The protective effect of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers on radiation-related heart disease and radiation-related lung injury

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ABSTRACT: Radiotherapy involving the thorax increases the risk of cardiovascular disease and lung dysfunction. Several studies show that angiotensin converting enzyme (ACE) inhibitor and angiotensin II receptor blocker mitigate the radiation induced injuries. Angiotensin converting enzyme captopril results in a superior mitigation compared to angiotensin II receptor blocker Losartan. Therefore, the protective effect of captopril on heart and lung tissue is the interest of this study. Captopril could act RAAS independent and prevent degradation of the vasodilator and growth inhibitor bradykinin. Besides, captopril is an ACE inhibitor with a thiol group. This side group can act as an antioxidant to reduce inflammatory reactive oxygen species and could play an important role in the superior mitigation of captopril by radiation induced injuries. The protective effect of captopril on heart and lung tissue after radiotherapy can be due to preventing degradation of bradykinin and due to the antioxidant side group.

Key words: radiation, cardio toxicity, lung dysfunction, RAAS system, ACE inhibitor captopril

INTRODUCTION

Radiotherapy is generally used in cancer treatment to control or kill malignancies. The ionizing radiation works by damage the DNA of exposed tissue leading to cell death. To spare normal tissue, the radiation is given in several angles, to provide a much larger absorbed dose in the tumor tissue than in the surrounding healthy tissue. The amount of radiation used in photon radiation therapy is measured in gray (Gy). The dose in gray varies depending on the type and stage of cancer being treated.

Radiotherapy used to treat patients with malignancies involving the thorax increases the risk of cardiovascular diseases. Radiation-related heart disease is shown in breast cancer survivors, testis cancer survivors and Hodgkin's lymphoma survivors (1). The cardiac effects due to radiotherapy can be roughly categorized in four conditions: pericarditis, pericardial fibrosis, diffuse myocardial fibrosis and coronary artery disease (2, 3). These conditions are caused by molecular events and vascular changes.

Radiation of the thorax is not only involving heart injury. The lung is also sensitive for the exposure to ionizing radiation. Radiation on the lung tissue results in pneumonitis in the early phase and fibrosis in late phase (4). The vascular changes induced by radiation seem similar to pulmonary arterial hypertension (PAH). Pulmonary hypertension can lead to failure of the right heart and premature death (5).

Researchers are interested in developing drugs for mitigation lung dysfunction and cardio toxicity after radiotherapy. Free radical scavengers (6),

anti-oxidants (7), blockers of growth factors and inhibitors of the renin-angiotensin-aldosterone system have demonstrated efficacy in mitigation of radiation injuries in animal studies (8).

Renin-angiotensin-aldosterone system (RAAS) can be inhibited by angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor type 1 blocker. Ghosh et al. shows that ACE inhibitor Captopril mitigated the radiation-related injury in rats when the captopril treatment begun one week after radiotherapy. Losartan, an angiotensin II receptor 1 blocker, is less effective in protecting against radiation injuries (9). Because of the previous finding, the aim of this study is to describe the possible protective mechanisms of captopril on radiation-related heart disease and radiation-related lung injury

RADIATION-RELATED HEART DISEASE

Since the 1960s it has been recognized that the heart can be damaged by substantial doses of radiation. This is demonstrated during radiotherapy for Hodgkin lymphoma. At doses above 30Gy, there is an increased risk of radiation-related heart disease (RRHD) within a year of two after exposure. Patients have greater risk of developing RRHD when the radiotherapy doses and volume goes up. Also age and the presence of conventional risk factors for heart diseases contribute to RRHD (1).

The pathological expression of radiation-related heart disease can roughly be divided in four conditions: pericarditis, pericardial fibrosis, diffuse myocardial fibrosis and coronary artery disease (2, 3). Radiation can also cause valvular disease; this has been demonstrated in an autopsy study of Veinot et al. (10). Although, the evidence for radiation-related valvular diseases is not strongly valid.

Radiation-related pericarditis is characterized by a protein-rich fluid in the pericardial sac, also known as pericardial effusion. Accumulation of this protein-rich fluid can potentially cause fatal cardiac tamponade. Pericardial fibrosis consists of collagen deposition, usually in the parietal pericardium. This increases the thickness of the fibrous layer and results in a rigid pericardial sac. A rigid pericardial sac encircles the heart and inhibits the normal filling of the cardiac chambers (1). For example, as blood passes from the right atrium into the right ventricle during diastole, the right ventricle expands and reaches a limit due the rigid pericardial sac. At that point, further filling is suddenly arrested and venous return to right heart is blocked. Consequently, systemic venous pressure rise and it results in signs of right-sided heart failure.

Diffuse myocardial fibrosis consists of diffuse proliferation of bands of collagen separating and replacing cardiac myocytes. It often occurs in the anterior wall of the left ventricle. The study of Fajardo et al. has demonstrated that this condition is a result from endothelial damage of myocardial blood capillaries. It can lead to ischemia and fibrosis, which finally can lead to heart failure (11). Radiation-related coronary artery disease (CAD) is morphologic essentially the same as the CAD resulting from atherosclerosis. Proliferation of myofibroblasts and lipid-containing macrophages causes the formation of plaques. These plaques reduce the lumen of the artery, as shown in figure 1. This can cause ischemia of the surrounding tissue. Ischemia of the surrounding tissue can result in a clinical manifestation of ischemic heart diseases like angina pectoris, myocardial infarction and chronic ischemic heart disease (12).

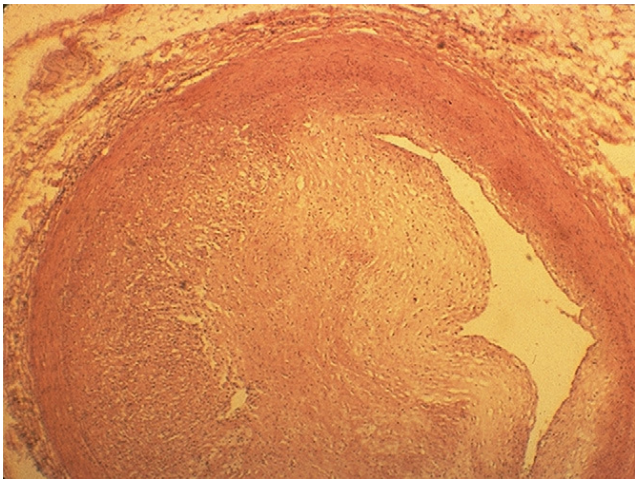

Figure 1. Left anterior descending coronary artery in a 16-year-old boy 1 year after receiving 40 Gy mantle radiotherapy for Hodgkin's disease. Myointimal proliferation has considerably narrowed the lumen. Fatal cases like this in a patient who had no cardiac risk factors other than radiation illustrate that the morphology of arterial disease due to radiation is essentially no different from that of age-related atherosclerosis. Hematoxylin-eosin stain. (12)

Blood vessel damage by radiation was already stated by radiation workers in 1899 (13). The types of lesions that cause the blood vessel damage are specified for each segment of the blood vessel. The lesions are important in pathogenesis of the delayed radiation injury. The micro vessels are more affected than the larger vessels and veins are, overall, less affected than arterial counterparts (12). The smallest elements of vasculature seem to be high radiation sensitive. This is due to the fact that endothelial cells are highly sensitive for radiation. Radiation causes detachment of the endothelial cells, lesions of the vessels, irregularity of cytoplasm and rupture of plasma membrane (12).
The small-sized arteries develop necrosis in the early event or in the delayed phase after radiotherapy. Medium-sized arteries develop lesions in the late phase, such as fibrosis, deposition of fibrosis and plaque formation. These lesions can result in ischemia and heart failure. (12).

Acute vasculitis after radiotherapy may occur as an uncommon delayed lesion. The infiltrate is lymphocytic and located in the media, adventitia or, les commonly, in the intima layer. Studies recognize scars of presumed vasculitis in small en medium size vessels (14). Radiation-associated vasculitis is self-limiting and heals without a therapy. Fajardo et al. have detected acute vasculitis with fibrinoid necrosis in the arterioles and arteries after endovascular brachytherapy. Endovascular brachytherapy is a treatment to prevent restenosis, which is when after a blood vessel stenosis had been opened by angioplasty, it becomes blocked again. It has been proven that radiation prevents restenosis. The vasculitis that Fajardo et al. have recognized after endovascular brachytherapy, were seen 28 days after exposure in 51% of samples around coronary arteries and 100% of those around iliac arteries, as shown in figure 2. The incidence of vasculitis after radiotherapy decreased with time and therefore vasculitis is called an early lesion after radiotherapy. (14)(15).

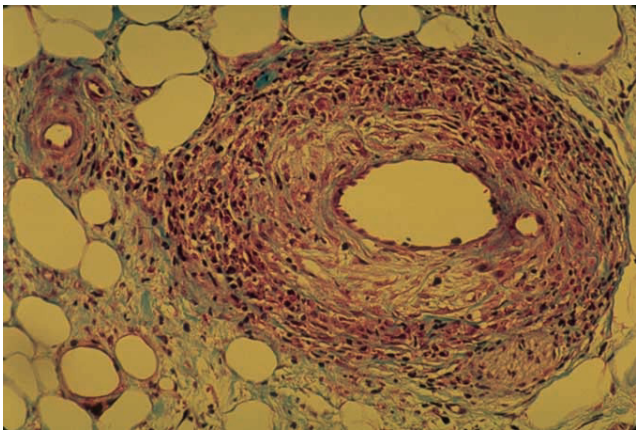

Figure 2. Acute lymphocytic vasculitis in a porcine epicardial arteriole adjacent to a major coronary artery. The coronary artery had been exposed, 28 days previously, to 35 Gy of endovascular brachytherapy. Fibrinoid necrosis is shown in the arteriole, with HE staining. (12)

Large arteries are less often affected than the smaller vessels. However, lesions of large arteries have dramatic effects: myointinmal proliferation, thrombosis, and finally rupture of the artery. Rupture of the large artery is often a fatal complication. It may not result from irradiation alone; it can be caused by other factors such as infections, digestive enzymes, or exposure to air (16).

Cardiac myocyten are terminally differentiated cells and are therefore relatively resistant to direct cytotoxic effect of irradiation. Experimental evidence suggests that radiation-related heart disease is an effect of myocyten toxicity secondary to microvascular damage and ischemia. Darby et al. developed hypotheses for the biological mechanisms that lead to increased mortality from coronary artery disease after radiation exposure in humans, shown in figure 3. The first hypothesis is that radiation increases the frequency of myocardial infarct by interacting with the pathological pathway of age-related coronary artery atherosclerosis. The second hypothesis is that radiation increased the lethality of age related myocardial infarction by reducing the heart tolerance to acute infarction as result of microvascular damage to myocardium. The hypotheses of Darby et al. give two possible routes for the radiation-related heart disease (1).

After radiotherapy pericarditis and myocardial disease are less common today than in the past. This is a result of modification in radiation techniques. Today lower radiation doses and smaller radiation volume are used. Acute pericarditis occurs in the early phase after radiotherapy, within weeks after exposure. This manifests in pleuritic chest, pain, fever, and tachycardia. These symptoms disappear rapidly with the use of non-steroidal anti-inflammatory

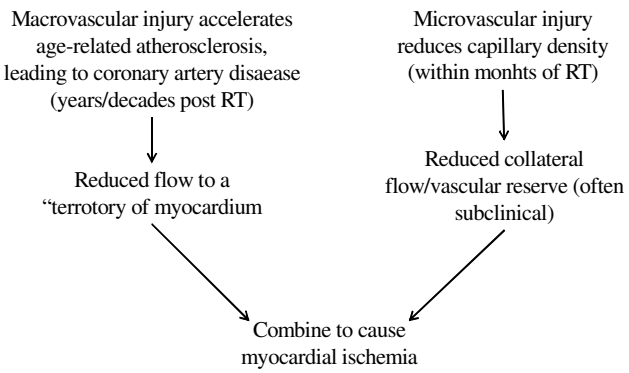

Figure 3. Hypotheses of Darby et al. Radiation increases the frequency of myocardial infarct by interacting with the pathological pathway of age-related coronary artery atherosclerosis. And second, radiation increases the lethality of age related myocardial infarction by reducing the heart tolerance to acute infarction as result of microvascular damage to myocardium. (1)

drugs (NSAIDs). A proportion of the irradiated patients develop chronic pericarditis after ten years. The severity of the disease is variable, from asymptomatic pericardial thickening to cardiac tamponade requiring urgent treatment. (1)

Radiation-related myocardial fibrosis is often asymptomatic and is picked up only incidentally on echocardiography more than 10 years after radiotherapy (17). Therefore, myocardial fibrosis is a characteristic example of delayed cardio toxicity after radiotherapy. Coronary artery disease is also a disease that occurs only in the late phase of radiation induced injury. CAD manifest after ten or more years after radiation. Usually coronary artery disease is not reflected in patient under 50 years old, but young patient who have received radiotherapy for Hodgkin lymphoma develop CAD before their 20th birthday. This phenomenon corresponds to one of the hypotheses of Darby et al. that radiation interacts with the age-related atherosclerosis (1).
In studies of patients with Hodgkin lymphoma, the death rates from heart disease have often been

so large that comparisons with rates in general population gave clear indication of the magnitude of the risk. Patients who have undergone radiotherapy for breast cancer have lower risks for developing CAD compared to patient with Hodgkin lymphoma. This can be due to a lower radiation doses and therefore lower cardiac radiation doses. The phenomenon of radiation-related heart disease is less obvious in breast cancer patient than in Hodgkin lymphoma patients. A meta-analyses by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has shown that mortality from heart disease is increased with 27% in women randomized to surgery plus radiotherapy compared to women randomized to surgery alone. This increase is especially due to coronary artery disease. The risk of death from heart disease after radiation increases by 3% per Gy (18). The relative risk of heart disease increases by the radiation dose; this is demonstrated in several studies. Preston et al. and Yamada et al. have shown that cardiac mortality in atomic bomb survivors was higher than in the general population (19, 20). Carr et al. reported an increase in mortality from coronary artery disease ten years after radiation of peptic ulcers (21). Finally, Darby et al and EBCTG analyzed mortality from heart disease after radiotherapy for breast cancer and concluded the same statement that the relative risk of heart failure increases with the radiation dose (18, 22).

Comparisons of mortality after various different treatments are often misleading because the prognoses of patients with different treatments will vary. Therefore, the effect of radiotherapy on heart disease is obtained by comparing irradiated women with left-sided breast tumors with women with right-sided breast tumors. The dose of the radiotherapy is equal for left-sided and right sided breast cancer. However, the cardiac radiation doses in women given radiotherapy for left sided tumors are usually larger than the cardiac radiation doses in right sided tumors. This is due the fact that the heart is on the left side and will be more affected by left sided radiation. The study of Darby in 2005 has demonstrated that there is an increasing trend in left-sided versus right-sided mortality. This increase seems to be causes by radiotherapy, especially 10 or more years after radiation exposure (22).

Marks et al. demonstrated that myocardial perfusion defects persisted by scanning at 3 to 8 years after radiotherapy. Such defects have been associated with wall motion abnormalities. Their clinical significance remains unproven. However, Marks et al. suggest that perfusion defect is related to long term manifestation of radiation (4). The perfusion abnormalities are likely to represent a radiation-related microvascular injury to the myocardial capillary network. If this is true, it can cause myocardial infarction, as illustrated by one of the hypotheses of Darby et al. in figure 3.

There are other pathogeneses possible to explain the cardio toxicity after radiotherapy. Radiation can cause impaired myocardial catecholamine and increased B receptor density (23). This is a finding that could explain the functional compensation. Another study suggests that capillary loss is associated with a focal loss of endothelial cell marker enzyme alkaline phosphatase (24). This results in swelling, lymphocyte adhesion, extravasations and cell proliferation (3).
Pro-inflammatory molecules have been reported to be upregulated by endothelial cell irradiation. ICAM is upregulated by a total body irradiation

(25). ICAM upregulation is associated with Nf-kB activity (26). This study suggests that Nf-kB play a key role in early reaction of endothelium. Nf-kB mediated inflammatory response results in LDL accumulation in intima. Innate immunity reacts by increased levels of IL-6, Il-8, C - reactive protein and serum amyloid A. The release of these mediators leads to local plaque formation, which is one of the events that can result in coronary heart disease. Radiation can interact in this pathway on different sides, as illustrated in figure 4 (3).

Radiation of the thorax can induce microvascular and macrovascular injury, which combine to cause myocardial ischemia and infarction. The exact mechanism of radiation-related heart disease is still unclear, but epidemiologic and experimental studies relate the radiation-related heart effects to vascular damage.

RADIATION-RELATED LUNG INJURY

Radiotherapy for the thoracic region is not only toxic for the heart tissue, but radiation also causes lung injury. 5-15% of the patients treated for breast cancer and 5-20% of the patient who are treated for lung cancer develop lung dysfunction (4). These patients experience reduction in the whole lung function. Within a few months after radiotherapy there is an acute inflammation seen on chest x rays or a CT scan. Pleural, interlobar and pericardial effusion may be present. These tissue changes are asymptomatic and resolve spontaneously. The majority of patients have radiologic evidence of lung fibrosis at 12-24 month after radiotherapy (4). The radiation-related lung injury can be divided in

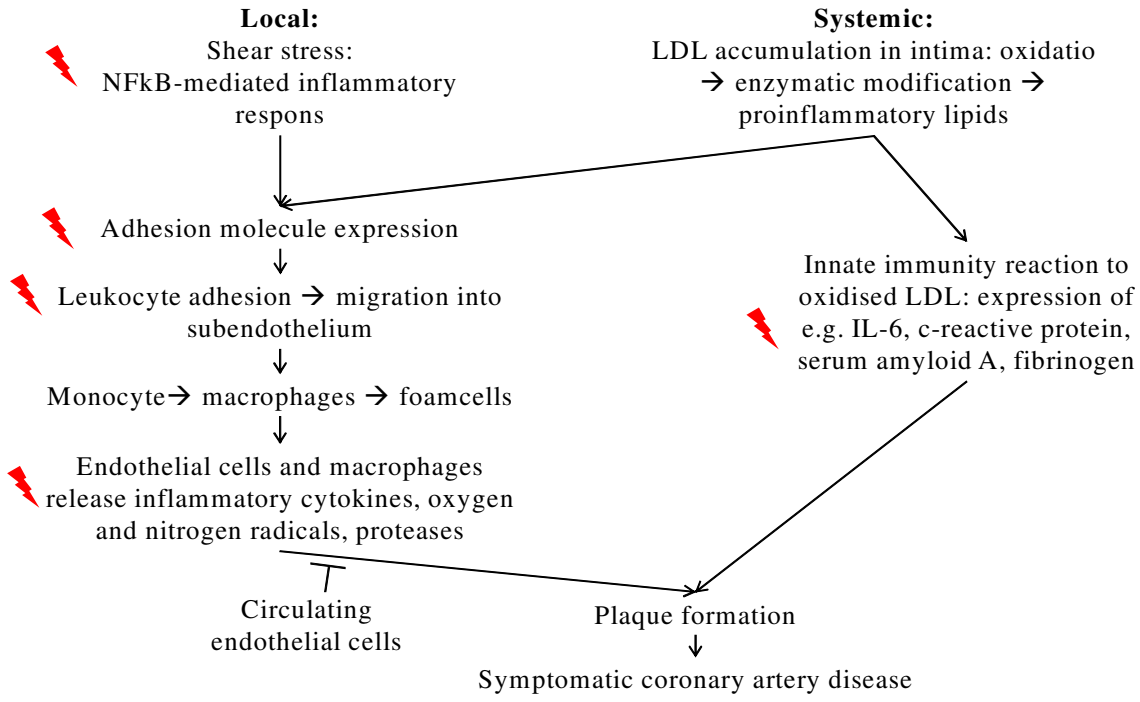

Figure 4. Possible interaction with radiation effects. Radiation can result in a Nf-KB mediated inflammatory response. This leads to LDL accumulation in intima. The innate immunity reacts by increased levels of IL-6, Il-8, CRP and serum amyloid A. This leads to local plaque formation, which is one of the events that can result to coronary heart disease. Radiation can interact in this pathway on different sides, indicated by the red flashes. (3)

early and late manifestations, as with radiation-related heart disease. Acute pneumonitis presents itself one to six months after radiotherapy. The pneumonitis results in shortness of breath, cough, and mild fever. It responds well to the treatment with steroids. Radiation induced fibrosis is typically described as progressive chronic dyspnea associated with scarring of the irradiated lung. Fibrosis occurs typically months to years after radiotherapy and is therefore considered as a late manifestation of radiation. Fibrosis of the lung tissue cannot be cured, but the treatment is aimed to relief the symptoms (4).

The function of the lungs is quantified by several components of standard pulmonary function test. The most commonly measured parameters is the forced expiratory volume in first second (FEV/1), the forced vital capacity (FCV), total lung capacity (TLC) and residual volume (RV). Several studies have reported radiation-related reduction in aforementioned parameters, which indicates that radiation causes reduction in lung function (4).

In healthy lungs, the inferior lung zones have a more favorable ventilation/perfusion ratio than the apical lung. Single-photon-emission computer tomography perfusion and ventilation scans can detect radiation-related lung injury (27, 28). There is both a reduction of ventilation and perfusion after radiotherapy of the thorax. However, perfusion seems to be more sensitive to reduction of function due to radiation therapy than ventilation (4). In mice, in which the heart is located in the inferior thorax, radiotherapy of the inferior lung is more associated with lung toxicity than is radiotherapy to superior lung (29). In rats, however, in which the heart is located in superior thorax, the reverse has been noted (30). This indicates that there is a relation between the cardiac irradiation and the severity of lung injury. The precise link between cardiac irradiation and radiation-related lung injury is still unclear.

The molecular changes of radiation-related lung injury occur earlier than the clinical changes. Radiotherapy triggers a cascade of genetic and molecular events. This is a process, involving several cytokines, cell types, and gene products Radiation generates tissue damage by direct action of reactive oxygen species (ROS) on DNA. Production of ROS causes endothelial dysfunction with an increase in permeability and can eventually result in edema. Tissue damage is also manifested in ischemia and fibrin accumulation. This is followed by an inflammatory response including macrophage activation Macrophages are able to release cytokines and ROS. Both vascular changes as well as an increase in oxygen consumption (because of the macrophages activation) contribute to development of hypoxia. Hypoxia further stimulates the production of ROS and profibrogenic and proagniogenic cytokines. Therefore hypoxia perpetuates a nonhealing tissue response leading to chronic radiation injury (4).

Vascular damage after irradiation of large volumes with relatively low dose is demonstrated in a preclinical model (31). Gosh et al. shows that irradiation increases the vascular resistance, and that it decreases pulmonary arterial ability to stretch (32). These features seem similar to those observed in patient with pulmonary arterial hypertension (PAH). PAH is a severe and progressive form of pulmonary hypertension that leads to right heart failure and premature death. Ghobadi et al. create the hypothesis that vascular damage resulting from radiation of the lung may develop into PAH (5). Lung irradiation causes muscularisation of media layer, thickening of the

adventitia and more advanced lesions. This is also observed in the part of the lung which receives no radiation, suggesting that there is a vascular effect throughout the entire lung. These vascular changes induced by radiation causes an increase in vascular resistance and an increase in pulmonary blood pressure. The pulmonary hypertension results in impaired lung function, measured by the aforementioned parameters (4).

Radiation can cause reduction in the whole lung function, measured by lung function parameters. This is due to pneumonitis in the early phase and fibrosis in the late phase after radiotherapy. The tissue which receives no radiation is also affected. Consequently it seems that vascular changes play an important role in radiation-related lung injury, as also seen in the radiation- related heart disease.

Research has indicated that radiation induced injuries might be treatable, although no therapies have yet been approved by FDA. Free radical scavengers (6), antioxidants (7), blocker of growth factors and inhibitors of renin-angiotensin-aldosterone system (RAAS) seem to efficacy mitigates the radiation injuries in animal models (8). Our interest is the mechanism of mitigating the radiation-related heart injury and radiation-related lung injury by blocking the RAAS system.

RENIN-ANGIOTENSIN-ALDOSTERON SYSTEM

The body senses changing in effective circulating volume by volume receptors. These receptors activate a series of effectors to restore the volume by varying vascular resistance, cardiac output and renal salt and water excretion. The primary volume receptors are located in the carotid sinuses, in the aortic arch and in the glomerular arterioles in the kidneys (33). The receptors in the kidneys regulate the volume by the renin-angiotensin-aldosterone system. When the blood pressure drops, renin is secreted by the kidneys and converting angiotensinogen in angiotensin I. Next, angiotensin converting enzyme (ACE) will convert angiotensin I in angiotensin II. Angiotensin II causes the production of aldosterone and vasoconstriction. Both contribute to an increase in blood pressure as shown in figure 5 (34).

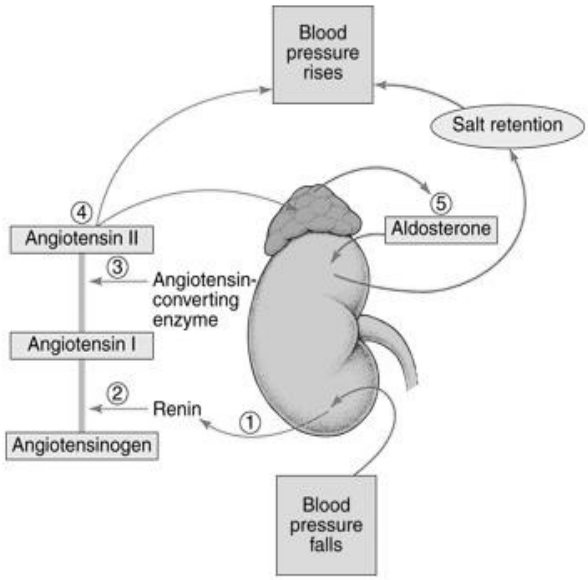

Figure 5. Renin-angiotensin-aldosterone system. As the blood pressure drops, renine will be released by the kidneys. Renine causes the conversion of angiotensinogen in angiotensin I. Angiotensin-converting enzyme is responsible for the conversion of angiotensin I in angiotensin II. Angiotensin II causes vasoconstriction and aldosterone secretion. The increase of angiotensin II and aldosterone levels result in rise of the blood pressure. (34)

Inhibition of the renin-angiotensin-aldosterone system is often used in the treatment of heart failure (35). The RAAS system can be inhibited by an angiotensin converting enzyme inhibitor and by an angiotensin II antagonist. The ACE inhibitor is the most common therapy in patients with heart failure. It inhibits the conversion of

angiotensin I into angiotensin II. This results in less angiotensin II and subsequently less constriction of blood vessels. ACE inhibitors lead to symptomatic improvement, reduced hospitalization and enhanced survival in patients with heart failure. Angiotensin II antagonist is an alternative to ACE inhibitors in patients who cannot tolerate these drugs. Angiotensin II antagonist blocks the Angiotensin II receptor type 1 and therefore the effect of angiotensin II is inhibited (36).

Bezapril, cilazapril, enalapril and ramipril are ACE inhibitors. These ACE inhibitors are pro drugs; this means that the drugs first have to be hydrolyzed to an active substance. Captopril and lisinopril are also ACE inhibitors, but they are immediately in an active conformation. All ACE inhibitors interfere with the renin-angiotensin aldosterone system. The anti-hypertension effect of ACE inhibitors is mediated by lower angiotensin II levels. Angiotensin I is not only converted by ACE, but also by other enzymes. Therefore, by a prolonged treatment with an ACE inhibitor, it is possible that the angiotensin II concentration returns to normal and the anti-hypertension effect of ACE inhibitor disappears (36).

Inhibition of angiotensin II in hypertensive patients results in regression of hypertrophy and hyperplasia. As shown in figure 6 this regression is caused by impaired sympathetic activity and impaired aldosterone levels. Angiotensin converting enzyme equals the action of enzyme kinase II. It is degraded bradykinin, a vasodilator. Bradykinin promotes the formation of vasodilator

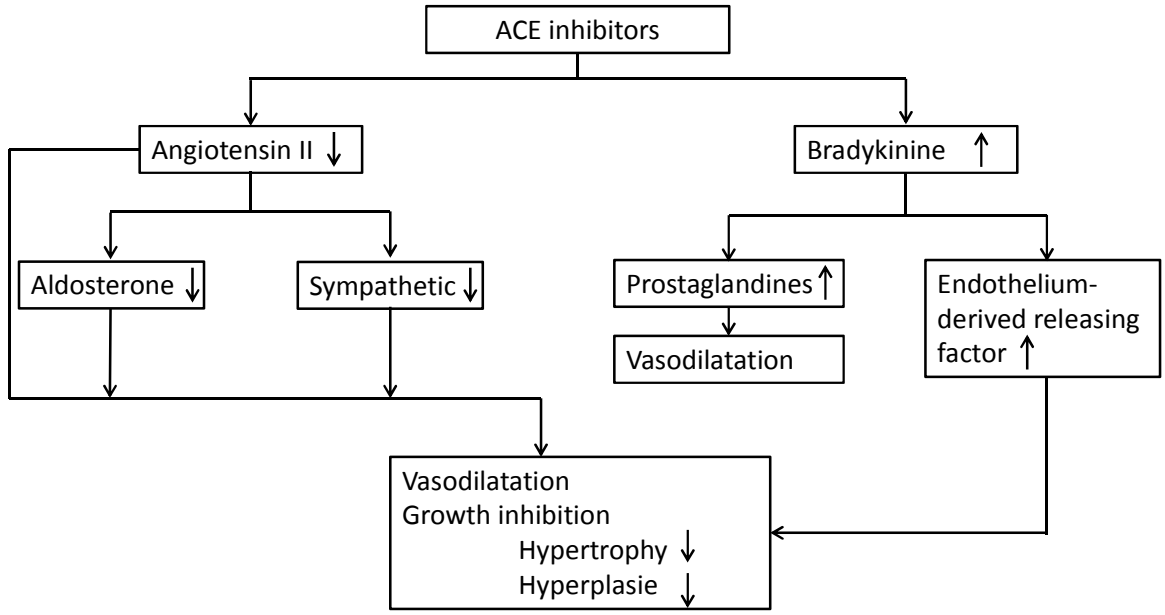

Figure 6. Angiotensin converting enzyme inhibitor. ACE inhibitors suppress the conversion of angiotensin I in angiotensin II. This results in less angiotensin II and subsequently less constriction of blood vessels by impaired aldosterone levels and impaired sympathetic activity. Angiotensin converting enzyme equals the action of enzyme kinase II. It is degraded bradykinin, a vasodilator. Bradykinin promotes the formation of vasodilator substances such as endothelium-derived relaxing factor (EDRF), Nitric Oxide (NO) and prostaglandin E2 en I2. Inhibition of ACE causes vasodilatation and growth inhibition due increase of bradykinin and decrease of angiotensin II. (36)

substances such as endothelium-derived relaxing factor (EDRF), nitric oxide (NO) and prostaglandin E2 en I2. Inhibition of ACE causes vasodilatation and growth inhibition due to the increase of bradykinin and decrease of angiotensin II. Growth inhibition is caused by enhanced EDRF and results in inhibition of ventricle and vascular smooth muscle cells (36).

The positive effect on symptoms of cardiovascular disease is due to arteriole and venues vasodilatation. This results in impaired pre- and afterload. Besides, ACE inhibitors can protect the endothelial function. This effect is probably due to increased nitric oxide and bradykinin (36).
ACE inhibitors differ little in hemodynamic, cardiovascular and therapeutically terms. All ACE inhibitors inhibit circulating and tissue RAAS system. The extent in which various ACE inhibitors can inhibit the tissue RAAS system is various. The exact differences, as well as the clinical relevance are still unknown (36).

ACE INHIBITOR CAPTOPRIL

Inhibitors of the renin-angiotensin aldosterone system have demonstrated efficacy in mitigation of radiation-induced injuries. This has been demonstrated by several studies. Moulder et al. reported that ACE inhibitor and angiotensin II receptor blocker is effective in mitigation of radiation-induced nephropathy. However, the angiotensin II receptor blocker seems to be more effective than ACE inhibitor (8).

Angiotensin II receptor blocker mediates the pro-apoptic, inflammatory and profibrotic action of angiotensin II that can contribute to vascular remodeling. The receptors also generate reactive oxygen species, which could exacerbate radiation injury (9). Therefore it is logical that blocking this angiotensin II receptor would benefit mitigation of radiation-related injury.

Ghosh et al found unexpected results with their study in 2009. They demonstrated that lung injury caused by a single whole thoracic radiation dose can be mitigated by ACE inhibitor captopril and by the angiotensin II receptor blocker losartan. This study shows a superior mitigation due to ACE inhibitor captopril compared with the mitigation of angiotensin II receptor blocker losartan. This was a surprising result because the opposite effect was shown by Moulder et al. on the radiation nephropathy (8, 9, 32).

ACE inhibitors and angiotensin II receptor blockers are effective in mitigation of radiation-related lung injury. Radiation-induced pneumonitis and the development of lung fibrosis are impaired by ACE inhibitors and angiotensin II receptor blockers in rats (37) (38). Angiotensin II plays an important role in the regulation of transforming growth factor-beta (TGF-beta) and alpha-actomyosin (alpha-SMA), two proteins involved in the pathogenesis of pulmonary fibrosis. The finding that ACE inhibitors or angiotensin II receptors blockers protect radiation-related lung injuries reaffirms the role that angiotensin II plays in this inflammatory process and suggests an addition indication of treatment of radiation-related lung injury (39)

The mitigation of the injuries due to ACE inhibitors captopril is not only determined by the effect on the RAAS system, because captopril has a superior effect over losartan, which also involves the RAAS system (8). Consequently, there should be another mechanism involved. Captopril could act by RAAS independent

proteolysis activities and prevent degradation of the vasodilator and growth inhibitor bradykinin. Possible mechanisms underlying bradykinin enhancement by ACE inhibitors in endothelial cells are shown in figure 7. The ACE inhibitor increases the bradykinin (BK) levels in micro environment of the B2 receptor, the ACE inhibitor increases the number of B2 receptors, the ACE inhibitor affects ACE-B2 receptor heterodimer interaction, thereby more signal transduction or the ACE inhibitor induces B1 receptor upregulation and act as B1 receptor agonist (40). All four possible mechanism of enhance bradykinin results in more nitric oxide synthase and therefore for more vasodilation.

Besides, captopril is a thiol-containing ACE inhibitor. Thiol is a side group that may act as an antioxidant to reduce inflammatory reactive oxygen species, therefore captopril is called a free radical scavenger. Molteni et al. demonstrated that an ACE inhibitor with a thiol side group is more effective in controlling fibrosis and growth of neoplastic cells than ACE inhibitors without a thiol side group (41). This side group of captopril can be important in the superior mitigation of captopril on the radiation-induced injuries.

CONCLUSION

Radiotherapy used to treat patients with malignancies involving the thorax increases the risk of cardiovascular diseases and increases the risk of lung dysfunction. Radiation-related heart disease is shown in breast cancer survivors, testis cancer survivors and Hodgkin's lymphoma survivors (1). Radiation of the thorax can induce microvascular and macrovascular injury, which

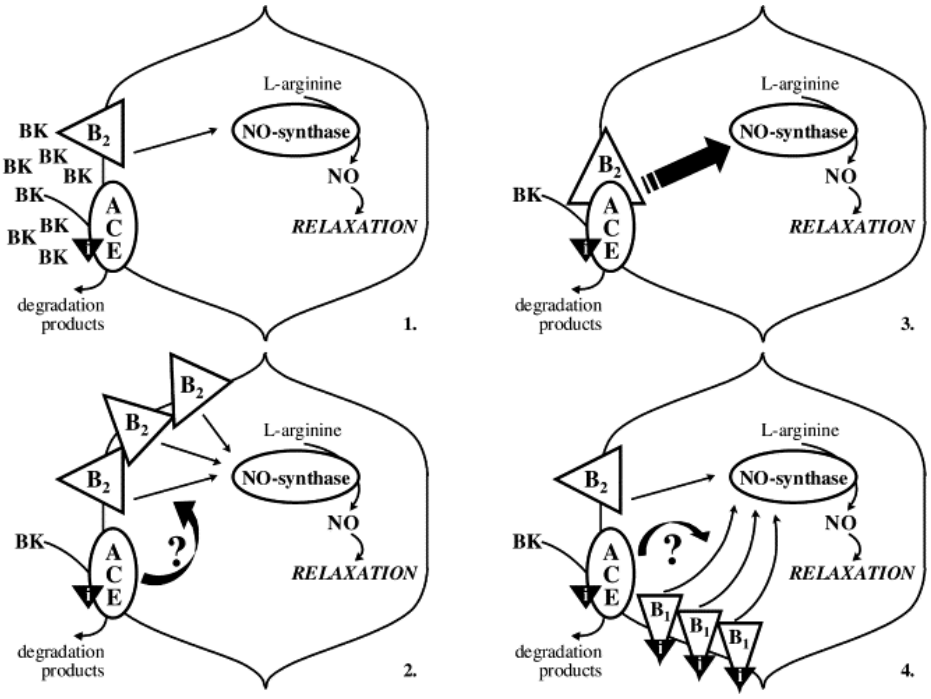

Figure 7. Possible mechanism underlying bradykinin potentiation by ACE inhibitors. ACE inhibitors either 1. increase the bradykinin (BK) levels in micro environment of the B2 receptor, 2. increase the number of B2receptoren, 3. affect ACE-B2 receptor heterodimer interaction, thereby more signal transduction, or 4. induce B1 receptor upregulation and act as B1 receptor agonist (40). These four possible mechanism results in higher nitric oxide (NO) production and therefore vasodilatation.

combine to cause myocardial ischemia and infarction. The exact mechanism of radiation-related heart disease is still unclear, but epidemiologic and experimental studies relate the radiation-related heart effects to vascular damage.

The lung is also sensitive for the exposure to ionizing radiation. Radiation on the lung tissue results in pneumonitis in the early phase and fibrosis in the late phase (4). Lung tissue which receives no radiation is also affected. Consequently, it seems that vascular changes play an important role in radiation-related lung injury, as also seen in the radiation- related heart disease.

Researchers are interested in developing drugs for mitigation radiation-related injuries. Blockers of the renin-angiotensin-aldosterone system have demonstrated efficacy in mitigation of radiation injuries in animal studies (8). Renin-angiotensin-aldosterone system can be inhibited by angiotensin converting enzyme inhibitor or angiotensin II receptor type 1 blocker. Ghosh et al. shows that ACE inhibitor captopril mitigated the radiation-related injury in rats when the captopril treatment begun one week after radiotherapy. Losartan, an angiotensin II receptor 1 blocker, is less effective in protecting against radiation injuries (9). Captopril has a superior mitigation effect on the radiation-related injuries compared to losartan. Consequently, there should be another mechanism involved and not only the inhibition of RAAS system.
Captopril can act by RAAS independent proteolysis activities and prevent degradation of the vasodilator and growth inhibitor bradykinin. The ACE inhibitor increases nitric oxide (NO) synthase and thereby vasodilatation of the blood vessels. There are four possible mechanisms for the bradykinin potentiation by ACE inhibitor. The ACE inhibitor increases the bradykinin (BK) levels in micro environment of the B2 receptor, the ACE inhibitor increases the number of B2 receptors, the ACE inhibitor affects the ACE-B2 receptor heterodimer interaction, thereby more signal transduction or the ACE inhibitor induces B1 receptor upregulation and act as B1 receptor agonist (40).

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The effect of ACE inhibitor captopril on mitigation of the radiation-related injury can be due to the thiol side group of captopril and to the preventing effect of bradykinin degradation by captopril. Ideally you want to give captopril before radiation to protect the tissue against radiation. However, captopril cannot be given before radiation because the free radical scavenger function of this medicine will influence the radiation dose. Therefore, it is interesting to research what the effect is of bradykinin alone in mitigation radiation-related injury. If bradykinin plays a major role in the mitigation of radiation-related injury, the bradykinin level can be upregulated before radiotherapy starts. This is one direction in which research can continue to find promising drugs that can reduce radiation-related injuries.

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