

Differences Between the Pathophysiology of Myocardial Infarction Related Cardiomyopathy and Anthracycline Related Cardiomyopathy

Bachelor thesis pathophysiology

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Abstract

Anthracyclines have shown to be very useful in treating cancers, but have received a lot of attention lately due to their cardiotoxic side effects causing cardiomyopathy (CM). Sufficient therapy has not yet been developed due to differences in injury pathways and mechanisms compared to other CM's. Moreover, the pathophysiology of anthracycline caused CM is not fully understood. Therefore, the aim of this review is to inform the reader about specialities of this type of cardiomyopathy, along with the latest therapeutic insights. This is done by comparing differences and similarities with a more known type of CM, namely myocardial infarction caused CM.

Differences and similarities in the pathophysiology between the two CM's originate from typical molecular mechanisms causing cardiac injury. They share ROS generation as a big injury mediator, but also have its own unique pathways of causing cardiac injury like Ca²⁺ overload and Topoisomerase IIB binding.

Cellular apoptosis and necrosis is witnessed in both cases, but cardiomyocytes differ in their reaction to the disease when looked at size adaptation. Cardiomyocytes after MI undergo eccentric hypertrophy while they undergo atrophy after anthracycline treatment. More differences are seen in autophagy regulation and the way of collagen deposition.

Cellular changes eventually lead to physiological changes characterised by LV wall thinning, unevenly divided wall tension, scar formation, left ventricle (LV) dilation and LV dysfunction. Only the last two characteristics are shared by anthracycline mediated CM, which is further distinguished by its loss in LV wall mass.

Both forms of CM have shown to respond positively to ACE inhibitors. Further current therapies, though not sufficient enough, are already present for MI related CM, but not for anthracyclines. Promising new therapies for Anthracycline treatment are mostly aimed at preventing oxidative damage. Targeting Nrf2, NF-kB and autophagy/mitophagy pathways have all shown very promising results in animal studies. However, clinical studies remain to be executed.

Introduction

Cardiomyopathy is a worldwide disease, with occurrence of its most common form being as high as 1 in 500. Cardiomyopathy is thought to be mostly of familial origin, but can also originate from a different cause (1). Lately, cardiomyopathy caused by chemotherapy has drawn a lot of attention. Chemotherapy has developed significantly in its effectiveness of treating cancer, but cardiotoxic side effects have come to the light over the last couple of years. Of all cytostatica, anthracyclines have been most discussed for both its outstanding clinical use and well noticed adverse side effects (2). Another non-familial origin of cardiomyopathy is the event of an acute myocardial infarction (AMI). With cardiovascular disease (CVD) continuing to be a rising problem in today's society, AMI related cardiomyopathy becomes more applicable as well (3). This is partly due to the fact that risk factors for developing a myocardial infarction (MI) are mostly modifiable, with lifestyle being a major one (4).

In this review, differences between anthracycline related cardiomyopathy and MI related cardiomyopathy pathophysiology will be discussed. Topics that will be covered are the pathogenesis, physiological changes and current and promising treatments for both diseases.

What is cardiomyopathy?

The term cardiomyopathy is used to refer to a group of disorders associated with a disease of the heart muscle. These diseases often lead to remodelling of the heart muscle, resulting in ventricular hypertrophy or dilatation. Changes in heart structure often result in contractile dysfunction and, when not treated accordingly, progressive heart failure or sudden cardiac death (1,5).

Dependent on the physiological changes the heart is submitted to, cardiomyopathy can be divided in subtypes: hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic cardiomyopathy. Cardiomyopathies can also be classified in primary and secondary myopathies. The American Heart Association (AHA) categorized primary cardiomyopathies as diseases where mainly or only the heart itself is affected. Secondary cardiomyopathies are indicated to be of a systemic origin (5). However, there is overlap between the two.

Hypertrophic cardiomyopathy (HCM) is one of the most common cardiomyopathies. Its definition is that of abnormal non-dilated left ventricular hypertrophy, without systemic or other cardiac causes (6). Left ventricular (LV) thickening is usually asymmetrical, but can also be diffuse, focal or concentric. A reduction of ventricular chamber volume is seen as a consequence of LV wall thickening (7).

Another, common cardiomyopathy, dilated cardiomyopathy (DCM) is a disease of the heart muscle with LV and/or right ventricular (RV) dilation, systolic dysfunction, and impaired contractility. This impaired contractility is almost always correlated with a reduced left ventricular ejection fraction (LVEF). Here, ventricular wall thickness is normal or decreased (5,8).

Restrictive cardiomyopathy (RCM) is characterized by an impaired diastolic function without ventricular dilation. Impaired diastolic function is usually due to increased myocardial stiffness impairing proper filling of either or both ventricles. Systolic function is preserved. Restrictive cardiomyopathy is a less common subtype (9,10).

Arrhythmogenic cardiomyopathy (AC) is one of the rarer diseases. It is characterized by ventricular arrhythmias with myocyte loss, progressive dystrophy and fibrofatty replacement of the right ventricular myocardium. (11,12).

Cardiomyopathies can be asymptotic or asymptotic. Symptoms of cardiomyopathies

overlap, with frequent symptoms being shortness of breath, fatigue, coughing, orthopnea, dyspnea and edema. However, early cardiomyopathies can also be asymptotic. Often used methods for diagnosis of both symptomatic and asymptomatic cardiomyopathy are ECG and echocardiography.

Molecular pathways

Myocardial infarction related cardiomyopathy

A myocardial infarction is defined as the occasion where acute myocardial ischemia is consistent with the presence of myocardial necrosis, leading to injury of the heart (13). The most common cause of a myocardial infarction is that of coronary atherosclerosis, where thrombus formation leads to an obstruction within the coronary artery (14). Known risk factors are those which can't be modified (gender, age), modifiable risk factors (with lifestyle being the major risk factor), and emerging risk factors like C-reactive protein. All these risk factors contribute to the probability of developing a myocardial infarction, leading to an obstruction of the coronary artery and eventually ischemia of the heart and its cardiomyocytes (15).

Uehata A. et al. already described the effects of coronary occlusion in 1992, where they monitored the effect of total coronary occlusion and reperfusion in dog hearts. An hour of ischemic conditions in the myocardium, followed by an hour of reperfusion, was enough to cause irreversible myocardial damage (16).

The exact pathogenesis of how ischemia and reperfusion cause injury to the myocardium remains unknown. A lot of different pathways are suggested to be involved in the disease, with one being more prominent than the other. However, the involvement of ROS and an overload of Ca^{2+} have been widely accepted (17). Several studies have shown elevated levels of Ca^{2+} in cardiomyocytes during ischemia (18, 19). During ischemia, blood flow to

cardiomyocytes has been interrupted, impairing the delivery of components needed to produce ATP. Sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA) activity is impaired by low ATP concentrations during ischemia, leading to elevated levels of Ca^{2+} . During early reperfusion, more Ca^{2+} influx is stimulated through a rise in Na^+ after reactivation of Na^+/K^+ ATPase (20). Studies have shown that abnormally high levels of intracellular Ca^{2+} , for example during the early reperfusion, are capable of causing hypercontracture leading to cardiomyocyte death (21). Elevated cytosolic Ca^{2+} levels are also shown responsible for an overload of mitochondrial Ca^{2+} , leading to the production of reactive oxygen species (ROS) (22). Elevation of ROS levels has been correlated with many destructive

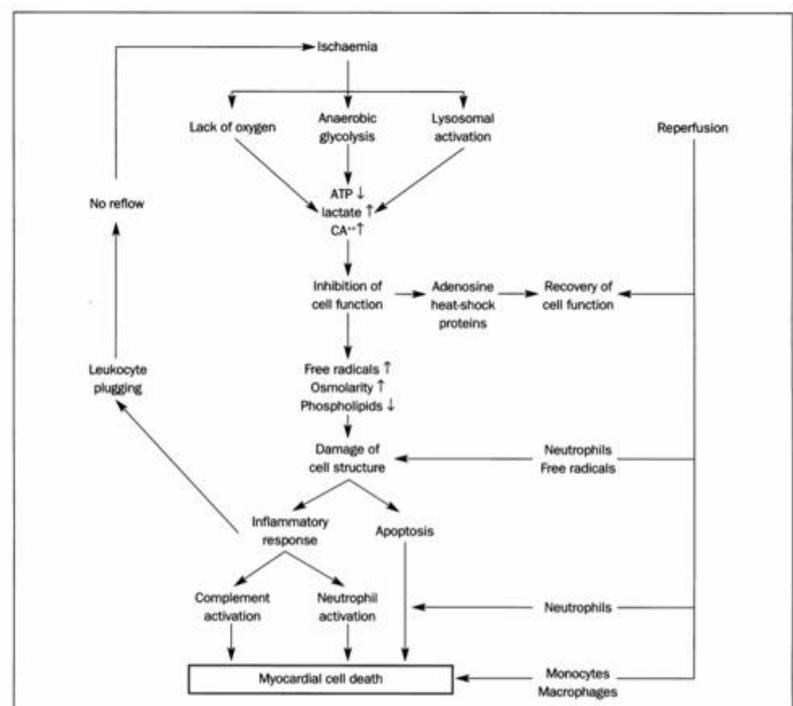


Figure 1 (26). Overview of several pathways contributing to myocardial cell death.

pathways during myocardial infarction. Generation of ROS has been shown to open mitochondrial transition pores (mPTP), leading to cardiac cell death. Elevated ROS levels have also shown to promote cytochrome C release and rupture of mitochondria which lead respectively to apoptosis and necrosis of cardiomyocytes (23). Mechanisms suggested for triggering ROS production during ischemia and reperfusion are the rapid normalization of pH, oxidative stress (24) and neutrophil infiltration (25).

More mechanisms thought to contribute in cellular injury are: osmotic cell stress and subsequent sarcolemma disruption, activation of the complement system and inflammatory cell recruiting, as seen in figure 1 (26).

Thus, coronary occlusion and reperfusion leads to cardiac cellular damage, apoptosis and necrosis with an overload of Ca^{2+} and ROS being the main contributors.

Anthracycline related cardiomyopathy

With every drug, side effects come along. Chemotherapy has shown great improvements in the treatment of cancer, but adverse side effects regarding cardiac function are noted as well. Arrhythmias, hypotension, tachycardia and even heart failure have been found to arise more frequently as a consequence of anthracyclines (27). Several chemotherapeutic drugs are known to cause cardiotoxicity, with anthracyclines being the most prominent one.

Anthracyclines are a group of chemotherapeutic drugs and are widely used to treat cancers like lymphomas, breast cancer and leukaemia's. The mechanism of Anthracyclines by which they reduce cancer development is known to be multifactorial. The most prominent mechanism is thought to be that of ROS development. Elevated levels of ROS, as described above, are able to induce cellular damage and ultimately cell death. A more recent researched mechanism is that of anthracycline binding to DNA and topoisomerase (Top) 2 β isoenzymes, causing double-strand breaks. It hereby inhibits DNA replication, puts the cell in cell-cycle arrest and induces apoptosis. These effects of anthracyclines are particularly useful to treat cancers. Unfortunately, adverse effects can occur in the heart, causing cardiac injury (28).

The amount of cardiotoxicity caused by anthracyclines is dependent on various risk factors. Patients with previous cardiac diseases, diabetes mellitus, hypertension and liver disease are known to have a higher change of developing cardiac injury after anthracycline treatment. Another large influencer of risking cardiotoxic effects is the route of administration and the cumulative dose used to treat cancers (29). Doxorubicin (DOX), the most well-known and used anthracycline, is shown to have a massive increase in the risk of developing CHF when it's dose exceeds 500 mg/m². A clinicopathologic analysis showed that when the dose exceeds 600 mg/m², the risk of developing CHF could rise up to 36% (27).

As said earlier, the exact mechanism of anthracycline induced cardiotoxicity remains unelucidated, but the most widely accepted mechanism remains that of ROS mediated oxidative stress. Most of the ROS production within cells takes place in mitochondria. Since the heart has a great need for ATP to pump blood through the body, its proportion of mitochondria is high. Under normal circumstances, excessive ROS levels can be neutralized by antioxidant enzymes as superoxide dismutase (SOD). However, when ROS production is elevated by DOX it exceeds the detoxification ability of antioxidant enzymes, leading to harmful effects (27). The MAPK's and siRNAs mediated Nrf2 pathway is a known key player in modulating oxidative balance, and thus an important pathway to be understood (3).

DOX can lead to the production of ROS by being transformed back and forth. DOX can be transformed from quinone to semiquinone. Mitochondrial enzymes as NADPH oxidase, xanthine oxidase (XO) and cytochrome P-450 reductase can help in this procedure. Rapid transformation from the formed semiquinone back to quinone generates superoxide anions (O₂⁻) (28). O₂⁻ can be further transformed leading to the production and elevated

levels of ROS and reactive nitrogen species (RNS) (27). It is shown that free cellular iron may also be responsible for elevating ROS levels by forming complexes with DOX. (31). Elevated levels of ROS can lead to mitochondrial membrane depolarization, where after the mitochondria can induce the release of cytochrome C and subsequent apoptosis (32). More effects of elevated ROS levels are lipid peroxidation, alterations in energy metabolism, sarcomere degradation and suppression of protein synthesis (33).

A more recent propose is that of Top-DOX interactions. Top 2A is known to be highly expressed in tumour cells, and is able to induce single or double-stranded breaks. DOX, and other anthracyclines, can bind with Top 2A and DNA, stabilizing a reaction intermediate. In this reaction intermediate, a double stranded brake is made, but can't be resealed. This results in growth arrest and ultimately in programmed cell death of tumour cells (34). Unfortunately, its isozyme Top 2 β presence is highly expressed in cardiomyocytes, where it can, in combination with DOX, exert toxic effects. Top 2 β -DOX binding is responsible for the suppression of peroxisome proliferator-activated receptor (PPAR). PPAR regulates oxidative metabolism, and its suppression can lead to mitochondrial dysfunction (28). An overview of cardiotoxic effects via ROS and Top2 β can be seen in figure 2.

It is also suggested that DOX plays a role in suppressing or inducing autophagy. As Shabalala et al. described in their paper, there is no consensus yet what the exact role of DOX is in controlling autophagy. Several studies show different effects of DOX on autophagy. Where some note that DOX suppresses autophagy, other find autophagy to be activated. These findings can partly be explained by the fact that the effect of DOX defers between animals. Where in mice autophagy is suppressed, it is activated in rats (35).

Next to autophagy and apoptosis, necrosis has been noted as an effect of increased oxidative stress through ROS formation and lipid peroxidation. Mitochondrial dysfunction for example, as a cause of impaired glucose metabolism and respiration rates, can result in necrosis (35).

Physiological changes

Myocardial infarction related cardiomyopathy.

The molecular pathways described above, lead to cellular injury and eventually to apoptosis and necrosis of cardiac myocytes. Cell injury and death of myocytes lead to reduced contractile power, followed by LV remodelling. LV remodelling is meant to be helpful and can have positive effects in the beginning but can eventually be catastrophic.

Before the chronic cardiac remodelling takes place, early cardiac repair is performed. Cardiac damage and cellular death trigger repair responses, eventually leading to altered tissue composition and structure. Cardiac repair is a complex process. Cardiomyocytes, endothelial cells, neutrophils, lymphocytes and fibroblasts are all involved. The repair

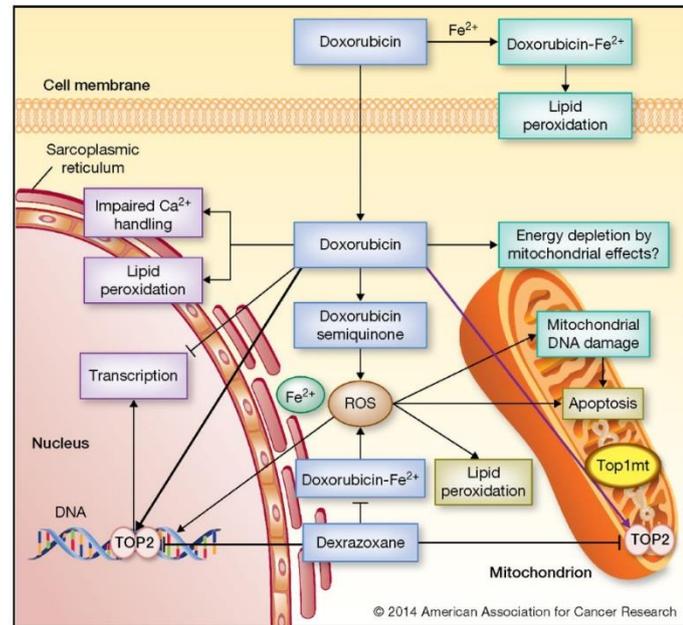


Figure 2 (28). Overview of the cardiotoxic effects of DOX via ROS and Top2 β .

response can be divided in different stages: Inflammatory phase, proliferative phase and reparative phase (36). At first, there is massive necrosis and apoptosis of cardiomyocytes. Hereafter, inflammatory cells help with the removal of dead myocytes, and the destruction of collagen scaffolding by MMP's to retain ventricular shape (37). However, this also leads to thinning of the ventricular wall. To later strengthen the ventricular wall again, myofibroblasts are recruited to the area where they proliferate and produce new collagens. These collagens also prevent the wall against rupture (38). However, this collagen deposition can eventually result in scar formation. This happens in the last phase. Myofibroblasts inflammatory cells disappear from the wound area, and collagens cross-link with each other, leading to scar formation (39).

In the following weeks and months, cellular and cardiac changes are still seen. To preserve cardiac output, cellular hypertrophy of non-infarcted cardiomyocytes is executed (40). Cardiac death reduces contractile power, and scar formation leads to a more stiffed myocardium, reducing ventricular elasticity. Both lead to reduced cardiac output, and eventually eccentric hypertrophy as a compensatory mechanism. Eccentric hypertrophy of cardiomyocytes is one of the causes of LV dilatation. In eccentric hypertrophy, cardiomyocytes grow in the length, aiding to wall thinning. This has not only been seen in cardiomyocytes surrounding the fibrotic scar, but also in the rest of the myocardium (41).

Scar formation can contribute in another way to LV dilatation (42). Scar formation and its correlated ventricular stiffness decrease LV elasticity and thus increase the stress put on the ventricular wall. More stress automatically leads to elevated stretching of the LV (43). Moreover, contraction in the ventricle is not symmetric due to necrotic and fibrotic areas, leading to a heterogenous distribution of wall tension. Contraction force is not counterbalanced by the necrotic part of the wall. This part will stretch out abnormally much due to extra stress, subsequently leading to enlargement of the LV, as seen in figure 3. This is promoted by hypertrophy of the non-infarcted part. Hypertrophy and an increase in wall stress are thought to be responsible for further collagen deposition, leading to an even more stiff environment and creating a viscous circle. An overview of these events can be seen in figure 4 (42, 44).

Dilatation of the LV, hypertrophy of cardiomyocytes, scar formation and an increased wall stiffness lead to LV dysfunction and reduced LVEF. All these disease mechanisms are related to a lot of different complications, as arrhythmias (38), HF and sudden cardiac death (SCD). All the mechanisms described above also cause the end-systolic LV volume to rise, which is shown to correlate with a worse prognosis of life (45).

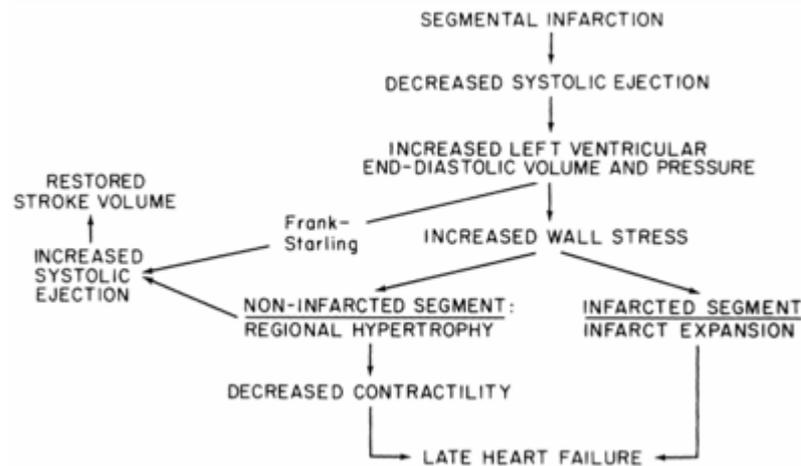


Figure 4 (34). Overview of the mechanisms involved in cardiac remodelling after MI.

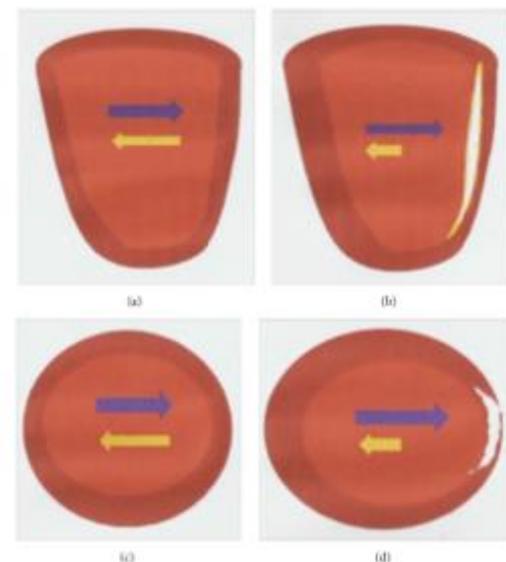


Figure 3 (40). Cardiac remodelling due to heterogeneity in LV wall tension distribution after MI. A and C: normally divided LV wall tension without scar formation and hypertrophy. B and D: Heterogenous divided LV wall tension as a consequence of scar formation and hypertrophy, leading to dilation.

Anthracycline related cardiomyopathy

A big difference between the pathophysiology following myocardial infarction and anthracyclines, is the time spectrum over which damage is done. In a myocardial infarct, immediate damage is done through acute oxygen depletion and reperfusion damage, in one hit. In anthracycline related cardiomyopathy, it is spread over a much longer period. The heart must withstand multiple doses of cardiotoxic cytostatica, with doses divided over a period often as long as multiple months or even years. However, the necrotic and apoptotic effects on cardiomyocytes after a myocardial infarct are well in anthracycline related cardiomyopathy.

The physiological changes of anthracycline related cardiomyopathy are much less understood than MI related cardiomyopathy. However, since it became clear that cytostatica could induce cardiomyopathy, research to the morphological changes has been done in abundance. Anthracycline-induced cardiomyopathy can be divided in an early, subacute and late onset phase (45). In several studies, an acute substantial decrease of heart and LV mass after anthracycline treatment in patients was noticed (46,47). A study of anthracycline effects in long-term cancer survivors showed larger declines in LV mass respectively to higher doses of anthracyclines (46). Necrosis, apoptosis and autophagy of cardiomyocytes are most probably responsible for the mass reduction. However, atrophy of cardiomyocytes is also proposed to be a contributing mechanism. In a study done by de Souza et al., patients who underwent anthracycline therapy showed a significant decrease in cardiomyocyte mass (48). Studies done on mice to further understand the mechanisms of cardiac atrophy found the same results (49). These results are in contrast with those found after myocardial infarction, where myocyte hypertrophy is seen. Atrophy is, among other mechanisms, shown to lead to an increase in extracellular volume (ECV) (48).

Clinical studies have also identified the presence of acute cardiac edema and myofiber disarray after DOX treatment (50). Mouse models done to study the emerging of edema more closely state that the increase of edema after treated with anthracyclines is of acute origin (51). Moreover, substantial disarray of cardiomyocytes has been seen in rats shortly after treatment with DOX. Medeiros-Lima et al. believe that the early onset of cardiotoxic effects is coupled to late cardiomyopathy. They believe that initial cell damage like apoptosis and proteolysis is followed by increased collagen and ECM formation and eventually adverse cardiac remodelling (52). Supporting this view, it was found that acute edema and fibrosis could predict late mortality (51). Decreased LV mass seen acutely after anthracycline treatment has been seen 6 to 9 years after anthracycline treatment as well (47).

Thus, it is believed that early cardiotoxicity eventually leads to left ventricular dysfunction. Impaired contractility, reduced systolic and diastolic function and dysrhythmias in the LV are seen after DOX treatment, with variation in onset time. Dysrhythmias and cardiac failure induced by DOX are for example noticed even after 6-19 years of treatment (53) but is also found within 24 hours after treatment (54). As for clinical symptoms of cardiac dysfunction, it can for example be in the form of reduced LVEF and a reduced shortening fraction (55).

Current and promising treatments

Myocardial infarction

Trying to limit cardiotoxic effects and cardiac remodelling after myocardial infarction is a fight which takes place at two fronts. Firstly, you can prevent acute cardiotoxicity as much as possible. Secondly, you can try to restore cardiac function after its harmful remodelling. During a myocardial infarction, damage can be minimized by making sure the ischemic period is as short as possible. Next to that, reperfusion injury could be limited. Small-size clinical studies have shown that ischemic postconditioning has a positive effect on the myocardium by reducing infarct size (56,57). Ischemic postconditioning is a process where blood flow returns to the ischemic part in steps, instead of at once. This partly prevents both the incidence of sudden extreme reoxygenation and Ca^{2+} overload, reducing cell damage (58). These clinical studies found an improvement in cardiac contractility and infarct size because of less reperfusion injury correlated apoptosis. These results were found shortly after the infarct, but also after one year (56,59). Unfortunately, clinical experiments based on other mechanisms to prevent reperfusion injury have shown disappointing results (60).

Intervening in cardiomyopathy long after the myocardial infarction is an option to improve cardiac functioning once cardiotoxic events have already taken place. Angiotensin converting enzyme (ACE) inhibitors like captopril have shown cardiac improvements in clinical studies. It is thought ACE inhibitors exert positive effects through influencing cardiac remodelling like ventricular dilatation. Inhibition of cardiomyocyte hypertrophy, coronary circulation and ventricular unloading are suggested mechanisms of ACE inhibitors (61). Next to that, Beta-blockers, RAAS blockers, antiplatelet agents and statins have all shown to reduce mortality after MI. However, disadvantages and lacking knowledge about long-term effects create the need for new or additive therapies (62).

Decreased LV contractility and function are partly due to the loss of cardiomyocytes. Many experiments have been done to try and restore cardiomyocyte to normal amounts. Regenerative trials using stem cells or progenitor cells have been done in abundance but have failed to realize their clinical expectations. This is for the most part due to a lack of understanding. Clarification on development, differentiation and maturation pathways of cardiomyocytes could strongly contribute (63). Nonetheless, knowledge about these principles continues to be gathered. Besides that, preclinical animal studies still show cardiac improvements which suggests that regenerative strategies could become promising in the future (64,65).

Anthracycline related cardiomyopathy

ACE inhibitors also showed to be promising in patients who received anthracycline treatment. ACE inhibitors prevented LVEF decline in patients who received high doses of DOX and had high levels of troponin I (66). Dexrazoxane could be used to counteract the toxic effect of generated ROS through DOX-iron interaction. Dexrazoxane is an iron chelating agent, which prevents the DOX-iron reaction and can thus decrease oxidative stress. Dexrazoxane can also bind to topoisomerase-2, suggesting prevention of DOX-Top2B binding toxic effects (28).

Studies of other antioxidant treatments like carvedilol and probucol to reduce ROS levels have shown very promising in animal experiments. (67). Unfortunately, these failed to deliver consistent results in clinical trials (68). Up until now, the ACE inhibitor dexrazoxane is the only drug approved for treatment by Food and Drug Administration (69).

Newest promising findings

Anthracycline related cardiomyopathy

The most research done to prevent toxic effects of anthracyclines is aimed at decreasing the toxic effects of ROS. Cardiomyocytes have a low number of antioxidants, which is why they are extra vulnerable to ROS. A lot of studies aim to elevate these levels. As described above, Nrf2 is a key player in modulating oxidative balance by being able to elevate anti-oxidant levels (70). Therefore, a lot of studies target this pathway.

Zhu et al. show how Klotho, a protein associated with ageing processes, can activate MAPK signalling and thereby protect cardiomyocytes from ROS in rats. Klotho was able to reduce intracellular ROS accumulation and apoptosis by elevating antioxidant enzyme synthesis. Inhibition of MAPK signalling resulted in cardiac apoptosis and dysfunctions (70). Other studies done targeting the MAPK pathway showed the same results. COS was able to activate the MAPK mediated Nrf2 pathway and thereby protect cardiomyocytes against DOX induced oxidative stress and apoptosis in vivo (71). However, the MAPK pathway remains to be completely clear, as other studies suggest the MAPK pathway to be of destructive origin. Das et al. showed that taurine mediated inhibition of the MAPK signalling molecules p53, p38 and JNK resulted in decreased apoptosis in rats (72). However, many other studies showed that stimulation of the Nrf2 signalling pathway leads to an increase in antioxidants and thereby protection against oxidative stress. Most of these studies were done in mice or rats. Clinical studies targeting Nrf2 pathways remain to be executed (73,74,75).

Other studies target NF- κ B signalling pathways. NF- κ B can promote DOX-induced apoptosis in cardiomyocytes and can among others be activated by ROS. Apremilast (AP) is seen to inhibit gene transcription of NF- κ B activated genes, thereby impairing NF- κ B induced apoptosis in rats (76). These results are supported by other experiments (77). NF- κ B is also known as a regulator of inflammatory responses. It is thought that inhibition of NF- κ B and thus inflammatory responses can have protective effects against DOX related cardiotoxicity (78).

Targeting mitochondrial dysfunction via SIRT3 has also shown to be promising. SIRT3 is a deacetylase involved in mitochondrial function through regulating ROS production and protection against oxidative stress (79). Its suggested protective effects are multiple. SIRT3 is thought to activate antioxidants, preserve mitochondrial structures and regulate ROS formation through influencing the electron transport chain. Du, Q. et al. showed that overexpression of SIRT3 resulted in suppressed mitochondrial disruption in vivo (80). To observe the effect of an SIRT3 activator, Honokiol treatment was done in mice. Honokiol mediated SIRT3 activation resulted in prevention of DOX-induced mitochondrial injury and cell death in rats' cardiomyocytes (81).

Others have shown cardioprotective mechanisms through preventing mitochondrial fission. Fission is a process of the mitochondria where mitochondria divide from a single organelle into multiple (82). Mitochondrial fission has been associated with cellular apoptosis, though underlying pathways are not entirely understood. However, a known mediator of mitochondrial fission is Ndm1. In vitro inhibition of Ndm1 function by knocking down one of its activator Mtfp1 resulted in a decrease of myocyte death. Mitochondrial fission through Ndm1 signalling is associated with cytochrome-c release, and inhibition of this occurrence is thought to be the driving cardioprotective factor of Mtfp1 knockdown (83). Inhibition of Ndm1 through LCZ696 administration in mice showed cardioprotective functions as well (84).

Autophagy and mitophagy disruption is believed to contribute in myocardial damage

as well. Dysfunctional mitophagy could lead to inhibited clearance and accumulation of damaged mitochondria (85). Wang, p et al. found that the protein SESN2 was able to re-establish functional mitophagy, paving the way for removal of damaged mitochondria and reducing cardiotoxic effects in vivo (86). However, consensus about the toxic mechanisms of disrupted mitophagy in DOX induced cardiomyopathy is still not reached. Another recent experiment states the opposite, supporting a theory of DOX-induced mitophagy to be harmful. They noticed an increase of autophagosomes in mitochondria after DOX treatment in vitro. Addition of a mitophagy inhibitor resulted in decreased mitochondrial toxicity (87). As for autophagy, no consensus is reached as well. Results concerning autophagy in DOX-treated cells are controversial, with both suppressed and activated autophagy observed following DOX-treatment. Tang, et al suggest inhibition of autophagy to be cardioprotective. DT-010, an autophagosome formation inhibitor, showed cardioprotective functions. Dt-010 was able to inhibit autophagy which was correlated with reduced myocyte apoptosis in cardiomyocytes of zebrafish. Autophagy is thought to be an inducer for apoptosis, which is why inhibiting autophagy is a suggested cardioprotective mechanism (88). These results are supported by Ma, et al. (89). On the other side, autophagy is thought to be positive for cardiomyocytes. Others suggest that autophagosome accumulation due to suppressed autophagy can be harmful and contribute to the detrimental effects of DOX (90). More research towards understanding the pathways involved in autophagy are needed to draw conclusions.

Conclusion

In conclusion, the pathophysiology of MI related CM and anthracycline related CM differ in their molecular injury mechanism, leading to corresponding variation in physiological changes and therapeutic strategies. However, similarities in the pathophysiology have also been found. An overview of differences and overlapping pathophysiological processes can be seen in figure 5.

What is obvious is that the origin of CM development is different. While cellular injury in AMI is done in a short period of time, anthracycline mediated injury is process of multiple hits. Molecular pathways differ from each other as well. Occlusion of a coronary artery leads to the abrupt termination of oxygen supply and other needed molecules. This results in Ca²⁺ overload and elevated ROS production as the main contributors of the disease. A big part of anthracycline caused cellular injury is caused by elevated ROS levels as well. Here, excessive ROS is accumulated every time a patient is treated with DOX. However, anthracyclines also have effects which are not seen in AMI. DOX interaction with Top2 β is believed to be another big part of injury development, which does not happen after AMI.

Since ROS production is one of the leading causes for injury in both diseases, cellular and hereafter physiological changes share some features. In both cardiomyopathies apoptosis and necrosis of cardiomyocytes is witnessed, with ROS being responsible for a big part. Collagen deposition does also happen in both cases, but is thought to be more outstanding in AMI related CM. Furthermore, eccentric hypertrophy witnessed after AMI has not been seen after DOX treatment. Surprisingly, atrophy of cardiomyocytes did occur after DOX treatment. Myofiber disarray and disrupted autophagy are other consequences witnessed more frequent in anthracycline related CM.

These cellular consequences lead to physiological changes. Due to necrosis and apoptosis of cardiomyocytes witnessed correspondingly, contractility is impaired. Furthermore, LV dilation and dysfunction and systolic dysfunction is witnessed in either cardiomyopathy. LV dilation in AMI is caused by collagen deposition and subsequent scar formation and increased ventricular stiffness, with heterogenous divided wall tension also

playing a role. Wall thinning due to eccentric hypertrophy further mediates LV dilation. In anthracycline related CM, fibrosis and reduced LV mass are characteristic physiological changes. Atrophy, necrosis and apoptosis lead to reduced LV wall mass. Persistent physiological injury and dysfunction can lead to arrhythmias, heart failure and sudden cardiac death.

Treatment of both cardiomyopathies differs mostly in the moment of intervention. In

AMI treatment, it is mostly preventing physiological changes after damage has already been done. Preventing damage from a MI is hard, since ischemic periods will always be present before reperfusion can be realized in the hospital. Treatment of AMI is based on reducing reperfusion damage as much as possible and preventing detrimental physiological changes with the help of Beta blocker, RAAS blocker and antiplatelet agents. Significant loss in the number of cardiomyocytes could possibly be counteracted by the help of regenerative therapies. Anthracycline treatment is more focussed at preventing damage by reducing ROS accumulation. Promising therapies are those intervening oxidative stress via Nfr2 and NF-kB signalling. ACE inhibitors have also shown to be promising. Furthermore, antioxidants and autophagy/mitophagy disruption are thought to be valuable to target in clinical therapies.

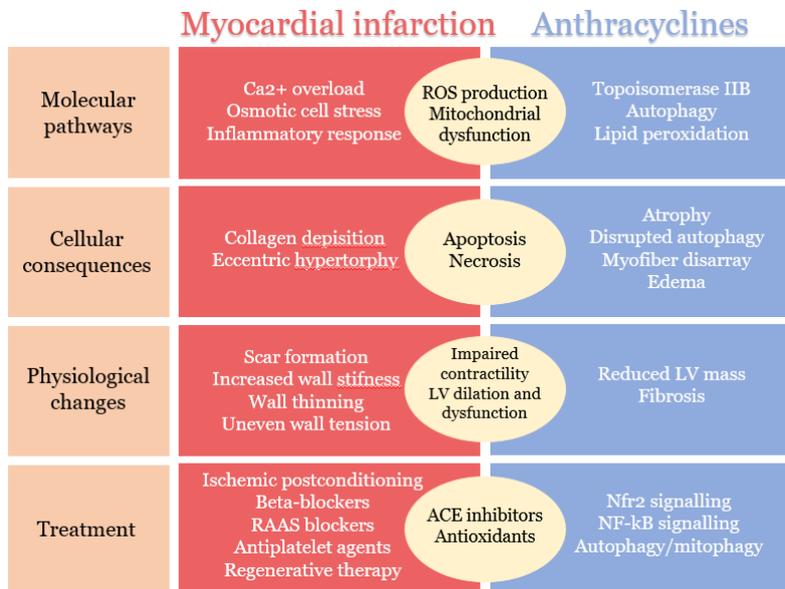


Figure 5. Overview of differences and overlapping characteristics between MI related CM and anthracycline related CM. Differences are stated in the red and blue squares. Overlapping characteristics are stated in the circles.

Future perspectives

As for MI related cardiomyopathy, damage done to the myocardium after MI seems to be inevitable. I think that necrosis and apoptosis of cardiomyocytes after MI can not be prevented, or in very low amounts at maximum. However, regeneration of the heart after myocardial injury could in my opinion still be a promising therapeutic pathway to restore myocardial power. Regenerative medicine has shown promising results in animal studies, but remains to be effective in clinical trials. A major reasons for these clinical disappointments is the lack of knowledge about cellular mechanisms and processes regarding cells in and around the myocardium. I think that regenerative medicine could become an effective way to treat MI related cardiomyopathy when understood better.

Anthracycline related cardiomyopathy is an other story. Here, I think it is best to appoint the prevention of cellular damage as the main therapeutic target. Studies have been mostly done in animals, targeting a lot of different cellular events. Examples of targets are mitochondrial disruption and fission, disrupted mitophagy and autophagy and apoptotic pathways. The main initiator of these events and myocardial injury is thought to be that of excessive ROS accumulation, which I think would be best to target. Many of the experimental studies have tried to prevent the harmful pathways stimulated by ROS instead of targeting ROS accumulation directly. Studies have for example tried to prevent the impairment of mitophagy or preserve mitochondrial structures, but I think that targeting the initiating factor is the most promising. Antioxidants have shown to decrease ROS levels and thus its harmful effects by breaking it down. Intervening directly in ROS formation instead of

accumulation could also be promising. SIRT3 has shown to decrease ROS formation through having an influence in the electron transport chain, leading to decreased harmful events. Thus, preventing the accumulation of the cellular injury initiator ROS is the most promising therapeutic mechanism in my opinion.

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