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Cardiovascular Disease Following Hematopoietic Stem Cell Transplantation: Pathogenesis, Detection, and the Cardioprotective Role of Aerobic Training

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Abstract

Advances in hematopoietic cell transplantation (HCT) techniques and supportive care strategies have led to dramatic improvements in relapse mortality in patients with high-risk hematological malignancies. These improvements, however, conversely increase the risk of late-occurring non-cancer competing causes, mostly cardiovascular disease (CVD). HCT recipients have a significantly increased risk of CVD-specific mortality, including elevated incidence of coronary artery disease (CAD), cerebrovascular disease, and heart failure (HF) compared to age-matched counterparts. Accordingly, there is an urgent need to identify techniques for the detection of early CVD in HCT patients to inform early prevention strategies. Aerobic training (AT) is established as the cornerstone of primary and secondary disease prevention in multiple clinical settings, and may confer similar benefits in HCT patients at high-risk of CVD. The potential benefits of AT either before, immediately after, or in the months / years following HCT have received limited attention. Here, we discuss the risk and extent of CVD in adult HCT patients, highlight novel tools for early detection of CVD, and review existing evidence in oncology and non-oncology populations supporting the efficacy of AT to attenuate HCT-induced CVD. This knowledge can be utilized to optimize treatment, while minimizing CVD risk in individuals with hematological malignancies undergoing HCT.

Keywords

cardiovascular disease; exercise; detection; hematopoietic stem cell transplantation

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Conflict of Interest

The authors declare no conflicts of interest.

1.0 Introduction

More than 60,000 individuals are expected to undergo allogeneic or autologous hematopoietic cell transplantation (HCT) annually worldwide for treatment of hematological malignancies.[1] Advances in transplantation techniques and supportive care strategies have dramatically improved cancer specific survival rates in the past 30 years; 10-year survival rates now exceed 80% following HCT.[1,2] However, with prolonged survival, the risk of treatment-induced late-occurring morbidity and mortality from competing (non-relapse mortality; NRM) causes has substantially increased. Specifically, in comparison with age-sex-matched counterparts from non-oncology settings, HCT recipients have a 2.3 to 4.0-fold increased risk of cardiovascular-specific mortality, a 0.6 to 5.6-fold increased risk of cardiovascular disease (CVD) including coronary artery disease (CAD), cerebrovascular disease, and heart failure (HF), and a 7.0 to 15.9-fold increased risk of CVD risk factors such as hypertension, diabetes, and dyslipidemia.[3–11] This excess CVD risk[23–26] is likely a consequence of acute direct (i.e., direct cytotoxic/radiation-induced injury) as well as indirect (i.e., impacts secondary to therapy such as deconditioning) effects of HCT therapy.[12] A research agenda that comprehensively and systematically tackles the issues related to CVD prevalence, pathogenesis, detection, and treatment in HCT recipients is urgently required.

Current cardiovascular screening and monitoring guidelines for post-HCT adult survivors recommend yearly cardiovascular risk factor screening, with assessment of global cardiac function (left ventricular ejection fraction, LVEF), and resting electrocardiography (ECG) in patients at high-risk for cardiovascular complications.[13] However, HCT-specific recommendations are based on retrospective studies that have identified cardiovascular complications in long-term survivors rather than optimal screening strategies developed by US Preventative Services Taskforce for the general population.[13,14] Moreover, assessment of resting LVEF and ECG in high risk patients may fail to detect early signs of alterations in cardiovascular morphology, function, and coronary artery narrowing,[15,16] suggesting that complementary stratification tools are required to fully evaluate CVD risk and identify those individuals at highest risk of future events.

Interventions that prevent and/or treat CVD risk factors and CVD in HCT patients will be of the utmost importance to mitigate CVD-specific mortality. In particular, an approach taking into account four intervention time points is needed:[16] (1) primordial prevention (prophylactic therapy given before or during HCT to prevent anticipated injury), (2) primary prevention (therapy provided to selected patients with early signs of myocardial and/or coronary vascular damage to treat injury and prevent progression), (3) secondary prevention (therapy provided after the detection of LVEF decline or coronary artery calcification to treat impairment), and (4) tertiary treatment (therapy provided after detection of HF or CAD clinical symptoms). Aerobic training (AT) is established as the cornerstone of disease prevention and treatment in multiple clinical settings,[17] and is well documented to improve insulin sensitivity, decrease lipids, and lower blood pressure with concomitant improvements in cardiovascular function and overall mortality in non-oncology settings.[18–21] Similarly, promising data in the oncology setting indicates that AT is safe and is associated with significant improvements in CVD risk factors.[22,23] AT may confer similar benefits in HCT

patients at high risk of CVD; however, the potential cardioprotective properties of AT in the context of HCT have received limited attention.

Here, we briefly discuss the risk and extent of CVD in adult HCT recipients, highlight novel tools for early detection of CVD, and review existing evidence in oncology and non-oncology populations supporting the potential role of AT as a viable therapeutic modality to abate/attenuate HCT-associated CVD.

2.0 Accelerated CVD Following HCT: Current Evidence

For a comprehensive overview of CVD risk factors and CVD in HCT patients, the reader is referred to prior excellent reviews;[4,15,24] a summary of CVD following HCT is provided in Table 1. In the following sections we briefly review the incidence of CVD risk factors, CVD, and CVD-specific mortality.

2.1 Prevalence of CVD Risk Factors

The third National Cholesterol Education Program Adult Treatment Panel III (ATP III) report indicates that the age-adjusted prevalence of CVD risk factors such as hypertension, diabetes, and dyslipidemia in US adults is approximately 22%.[25] Importantly, the same level and extent of CVD risk factor prevalence occurs at much earlier age following HCT. In a study that assessed the 10-year cumulative incidence, Armenian et al.[7] found the prevalence of hypertension, diabetes, and dyslipidemia was 43.0%, 18.7%, and 48.3% respectively, in 1087 HCT recipients (median age of HCT: 44 years) compared to 34.6%, 8.5%, and 40.0% in the general population. Furthermore, Chow et al.[26] found that compared to pre-HCT, use of antihypertensives and diabetes medications was significantly higher 1-year post-HCT (6.7% vs. 19.6% and 4.1% vs. 12.9%, respectively) in 1,379 HCT recipients (median age at time of HCT: 40 years), while Blaser et al.[27] reported that a mean of two years following HCT, 73.4% and 72.5% had hypercholesterolemia and hypertryglyceridemia respectively in 761 HCT survivors (median age at transplantation: 49 years). These findings indicate there is a characteristic pattern of changes in CVD risk profiles early after HCT,[26] which persist for up to 10 years.[7] Importantly, there is no reason to expect that these rates will improve over time, likely making patients more susceptible to normal pathologies of aging.

2.2 Prevalence of CVD and CVD-Related Mortality

In the non-oncology setting, the presence of one or more comorbidities such as hypertension, diabetes, and dyslipidemia increases the risk of CVD by 29% to 67%.[28,29] Thus, the heightened prevalence of CVD risk factors in HCT survivors likely increases risk of developing CVD. Indeed, in a cohort of 1244 HCT survivors (median age at HCT: 45; median follow-up 5 years), Armenian and colleagues[8] reported that HCT survivors treated with high-dose anthracyclines are at a nearly 5-fold risk of HF when compared to age- and sex-matched individuals from the general population. The risk of HF increased substantially in patients with hypertension (OR: 35.3) or diabetes (OR: 26.8).[8] The risk of CAD is up to 40% higher in HCT patients compared to matched counterparts.[30–32] For example, Chow et al.[26] examined the risk of developing CAD in 1379 HCT survivors (median age at HCT: 40 years; median follow up: 7 years); patients with hypertension or diabetes had 3.6-fold and

2.8-fold higher risk, respectively. Importantly, there appears to be premature onset of CVD in HCT survivors. Tichelli and colleagues[33] reported that the median age of first CVD event (cerebral, coronary, or peripheral ischemic event) was 49 years in 265 HCT patients (median age of HCT: 27 years); almost 20 years earlier than the first CVD event reported in the general population from the Framingham Heart Study (67 years).[28,34] A larger, multicenter study in 548 HCT patients (median age of HCT: 27 years; median follow-up: 9 years) also reported premature development of overt CVD (cerebral, coronary, or peripheral ischemic event) after HCT; the median age of the first CVD event was 54 years.[30] Accordingly, evidence suggests that not only is there is a greater magnitude of CVD in HCT patients, but also that the occurrence of CVD occurs earlier.

Not surprisingly, the risk of premature CVD-related mortality is significantly higher in HCT recipients.[5,35] The Bone Marrow Transplant Survivor Study[35,36] evaluated mortality in 1479 HCT patients (median age at HCT: 26 years; median follow-up: 10 years); results indicated that there is a 2–4-fold increased risk of CVD death among HCT survivors compared with the general population. Chow et al.[5] examined CVD-related mortality in 1491 HCT recipients (median age at HCT: 41 years), and found that transplant recipients experienced nearly a 4-fold increased risk of CVD death (adjusted incidence rate difference, 3.6 per 1000 person-years [95% CI, 1.7 to 5.5]) compared with an age-sex-matched population cohort. Together, these findings provide mounting credence to the notion of HCT as a model of ‘accelerated CVD phenotype’ and provide compelling rationale to examine HCT-related CVD sequelae.

3.0 Pathogenesis of HCT-Induced Accelerated CVD

3.1 ‘Direct’ Cardiovascular Injury

Cardiovascular injury may occur during treatment of primary malignancy (anthracycline or radiation exposure prior to relapse or during primary remission), or during HCT-associated therapeutic exposures (total-body irradiation (TBI) and/or high dose alkylating exposures to obtain immuno- and myelosuppression and to create space in the marrow to allow engraftment of transplanted cells).[36] Radiation and/or chemotherapy causes direct cardiovascular injury contributing to the manifestation of two distinct but related forms of CVD morbidity and mortality: cardiomyopathy associated with HF, and CAD.[37]

3.1.1 Therapy-related HF—We have previously summarized the potential mechanisms underlying chemotherapy-induced cardiovascular alterations (Figure 1A; **modified from**[38–40]). In brief, anthracycline-induced generation of reactive oxygen species (ROS) are a primary contributor to cardiotoxicity via activation of multiple pathways including: the tumor suppressor protein, p53,[41,42] and suppression of sarcomere protein synthesis through depletion of GATA-4 dependent gene expression[43,44] and cardiac progenitor cells (CPCs).[45,46] The resulting cardiac myocyte apoptosis ultimately contributes to impairments in LV systolic (contractile) and diastolic (lusitropic) function,[47–49] and elevated afterload (increased wall stress).[50]

3.1.2 Therapy-related CAD—Oxidative stress and up regulation of pro-inflammatory molecules[51,52] are key pathways thought to contribute to radiation-induced CAD (Figure

1B).[53,54] Evidence suggests that activation of the nuclear transcription factor NF-κB[55] or downregulation of endothelial cell-specific p53[56] induce oxidative stress and chronic inflammation, which ultimately up-regulates numerous pathways pertinent to vascular disease, including matrix metalloproteinases, adhesion molecules, pro-inflammatory cytokines, while inactivating vasculoprotective nitric oxide.[57–59] Eventually, coronary vascular injury characterized by endothelial cell proliferation, intimal thickening, medial scarring, lipid deposits and adventitial fibrosis may occur.[60–63]

3.2 'Indirect' Cardiovascular Injury

Direct insults may occur in conjunction with indirect injury resulting from pre-existing CVD risk factors at diagnosis, lifestyle modifications during and following HCT, and HCT-specific complications such as graft versus host disease (GVHD) and type of transplantation (autologous vs. allogenic). Indeed, the incidence of pre-HCT comorbidities such as hypertension, diabetes, and hyperlipidemia are reported to be as high as 25%,[11] 5%,[11] 32%,[27] respectively. Pre-HCT CVD risk profile is, in turn, a strong predictor of post-HCT CVD risk, with ≥2 of the following factors: obesity, dyslipidemia, hypertension, and diabetes associated with a 5.2-fold increased risk of CAD or cerebrovascular disease.[10]

3.2.1 Lifestyle Modifications—Acute and chronic alterations in lifestyle (e.g., deconditioning, weight gain) also contribute to increased CVD risk. Immediately following HCT, patients undergo ≥30 days of inpatient bed rest. The impact of acute inpatient bed rest on CVD sequelae has not been examined in HCT patients; however, the changes in cardiovascular structure and function during short- and long-term bed rest have been under investigation for many years. A landmark 1966 study by Saltin and colleagues[64] found that 20 days of bed rest in healthy young males caused a 27% decrease in peak oxygen consumption (VO_{2peak}), a 25% decrease in stroke volume, a 7% decrease in left ventricular mass, and a 20% increase in resting heart rate. Remarkably, a 30-year follow-up of subjects previously studied in 1966 established that 3 weeks of bed rest at 20 years of age had a more profound impact on VO_{2peak} than did 3 decades of aging.[65] Importantly, VO_{2peak} is inversely correlated with cardiovascular and all-cause mortality in a broad range of adult populations,[66–69] while Cooney et al.[70] found that among 10,519 men and 11,334 women followed in a Finish population-based study, a 15 beat increase in resting heart rate was associated with a 24% and 32% increase in future cardiovascular death in men and women, respectively. Other acute disuse-induced cardiovascular alterations include significant declines in left ventricular systolic and diastolic function,[71–73] marked conduit artery wall thickening,[74] and endothelial dysfunction.[75] Studies characterizing both the acute cardiovascular effects of bed rest and the long-term consequences of disuse-induced changes in cardiovascular structure and function are now required in HCT patients.

Epidemiological evidence indicates that long-term physical inactivity increases the relative risk of CAD, stroke, and hypertension, by 45%, 60%, and 30%, respectively.[76] Initial evidence suggests that physical inactivity may also contribute to CVD risk in HCT patients. Tichelli and colleagues[30] reported that among 548 HCT survivors, patients with an arterial event (cerebral, coronary, or peripheral ischemia) were more often sedentary (75% vs. 44%). Chow et al.[77] compared 2362 HCT survivors (median age, 55.9 years; median 10.8 years

since HCT) with a general population sample (National Health and Nutrition Examination Survey [NHANES]; n = 1192), and found that HCT survivors with CVD were less likely to be currently physically active (ORs, 1.7 to 3.1).

3.2.2 HCT-specific Complications—Graft versus host disease (GVHD) has been hypothesized to contribute to increased CVD risk, where an allo-immune response results in a sequential influx of lymphocytes, macrophages and neutrophils.[78] Such an inflammatory environment promotes plaque instability, ultimately resulting in plaque rupture, thrombus formation, and infarction.[79] Indeed, biomarkers of endothelial injury such as von Willebrand Factor (vWF) show a close relation to chronic GVHD, suggesting that an immunological mechanism may result in chronic endothelial dysfunction and accelerated atherosclerosis.[80]

After accounting for effects of active chronic GVHD, allogeneic HCT survivors appear to have an increased risk of developing hypertension, dyslipidemia, and diabetes which predispose towards more serious CVD compared with other cancer survivors or the general population.[3,30,33] For example, Armenian and colleagues[7] examined the incidence and predictors of CVD risk factors and subsequent CVD in 1885 1+year survivors of HCT (median age, 44.4 years; median 5.9 years since HCT), and reported that allogeneic HCT recipients were at a significantly higher risk of hypertension, diabetes, and dyslipidemia compared with autologous HCT recipients. Furthermore, in 1491 HCT recipients (median age at HCT: 41 years), Chow et al.[5] found that although most outcomes did not markedly differ between patients who received allogeneic versus autologous grafts, the hazard of hypertension was increased after allogeneic HCT (HR,1.8 [CI, 1.3 to 2.5]). Although the mechanisms underlying HCT allogenic-specific CVD have not yet been well described, certain generalizations can be extrapolated from solid organ transplant recipients where immunosuppressive agents (including glucocorticoids, calcineurin inhibitors, and sirolimus) are well-known to contribute to CVD pathogenesis.[81 82–84] For instance, dyslipidemia has been reported in up to 80% of solid-organ transplantation patients on immunosuppressive agents, and insulin resistance and hypertension are frequently encountered side-effects of immunosuppressive medications.[7,11,85]

3.3 ‘Multiple-Hit’ Hypothesis

As HCT patients progress through treatment regimens, they are subjected to multiple cardiovascular insults coupled with lifestyle perturbations that collectively leave patients with significantly elevated risk of CVD risk factors, overt CVD, and ultimately, CVD-related mortality (Figure 2). There is currently limited data available to support the contention of the “multiple hit” in HCT patients. Future, large-scale, prospective studies are urgently required to comprehensively evaluate CVD sequelae associated with HCT therapy.

4.0 CVD Detection

The assumption behind cardiovascular screening is that detection of subclinical disease would result in interventions that may delay or even prevent the onset of clinically apparent disease; however, this notion has not been rigorously investigated in HCT recipients. Current HCT-specific recommendations for yearly fasting lipid and blood sugar assessment in all HCT patients, and evaluation of global cardiac function (LVEF) and ECG in symptomatic

patients,[13] are based on retrospective studies that have identified CVD risk factors and overt CVD in long-term survivors rather than screening strategies developed by US Preventative Services Taskforce for the general population.[13,14] Accordingly, current HCT screening tools may fail to detect early signs of CVD pathogenesis when interventions would be most beneficial.[15] Early identification of patients at high-risk of HCT-induced CVD may optimize long-term overall survival after HCT. To this end, novel assessment techniques incorporating exercise testing, blood and imaging markers could enable the detection of early CVD, and thus provide unique insight into both the type and timing of subsequent interventional approaches. For example, reduced strain and strain rate revealed impaired myocardial function prior to LVEF decline[86,87] and heart failure symptoms [88] in patients treated with anthracycline-containing therapy. Optimal timing for subclinical cardiac assessments in HCT recipients remains undetermined, but emerging evidence suggests it has a potential role for predicting therapy-related CVD that merits further investigation. Indeed, in the contexts of CAD, HF, and diabetes, identification of cardiovascular phenotypes has initiated research into individualization and optimization of exercise training programs based on morphology and function [89–93] – concepts that could be readily applied in the HCT setting. Here, we briefly review evidence detailing novel methods of CVD detection.

4.1 Imaging-Based Approaches

4.1.1 Echocardiography—The use of more sensitive and specific echocardiographic techniques to evaluate LV function may address the current limitations of conventional cardiac imaging techniques employed in the oncology setting for detection of HF. Specifically, speckle tracking assessment of systolic function with strain and strain rate is more sensitive for detecting altered myocardial performance beyond LVEF[94] and, in the case of strain rate, less susceptible to alterations in loading conditions compared to LVEF.[95] In the clinical setting, reduced strain and strain rate revealed impaired myocardial function prior to LVEF decline[86,87,96] and HF symptoms[88] in conventionally treated cancer patients treated with anthracycline-containing therapy. Changes in LV torsion have also been shown to improve CVD risk prediction in several cardiac patient populations.[97–99] Novel indices of diastolic function such as tissue Doppler imaging (TDI), flow propagation velocity (Vp), and diastolic strain and strain rate measures may also provide early markers of alterations in cardiac function. In anthracycline-induced cardiotoxicity, changes in diastolic function have been shown to precede systolic dysfunction.[100–102] Optimal echocardiography assessment techniques remain undetermined in HCT patients; studies are needed to specifically define the potential role of novel echocardiography techniques for predicting therapy-related HF.

4.1.2 Computer Tomographic (CT)-based Imaging—In non-oncology populations, CT-based imaging (coronary artery calcium scoring, CT angiography [CTA]) has emerged as an accurate, non-invasive measure of CAD risk. Over the last decade, multiple retrospective cohort studies have demonstrated the strong independent prognostic value of coronary artery calcium in predicting CAD events.[103] As a result, the recent American College of Cardiology Foundation/ American College of Cardiology Guidelines for assessment of cardiovascular risk in asymptomatic individuals contain an indication for evaluation of coronary artery calcium.[103] The extent of coronary artery calcification provides valuable prognostic information regarding CAD risk; however, significant atherosclerosis may be

present in the absence of calcium.[79] Accordingly, CTA allows a more direct, yet still non-invasive, measurement of total plaque in the coronary arteries.[104] Each of the 17 coronary segments are visually assessed and classified on the basis of stenosis severity, and each plaque is classified as calcified, non-calcified, or mixed. CTA therefore enables visualization of ulcerated lesions as well as accurate assessment of plaque morphology. There is a paucity of studies evaluating the utility of coronary artery calcium or CTA in assessment of coronary atherosclerosis in cancer survivors at high risk for CAD. In the only study to date that evaluated a CT-based approach to CAD detection, Jain and colleagues[105] examined coronary calcium scoring with concomitant CTA in 20 (median age at study: 46 years; median follow-up: 6 years) HCT recipients. CAD was detected in 4 of 15 (26.6%) patients who would be considered 'low risk' by conventional Framingham Risk Score stratification;[105] highlighting how conventional risk classification algorithms may not be adequate or appropriate for HCT patients. Large-scale prospective investigations are clearly required to examine the clinical use of these screening strategies in HCT recipients.

4.2 Blood-Based Approaches

4.2.1 Biomarkers—Biomarkers that individually or in aggregate predict risk of CVD could aid in developing targeted prevention strategies during the preclinical phase of CVD, when intervention may be more likely to alter disease progression. The advent of highly sensitive assays has made detection of extremely low concentrations of biomarkers possible, and provides prognostic information above and beyond that provided by traditional risk factors (Table 2).[106] For example, a transient rise in cardiac troponin I has been demonstrated to predict the occurrence [107] as well as the magnitude of LVEF decline [108–110] in patients with hematologic and solid malignancies. The role of conventionally used CVD biomarkers in the HCT setting has yet to be determined.

A single marker may not provide sufficient biological information for an accurate assessment of cardiac and vascular damage.[111] In fact, several studies have reported that multiple biomarkers are superior to individual biomarkers in predicting subclinical and clinical CVD.[112–115] Wang et al.[115] measured 10 biomarkers in 3209 Framingham Heart Study participants and noted that persons with "multimarker" scores (based on regression coefficients of significant biomarkers) in the highest quintile as compared with those with scores in the lowest two quintiles had elevated risks of death (adjusted hazard ratio, 4.08; $P<0.001$) and major CVD events (adjusted hazard ratio, 1.84; $P=0.02$). In a subsequent study from the Framingham Heart Study (n=3428), a panel of high sensitivity biomarkers including soluble ST2 (sST2), growth differentiation factor-15 (GDF-15), and ultra-sensitive cardiac troponin (hsTnI), individuals with multimarker scores in the highest quartile had an elevated risk of future CVD events.[106] Integration of comprehensive biomarkers may identify risk factors before the onset of overt disease, and thereby potentially lead to earlier and more accurate identification of HCT patients at high CVD risk.

4.2.2 High-Throughput 'Omics' – Metabolomics—Metabolites are closely linked to cellular and whole-body phenotypes, thus providing "proximal reports" of cellular states. Metabolomics, the systematic analysis of metabolites, has been established as a clinical diagnostic tool that can predict future diabetes,[116] chronic kidney disease, and

CVD.[112,117–120] for example, Wang et al.[97] performed a nested case-control study of 188 individuals in the Framingham Heart Study who developed diabetes and 188 propensity-matched controls, and found that individuals with the metabolite 2-aminoadipic acid concentration in the top quartile had a 4-fold higher risk of developing diabetes over a 12-year follow-up period compared with those in the lowest quartile (adjusted OR: 4.49, 95% CI, 1.86 to 10.89). To determine whether a metabolite score was related to functional consequences of CVD, Lewis and colleagues[121] examined the relationship of a metabolomic amino acid score to exercise-induced myocardial ischemia in 166 subjects referred for diagnostic exercise stress testing. Of great interest, compared with the lowest quartile of the amino acid score, the top quartile of the score was associated with a nearly 5-fold risk (adjusted OR: 1.47–16.09) of inducible myocardial ischemia.[122] Future studies will need to evaluate the predictive value of metabolomics for prediction of CVD in HCT survivors. Ultimately, integration of comprehensive biomarkers with metabolomic profiling may be an innovative way to unravel the etiology and pathophysiology of HCT therapy-induced CVD.

4.3 Exercise-Based Approaches

4.3.1 Incremental Exercise Testing—Resting cardiac function, in contrast to exercise-based measures such as cardiopulmonary exercise testing (CPET), does not provide assessment of the integrative nature of cardiovascular function, assess cardiovascular reserve, or reliably predict VO_{2peak}. Our group has shown that CPET is a safe and feasible tool to provide an objective assessment of cardiovascular reserve and VO_{2peak} in select cancer populations.[68,69,123,124] In addition, these studies demonstrate that cancer patients have significant and marked reductions in VO_{2peak} and submaximal [e.g., ventilatory threshold (VT), minute ventilation – carbon dioxide production relationship (VE/VCO_2), oxygen uptake efficiency slope (OUES)] measures of exercise capacity across the entire survivorship continuum.[69,123,124] Of particular importance, we explored the utility and prognostic value of CPET prior to allogeneic HCT in 21 patients (mean age 44 years) with high risk hematological malignancies. After 25 months of follow-up, CPET-derived peak and sub-maximal measures were strong independent predictors of NRM.[125] Wood et al.[126] also evaluated CPET in 29 patients (mean age 55 years) prior to HCT and found that patients with pre-HCT VO_{2peak} <16 mL/kg/min had higher risk of mortality post HCT (HR: 9.1). CVD-specific mortality was not evaluated in these two preliminary studies; however, there is now strong rationale for further investigations into the utility of CPET to improve CVD risk stratification in HCT patients.

5.0 Aerobic Training to Attenuate HCT-induced Cardiovascular Disease

There is a wealth of observational data demonstrating that higher exposure to exercise is associated with substantial decreased incidence of CVD mortality in non-oncology settings.[23,127–129] For example, in 44,452 men from the Health Professional Study, increased metabolic equivalent tasks (METs) was associated with a 42% risk reduction (RR, 0.58; 95% CI, 0.44–0.77) of myocardial infarction,[130] while Mora et al.,[131] in a prospective study of 27,055 women, found that the adjusted CVD rate ratio was 41% in the least active group compared with the most active group. Evidence from adult survivors of childhood cancer with a history of HCT indicates that weekly exercise time is also associated with decreased

CVD risk. Specifically, Jones et al.[132] examined the association between exercise exposure (MET hours/week) and risk of major CVD events in adults survivors of childhood Hodgkin lymphoma (n = 1,187; median age, 31.2 years, median follow up, 11.9 years). Compared with survivors reporting 0 MET hours/week, the adjusted rate ratio for any CVD event was 0.47 (95% CI, 0.23 to 0.95) for those in the highest exercise exposure quartile.[132] Additionally, adherence to national exercise guidelines was associated with a 51% lower risk of any CVD event in comparison with not meeting the guidelines (< 9 MET hours/week).[132] The above findings indicate that adoption of regular exercise consistent with national vigorous exercise recommendations could confer substantial cardiovascular benefits in HCT recipients. However, there are significant limitations -- such as reverse causality -- associated with observational studies. Indeed, it is not possible to delineate whether higher levels of exercise simply reflect lower CVD burden as opposed to a direct exercise-induced effect. Phase 2 trials wherein the dose of exercise is carefully quantified are required to inform the design of confirmatory randomized controlled trials (RCTs).

To examine the current evidence outlining the effects of AT on CVD sequelae in the HCT setting, we searched PubMed using the following MeSH terms and text words: hematological, malignancies, stem cell transplantation, exercise, exercise therapy, exercise training, aerobic training, exercise capacity, cardiorespiratory fitness, VO_{2peak}, cardiac, CAD, CVD, CVD risk factors, myocardial infarction, stroke, HF, LV dysfunction, heart rate (HR), LVEF, LV mass, LV end diastolic volume, LV end systolic volume, hypertension, blood pressure, echocardiography, systolic function, diastolic function, body weight, body fat, vascular, endothelial function, biomarkers, tumor necrosis factor alpha (TNF-α), cholesterol, triglyceride, C- reactive protein (CRP), insulin, glucose, leptin, c peptide, interleukin-6 (IL-6), and hemoglobin. RCTs or single-arm (pre-post) of structured exercise training involving adults (≥18 years of age) with hematological malignancies undergoing HCT were included. Studies with a participant mean age <18 years, not written in English, review articles, and animal studies were excluded.

Study characteristics are presented in Table 3. In brief, studies consisted of 9 (82%) RCTs and 2 (18%) single-arm studies including a total of 820 patients (n=430, exercise training; n=390, usual care; n=479 male; n=313 female). Ten studies excluded patients with pre-existing documented CVD; one study did not report exclusion criteria. In terms of baseline (pre-intervention) CVD risk factor profile, only 1 study reported history of hypertension (prevalence of 29%) and hypercholesterolemia (prevalence of 30%); no studies reported history of type II diabetes. In general, exercise prescriptions followed the standard exercise guidelines for healthy individuals: 3–5 days per week for ≥30 min per session for moderate-intensity exercise or 3 days per week for ≥20 min per session for vigorous-intensity exercise.[114,115] Eight studies (73%) prescribed intensity based on estimated peak HR or perceived exertion, while all studies (100%) used a conventional (linear) approach to exercise prescription which maintains a static intensity, frequency, and duration after an initial lead in period.[133]

Reported cardiovascular end points included estimated (n=5; 45%) or measured (n=2; 18%) VO_{2peak}, body weight (n=2; 18%), and hemoglobin (n=2; 18%). Overall, findings indicate that AT has beneficial cardiovascular effects during and following HCT. For example

Courneya et al.[134] found that following a 12 week intervention during therapy, VO_{2peak} increased 19% in AT patients, compared to a 1% decrease in sedentary controls, while Coleman and colleagues[135] demonstrated that AT attenuated a decrease in hemoglobin compared to controls. These preliminary investigations indicate that AT is a promising strategy to prevent and/or treat HCT-induced CVD; however, further high quality research is clearly required. A more personalized approach incorporating the principles of training may be required for optimal mitigation of CVD-related morbidity and mortality in HCT patients, including individualization, specificity, progressive overload, and rest and recovery.[133] An essential prerequisite in the design of all exercise training trials is the objective assessment of patients' VO_{2peak} and peak heart rate, as well as their submaximal cardiopulmonary responses to exercise, thus permitting precise tailoring of training to the individual patient. These individualized approaches are currently being used in an ongoing trial in breast cancer patients;[136] future investigations should examine the efficacy of personalized AT in HCT patients. To this end, adequately powered multicenter RCTs with appropriate CVD endpoints are required to evaluate the efficacy of AT to prevent/treat HCT-induced CVD.

6.0 Conclusions

CVD is a frequent and devastating adverse complication of HCT leading to morbidity, poor quality of life, and premature mortality. As reviewed here, there is evidence indicating that HCT patients are subjected to direct and indirect cardiovascular injury that collectively leave patients with an increased prevalence of CVD risk factors, overt CVD, and CVD-related mortality. It is important to stress that the current evidence base is emergent with a small number of studies; many areas of HCT-induced CVD remain to be defined and addressed. A summary of future investigations needed in the HCT setting is provided in Table 4. To this end, we propose that in combination with continual advancements in anticancer therapy, expansion of screening and surveillance of CVD with multimodal techniques is required. Additionally, preliminary evidence indicates that AT may abate HCT-induced cardiovascular injury. These findings provide a sound rationale to test the efficacy of a new exercise paradigm that focuses on a personalized medicine approach to optimize health and longevity in the HCT setting by preventing and/or attenuating HCT-associated CVD.

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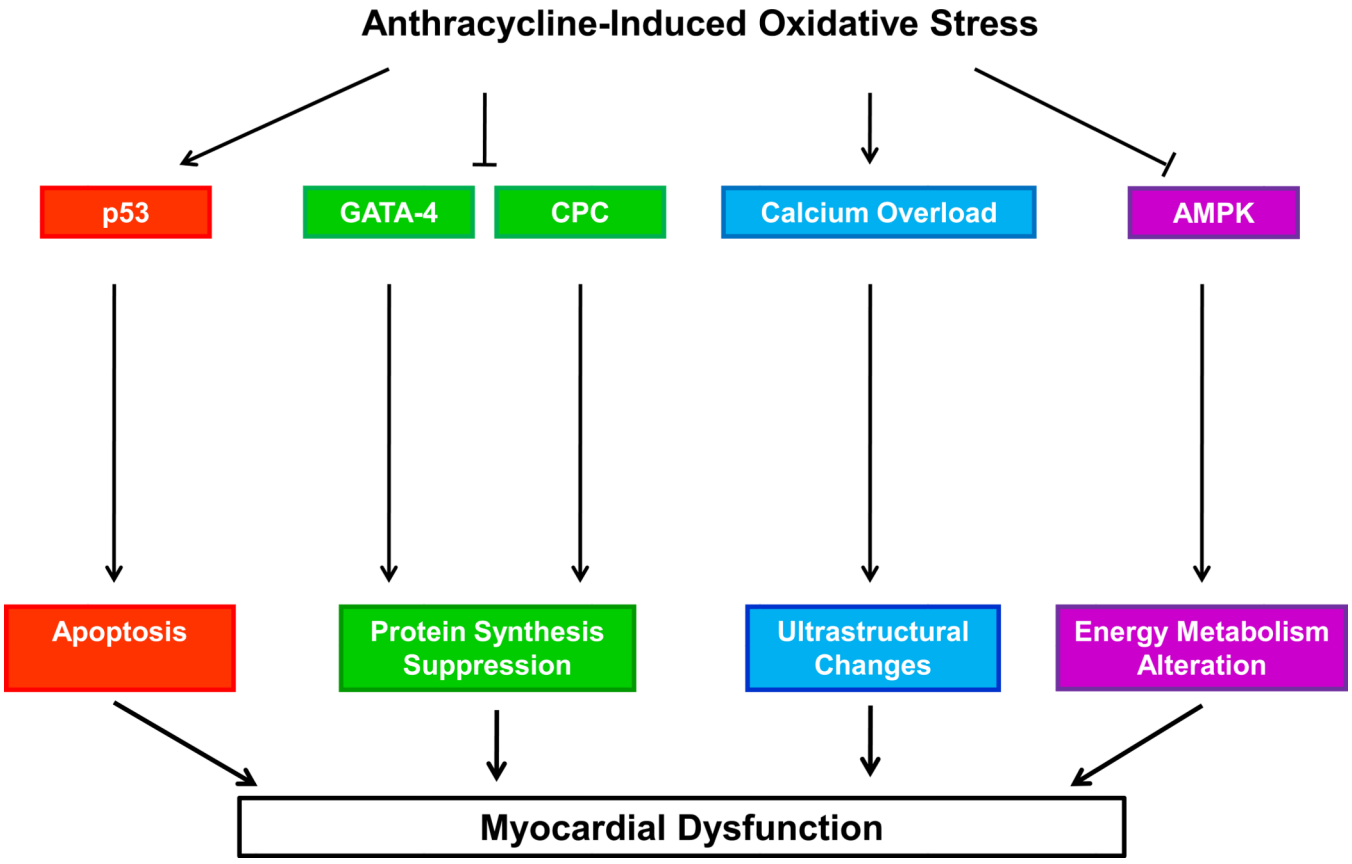

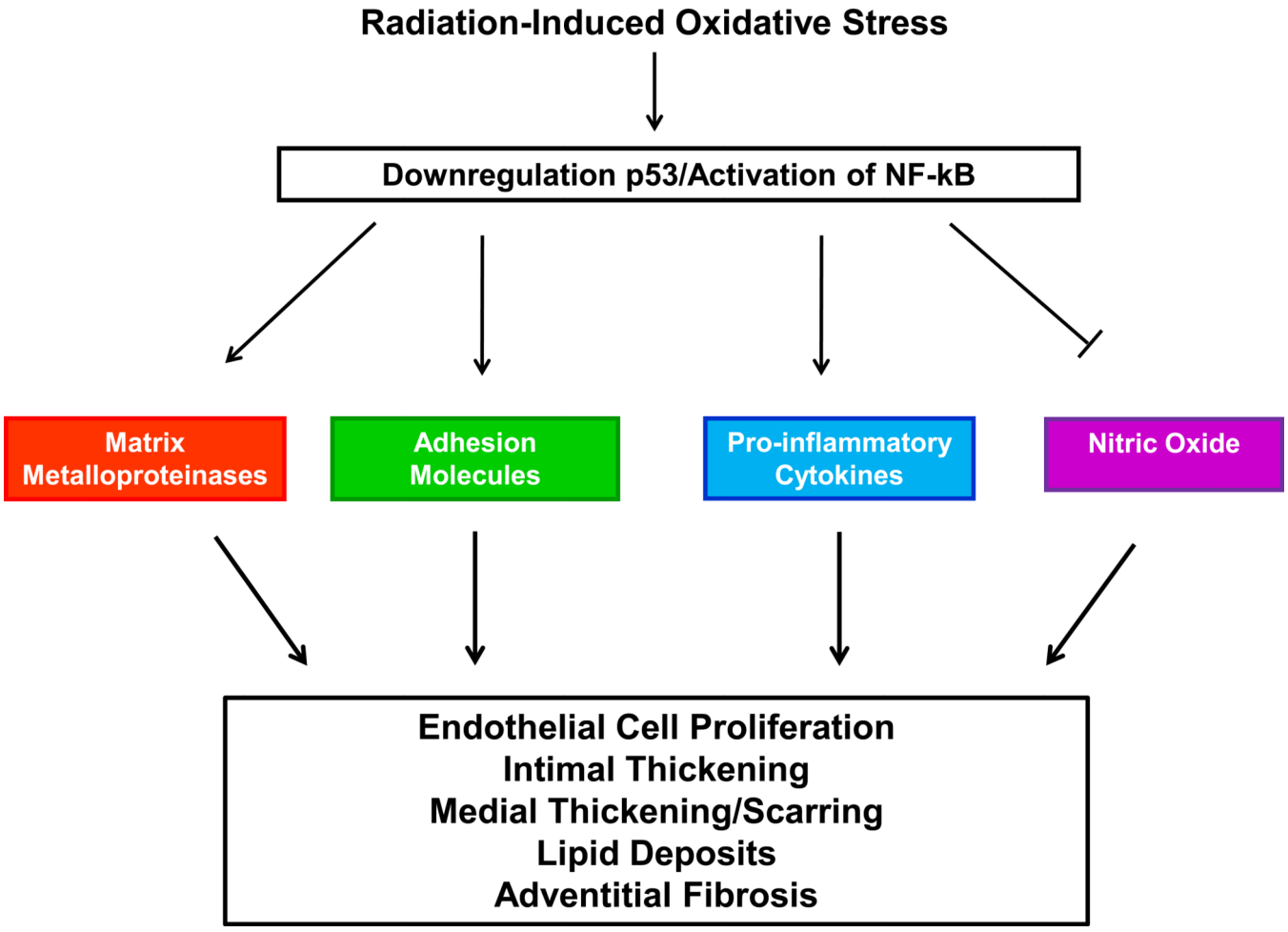

Figure 1. Mechanisms underlying 'direct' cardiovascular hits

A) Anthracycline-induced generation of ROS is a central mediator of: 1) accelerated myofilament apoptosis via upregulation of p53 pathway, 2) suppression of myofilament protein synthesis via inhibition of CPCs and GATA-4, 3) alterations in cardiac energy metabolism via downregulation of AMPK, 4) ultrastructural changes to myocytes via calcium overload. These changes lead to myocardial and vascular dysfunction. B) Radiation-induced vascular injury occurs via downregulation of endothelial cell-specific p53/activation of nuclear transcription factor NF-κB, which ultimately up-regulates matrix metalloproteinases, adhesion molecules, pro-inflammatory cytokines, while inactivating vasculoprotective nitric oxide. Eventually, coronary vascular injury characterized by endothelial cell proliferation, intimal thickening, medial scarring, lipid deposits and adventitial fibrosis may occur. ROS, reactive oxygen species; mitogen activated protein kinases, MAPK; cardiac progenitor cells, CPCs; AMP-activated protein kinase, AMPK.

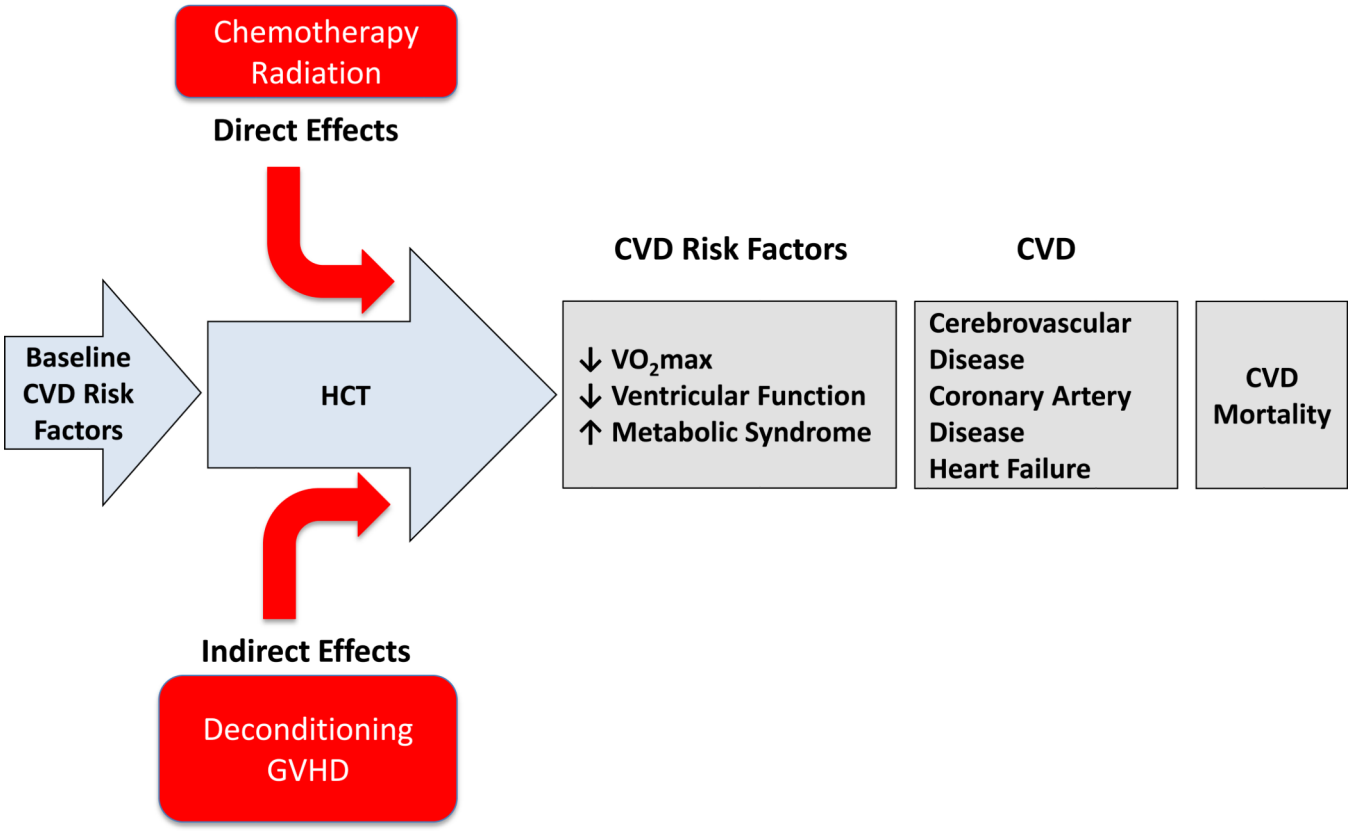

Figure 2. Model of accelerated CVD phenotype

At diagnosis, a significant proportion of HCT patients present with pre-existing or heightened CVD risk factors, which increase the risk of therapy-associated cardiovascular injury. Independently, total-body irradiation and/or high dose chemotherapy are associated with direct adverse effects on the cardiovascular system. These direct effects occur in the context of concomitant lifestyle perturbations (indirect effects: deconditioning, GVHD). Collectively, these direct and indirect insults enhance susceptibility to CVD risk factors, CVD, and premature CVD mortality. CVD, cardiovascular disease; HCT, hematopoietic cell transplantation; GVHD, graft versus host disease.

Table 1

Incidence of CVD risk factors and overt CVD following HCT.

Outcome	Incidence
CVD Risk Factors	
Hypertension	28%–74%[7,10,137,61,27,138]
Dyslipidemia	33%–58%[7,10,26,137,23]
Diabetes	10%–41%[7,10,26,137,23]
Obesity	20–44%[26,61,23]
Low exercise tolerance	100%[125]
Decreased LVEF	5%–43%,[139,140]
Overt CVD	
Arrhythmia	2%–13%[7,10,137]
Stroke	0.2%–4.8%[7,10,26,137,61]
Transient ischemic attack	0.3%[4]
Myocardial ischemia	1%–6%[7,10,77,137]
Heart failure	1% to 9%[3–5,61]

Table 2

CVD Specific Biomarkers.

Cardiac Markers	Definition	CVD Outcomes
Ultra-sensitive cardiac troponin (hsTnI)	Marker of proteolysis and turnover of myocardial contractile proteins.[141]	Associated with all-cause and cardiovascular mortality.[106]
Soluble ST2 (sST2)	Marker of myocardial stress and myocyte stretch.[142]	Associated with the risk of CVD events [142]
Growth differentiation factor-15 (GDF-15)	Marker of myocardial[143,144] and vascular[145–147] inflammation and tissue injury.	Associated with the risk of CVD events.[106,148,149]
N-terminal-pro-B-type natriuretic peptide (NT-proBNP)	Marker of cardiovascular remodeling.[150]	Associated with the risk of CVD events and death.[151]
High-sensitivity C-reactive protein (hsCRP)	Marker of inflammation.[79]	Associated with the risk of CVD events.[152]
Homocysteine	Marker of oxidative stress and inflammation.[153]	Associated with endothelial dysfunction, atherosclerosis[113,115,154,155]

Table 3

Summary of Exercise Interventions Aimed at Attenuating HCT-Induced CVD.

Author	N	Cohort/Design/Setting	Exercise	Outcomes
Battaglini et al. (2009)[156]	10	Acute leukemia/intervention during treatment	30min/d; 3d/wk; 40–50% estimated HRR; 3–5 weeks	Total minutes on bicycle ergometer at 60% HRR: ↑ 88% Body weight: ↓ 4%
Coleman et al. (2003)[157]	14	Multiple myeloma/RCT during treatment	60min/d; 3d/wk; 12–15 Borg scale; 22 wks	6-Minute Walk Test: ↓ 2% in AT; ↓ 2% in control
Coleman et al. (2008)[135]	60	Multiple myeloma/RCT during treatment	20min/d; 3d/wk; 11–13 Borg scale; 15 wks	Hemoglobin: ↓ 7% in AT; ↓ 10% in control
Coleman et al. (2012)[158]	95	Multiple myeloma/RCT during treatment	30min/d; 5d/wk; 11–13 Borg scale; 15 wks	Hemoglobin: ↓ 6% in AT; ↓ 5% in control
Courneya et al. (2009)[159]	60	Lymphoma/RCT during treatment	15–45min/d; 3d/wk; 60–75% peak power output; 12 wks	Body weight: ↓ 0.4% in AT; ↓ 0.6% in control
Courneya et al. (2009)[134]	60	Lymphoma/RCT during treatment	15–45min/d; 3d/wk; 60–75% peak power output; 12 wks	Measured VO_{2peak}: ↑ 19% in AT; ↓ 1% in control
Groeneveldt et al. (2013)[160]	28	Multiple myeloma/Intervention post treatment	15–30min/d; 3d/wk; 50–60% HRR; 24 wks	Measured VO_{2peak}: ↑ 1%
Jarden et al. (2009)[161]	21	Allogeneic HCT/ RCT during treatment	15–30min/d; 5d/wk; 45–75% estimated max HR; 4–6 wks	Estimated VO_{2peak}: ↑ 0.01% in AT; ↓ 28% in control
Oechsle et al. (2014)[162]	24	Myeloablative chemotherapy/ RCT during treatment	10–40min/d; 5d/wk; intensity NR; 4 wks	Estimated VO_{2peak}: ↑ 11% in AT; ↓ 26% in control
Shelton et al. (2009)[163]	30	Allogeneic HCT/ RCT post treatment	20–30min/d; 3d/wk; 60–75% estimated max HR; 4 wks	6-Minute Walk Test: ↑ 12% in AT; ↑ 10% in control
Streckmann et al. (2014)[164]	28	Lymphoma/RCT during treatment	60min/d; 2d/wk; 60–80% estimated max HR; 36 wks	Incremental step test: ↑ in AT; ↓ in control (values NR)

Abbreviations: HCT, hematopoietic cell transplantation; HRR, heart rate reserve; RCT, randomized controlled trial; AT; aerobic training; HR; heart rate; NR, not reported.

Table 4

Future Directions in HCT Research.

Underlying mechanisms of HCT-induced CVD

- Identify baseline cardiovascular phenotypes that may predict susceptibility to HCT-induced CVD
- Elucidate the time course of HCT-induced CVD from:
  - **i.** 'direct' injury (primary malignancy therapy and HCT-associated chemotherapy and radiation)
  - **ii.** 'indirect' injury (disuse, GVHD)
- Examine differing pathophysiology of HCT-induced HF and CAD

Detection of HCT-induced CVD

- Determine the optimal strategy (type of test, timing, and frequency) for detection of CVD risk factors (hypertension, diabetes, hyperlipidemia), HF, and CAD
- Evaluate HCT-induced CVD in older patients
  - **i.** Most of the research performed to date has focused on children or young adults, however, data from the Center for International Blood and Marrow Transplant Research demonstrated that the median age of patients undergoing HCT has risen significantly over the last 10 years due to better supportive care and the impact of reduced intensity conditioning regimens.[165] A significant proportion of these patients have cardiac comorbidities and cardio-pulmonary complications. Strategies specifically aimed at this patient population need to be developed and prospectively explored.

Clinical importance of HCT-induced CVD

- Delineate the short- and long term impact of positive blood, imaging, and cardiopulmonary exercise test results and relationship with clinical CVD events

Prevention/Management of HCT-induced CVD

- Establish the most effective timing (pre-HCT, peri-HCT, post-HCT, late post-HCT) to perform AT
- Determine the optimal AT dose required to prevent/treat CVD at each intervention time point (pre-HCT, peri-HCT, post-HCT, late post-HCT)
- Assess the impact of AT on CVD risk factors (e.g. hypertension, diabetes, hyperlipidemia), CVD events (e.g. HF, CAD), and CVD-mortality
- Conduct:
  - **i.** Phase 2 trials wherein the dose of AT is carefully quantified to inform the design of confirmatory randomized controlled trials (RCTs)
  - **ii.** Adequately powered multicenter RCTs with appropriate CVD endpoints to evaluate the efficacy of AT to prevent/treat HCT-induced CVD

Evaluation of HCT-induced injury to other organ systems

- Cardiac function is one component of a highly integrated system responsible for the transport of oxygen. When evaluating HCT-induced injury, research evaluating injury to other organs that impact exercise tolerance is also required:
  - **i.** Pulmonary system. Lifetime risk of chronic pulmonary dysfunction following HCT ranges from 30% to 60%.[166,167] HCT therapy may adversely impact respiratory muscle mechanics, airway resistance and gas exchange, contributing to dyspnea and exercise intolerance.
  - **ii.** Muscle system. Up to 70% of patients surviving for at least 5 years after HCT report moderate to severe symptoms of fatigue, muscle weakness, cramps, myalgias, or arthralgias.[168–170] HCT therapy may adversely blood flow in the peripheral circulation, transport of oxygen through the muscle cell via myoglobin, and skeletal muscle oxidative capacity, contributing to exercise intolerance.