANP suppress the activity of the renin-angiotensin-aldosterone system, antagonize the effect of endothelin-1 and angiotensin-II and thus prevent an increase in peripheral vascular resistance (TPR) as well as preserve the renal blood flow. Several studies revealed that ADM induced sustained reductions in plasma aldosterone levels despite a rise in plasma renin activity (Charles et al., 2001, 2003; Neri et al., 2002; Rademaker et al., 2002). Both of these peptides may contribute to the regulation of vascular tone through the cAMP-related mechanism and NO-cGMP signaling mechanisms (Hayakawa et al., 1999; Rebuffat et al., 2001).

Thus, it seems likely that the increase in plasma ADM and ANP secretion during prolonged exercise may be a compensatory mechanism against further elevation of blood pressure and plays an important role in maintaining cardiac performance.

Adrenomedullin and static exercise

There are only few studies focusing on changes in plasma ADM concentration induced by static exercise in healthy men. The results of a study performed during static handgrip exercise (6 min at 30% MVC) in healthy young and older men (Krzeminski et al., 2002, 2012) showed significant increases in plasma ADM and ET-1 concentration, and in PRA only in the older subjects. The increases in plasma NA and A were significantly greater in the older than in the younger subjects. The exercise-induced increases in plasma ADM correlated positively with those of NA, PRA, ET-1 and left ventricular ejection time (LVET) as well as negatively with changes in TPR, stroke volume (SV), the pre-ejection period (PEP) and PEP/LVET ratio.

The authors suggested that a positive relationship between the exercise-induced changes in plasma ADM and those in plasma ET-1 and NA might indicate the interaction of these hormones in shaping the cardiovascular response to static exercise in healthy elderly subjects. It seems likely that ADM, ET-1 and angiotensin II with their opposite vasoactive properties can contribute to the maintenance of vascular tone during static exercise in older men.

The increased plasma catecholamines concentration indicates that static exercise causes a progressive activation of the sympathetic nervous system. Inverse relationships between exercise-induced changes in plasma ADM and those in TPR may be associated with vasodilator action of ADM on arterial vessels (Cockcroft et al., 1997). It has been shown that ADM increases both intracellular cAMP and nitric oxide (NO) in vascular endothelial cells and smooth muscle cells by activation of adenylyl cyclase and inducible endothelial NO synthase (Eguchi et al., 1994a; Hattori et al., 1999; Ishizaka et al., 1994; Kohno et al., 1995; Zhang and Hintze, 2001). It has been demonstrated that cAMP-dependent pathway is involved in cytokine-induced NO production by vascular smooth muscle cells (Hirokawa et al., 1994; Ikeda et al., 1996a; Imai et al., 1994; Koide et al., 1993). Some have authors found that ADM can act by both NO-dependent and potassium ATP

(K_{ATP}) channel-dependent mechanisms (Sabates et al., 1997; Terata et al., 2000). Bolotina et al. (1994) demonstrated that NO may directly activate calcium-dependent potassium channels in vascular smooth muscle cells. Shimekake et al. (1995) demonstrated that not only the cAMP-related mechanism, but also the NO-cGMP pathway may be involved in the mechanism of ADM-induced vasodilation. Nitric oxide stimulates soluble guanylyl cyclase, producing increased concentrations of cyclic GMP in vascular smooth muscle cells. The cyclic GMP activates GMP-dependent kinases that decrease intracellular calcium, producing relaxation (Majid et al., 1996; Moncada et al., 1991). It has also been demonstrated that NO reduces the production of vasoconstrictive substances such as endothelin-1 through a cGMP-dependent mechanism as well as inhibits the release of norepinephrine from sympathetic nerve terminals (Boulanger and Luscher, 1990).

Inverse relationships between static handgrip-induced changes in plasma ADM and those in PEP, PEP/LVET ratio, peak velocity and mean acceleration of the blood flow in the ascending aorta, and mean velocity of circumferential fiber shortening might be at least partly associated with inotropic action of ADM on the heart (Krzeminski et al., 2009, 2012; Krzeminski and Pawlowska-Jenerowicz, 2012). It should be noted that the PEP/LVET ratio has been proposed as a sensitive inverse index of left ventricular myocardial performance (Lewis et al., 1977; Martin et al., 1971; Weissler et al., 1969, 1972, 1980). A significant correlation was found between the PEP/LVET ratio and the left ventricular ejection fraction determined angiographically in patients with cardiovascular diseases (Ahmet et al., 1972; Garrad et al., 1970; Lewis et al., 1980; Stack et al., 1981; Weissler et al., 1980).

Similarly, the peak velocity and mean acceleration of the ascending aortic blood flow correlate well with the ratio of rise in pressure during isovolumetric contraction to the isovolumetric contraction time (peak dP/dt). The peak dP/dt ratio is sensitive to changes in myocardial contractility, insensitive to changes in the afterload and only mildly affected by changes in the preload (Rhodes et al., 1993). An inverse relationship between changes in left ventricular dp/dt and PEP was found in healthy man (Martin et al., 1971).

Adrenomedullin has been reported to activate the adenylate cyclase-cAMP system in isolated cardiac myocytes, which is one of the major pathways for the regulation of myocardial contractility (Sato et al., 1997; Stangl et al., 2000; Szokodi et al., 1996). Some authors have reported that ADM increases cardiac contractility via a specific adrenomedullin, calcium-dependent mechanism. The authors have suggested that ADM-induced inotropic positive action that may involve Ca^{2+} release from intracellular ryanodine- and thapsigargin-sensitive Ca^{2+} stores, enhances Ca^{2+} influx from sarcoplasmic reticulum through L-type Ca^{2+} channels as well as activation of protein kinase C and protein kinase A (Bell and McDermott, 1994; Huang et al., 1999; Ihara et al., 2000; McLatchie et al., 1998; Szokodi et al. 1998). Bäumer et al. (2002) reported that ADM can indirectly increase cardiac contractility by improving myocardial perfusion.

Thus, it seems likely that ADM acts to increase left ventricular function during static exercise by both a decrease in systemic vascular resistance (afterload) and an increase in myocardial contractility.

Conclusions

There is little data available on the effect of different types of exercise on plasma adrenomedullin concentration in healthy man. Moreover, the results of studies on the effect of dynamic exercise on plasma ADM are contradictory. However, they provide evidence that the sympathetic nervous system and cytokine induction may be involved in ADM release during prolonged endurance exercise. Increased secretion of ADM and ANP during this type of exercise may be a compensatory mechanism attenuating elevation of blood pressure and preventing deterioration of cardiac function such as cardiac fatigue. The inverse relationship between plasma ADM and mean blood pressure observed during maximal exercise supports the concept that ADM might blunt the exercise-induced systemic blood pressure increase.

There is little data showing increases in plasma ADM during static exercise and the investigations were related to older healthy man. Positive correlations between exercise-induced

increases in plasma ADM and those in plasma noradrenaline and endothelin-1 indicate the interaction of these hormones in shaping the cardiovascular response to static exercise. Relationships between static exercise-induced changes in plasma ADM and those in cardiovascular indices might be at least partly associated with inotropic action of ADM on the heart.

Interactions of ADM with vasoactive peptides, catecholamines and cardiovascular indices demonstrate the potential involvement of this peptide in the regulation of blood pressure and myocardial contractility during both dynamic and static exercise. It seems likely that ADM contributes not only to cardiovascular adaptation to exercise, but also to the prevention of acute and long-term cardiovascular complications in endurance athletes. Determination of plasma ADM levels might be considered as a useful and non-invasive tool for evaluation of hemodynamics and cardiac function. Thus, plasma ADM levels could potentially be used as a biomarker or early indicator of cardiovascular dysfunction in endurance athletes and powerlifters or weightlifters.

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