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OPINION

The effect of GnRH agonists on angiogenesis and its implications for the myocardium in patients with cardiac risk

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ABSTRACT
Gonadotropin-releasing hormone agonists were described as anti-angiogenic factors in tumors. Simultaneously they were associated with increased cardiovascular risk in patients treated for prostate cancer, especially in those with preexisting cardiac disease. Studies aiming to elucidate the mechanisms by which androgen deprivation therapy causes cardiovascular effects are rare. We believe that gonadotropin-releasing hormone agonists can impair myocardial angiogenesis. That, in patients with myocardial disease can deepen hypoxia, significantly worsen the condition of the myocardium, and therefore increase the risk of cardiac failure. Careful assessment of the myocardial status and consequent timing and typing of therapy can minimalize the adverse effects. Ideally through close cooperation between cardiologists and oncologists *(Fig. 1, Ref. 25).* Text in PDF *www.elis.sk.*
KEY WORDS: angiogenesis, cardiovascular risk, follicle stimulating hormone, GnRH agonist, testosterone.

Introduction

GnRH agonists are the most common type of the androgen deprivation therapy (ADT) for the treatment of patients with prostate cancer. Despite that, the relationship between GnRH agonists and cardiovascular (CV) disease remains controversial (1, 2, 3). Multiple studies have reported that low testosterone levels correlate with poor CV health and increased risk of CV events (4).

Keating et al. (5) as first authors pointed out that the use of GnRH agonists was associated with increased risk of myocardial infarction (adjusted HR, 1.11; P = 0.03). In conditions where low testosterone levels are induced by therapy with GnRH agonists for prostate cancer, the increase in CV disease supports the hypothesis that testosterone insufficiency increases risk of CV events. Mainly when it occurs in patients with no other associated CV risk factors. However, there is no evidence that testosterone therapy either increases or decreases CV disease risk (4).

The mechanisms of CV effects of GnRH agonists are not well described. Based on the finding that GnRH agonists significantly reduce the expression of VEGF (6), we believe it is necessary to investigate their possible role in the impairment of myocardial angiogenesis.

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Angiogenesis in the infarcted myocardium

Cardiomyocytes require sufficient blood flow to maintain the high metabolic and oxygen demand. Adequate perfusion of the cardiac muscle improves cardiac function. After an ischemic event, the myocardium undergoes extensive remodelling, which can be divided into three different, but overlapping phases (7).

In the initial inflammatory phase; macrophages and neutrophils clear off necrotic cardiomyocytes. This is followed by a proliferative phase, where endothelial cells and fibroblasts proliferate and create vascularised granulation tissue, which later matures into collagen rich scar tissue. This whole process has the tendency to increase the physical strain on the neighbouring viable myocardium. Even though angiogenesis occurs in the granulation tissue, and plays a role in the formation of the infarction scar, neovascularisation of the adjacent uninjured myocardium is a key factor in the process of tissue remodelling. Neovascularisation is also important for the prevention of heart failure through the regulation of hypertrophy and contractility of cardiomyocytes. Failure to induce sufficient neovascularization results in deficient oxygen supply and subsequently in loss of cardiomyocytes, atrophy and interstitial fibrosis, and may represent a major cause of myocardial dysfunction and heart failure (7)

Angiogenesis is a natural mechanism to restore perfusion to the ischemic myocardium after acute myocardial infarction and it is one of the determinants of patient prognosis. Coronary angiogenesis is a form of adaptation of the myocardium to ischemic injury. Renewal of tissue perfusion is decisive for preventing larger infarction, systolic deterioration, remodelling of the left ventricle and poor patient outcome (8, 9). Angiogenesis can improve blood flow, revascularisation and myocardial function. It also supports new mechanisms for myocardial repair and survival. Impaired

neovascularisation in the infarct area and consequent metabolic imbalance are important contributors to the development of cardiac failure, which is the main cause of death in patients with acute myocardial infarction (AMI) from the long-term perspective. Angiogenesis therefore plays a decisive role in myocardial repair during the first days and weeks after AMI (10). It is a multilevel highly regulated process; including the expression of proangiogenic factors, migration and proliferation of endothelial cells and formation of capillary vessels (11).

Vascular endothelial growth factors (VEGF), primarily VEGF-A, is related to angiogenesis and can potentially protect the ischemic myocardium during the initial phases after AMI. VEGF as a selective mitogen for endothelial cells can directly stimulate the growth of news vessels. Increased VEGF-A levels were demonstrated in ischemic myocardium as well as in the serum of patients post AMI (12). Despite the high levels of VEGF-A after acute ischemia, the level of neovascularisation in the infarction area remains insufficient (12, 13).

GnRH agonists inhibit angiogenesis

Several studies dealt with the effect of ADT therapy on cardiovascular risk in patients with prostate cancer. They described different results based on modality, duration of follow up and patient. Studies aiming to elucidate the mechanisms by which GnRH agonists and other forms of ADT affect CV structures are rare. Asai et al (6) suggested that GnRH agonists impair the angiogenic process and inhibit the expression of pro-angiogenic VEGF-A. They directly induce apoptosis in different types of cells (14). It is well known that testosterone levels can drop after acute myocardial infarction. The absence of androgens after myocardial infarction can lead to increased apoptosis of cardiomyocytes (15). The ability of GnRH to inhibit angiogenesis is considered very important in the context of tumour angiogenesis in prostate cancer. This inhibitory effect on the other hand can potentially affect cardiac angiogenesis and interfere with cardiovascular adaptation and regeneration.

GnRH agonists bind to GnRH receptors and initially result in marked increase of testosterone and dihydrotestosterone, but after 1 to 3 weeks of treatment, testosterone is suppressed to < 0.5 ng/ml (< 1.7 nmol/l). They also induce an initial increase in follicle-stimulating hormone (FSH) levels followed by a gradual decrease to approximately 50% of normal levels, later FSH rises gradually (16, 17). Receptors for androgen and FSH are present on endothelial cells and regulate VEGF expression. Thus, the mechanism through which GnRH agonists might inhibit angiogenesis could be through influencing the levels of androgen and FSH.

- **Testosterone and angiogenesis**

Testosterone is the most important androgen in male physiology. Over 90 % of released testosterone directly binds and activates intracellular androgen receptors. The VEGF promoter is regulated though several mechanisms via nuclear receptors, including the androgen receptor. Androgens participate in the regulation of expression of HIF-1a and VEGF-A (18). Despite that, angiogenic signalling molecules differ in their regulation via androgens; e.g.

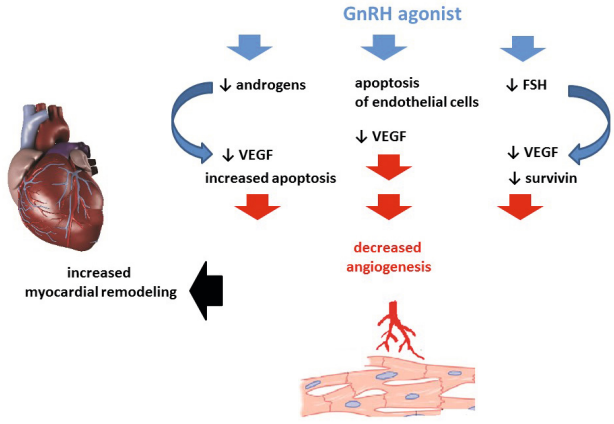

Fig. 1. Potential relationship of GnRH agonist and angiogenesis. GnRH agonist can inhibit expression of the angiogenic factors VEGFs and induce apoptosis of endothelial cells. GnRH agonist also reduces androgens and FSH synthesis. Receptors for androgen, FSH are present on the endothelial cells and these signal molecules regulate VEGF expression. Castration downregulates VEGF in normal tissues and can lead to increased apoptosis of various cells. FSH acts as a mitogen and a positive trophic factor. FSH promotes angiogenesis through a VEGF-dependent mechanism and inhibits apoptosis by the expression of survivin.

castration inhibits VEGF but not bFGF while a decrease in androgens causes vascular regression, which is the result of reduced expression of VEGF in cells and apoptosis of endothelial cells (19). Furthermore, in comparison to healthy controls, hypogonadal males demonstrated lower levels of circulating endothelial progenitor cells, which were refractory to testosterone administration (20).

- **Follicle-stimulating hormone and angiogenesis**

The expression of receptors for follicle-stimulating hormone was demonstrated on endothelial cells. FSH stimulates angiogenesis through the VEGF-dependent mechanism (21). *In vitro* treatment with FSH significantly increased VEGF expression in a dose- and time-dependent manner (22). FSH stimulates the expression of HIF-1 and is a strong inductor of reactive oxygen species which in turn also influence the expression and regulation of VEGF and angiogenesis (23). Additionally, FSH increased the expression of survivin, which promotes the survival of endothelial cells. The production of survivin in rats' myocardium after acute myocardial infarction was demonstrated to significantly inhibit the expression of apoptotic factors. Thus, survivin decreases the apoptotic index of myocardial cells and size of the infarction (24). We assume, that FSH decline can impair angiogenesis. However, the effect of ADT on FSH levels is variable; for example: FSH decreased from pre-ADT levels by a median of 93 % among patients with antagonist therapy compared to 27% reduction in the agonist group (25).

Conclusion

The mechanisms of CV effects of GnRH agonists are not well described. Based on the finding that GnRH agonists significantly

reduce the expression of VEGF (6) through decreasing the levels of FSH and androgens, we believe it is necessary to investigate their possible role in the impairment of myocardial angiogenesis. The efforts to define patient groups with prostate cancer who could benefit from androgen deprivation and "tailored therapy" are still ongoing. It appears that post-myocardial infarction patients should receive specific attention at the time when angiogenesis is the prevention of cardiac failure.

Even though MI causes a spontaneous angiogenic reaction, which has the potential to restore myocardial blood flow, this defence mechanism is often insufficient for re-establishing physiological levels of perfusion (12, 13). Further studies are required to investigate the interactions between hormonal therapy and vasculature. The effect of GnRH agonists on angiogenesis is an important aspect. Local hypoxia stimulates angiogenesis in the myocardium, but it also stimulates apoptosis. This in our view will result in simultaneous regeneration and injury. Re-evaluation of current views based on novel discoveries and studies of complex relations is needed. A question emerges as to whether such studies could be used in the future for determining the areas of hypoxia in the myocardium.

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