Chapter

Predicting Risk of Emerging Cardiotoxicity

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Abstract

Smoking, hypercholesterolemia, hyperlipidemia, obesity, diabetes, insulin resistance and family history all are well established general risk factors broadly associated with injury in the cardiovascular system. Similarly, echocardiography, electrocardiography, MRI, PET scans and circulating biomarkers like cardiac Troponin (cTn) provide indications that injury has occurred. Traditionally, cardiovascular injury has been attributed to conditions that exacerbate the potential for ischemia, either by producing excessive metabolic/work demands or by impairing the perfusion necessary to support the metabolic/work demands. This review summarizes additional factors that are underappreciated in contributing to the risk of injury, such as iatrogenic injury secondary to treatment for other conditions, infection, environmental exposures, and autoimmune processes.

Keywords: cardiovascular, cardiac, heart, myocardial, vascular, endothelium, COVID-19, auto-immunity, autoantibody, anthracycline, diabetes, mitochondria, air pollution, nanomaterials, nanoparticles

1. Introduction

The risk factors generally associated with risk for atherosclerotic cardiovascular disease include age, sex, race, systolic and diastolic blood pressure, total, Total cholesterol, high/low density lipoprotein (HDL and LDL) fractions, overweight and obesity, and history of diabetes or smoking [1, 2]. Evidence-based treatment guidelines based on these factors have been established [1]. Apps/tools for use by the general population to predict risk of a cardiovascular event have been published both by the American Heart Association [3], and by the American College of Cardiology [4]. The gold standard for establishing injury is typically direct histologic evidence of injury, which increasingly have become well correlated with surrogate markers such as circulating cardiac troponin (CTnT or cTnI) levels or natriuretic peptide levels (ANP or BNP).

The purpose of this chapter is to highlight potential areas of emerging concern that are not yet established as directly causing increased risk of cardiovascular disease. They may be iatrogenic toxicity effects associated with treatment for non-cardiovascular diseases and therefore no considered a general risk overall [5–7]. They

may be effects that alter the progression of an established risk factor, they may be factors that have only recently been considered, or that may not alter the risk of acquiring cardiovascular disease at all but may alter the severity and subsequent mortality of a cardiovascular event, were it to occur secondary to any of the established risk factors. Contributing elements might be disruption of mitochondrial function [8–11], or infectious disease [12–21]. Chronic diseases that have strong systemic inflammatory components such as Systemic Lupus Erythmatosis (SLE) [22–25] or asthma [26–28] may or may not alter the incidence of chronic CVD but may be associated with increased risk of acute events, or may modify the outcome from reperfusion therapies, especially those already known to be complicated by a major inflammatory component [29–32].

In addition, as large-scale health system databases become increasing robust and geo-mapping of environmental influences is increasingly refined, associations between air quality CVD outcomes can now be interrogated with much higher fidelity than before, and what had been experimental and/or local phenomenological observations are becoming increasingly more widely appreciated [33, 34]. Findings previously associated only with air pollution are becoming more generalized to other environmental influences as well [35].

Finally, emerging from across the spectrum of systemic challenges and with wide-ranging targets, the potential role of auto-immune responses as an aggravating risk factor that is becoming increasingly appreciated will be discussed [36–39].

2. Anti-neoplastic agent cardiotoxicity

2.1 Anthracyclines

Cardiovascular risk can be attributed to those things that directly damage the myocyte, those things that increase the likelihood of damage to the myocyte, or those things that impair the recovery following injury to the myocyte. Anthracyclines are effective anti-neoplastic agents, but with efficacy limited by cardiotoxic side effects. Clinically, there are specific guidelines based on serial cTnT levels to monitor of cardiotoxic effects, and experimentally, the cardiotoxicity is well-established enough that doxorubicin, a common anthracycline, is one of the most commonly used approaches to induce experimental heart failure independent of any neoplasm [40]. Anthracyclines cause a type I cardiotoxicity that is dose-limiting, often irreversible, and produces changes demonstrated on biopsy. While previous treatment for cancer is not considered a general cardiovascular risk factor per se, it is clear that at least some cancer therapeutics can produce persistent cardiac effects, and understanding those mechanism provides a great deal of insight regarding underlying mechanisms involved in increasing cardiovascular risk. This is particularly important when anthracyclines were used, but no overt toxicity was noted, which is to say only that ejection fraction, or CTnT NP remained within acceptable limits. It is worth reviewing the many ways that anthracyclines can induce injury so as to better appreciate how a sub-clinical event might have go undetected at the time, but could none-the-less create a vulnerable substrate for injury later.

Doxorubicin is toxic, in itself, and approximately half of the doxorubicin administered into the body is eliminated unchanged. However, the metabolized doxorubicin creates secondary effects/products that are at least as toxic as the parent compound.

Metabolism of doxorubicin occurs in one of three ways: two-electron reduction, one-electron reduction, and deglycosylation [5, 41, 42].

Two-electron reduction is the primary metabolic pathway for doxorubin and results in the formation of active secondary alcohol metabolites. The alcohol metabolites that are produced cause cardiotoxic side effects by disrupting intracellular and especially intramitochondrial calcium and iron homeostasis. Doxorubincinol, a secondary alcohol metabolite of doxorubicin, interacts with aconitase/iron regulatory protein 1 (IRP-1) and converts it to a "null protein". Normally, when iron levels are adequate, aconitase acts within the Krebs cycle to convert citrate to isocitrate. When iron levels are low, this enzyme does not contain a [4Fe-4S] cluster and will act as IRP-1, which has RNA-binding activity. IRP-1 helps to regulate the expression of genes involved in iron metabolism and homeostasis [5, 41, 42].

Doxorubicinol also is an inhibitor of a number of ATPases, including the mitochondria's proton pump and those which regulate intracellular calcium levels, which not only leads to inhibition of cellular oxidative phosphorylation and bioenergetic collapse, but also disrupts calcium homeostasis leading to intracellular calcium overload disruption of excitation-contraction coupling [5, 41, 42]. Anthracyclines, particularly doxorubicin, also increase activity of calpain and may suppress sarcomere protein synthesis via signaling pathways and transcription factors, such as GATA4 [5, 41, 42]. Increased Calpain activity likely is secondary to an increase in intracellular calcium. This increase in activity increases degradation of titin, a major myofilament of sarcomere, which further leads to an impaired diastolic relaxation. Calpain dysregulation is also known to activate caspase-12, which can cause apoptosis. Caspase-12 is localized in the endoplasmic reticulum and is often activated by ER stress [43].

Anthracycline alcohol metabolites also interfere with the activity of iron sequestering proteins which leads to an increase in intracellular free iron. Anthracyclines have a high affinity for ferric iron, forming a free radical that is capable of reducing oxygen [44]. This is one mechanism by which anthracyclines are capable of participating in "redox cycling". Doxorubicin also contributes to the generation of ROS by inactivating the cellular defense enzymes glutathione peroxidase (GPx) and superoxide dismutase (SOD) [5, 41, 42], essential enzymes critical to managing mitochondrial membrane potential.

In one-electron reduction metabolic pathway, doxorubicin's adverse effects are due to redox cycling. The quinone moiety accepts an electron from NADH or NADPH via the use of endothelial nitric oxide synthase (eNOS), leading to the formation of a semiquinone free radical. This free radical reduces oxygen and forms a superoxide radical. This contributes to the increase in ROS observed in cardiomyocytes after doxorubicin exposure [5, 41, 42]. Further, doxorubicin's interaction with eNOS shuttles the enzyme from a NO-producing enzyme to a superoxide-producing enzyme. This could contribute to an impaired cardioprotective mechanism. This "uncoupling of eNOS" has already been shown to be a contributor in heart failure [6].

The deglycosylation pathway is thought to be a less important contributor to anthracycline metabolism, but it creates a lipophilic molecule that has greater accumulation in the mitochondrial membrane than unmetabolized doxorubicin [5, 41, 42], and by interfering with such mitochondrial membrane proteins as cardiolipin, can also disrupt mitochondrial function, which can trigger any number of secondary effects, including energy depletion, ROS generation and DNA damage, as well as apoptosis [7–11].

Topoisomerase IIB is found in all quiescent cells, including cardiomyocytes. Anthracyclines inhibit this enzyme, leading to unrepaired ROS induced

double-stranded breaks, DNA damage and transcriptome changes in tissue with little regenerative capability [5, 41, 42]. It was demonstrated that mice with cardiomyocyte specific Top2b deletion were protected from the progressive heart failure effects of doxorubicin [45], clearly suggesting that the inhibition of topoisomerase IIB plays a major role in the cardiotoxicity induced by doxorubicin.

Stress to the heart generally shifts metabolic energy production away from the preferred free fatty acid substrate to one that is glucose based and more prone to lactate production. Typically, those shifts are driven by limitations in perfusion and access to sufficient oxygen to support electron transport chains. The same is true for anthracyclines, except that anthracyclines also directly disrupt multiple aspects of mitochondrial function. Doxorubicin causes p53 activation via its inhibition on topoisomerase IIB, leading to repression of PPARg co-activator alpha and beta, which normally promote mitochondrial biogenesis. Their signaling inhibition leads to aging and heart failure. Thus, doxorubicin's inhibition of topoisomerase IIB leads to a mitochondrial dysfunction that that is known to contribute to development of heart failure in doxorubicin-treated patients [46] and in other models of heart failure as well [7–11].

It has also been suggested that anthracycline-induced cardiotoxicity is partially due to the action of matrix metalloproteinases (MMP's). MMP-2 is highly abundant in cardiac myocytes and increased plasma levels have been observed following heart failure. It is possible that doxorubicin increases the concentration of MMP-2 in cardiac cells. Activation of MMP-2 by doxorubicin has been shown to play a role in the degradation of titin, further suggesting that this mechanism plays a role in sarcomere disruption and cardiac remodeling involved with doxorubicin-induced cardiomyopathy [47]. MMPs play an active role in regulating fibrosis in the heart and dysregulation can lead to disruption of the extracellular matrix, adverse remodeling and impaired relaxation.

Doxorubicin can have genomic effects as well. GATA4 is a zinc finger transcription factor that regulates multiple genes, including anti-apoptotic gene Bcl-x. GATA4 is not only involved in sarcomere integrity, but is also an essential survival factor in cardiomyocytes and has been shown to rapidly deplete after doxorubicin exposure. GATA4 depletion leads to cardiomyocyte apoptosis and is essential for adaptive stress response in the adult heart [48] and decreased GATA4 can occur secondary to p53 accumulation caused by doxorubicin exposure [49]. A GATA motif also was identified in an angiotensin II receptor (ATII-R). When stimulated, this receptor helps regulate the hypertrophic response to pressure overload. Mutations introduced into this binding site eliminated this response, demonstrating a role for GATA4 in the regulation of cardiac hypertrophic response [43].

Doxorubicin has a high affinity for the phospholipid cardiolipin. Cardiolipin is a mitochondrial membrane protein involved in many cellular mechanisms, including mitochondrial cristae morphology, electron transport chain function, steroid synthesis, mitophagy, and apoptosis. Cardiolipin turns over at a slower rate than other phospholipids of the mitochondrial membrane and a change in the cardiolipin pool is observed in multiple cardiovascular diseases and in the aged heart [5, 50]. When complexed to doxorubicin, cardiolipin is unable to perform some of its regular functions such as anchoring cytochrome c [7]. This high affinity for cardiolipin also enables doxorubicin to accumulate in the mitochondria. Additionally, it is possible that anthracyclines possess an affinity to intercalate into mitochondrial DNA and may have a higher affinity for mitochondrial DNA than for nuclear DNA [44], leading to mitochondrial genomic injury as well.

The intimate involvement of mitochondrial dysfunction in progression of cardiovascular injury is becoming increasingly evident [7–11]. It should not be surprising that anthracyclines also interfere with cellular energy metabolism in numerous ways, some of which already have been described. Doxorubicin is known to directly interfere with complex I of the electron transport chain and causes a dose-dependent opening of the mitochondrial permeability transition pore, preventing the mitochondria from creating a proton gradient [7–11]. Furthermore, doxorubicin acutely inhibits AMPK and causes a net metabolic shift from fatty acid oxidation to glucose oxidation and lactic acid production, and the observed alterations in redox and metabolic pathways caused by doxorubicin have been shown to persist beyond the half-life of the drug [7], suggesting a durable effect that would increase both the severity of injury but also recovery from future cardiac events.

In addition to the intracellular mechanisms of apoptosis already discussed, it has been shown that doxorubicin upregulates the expression of several death receptors, including TNFR1, DR4, DR5, and FAS [51]. In one study, Adriamycin was shown to induce apoptosis in a p53-independent mechanism, via a Fas-mediated pathway [52]. The cardiotoxic side effects of doxorubicin are also thought to be partially due to an inflammatory response. Doxorubicin has been shown to increase several specific cytokines, including IL-6 and COX-2, and the inflammatory response induced by doxorubicin can be mediated in part by the activation of the p38 MAPK/NF-κB pathway [53]. The activation of p38 MAPK in cardiac cells has been associated with the accumulation of ROS and the onset of apoptosis in ischemia–reperfusion injured hearts [43] and strategies to limit those effects have been a major feature of cardioprotection in ischemia–reperfusion settings [29–32].

Studies have demonstrated that specific inflammatory biomarkers are predictive of cardiotoxicity in anthracycline-treated patients [44]. For example, one study showed myeloperoxidase levels had predictive value for ANT cardiotoxicity [54]. Another study showed that patients with high baseline levels of IgE were at a lower risk of developing cancer therapy-related cardiotoxicity from doxorubicin and trastuzumab treatment [55]. These results indicate that an inflammatory response likely plays a significant role in the development of anthracycline-induced cardiotoxicity.

2.2 Additional cancer drug treatment related cardiovascular effects

Anti-neoplastic drugs also capable of causing cardiac injury are not limited to the anthracyclines. For example, Trastuzumab causes a type II cardiotoxicity that is often reversible after cessation of therapy; however, some degree of persistent cardiac dysfunction has been documented in a portion of patients [56]. Trastuzumab is a human epidermal growth factor receptor 2 (HER2/ErbB2) inhibitor. In the adult heart, HER2 plays a cardioprotective role and inhibits apoptosis. When the heart is subjected to biomechanical stress, neuregulin-1 (NRG1) secreted from endothelial cells binds to HER2/HER4 heterodimers on cardiomyocytes and activates PI3K and MAPK pathways [57]. ErbB2 inhibition is associated with a significant increase in Bcl-2 family proteins [58]. It has been demonstrated that mice with a cardiac-specific deletion of ErbB2 displayed evidence of dilated cardiomyopathy, suggesting ErbB2 signaling is essential for prevention of dilated cardiomyopathy during remodeling [59]. Further, downregulation of both ErbB2 and ErbB4 has been observed in pathological remodeling of the failing myocardium in humans [60].

Trastuzumab has also been shown to trigger oxidative stress and induce the expression and activation of proapoptotic proteins, ultimately leading to mitochondrial dysfunction, the opening of mitochondrial permeability transition pores, and activation of the cell death pathways [57, 59]. Trastuzumab and anthracycline combination treatment can be powerful in its therapeutic effect, but also is known to significantly aggravate the cardiotoxic effects of anthracyclines. It is thought that anthracycline induced cardiac injury triggers the activation of the HER2 survival pathways. When anthracyclines are treated in combination with trastuzumab, these cardioprotective survival pathways are inhibited and less protection is provided to the heart [57], explaining the aggravated progression of cardiac injury.

Another fairly common therapeutic, cyclophosphamide (CP), is an alkylating agent used to treat diseases such as neuroblastoma, as well as systemic inflammatory conditions such as Systemic Lupus Erythmatosis (SLE), and rheumatoid arthritis [61]. At lower doses, CP has an immunosuppressive effect, while at higher doses, it causes cardiotoxic effects. Cyclophosphamide and its metabolites, 4-hydroxy cyclophosphamide, aldophosphamide, and acrolein are cardiotoxic, with acrolein being the most cardiotoxic [61]. Acrolein forms cytoplasmic and nuclear protein adducts, as well as adducts with lysine and cysteine. When adducted to lysine, Acrolein can react with glutathione to cause oxidative stress. When adducted with cysteine, it leads to activation of caspases and NF-κB. Activation of caspases causes apoptosis and activation of NF-κB causes the production of inflammatory cytokines [61]. Cyclophosphamide also alters the energy pool in cardiomyocytes. Many anticancer drugs, including CP, alter the expression of heart-type fatty acid binding protein (H-FABP) and carnitine palmitoyltransferase 1 (CPT-1), leading to inhibition of fatty acid oxidation and diminished ATP production. When deprived of enough ATP, cardiac tissue alters contraction and relaxation, accumulates calcium in the mitochondria, and undergoes ER stress [61].

Like many other cytotoxic agents, CP causes oxidative stress in cardiomyocytes by decreasing antioxidant levels and generating free radicals. Nrf2 is a leucine zipper protein involved in the regulation of antioxidants. CP decreases antioxidant levels is through its action on Nrf2 [61], and by suppression of intracellular GSH and SOD [62]. In CP-treated rats, additional treatment with cyclosporin-A had a cardioprotective role against CP-induced cytotoxicity [63]. Cyclosporin binds cyclophilin and forms a complex that then binds calcineurin and inactivates it, suggesting that CP induces calcineurin-mediated effects. It is thought that CP causes calcineurin-mediated dephosphorylation of NFAT, which is involved in the transcription of hypertrophic genes and apoptosis via FasL and death receptors. Additionally, calcineurin causes activation of Akt, which participates in phosphorylation of GSK-3B and leads to cardiac hypertrophy [61].

Cyclophosphamide also was shown to increase the expression of pro-apoptotic proteins and decrease the expression of antiapoptotic proteins [64]. p53 inhibition is associated with reduced apoptosis, but CP and anthracyclines both upregulate expression of p53, promoting apoptosis [61], and CP was shown to increase the expression of caspase-3 and decrease the expression of Bcl-2, also pro-apoptotic mechanisms [65, 66]. Ultrastructural changes were observed in rat cardiomyocytes when treated with CP, including lysis of myofibrils, dilation of vesicles in the sarcoplasmic reticulum, and destruction of mitochondria [67] suggesting substantial potential for persistent effects long after therapy has ended.

2.3 Cancer radiation treatment related cardiovascular injury

Additional cancer therapy related adverse cardiovascular effects are not necessarily associated with pharmaceuticals of any kind and can take quite a long time for the association to become evident. In the WECARE prospective clinical trial, women receiving radiation to treat Stage 1 or Stage 2 breast cancer, 10.5% of those receiving left-sided radiation developed coronary artery disease over then next 27 years, nearly double the incidence when compared to those who received right-sided radiation (5.8%). Further, in those patients who were under age 40 at the time of treatment, 5.9% went on to develop heart disease, compared to none in the right-sided radiation treatment group [68]. The association is presumed to relate to the relative position of the underlying cardiac structures predominantly in the left thoracic compared to the right, with coronary artery disease presumed to be the result of direct injury to the coronary arteries. The association has been suggested previously [69] is consistent with findings from a meta-analysis of smaller cohorts [70], and in older patients with a specific subset of breast cancer (estrogen positive) [71]. It remains unclear whether the vascular injury hypothesis is correct, or if the disease progression/complication rate (restenosis, heart failure, arrhythmia) following the incident cardiovascular events also were worse. Perhaps what is becoming increasingly clear is that there is substantial potential for cardiovascular events as a consequence of successful management of other disease processes and heightened routine surveillance of cardiovascular end points may be warranted, even when direct cardiovascular symptoms are not immediately evident.

3. Micronutrient effects and metabolism-targeting drug effects

Micronutrient deficiency is associated with heart failure and is a potential cause of cardiomyopathy. Low vitamin D levels are known to be associated with cardiomyopathy though the mechanism by which vitamin D affects the heart is not fully understood. Vitamin D is known to have an antihypertrophic effect. Vitamin D deficient rats have been shown to have smaller myofibrils than vitamin D sufficient rats. Additionally, vitamin D helps to regulate the expression of MMP's and tissue inhibitors of metalloproteinases (TIMP's). Imbalance in their expression is associated with diastolic and systolic dysfunction [72]. Vitamin D levels are also thought to regulate heart energy metabolism and intracellular calcium handling [73]. Of note, Vitamin D deficits have been strongly identified with morbidity and mortality associated with SARS-2 COVID19 [74]. While COVID19 mortality is not exclusively a cardiovascular event, neither can substantial cardiovascular compromise be excluded as a significant contributing factor, simply suggesting that at least some micronutrient deficiencies likely are emerging as cardiovascular risk factors of note for the future. Consistent with that impression, thiamine deficiency deprives the heart of ATP and can lead to heart failure. Thiamine is an essential cofactor for aerobic metabolism, for example, as a cofactor for the pyruvate dehydrogenase complex.

CoQ10 deficiency may also be capable of causing cardiomyopathy, as it is involved in energy metabolism, stabilization of the cellular membrane, and has antioxidant effects [75]. Blood levels of CoQ10 have been reported to be low in patients taking statin class drugs. Statins are some of the most commonly prescribed drugs to manage risk of ischemic cardiovascular disease, and a recent meta-analysis indicated that

CoQ10 supplementation reduces the risk of Statin-induced peripheral myopathies (muscle weakness, muscle cramp, muscle tiredness) but without changes in creatine kinase levels [76]. Interestingly, while the peripheral myopathies are a known complication of statin therapy, there are few studies specifically questioning whether a cardiomyopathy could also develop in a subset of patients on statins. A recent study examined the potential relationship between heart failure and long-term statin use and reported a statin-associated cardiomyopathy that responded to discontinuation of the statin combined with CoQ10 supplementation. After a mean follow-up of 2.8 years, 34% had normalized diastolic dysfunction, and 25% showed improvement [77]. While encouraging that the adverse outcomes were somewhat reversible, the results also indicate that over 40% of the patients did not improve and had lasting deleterious cardiac effects at least partially attributable to statin therapy originally prescribed to prevent cardiovascular disease [77].

In a similar vein, thiazolidinediones (TZDs) are PPARg agonists used in the treatment of type II diabetes mellitus (DMTII). To the extent that DMTII is one of strongest predictors of cardiovascular risk overall, it makes sense that these would be beneficial drugs for reducing the risk, especially for ischemic heart diseases, and the drugs are effective in that regard. However, in the event an ischemic event occurs anyway, therapeutic doses of TZDs are associated with impaired recovery and increased mortality [78]. Experimental studies indicate that excess stimulation of fatty acid metabolism by upregulating PPAR signaling restricts the heart from transitioning away from fatty acid as a substrate in the setting of ischemia, augmenting injury and subsequent dysfunction [79]. In addition to findings associated with therapeutic doses, there also can be a direct cardiotoxicity associated with TZDs at supratherapeutic levels. At least some of the cardiotoxicity is not PPAR related but remains metabolic/mitochondrial in origin [78]. Thiazolidinediones also bind off-target sites that contribute to the cardiotoxic effects. These off-target sites include mitoNEET, mitochondrial pyruvate carrier 2 (Mpc-2), mitochondrial and cytoplasmic dehydrogenases, ion channels, and enzymes and modulators involved in glucose homeostasis and energy production. MitoNEET is an iron–sulfur cluster transporter on the outer mitochondrial membrane that inhibits mitochondrial iron transport. Altering expression of mitoNEET has been shown to affect ROS levels and damage induced by ROS [78].

Similarly, Rosiglitazone, another DMTII drug, also causes myocardial energy deficiency and oxidative stress in a PPARg-independent mechanism via inhibition of complex I and complex IV of the electron transport chain, resulting in an increase in the NADH/NAD ratio and a reduction in ATP synthesis. Additionally, rosiglitazone potentially decreases mitochondrial ROS-scavenging capacity and increases phosphorylation of p38-MAPK via a PPARg-independent mechanism, as well as inhibiting NF-κB activity, which all can contribute to cardiac hypertrophy [78].

Together, these findings suggest that a host of mechanisms can contribute to adverse cardiovascular outcomes. Many of them impact mitochondrial function, with consequences including excess ROS oxidative stress, decreased capacity to buffer the oxidative stress, energy depletion, and increased apoptosis. In some cases, the cardiovascular risks are unavoidable, but if they could be managed better, the therapeutic efficacy of the drugs might be improved. While managing dosing based on known toxicities and the emergence of symptoms works in some cases, in many cases the emergence of symptoms can be quite delayed, or in some cases, associated with beneficial outcomes in some other aspect of cardiovascular risk. What is increasingly clear is an appreciation that a need for a more sophisticated approach to anticipation and surveillance of cardiovascular risk is emerging.

4. Infectious inflammatory diseases

A more central role for inflammation processes in the progression of chronic cardiovascular disease is becoming increasingly appreciated both as a direct source of the injury, and also as an aggravating condition that accelerates dysfunction in chronic disease [14–16]. There also are concerns that emergence of immunotherapies for a variety of conditions has the potential for adverse cardiovascular impact [80]. Some infections can produce an inflammatory response in the heart that ranges from subclinical to lethal [16]. Persons who become infected with the parasite *Trigonoscuta cruzi* may develop Chagas disease. The acute phase in many is characterized by asymptomatic, mild myocarditis, but a subset can also develop myocarditis that is severe enough to produce irreversible damage and heart failure. If the infection is not identified and treated, it persists in the system and may remain symptomatic for decades. However, 20–30% of chronically infected individuals will develop dilated cardiomyopathy, heart failure with or without arrhythmia, and are at increased risk for sudden cardiac death [12]. The prevalence of Chagas disease is considered endemic in Central America, South America and portions of the United States. A common cardiac feature of the disease is progressive loss of parasympathetic autonomic drive, creating a proarrhythmic substrate, more labile blood pressure control, and increased spasticity in the coronary microvasculature. Persistent sympathetic over-stimulation is known to cause multi-focal micro-infarctions, excess bioenergetic burden and mitochondrial dysfunction, leading to ROS induced DNA damage, apoptosis and progressive loss of function, similar to what has been described with catecholamine cardiotoxicity [12]. Particularly worrisome, however, is that sudden cardiac death is fairly common, and often occurs without previous signs or symptoms of advanced cardiomyopathy.

Similarly, infections caused by the Coxsackie B virus have had a known association with significant cardiovascular complications for over 60 years [81] and account for 25% of all myocarditis in young adults [82]. The early stages of infection can produce directly cytopathic effects, which can progress to a chronic, pathologic immune response if the virus persists, and in a majority of the patients who progress with chronic manifestations, development of a cardiac specific autoimmune response [83]. In fact, Coxsackie N infection has been a well-established mouse model for studying mechanisms associated with the development autoimmune-mediated myocarditis and heart failure (EAM: Experimental Autoimmune Myocarditis) [84].

More recently, the emergence of HIV and then the development of effective anti-retroviral therapies has led to an appreciation that there is an early onset of cardiovascular diseases, complicated by an inability to determine the extent to which the cardiovascular impact is the direct result of the virus, or if the primary factors are more related to the therapies used to treat the infection [13, 85]. HIV has been associated with early onset ischemic heart disease [86], but also with early onset heart failure in patients without evidence of significant coronary artery disease [87].

Most recently, the worldwide experience with SARS2-COVID19 has once again highlighted the capacity for acute infectious effects on exacerbating cardiovascular diseases, highlighted by the increased early mortality rates among those with pre-existing disease [17, 19]. Initially attributed to hypoxia-induced ischemia or hemodynamic failure secondary to the pulmonary impact of the virus, it was established quickly that there was direct cardiac infection [18], and that extrapulmonary effects of the virus were numerous [20, 21]. Given the cellular route of entry vias the Angiotensin 2 Receptor, and the widespread expression of the receptor throughout

the body, it should be no surprise really that many tissues would have been impacted by the infection [88]. Driven in part by what was seen largely as microvascular injury, increased thromboembolism, and the prevalence of the receptor in the vasculature, several strong reviews strongly suggested that COVID-19 should be considered as an endothelial disease [89, 90]. The presence of cardiac specific autoantibodies in COVID19 patients [38, 39] together with MRI studies suggesting persistent cardiac dysfunction in recovered COVID patients [91] tend to suggest that there is a larger, more multi-mechanistic cardiovascular profile for the disease [92, 93]. One study is particularly concerning. Ratchford and colleagues studied vascular function in previously healthy, active young adults who had tested positive for the infection but had exhibited only mild symptoms that were resolved quickly. One month after resolution of symptoms, the group (male and female) showed persistent and consistent reductions in vasodilator capacity compared to a matched cohort of control subjects that had never been infected with COVID [94].

By the end of 2022, there will be more than 50 million individuals in the US alone who will have recovered from a COVID19 infection. It was widely observed that when COVID infection occurred in individuals who already had significant cardiovascular disease, they were at higher risk [17, 19]. It is highly likely that COVID infection prior to the subsequent development of cardiovascular disease, even if not directly responsible for the cardiovascular injury, will be associated with increased mortality from whatever disease process does evolve. Determining the best methods for identifying who has the highest future risk, and then considering the possibility of prophylactic risk mitigation could be a significant challenge for the next generation [92, 93], but it strongly highlights the need for an increased appreciation for the potential role of prior infection as an aggravating risk.

5. Non-infectious systemic inflammatory diseases

Systemic Lupus Erythematosus (SLE) also commonly known as lupus, is a chronic autoimmune disease that can affect the joints, skin, brain, lungs, kidneys, and blood vessels. Widespread inflammation and tissue damage occur in these affected organs. Patients with SLE have been reported to have a higher risk of cardiovascular events compared to the general population. Common risk factors known to increase cardiovascular disease are smoking, hypertension, hyperlipidemia, and diabetes, which are also frequent comorbidities in individuals with lupus [24]. Adding to these traditional risk factors, the systemic and vascular inflammation that occurs in individuals with lupus cause the atherosclerotic process to accelerate.

Figure 1 summarizes data indicating that Individuals diagnosed with lupus experience cardiovascular events more frequently. Patients recently diagnosed with lupus had a 3-fold increased risk of myocardial infarction and a 2-fold increased risk of ischemic stroke in the next 5 years [22]. It was also noted that the relative risk for MI and Stroke both were significantly increased within the first year of the diagnosis with lupus. The hazard ratio in the first year for cardiovascular diseases was 5.63 (95% CI 4.02–7.87), for myocardial infarction was 6.47 (95% CI 4.42–9.47), and for stroke was 6.28 (95% CI 4.83–8.17) [22].

When assessing heart failure and its relationship with SLE, patients with lupus are found to have increased short-term and long-term risk of heart failure compared to those without SLE [25]. Due to an increased risk of heart failure within a year of a lupus diagnosis, there is a need for earlier cardiac monitoring in this population.

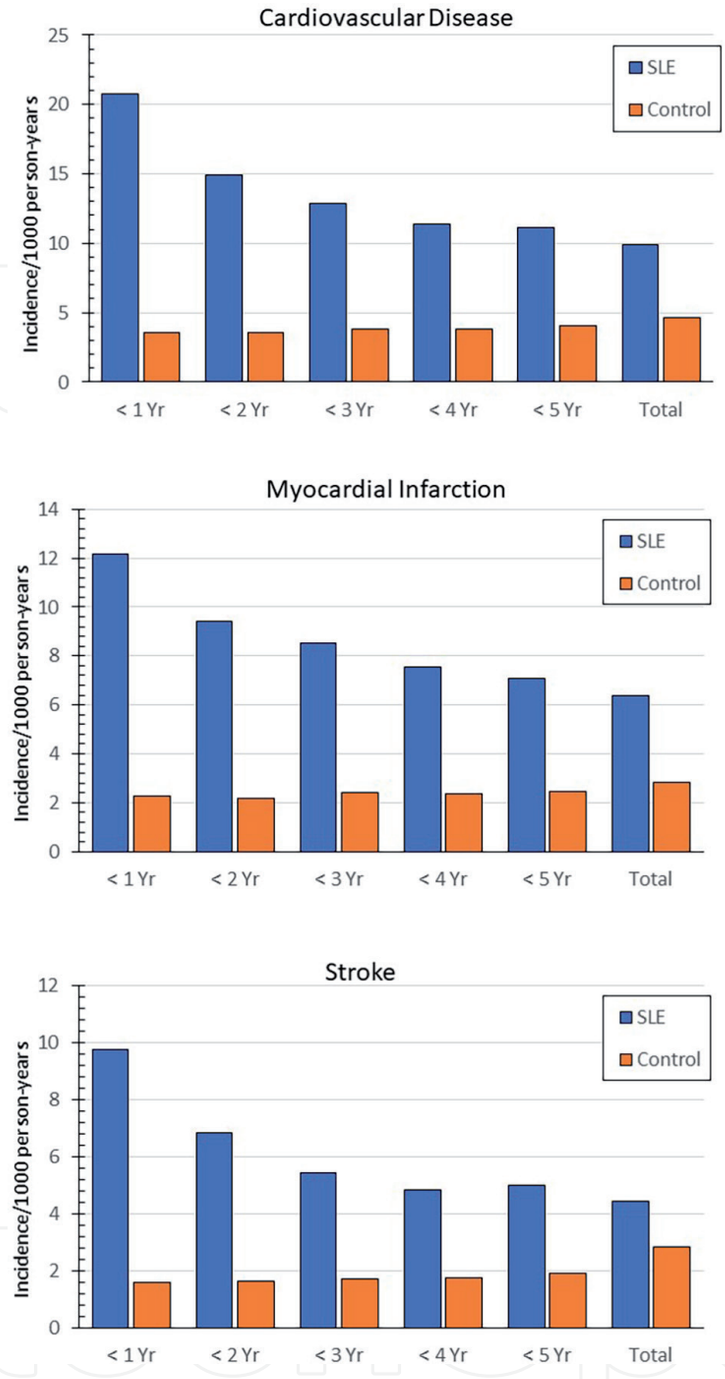

Figure 1.
Summary of cumulative incidence of cardiovascular disease (top panel), myocardial infarction (middle panel), or stroke (bottom panel) in individuals with systemic lupus Erythmatosis (SLE) compared to control (drawn from data in 22).

The median age for patients with SLE diagnosed with heart failure was 65 years old. When comparing this population of patients to those without lupus in any age group, the rate of heart failure still remained higher in those with lupus. Patients younger than the median age of 65 years had a higher rate of heart failure than older patients without lupus. This finding correlates with other research which suggests increased cardiovascular risk in younger patients who have lupus. Although there are no definite conclusions regarding the direct relationship between heart failure and lupus, there are several possible theories that extend beyond the common cardiovascular risk factors. For example, those with lupus who are also taking medications such as

glucocorticoids, NSAID's and hydroxychloroquine may enhance their chances of developing heart failure due to specific cardiotoxic drug interactions [25].

Interestingly, SLE affects women more often than men. The association between lupus and cardiovascular disease in women has been shown to be a major cause of premature mortality and morbidity. In a retrospective study looking at women who were diagnosed with lupus within the age range of 35–44 years old, the likelihood of myocardial infarction was increased 52 fold compared to the control group. Comparatively, women diagnosed with lupus who were 45–54 years old, showed a slight decline in the incidence rate for a myocardial infarction. Some plausible explanations include a prothrombic effects of estrogen in combination with hypertension, renal disease, and antiphospholipid antibodies in premenopausal women aged 35–44 years.

In contrast, women of menopausal age (45–54) have declining estrogen levels, which may play a role in providing a cardioprotective effect. While there was a decline in incidence rates for myocardial infarction in the 45–54-year-old women age group, the incidence rates rose again in women 55 and older. Women with SLE display an increase in the estrogen-to-androgen ratio which could explain the increased risk of the SLE during pregnancy and menses. Multivariate analysis of women diagnosed with SLE and having a cardiac event demonstrated that diagnosis of SLE at an older age (39 vs. 34), longer SLE duration (13 vs. 10 years), prolonged use of corticosteroids (11 vs. 7 years), diagnosis of hypercholesterolemia (18 vs. 4%), and postmenopausal status (48 vs. 29%) all contributed significantly to the increased risk of a cardiovascular event in women with SLE [23].

Asthma is a chronic inflammatory airway disease causing around 500,000 hospitalizations per year in America. Because there is a risk of overlapping effects in therapies, individuals with cardiovascular disease often are excluded from asthma studies, and individuals with asthma often are excluded from cardiovascular studies, making a relationship between asthma and cardiovascular disease more difficult to identify.

It is increasingly appreciated that the localized inflammatory airway process is supported by a more generalized systemic inflammatory state and inflammatory processes are major contributors to the evolution and severity of myocardial infarction and their associated reperfusion injuries [29–32]. As such, asthma may be considered as a potential risk factor for enhanced cardiac injury either with an acute myocardial infarction directly, or with reperfusion injury following revascularization therapy. The airway inflammatory response in asthma is driven by T Helper cells type 2 (Th2) and then followed by a systemic inflammatory response characterized by increases in pro-inflammatory biomarkers such as high sensitivity C-reactive protein (hsCRP) and Interleukin 6 (IL-6). Individuals with asthma have higher circulating levels of myeloperoxidase, consistent with higher potential for ROS generation. Asthma-triggered inflammation triggers endothelial release of Platelet-Activating Factor (PAF), which contributes significantly to the airway hyper-responsiveness in asthma, but also may play a role in the increased risk for an acute myocardial infarction in asthmatic patients [26].

Patients with asthma were found to have increased risk of myocardial infarction. Furthermore, the increased MI risk appears to "scale" with the severity of the underlying asthmatic disease. Those with active asthma (individuals on an asthmatic medication) had a risk that was 29% above the increased MI risk seen in patients classified as having non-active asthma (individuals not on asthma medication), but the

data are a bit more challenging since those with active asthma also were more likely to be older, diabetic and with increased BMI [26]. In a separate study, it was found that child-onset asthma did not increase the risk of a myocardial infarction, but adult-onset asthma was more likely associated with this elevated risk [27].

The elevated risk that is linked between active asthma and an acute myocardial infarction is primarily increased in the first week after an asthma exacerbation. During this study's reference period, the incident rate of MI was 25/100 person-years, but increased to 120.1/100 person-years in the 1–7 day risk period following an asthma exacerbation. In the 8–14 day risk period after an asthma exacerbation, the incident rate dropped to 50.1/100 person-years and further dropped to 38/100 person-years in the 15–28 days post asthma exacerbation [28].

There are many theories linking asthma exacerbation to increased risk of acute myocardial infarction. Acute respiratory infections are the most common cause of asthma exacerbation. Asthma propagates inflammatory pathways and cytokines leading to systemic vascular inflammation and platelet activation, fibrinolysis inhibition, and elevated CRP. Markers such as hsCRP will cause other inflammatory regulators to be upregulated resulting in leukocyte adhesion to the arterial endothelium. Arterial thrombosis results from platelet activation and endothelial dysfunction. The release of inflammatory cells resulting in the accumulation of neutrophils, platelets, fibrin, and red blood cells are characteristic of a Type 1 myocardial infarction [28]. Experimental studies in our lab, using a rag-weed sensitization to produce a hyper-responsive allergic airway model, demonstrated clearly that myocardial ischemia and reperfusion induced larger infarctions, that were associated with higher inflammatory infiltrates, and increased inducible expression of pro-inflammatory adhesion molecules in the contrary vascular that was present only on reperfusion, but was not expressed under basal sensitized conditions [95–97].

6. Environmental agents in cardiovascular risk

The relationship between air pollution and negative health outcomes has been well established in the literature over the years, first reported with outcomes following the Great London Smog of 1952 when health crises were observed following the event. While the initial correlation was thought to be tied to the pulmonary system, years later the reports were re-examined and showed that cardiac mortality – not pulmonary – was more directly associated with the increase in mortality [98]. In addition, the reexamination has prompted numerous others to delve further into this topic and with technological advancements, research has expanded to include other potential sources of cardiac toxicity such as nanoparticles of various heavy metals. Along with the pulmonary diseases commonly associated with these materials, acute myocardial infarction, atherosclerosis, and increased peripheral resistance have all been implicated with increased exposure [34, 35].

Such findings prompted the WHO to release air pollution guidelines in 2006 in hopes of reducing acute and chronic disease associated with different air pollutants worldwide. Air pollutants can be placed into two broad categories, natural phenomena and human activities [99–101]. Human activities are related to industrial processes and account for pollutants like CO and SO2, which cause most of the harmful adverse health effects. Natural phenomena on the other hand are related to volcanoes, wildfires, and land dust. In addition to this gaseous type of air pollution, particulate

matters (PM) are a major player in negative health outcomes. The two major categories of PM are based on size, which are PM2.5 and PM10 – each having a different symptom profile of which the mechanism of action has not completely been resolved. However, with size, the aerodynamic diameter varies. PM10 have an AD range from 2.5 to 10 μm which allows for deposition into nasal and upper airways while PM2.5 have an AD range of less than 2.5 and less than 0.1 μm, which allows them to penetrate lung alveoli and gain access to the bloodstream [33–35].

Likewise, research into the health effects of nanoparticles is more novel and has been less refined; thus, regulations regarding exposure to these materials are not fully resolved. However, there have been numerous studies highlighting the correlation between exposure to these materials and the resultant impacts on cardiovascular function. Six of the most common metal nanoparticles are titanium oxide, zinc oxide, silver, iron oxide, carbon and silicon oxide nanoparticles. Of this list, iron oxide, carbon, and silicon oxide nanoparticles are not only used commercially, but also are used for cancer therapies, drug delivery, as well as other diagnostics. Most of these nanoparticles are associated with increasing the generation of reactive oxygen species or are pro-inflammatory, thus increasing pro-inflammatory cytokines [103].

6.1 Ambient particulate matter

While PM10 has adverse associated health effects, acute exposure to PM2.5 resulted in higher death rate related to cardiovascular disease. Short term exposure to particulate matter can result in induction of the systemic oxidation, inflammation, and increased platelet reactivity as result of elevated serum fibrinogen. However, not all people are impacted to the same magnitude by exposure to these pollutants. Those with pre-existing cardiovascular disease, diabetes, smoking status, age, and pulmonary disease like COPD can have increased responses to exposure.

The relationship between ambient particulates has been most heavily studied in the context of impact on blood pressure. According to a study by Gold et al., with every ~5–6 μg/m^3 increase in PM2.5, there was a significant increase in cardiovascular disease ranging from 0.5 to 1.5% [104]. In addition, studies have shown that increases in PM2.5 are associated with increases in systolic and diastolic blood pressure. Brook demonstrated that in a period of 5 days in Boston, MA, an increase of 10.5 μg/m^3 in PM2.5 resulted in a 2.8 mmHg increase in SBP and 2.7 mmHg increase in DBP [98]. The increased blood pressure would be consistent with impaired endothelial reactivity and enhanced constrictor responses that we demonstrated in experimental animals exposed to ambient particulates [105–107]. While is tempting to consider that the effects are attributable to increased sympathetic autonomic balance, we also have demonstrated that in older, heart-failure prone animals, there was increased risk of heart failure exacerbation, but increased risk of brady arrhythmias, and increased cardiac parasympathetic tone [108].

Even when ambient particulates do not alter the incidence of event, we and others have demonstrated that prior exposure can increase the severity of infarction, reduce the effectiveness of reperfusion, and aggravate progression of heart failure [33–35, 99–101, 105–108]. We also have demonstrated that short, episodic exposure to particulates beginning 4–7 days after an ischemia–reperfusion event was associated with increased adverse remodeling in the ventricle, increased fibrosis and decreased cardiac function 30 days post MI, compared to un-exposed animals (**Figure 2**).

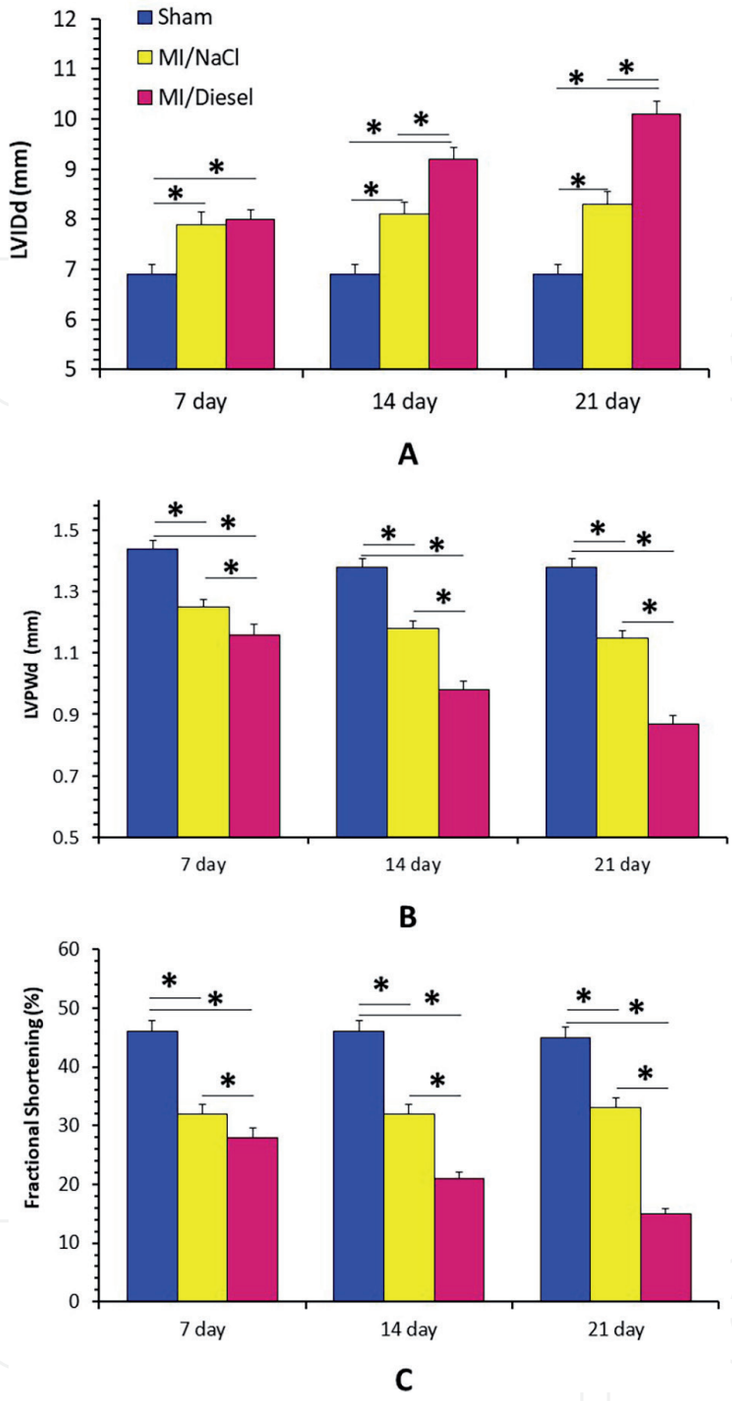

Figure 2.
Summary select echocardiographic findings on days 7, 14 ad 21 after LAD occlusion in a rat model of infarction in sham animals (blue), those with infarction/vehicle exposure (yellow), and those with MI and subsequent exposure to diesel particle on days 4, 11 and 18 (red) following myocardial infraction) on diesel particle exposure on days 4, 11 and 18. MI produced a dilation of the LV that was stable in the sham group, but progressively increased in the diesel exposure group (panel a). MI produced a thinning of the infarcted myocardial wall that was relatively stable in the sham group but progressed substantially in the diesel exposed group (panel B). Consistent with the structural changes, fractional shortening progressively decreased in the diesel group, while the decrease in the sham group was stable. (indicates $p < 0.05$ for the comparison indicated; previously unpublished data).*

6.2 Engineered nanomaterials (nanoparticles)

Nanomaterials have wide and varied commercial applications ranging from athletic equipment to clothing, to sunscreens, to drug delivery systems. Studies

Nanoparticle	Increased	Decreased
Titanium Dioxide	CK-MB	SOD
	Troponin T	GR
	LDH	GST
	Myoglobin	APX
	CK	
	Caspase 3	
	Cyto C release	
	DNA tail length	
Zinc Oxide	CK-MB	Heart rate
	Troponin T	
	CRP	
	IL-6	
	Myoglobin	
	TNF-alpha	
	Caspase-3	
	DNA tail length	
Silver	SOD	FGF-2 expression
	CAT	
	GSH	
	VEGFA expression	
Carbon	ET-1	GSH
	ACE	BFGF expression
	MCP-1	
	IL-6	
	IL-10	
	IO-12	
Silicon Oxide	CK-MB	MEF2C
	Troponin T	NKX2.5
	LDH	
	CRP	
	ET-1	
	D-dimer	
	IL-1 beta	
	TNF-alpha	
	IL-6	
	Inhibition p-VEGFR2	
	inhibition p-ERK1/2	
Iron Oxide	Vascular permeability	Heart rate
		cell proliferation

Table 1.
Summary of active mediators increased in blood or tissue following exposure to various forms of nanomaterials and known to have cardiac effects (assembled from data summarized in 103).

regarding the impact of nanoparticles on the cardiovascular system have shown various mechanisms of action. Three, general, well-accepted mechanisms for pulmonary exposure to nanoparticles have been proposed and demonstrated in several studies: 1) nanoparticles trigger lung-mediated systemic inflammatory response or oxidative stress – altering cardiac functioning 2) translocation of the nanoparticles from the lungs to the circulatory system through the alveoli (as seen with PM2.5) 3) alteration through a neurogenic pathway. These studies demonstrate the deleterious effects on the cardiovascular system from the nanoparticles though the exact mechanisms are not completely clear and likely involve a combination of the general proposed mechanisms [102]. The particular effect for any given nanoparticle varies as a function of its composition and is summarized in **Table 1**.

Iron oxide nanoparticles are commonly used in medicinal applications like drug and gene therapy delivery and cancer therapy [103]. The exposure to iron oxides can result in increased vascular permeability and decreased acute heart rate. However, the mechanism of action is not completely resolved though iron oxides are associated with oxidative damage through the generation of ROS.

Carbon nanoparticles are extremely versatile, resulting in them being found in a large range of substances. In medicine, carbon nanoparticles can be found in cancer therapies, drug delivery, gene therapy, sensors, and plastics. Their small particle size, large surface area, and association with catalytic metals are some of the reasons these nanoparticles (SWCNTs) are considered toxic agents which induce ROS generation and oxidative damage via the Fenton reaction. Exposure to these particles is often through the pulmonary route and due to their size, can be transported to secondary organs. Toxic effects can be oxidative damage and recruitment of inflammatory factors as seen in bronchoalveolar lavage fluids. These effects commonly present as decreases in thiol contents, elevation in lipid-peroxidation produces, and increase in liver and heart inflammatory markers like ET-1, ACE, MCP-1, IL-6, IL-10, and IL-12 [103]. Experimental studies of cardiac ischemia and reperfusion validate the increased risk of cardiac injury and the role of induced inflammatory pathways [109–113].

Silicon oxide nanoparticles are a commonly used commercial nanoparticle as well as their use in drug delivery, gene therapy, and diagnosis. These small particles readily mix in air and the common method of exposure is occupational during production. Ironically, silica NPs have recently been used for adenosine delivery for its cardioprotective effects [103]. However, these nanoparticles can also produce ROS which can lead to the release of cytokines and subsequently apoptosis. Study results in mice show an increase of CRP, TNF-alpha, and IL-6. Cardiac markers like ET-1, D-dimer, LDH, CK-MB, and eTNT increased after the silica exposure [103].

Many of the compounds discussed in this chapter have become ubiquitous today with increasing use of nanoparticles in products and ongoing air pollution of the industrialized world. Though strong correlations exist between common pollutants and cardiotoxicity, further research into the exact mechanisms, safe levels of exposure, and chronic effects need to continue.

7. Autoimmune mechanisms as an emerging source of cardiovascular risk

Idiopathic dilated cardiomyopathy (DCM) is a myocardial disease characterized by a progressive depression of myocardial function and ventricular dilation. DCM is the leading cause of severe heart failure, and the most common cause for heart

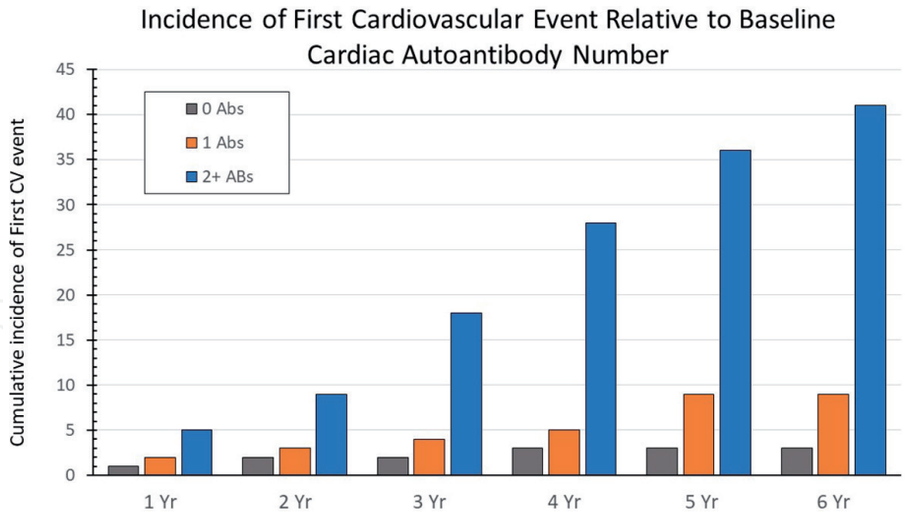

Figure 3.
Cumulative 6 year incidence of a first cardiovascular event in patients with diabetes as a function of pre-existing cardiac autoantibody number at the onset of the study (drawn from data in [117]).

transplantation. Chronic heart failure remains one of the most important sources of "all cause" morbidity and mortality, with a high frequency of hospital readmission, and a total health care expenditure burden more than twice the cost for all forms of cancer combined. The causes of DCM remain unclear, but research has been directed along three major avenues: genetic factors, viral persistence, and immunological abnormalities, including autoimmunity. Myocarditis is an inflammatory disease and some reports suggest that myocarditis and DCM represent acute and chronic stages of organ-specific autoimmune disease of the myocardium.

General characteristics supporting an autoimmune hypothesis are familial aggregation, a weak association with HLA-DR4, abnormal expression of HLA class II antigens on cardiac endothelium on endomyocardial biopsy, and the presence of organ and disease specific cardiac IgG class autoantibodies in the sera of affected patients and symptom free relatives. Supporting the genetic associations are several parallel lines of evidence. The incidence of cardiac complications is significantly higher in patients with Type I diabetes than it is in with other forms of diabetes. Type 1 diabetes is an autoimmune disease and relationship between Type 1 diabetes and autoimmune myocarditis has been suggested [114]. Similarly, Celiac disease, also with autoimmune components, has been associated with autoimmune myocarditis [115]. Type I diabetes and celiac disease, both autoimmune, have been associated with a high prevalence in Saudi children [116].

The incidence of cardiac complications is significantly higher in patients with Type I diabetes than it is in with other forms of diabetes, and the presence of cardiac autoantibodies in diabetic patients is strongly associated with the probability of subsequent cardiac event (**Figure 3**). Autoantibodies are present in between 30 and 90% of all patients with DCM [118–121]. Maguy has shown recently that there is an autoantibody signature associated with sudden cardiac arrest [36], the presence of autoantibodies against HSP65 is strongly associated with post-operative atrial fibrillation [126] and cardiac autoantibodies have been suggested as significant mediators in COVID related cardiac dysfunction and a possible source of increased cardiovascular risk in COVD survivors [38, 39]. Cardiac autoantibodies are present in at least 10% of post-myocardial infarction patients and may explain disproportionate loss of function in a subset of patients relative to that predicated on the ischemic injury

per se. Repeated infarctions, stabilized by repeated revascularization may also be repeated episodes for sensitization and expansion of an autoimmune signal leading to increased rates of deteriorating function and heart failure [39].

The possibility that an auto-immune process could complicate post-infraction recovery has been suggested for more than 40 years [122]. High titers of autoantibodies to the beta-1 adrenergic receptor were identified in patients with Chagas disease. The beta-1 adrenergic autoantibody is the most studied so far. It meets Witebsky's postulates for indirect and direct autoimmune etiology. The autoantibody is stimulatory, ultimately leading to increased apoptosis sufficient to cause loss of function. Those results are consistent with models of catecholamine cardiotoxicity and with premature DCM in transgenic mice with cardiac specific overexpression of beta-1 adrenergic receptors. Signaling may be ERK1/2 dependent, but some evidence suggests that the mechanism is independent/different from standard isoproterenol stimulated beta-adrenergic responses [118–120]. Kaya [37] has demonstrated a strong association between cardiac autoantibodies and heart failure, as have others [124, 125], with an emphasis on the myosin molecules as the primary antigenic drive [118–121, 125, 127, 128]. Serum levels of troponin are the single best indicator of myocardial injury, but immunizing mice with Troponin I caused T-cell activation and cardiac inflammation with elevated RANTES, MCP-1, MIP1-alpha, MIP1-beta, MIP2, T-cell activation gene 3, CCR1, CCR2 and CCR5. It's clear that the cardiac autoimmune response can be both antibody and T cell mediated [129]. General anti-inflammatory effects (carvedilol, prednisone) or macrophage dependent inflammation (Olmesartan) all have shown efficacy is reducing the progression in experimental models of DCM.

8. Summary

It appears that many of the risk factors generally associated with cardiovascular risk, like diabetes, endothelial dysfunction, sympathetic over stimulation, all may have an under- appreciated component that is immune/inflammation mediated, and that may include an autoimmune component. Systemic inflammatory diseases without infectious triggers, airborne particles, manufactured nanoparticles, and some therapeutics used in the treatment of other diseases all may exaggerate the consequences of a cardiovascular inflammatory reaction. Some compounds, like doxorubicin, have well established mechanistic profiles that may provide insight as to how each of the mediators is adding to the cardiovascular risk, or injury expansion progression profile. It seems clear that future management of cardiovascular risk will need to become more personalized, and with greater appreciation for a much larger menu of contributing factors, all of which will require development of better biomarker screens than what are currently in use. Immunomodulating agents likely will also have an increasingly important role in limiting progression of heart failure.

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