Characterization of arterial stiffness in cancer patients: making the case for clinical implementation

by

Shannon Kay Parr

B.S., Kansas State University, 2016
B.S., Kansas State University, 2016
M.S., University of Kansas, 2019

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Kinesiology
College of Health and Human Sciences

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Abstract

Monitoring changes in left ventricular function is the primary surveillance strategy in cardio-oncology practice for detecting cardiotoxicity in cancer patients actively receiving treatment and in the survivorship phase. The current clinical manifestation of cardiotoxicity is defined by reductions in left ventricular ejection fraction and global longitudinal strain, primarily reflections of cardiac systolic function. Recent evidence, however, has suggested that vascular function is reduced following anti-cancer chemotherapy. These vascular abnormalities manifest as reduced endothelial function, increased vascular smooth muscle tone, and arterial stiffness, and often occur in the absence of clinically significant changes in cardiac function. Of these, increased arterial stiffness has been linked to adverse cardiac outcomes including heart failure and cardiac remodeling, in the general and various clinical populations; but it has yet to be incorporated into regular clinical practice due to methodological challenges. Therefore, the primary aim of this dissertation was to fully characterize the association of arterial stiffness and cancer and develop a clinically feasible method to measure arterial stiffness into practice.

The first investigation of this dissertation (Chapter 2) demonstrates arterial stiffness increases in a diverse group of cancer patients after exposure to heterogenous therapy regimens. Our second investigation from Chapter 3 demonstrates that pulse pressure, an index of arterial stiffness, is predictive of all-cause mortality and cardiovascular mortality in a retrospective data set of participants with a history of cancer. From this work that established that arterial stiffness increases with cancer treatment and is predictive of long-term outcomes in cancer populations, we developed a clinically relevant method to measure arterial stiffness in the clinic for Chapter 4. Specifically, this method is focused on the evaluation of aortic arch stiffness leveraging the standard scanning views obtained during routine transthoracic echocardiography. Taken

together, our data suggests arterial stiffness increases following anti-cancer chemotherapy and predicts long-term adverse outcomes. This work begins to make a compelling case for monitoring stiffness in the clinic, and our newly proposed method represents an avenue to incorporate vascular measures into cardio-oncology risk stratification.

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Major Professor
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Preface

Chapters 2-3 of the present dissertation represent peer-reviewed articles that have been published in scientific journals. They are written in published format and the citations are listed below. These original investigations are reproduced with permission from the publishers.

Parr SK, Liang J, Schadler KL, Gilchrist SC, Steele CC, Ade CJ. Anticancer Therapy-Related Increases in Arterial Stiffness: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2020;9:e015598.

Parr SK, Steele CC, Hammond ST, Turpin VRG, Ade CJ. Arterial Stiffness is Associated with Cardiovascular and Cancer Mortality in Cancer Patients: Insights from NHANESIII. Int J Cardiol Hypertens 2021;9: 100085.

Chapter 1 - Introduction

"The physiologist is at the threshold of an unprecedented scientific era. To him or her will fall the task of making sense of the bits and pieces of new knowledge that are so rapidly accumulating. The whole is more than the sum of its parts but an intimate appreciation of the parts is needed to assemble a coherent whole. This is a challenge- and the privilege- of today's integrative physiologist"

- Claude Lefent (1995), Director of the National Heart Lung and Blood Institute.

The field of cardio-oncology was born in 1995 at the European Institute of Oncology in response to the growing need to provide cardiovascular care for cancer populations receiving treatments[1,2]. Development of this discipline arose with the discovery of new treatments in the late 1950's and 1960's, specifically anthracyclines, fluoropyrimidines, and alkylating agents that helped with the treatment of both adult and childhood cancers[3]. However, not long after these agents were introduced, it became clear they were associated with off-target cardiotoxic effects[4-6], including but not limited to acute electrocardiogram abnormalities, angina, hypotension, left ventricular dysfunction, heart failure, and sudden death[7]. The field has continued to grow as new, more targeted agents have been introduced such as antiangiogenic agents, hormone therapies, and immune-modulating therapies (i.e., immune checkpoint inhibitors and car-T cell therapies)[8]. Even with the development of these new drugs and improved outcomes, we are still faced with the same problem: all of these agents have off-target effects and are non-tissue specific, so cardiotoxicity remains a challenge in modern medicine[9].

Most research in this emerging field has focused on the heart and prevention of cardiotoxicity by investigating the damaged pathway from the cellular level to the entire clinical manifestation

of heart failure. The leading hypotheses for cardiac damage center around the cytotoxic mechanisms of action of these drugs; most elicit cell cycle arrest by inhibiting critical steps in DNA replication (i.e., anthracyclines inhibit topoisomerase IIb and 5-fluorouracil acts as uracil and inserts itself in the DNA sequence) and through the production of reactive species by drug metabolism within cells[10,11]. Within the last decade, it has become apparent that these processes are also occurring in vascular cells. Data from in vitro, animal, and human studies have highlighted that various cancer treatments can lead to endothelial dysfunction through reduced nitric oxide signaling[12,13], altered vascular smooth muscle cell tone[14,15], and vascular cell senescence[16,17]; all of which are known precursors to increased arterial stiffness[18]. The primary purpose of the vasculature is to provide steady blood flow to metabolically active tissues and cushion energy transmission from ventricular ejection within the elastic walls of the large arteries. As large arteries become stiffer with aging and proinflammatory conditions, these functions become dampened and can lead to adverse cardiac and microcirculatory outcomes[19]. Recent reports from our lab[20] and others[21] have shown that arterial stiffness is increased in cancer patients receiving treatment compared to cancer-free controls. Monitoring changes in large artery stiffness in this population could serve as a powerful marker for cardiotoxicity, as arterial stiffening is associated with subclinical indices of cardiac dysfunction outside of overt changes in left ventricular ejection fraction[22,23].

The primary aim of this dissertation is to describe the relationship between cancer and arterial stiffness comprehensively and to bring monitoring strategies into the clinic for improved cardiovascular care in these patients. In Chapter 2, we performed a meta-analysis to determine the association of chemotherapies and increases in arterial stiffness in a diverse group of cancer patients. Chapter 3 addresses whether pulse pressure, an index of arterial stiffness, is predictive

of outcomes in cancer patients using a retrospective data set from the national health and nutrition examination survey (NHANES). Chapter 4 represents an exploratory analysis of comparing a novel method of aortic arch stiffness measured by transthoracic echocardiography to the gold standard carotid-femoral pulse wave velocity. Taken together, the studies presented in this document are aimed to extend knowledge on large artery consequences of cancer and its associated therapies in hopes to better stratify the risk of adverse cardiac outcomes in this patient population.

References

1. Cardinale D. [A new frontier: cardio-oncology]. Cardiologia. 1996;41:887-891.

2. Cardinale D, Mills NL, Mueller C, Study Group on Biomarkers of the ESCAfACC. Cardiac biomarkers in the field of cardio-oncology. Eur Heart J Acute Cardiovasc Care. 2022;11:e1-e2. doi: 10.1093/ehjacc/zuac126

3. Chabner BA, Roberts TG, Jr. Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer. 2005;5:65-72. doi: 10.1038/nrc1529

4. Ghione M. Cardiotoxic effects of antitumor agents. Cancer Chemother Pharmacol. 1978;1:24-34. doi: 10.1007/BF00253143

5. Praga C, Beretta G, Labianca R. Cardiac toxicity from antitumor therapy. Oncology. 1980;37 Suppl 1:51-58. doi: 10.1159/000225497

6. Manente P, Buchberger R, Valmachino G, Fioretti D, Lo Giudice C, Gasparoni P, Conte N. [Cardiotoxicity induced by 5-fluorouracil. A case report]. Tumori. 1980;66:255-260. doi: 10.1177/030089168006600214

7. Cardinale D, Bacchiani G, Beggiato M, Colombo A, Cipolla CM. Strategies to prevent and treat cardiovascular risk in cancer patients. Semin Oncol. 2013;40:186-198. doi: 10.1053/j.seminoncol.2013.01.008

8. Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, Boriani G, Cardinale D, Cordoba R, Cosyns B, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J Cardiovasc Imaging. 2022;23:e333-e465. doi: 10.1093/ehjci/jeac106

9. Lenihan DJ, Cardinale D, Cipolla CM. The compelling need for a cardiology and oncology partnership and the birth of the International CardiOncology Society. Prog Cardiovasc Dis. 2010;53:88-93. doi: 10.1016/j.pcad.2010.06.002

10. Varricchi G, Ameri P, Cadeddu C, Ghigo A, Madonna R, Marone G, Mercurio V, Monte I, Novo G, Parrella P, et al. Antineoplastic Drug-Induced Cardiotoxicity: A Redox Perspective. Front Physiol. 2018;9:167. doi: 10.3389/fphys.2018.00167

11. van den Boogaard WMC, Komninos DSJ, Vermeij WP. Chemotherapy Side-Effects: Not All DNA Damage Is Equal. Cancers (Basel). 2022;14. doi: 10.3390/cancers14030627

12. Duquaine D, Hirsch GA, Chakrabarti A, Han Z, Kehrer C, Brook R, Joseph J, Schott A, Kalyanaraman B, Vasquez-Vivar J, et al. Rapid-onset endothelial dysfunction with adriamycin: evidence for a dysfunctional nitric oxide synthase. Vasc Med. 2003;8:101-107. doi: 10.1191/1358863x03vm476oa

13. Sutterfield SL, Caldwell JT, Post HK, Lovoy GM, Banister HR, Ade CJ. Lower cutaneous microvascular reactivity in adult cancer patients receiving chemotherapy. J Appl Physiol (1985). 2018;125:1141-1149. doi: 10.1152/japplphysiol.00394.2018

14. Mosseri M, Fingert HJ, Varticovski L, Chokshi S, Isner JM. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. Cancer Res. 1993;53:3028-3033.

15. Shen B, Ye CL, Ye KH, Zhuang L, Jiang JH. Doxorubicin-induced vasomotion and [Ca(2+)](i) elevation in vascular smooth muscle cells from C57BL/6 mice. Acta Pharmacol Sin. 2009;30:1488-1495. doi: 10.1038/aps.2009.145

16. Altieri P, Murialdo R, Barisione C, Lazzarini E, Garibaldi S, Fabbi P, Ruggeri C, Borile S, Carbone F, Armirotti A, et al. 5-fluorouracil causes endothelial cell senescence: potential

protective role of glucagon-like peptide 1. Br J Pharmacol. 2017;174:3713-3726. doi: 10.1111/bph.13725

17. Chen L, Holder R, Porter C, Shah Z. Vitamin D3 attenuates doxorubicin-induced senescence of human aortic endothelial cells by upregulation of IL-10 via the pAMPKalpha/Sirt1/Foxo3a signaling pathway. PLoS One. 2021;16:e0252816. doi: 10.1371/journal.pone.0252816

18. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25:932-943. doi: 10.1161/01.ATV.0000160548.78317.29

19. Bell V, Mitchell GF. Influence of vascular function and pulsatile hemodynamics on cardiac function. Curr Hypertens Rep. 2015;17:580. doi: 10.1007/s11906-015-0580-y

20. Frye JN, Sutterfield SL, Caldwell JT, Behnke BJ, Copp SW, Banister HR, Ade CJ. Vascular and autonomic changes in adult cancer patients receiving anticancer chemotherapy. J Appl Physiol (1985). 2018;125:198-204. doi: 10.1152/japplphysiol.00005.2018

21. Chaosuwannakit N, D'Agostino R, Jr., Hamilton CA, Lane KS, Ntim WO, Lawrence J, Melin SA, Ellis LR, Torti FM, Little WC, et al. Aortic stiffness increases upon receipt of anthracycline chemotherapy. J Clin Oncol. 2010;28:166-172. doi: 10.1200/JCO.2009.23.8527

22. Bell V, McCabe EL, Larson MG, Rong J, Merz AA, Osypiuk E, Lehman BT, Stantchev P, Aragam J, Benjamin EJ, et al. Relations Between Aortic Stiffness and Left Ventricular Mechanical Function in the Community. J Am Heart Assoc. 2017;6. doi: 10.1161/JAHA.116.004903

23. Spetko N, Rong J, Larson MG, Haidar M, Raber I, Peters K, Benjamin EJ, O'Donnell CJ, Manning WJ, Vasan RS, et al. Cross-Sectional Relationships of Proximal Aortic Stiffness and

Left Ventricular Diastolic Function in Adults in the Community. J Am Heart Assoc. 2022;11:e027230. doi: 10.1161/JAHA.122.027230

Chapter 2 - Anticancer therapy-related increases in arterial stiffness: a systematic review and meta-analysis

Abstract

Background- Cardio-oncology is a clinical discipline focused primarily on the early detection of anticancer therapy-related cardiomyopathy. However, there is growing evidence that the direct adverse consequences extend beyond the myocardium, to affect the vasculature, but this evidence remains limited. In addition, there remains a paucity of clinically based strategies for monitoring vascular toxicity in these patients. Importantly, arterial stiffness is increasingly recognized as a surrogate endpoint for cardiovascular disease and may be an important vascular outcome to consider. Therefore, the aim of this systematic review and meta-analysis was to summarize evidence of increased arterial stiffening with anticancer therapy and evaluate the effect of treatment modifiers. **Methods and Results**- Nineteen longitudinal and cross-sectional studies that evaluated arterial stiffness both during and following anticancer therapy were identified using multiple databases. Two separate analyses were performed, baseline to follow-up (12 studies) and control vs. patient groups (10 studies). Subgroup analysis evaluated whether stiffness differed as a function of treatment type and follow-up time. Standard mean differences (SMD) and mean differences (MD) were calculated using random effect models. Significant increases in arterial stiffness were identified from baseline to follow-up ([SMD]= 0.890, 95%CI= 0.448-1.332, P=<0.0001; [MD]=1.505, 95% CI= 0.789-2.221, $p \leq 0.0001$) and in patient vs. control groups ([SMD]= 0.860, 95%CI= 0.402-1.318, P=.0002; [MD]= 1.437, 95% CI= 0.426-2.448, p= 0.0052). Subgroup analysis indicated differences in arterial stiffness between anthracycline and non-anthracycline based therapies ([SMD]= 0.20, 95%CI= .001-0.41 P= .048),

but not follow-up time. **Conclusions**- Significant arterial stiffening occurs following anticancer therapy. Our findings support the use of arterial stiffness as part of a targeted vascular imaging strategy for identification of early cardiovascular injury during treatment and for detection of long-term cardiovascular injury into survivorship.

Introduction

Anticancer treatments, including anthracyclines, alkylating agents, and vascular endothelial growth factor inhibitors, are associated with direct vascular damage[41] and an increased risk of adverse vascular outcomes, that can occur after the first treatment and persist into survival[19,64,69]. As such, recent reports in vascular cardio-oncology have highlighted the critical need to continuously monitor vascular health during treatment and into survivorship, sothat effective primary and secondary preventative strategies can be prescribed. However, while clinical monitoring for ventricular toxicities such as cardiomyopathy have been described (e.g., echocardiography), there have been no systematic reports evaluating potential clinical strategies for monitoring vascular toxicity during and following anticancer treatment, reflecting a serious gap in our current knowledge and the need to identify potential imaging approaches[2,6,9].

An increasingly recognized surrogate endpoint for cardiovascular disease (CVD) is local and regional measurements of arterial stiffness. In non-cancer populations, arterial stiffness is independently predictive of all-cause mortality and fatal/non-fatal cardiovascular outcomes, and is used in CVD risk stratification[11,17,32,37,40,70]. We and others have demonstrated that cancer patients and survivors exhibit increased arterial stiffness, above levels expected with aging alone[1,16,19]. Therefore, since arterial stiffness is central to a comprehensive evaluation of vascular health and a surrogate endpoint for general CVD, monitoring of arterial stiffness may serve as an important clinical approach in cancer populations receiving systemic anticancer therapies. However, the current evidence base is limited due to several factors, including small sample sizes, different measurement strategies, various study designs, and different durations of follow-up. Therefore, to clarify these issues, we conducted the present systematic review and meta-analysis with the primary aim to provide an overview of the current evidence for increases in

arterial stiffness after anticancer therapy. A secondary aim was to examine whether changes in arterial stiffness differed as a function of follow-up time and anticancer treatment type.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

Data searches and sources

Studies evaluating the relationship between arterial stiffness and anticancer therapy were retrieved from a systematic review of English literature in Cochrane, PubMed, Google Scholar, and Web of Science databases until January 2019, by members of the research team (S.P, C.A) with assistance from University research data informationists. The population search terms included “cancer”, “chemotherapy”, “cardiotoxicity”; and descriptor search terms “arterial stiffness”, “pulse wave velocity”, and “augmentation index”. Data sources were also identified through manual search of the references of articles. All search results were downloaded to a research management system (Endnote, Clarivate Analytics) where data extraction began by removing duplicates, review papers, and letters to the editor. All remaining results underwent a full text review to determine eligibility into the analysis. The literature search and selection of studies was done by two independent reviewers (C.A., S.P.), disagreements were resolved by consensus. This analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and registered at the International Prospective Register of Systematic Reviews (PROSPERO ID:150246).

Study eligibility

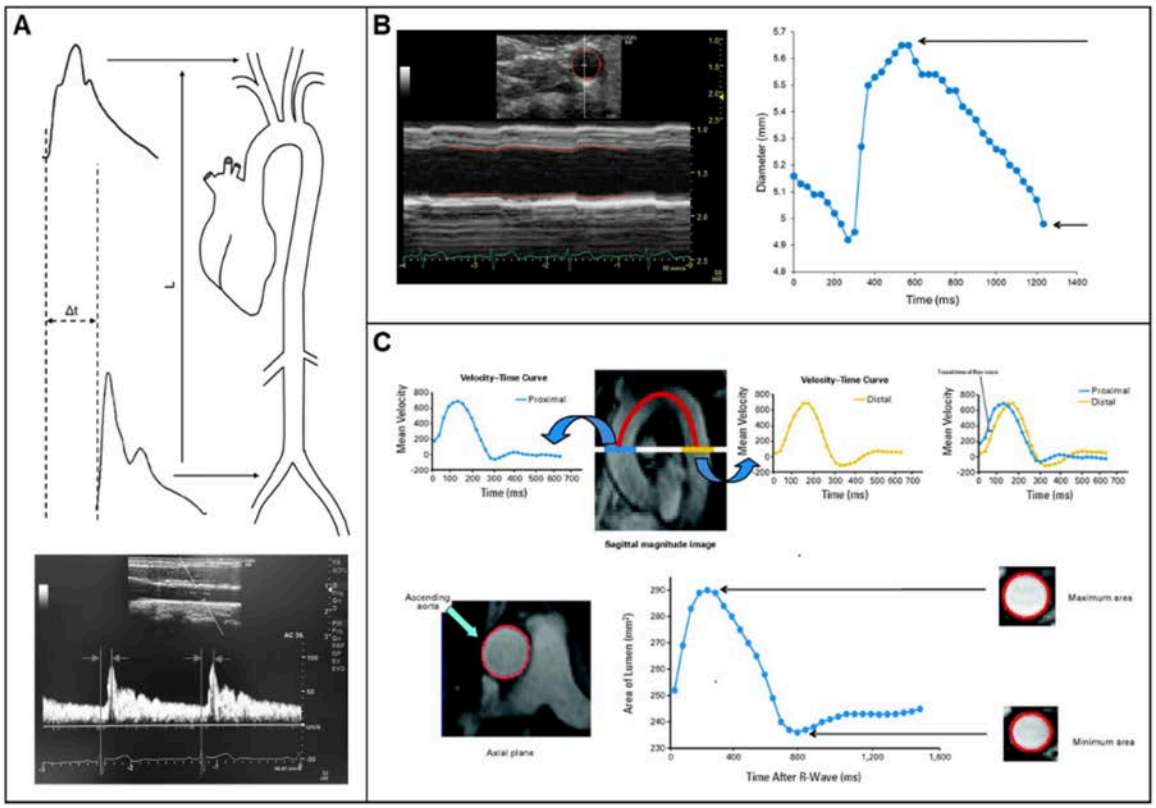
Studies were considered eligible if they met the following criteria: 1) full-length publication in peer-reviewed journal; 2) evaluated arterial stiffness via pulse wave velocity and or aortic/carotid

stiffness; and 3) reported anticancer drugs used to treat cancer that have previously been associated with long-term CVD risk[75]. Due to the nature of our research question, the effect of anticancer therapy on arterial stiffness could be assessed via either longitudinal comparison of pre-treatment baseline to post-treatment follow-up or comparison of an anticancer treatment group to that of an age, gender, CVD risk factor matched healthy group. Exclusion criteria were studies lacking sufficient information on anticancer treatment or cancer type, longitudinal studies lacking sufficient information on baseline patient characteristics and stiffness data, and case-control studies where the control group had a history of anti-cancer therapy. No restriction criteria were imposed regarding type of cancer, follow-up time, or population age due to limited number of studies.

Modalities included in the study

We included three separate modalities in our analyses that evaluated arterial stiffness both as a local measurement of specific vessels via aortic distensibility (AoD) and β-Stiffness index (carotid artery and aorta) and regional assessments of pulse wave velocity (PWV) that gives an index of global arterial health (aortic, carotid-femoral and brachial-ankle). In our literature search, PWV, AoD, and β-Stiffness index were the most commonly reported and more importantly, are validated measurements for assessing arterial stiffness[33,36,49]. PWV is reported in m/s and is calculated as the ratio of the distance between two points and the time taken to reach those two sites[33]. AoD is calculated by the change in cross-sectional area relative to the changes in arterial pressure and β -Stiffness index is calculated as the ratio of changes to relative changes in pressure and diameter[36]. **Figure 2-1** provides a visual representation of how arterial stiffness was measured in the studies included in our meta-analysis.

Figure 2-1 Determination of arterial stiffness



A, Pulse wave velocity can be calculated by dividing the distance (L) between 2 arterial sites by the difference in transit time (Δt) of pressure wave obtained via applanation tonometry or velocity wave obtained via Doppler ultrasonography (illustrated here) arrival between those two sites. **B**, Carotid β- stiffness can be calculated from B-mode and M-mode visualizations of the common carotid artery. From this image, maximal and minimal carotid diameters over the cardiac cycle can be determined by tracing the region of interest (red boundaries). **C/Upper**, Pulse wave velocity can be calculated from phase-contrast cardiovascular magnetic resonance images of the aorta by dividing the distance between the ascending and descending thoracic aorta by the transit time of the flow computed on the basis of time difference of the velocity-time curve at 2 different regions (blue line). **C/Lower**, Aortic distensibility can be calculated from phase contrast cardiovascular magnetic resonance imaging of the thoracic aorta. From these images, maximum and minimum aortic areas over the cardiac cycle can be determined by tracing the region of interest (red boundaries). **C**, Reprinted from Chaosuwannakit et al[30] with permission. Copyright © 2010, American Society of Clinical Oncology.

Extraction of data

Data were extracted by two authors (C.A., S.P.) according to the PRISMA Statement[42], discrepancies were resolved by consensus. For each study, we obtained population characteristics, measures of arterial stiffness, follow-up duration, underlying malignancy, cancer treatment utilized, treatment duration, and reported measures of arterial stiffness via PWV, AoD, or β -Stiffness index. Some studies reported multiple measures of arterial stiffness; we agreed to extract PWV if reported since it is the gold standard for measuring arterial stiffness. The two authors agreed on consensus for extraction if both β stiffness and distensibility were reported. Upon review, two study design types were identified in the search results; longitudinal and cross-sectional. Risk of bias was evaluated with the Newcastle-Ottawa Scale[62]. Briefly, the quality of each study was determined using questions that assessed the categories of bias: selection, comparability, and exposure. No study was excluded on the basis of quality alone.

Statistical analysis

All statistical analyses were performed using the software R (version 3.5.1) with package meta. The effect sizes were calculated using the inverse variance method. Heterogeneity was evaluated using the Cochran's Q test and Higgin's I^2 statistic. After examining the Cochran's Q test and I^2 statistic, significant heterogeneity was revealed so we proceeded with a random-effects model to minimize bias[52]. We performed both a standard mean difference (SMD) analysis to account for different methods used to measure arterial stiffness and mean difference (MD) analysis to examine overall difference in PWV longitudinally in cancer patients through treatment and in cancer patients compared to cancer-free controls. We felt it was appropriate to conduct both SMD and MD analyses in order to fully summarize the current literature and provide clinically

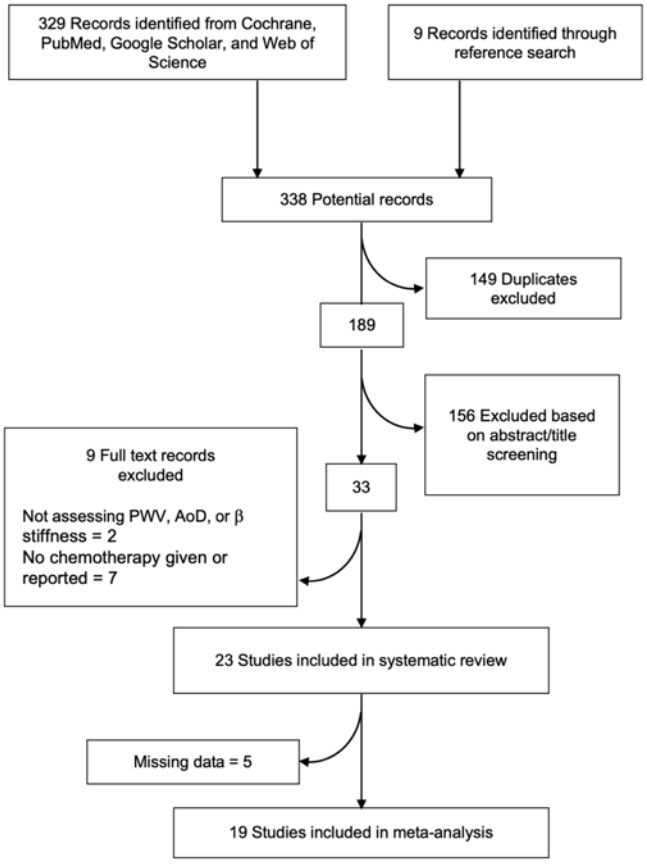
relevant insights. Using the SMD method allowed us to include various methods used to evaluate arterial stiffness (PWV, AoD, Beta) and MD allowed us to determine the mean effect of changes in arterial stiffness measured by PWV, the current clinical gold standard. For the SMD analysis evaluating longitudinal changes in arterial stiffness we had to correct differences in scaling (i.e., increases in PWV=increases in stiffness, decreases in AoD=increases in stiffness). This was done by multiplying the mean values by -1 as directed by the Cochrane handbook for SMD meta analyses[24]. The forest plots are provided with the SMD and MD with respective confidence intervals for the comparison between previous research. The primary analysis evaluated the association between anticancer therapy and arterial stiffness, regardless of type of anticancer drug or follow-up time. Subgroup analysis investigated whether differences in arterial stiffness differed as a function of follow-up time (<6 months vs. 6-12 months, 6-12 months vs. >12 months, and <6 months vs. >12 months following last anticancer treatment) and anticancer treatment type (anthracycline based vs. non-anthracycline based treatments). Additionally, we performed a sensitivity analysis because of our high heterogeneity score with each analysis to determine if any one study was driving the results of the analyses[52]. The sensitivity analysis was performed by calculating the pooled treatment effect of the studies that measured stiffness by PWV (i.e., excluding studies that used AoD or carotid β -Stiffness) after excluding each study one at a time and calculating SMD and MD. The treatment effect was considered significant if $p < 0.05$.

Results

Systematic review

Our search identified 338 publications, which was narrowed by preliminary review to 189 after removing duplicates (**Figure 2-2**). Articles were excluded due to anticancer therapy not given or reported or using a method to measure stiffness that was not PWV, AoD, or β -Stiffness index. Twenty-four studies measuring stiffness were eligible; of those, six were missing data, the authors were contacted via email and one responded. In the final analysis, twelve studies[1,10,13,16,20,27,39,41,53,55,60,72] were considered longitudinal or cohort studies. Ten studies[8,10,19,20,22,26,28,29,55,76] were case-control studies with age, sex, cardiovascular risk factor matched controls. Three studies[10,20,55] included a cross-over case-control design. In total, the included studies analyzed 2147 subjects (1043 patients, 1104 controls) and all studies were published from 2008 to present.

Figure 2-2 Flow chart of selection process of eligible studies



Flow through of the identification and selection of studies included in the systematic review and meta-analysis. AoD indicates aortic distensibility; and PWV, pulse wave velocity.

Association of increased arterial stiffness based on drug class

Anthracycline exposure and arterial stiffness

Fourteen of the included studies assessed arterial stiffness in patients who received primary anthracycline chemotherapy[8,10,13,16,19,22,26-29,39,41,60,76]. Of those, nine assessed acute (< 1 year) arterial stiffness from baseline to completion of treatment or during treatment, with a follow up time that ranged 1-9 months. All but two of these studies reported a significant increase in arterial stiffness (range: ~1-95%). We recently reported a ~20% increase in carotid artery stiffness in patients currently receiving anthracycline chemotherapy compared to matched non-cancer controls[19], which is similar to several reports of patients in the months following treatment[20,27,76]. Additionally, some investigations have reported >50% increases in arterial stiffness within 4-6 months following treatment. Chaosuwannakit et al. (2010) demonstrated a two-fold increase in carotid-femoral PWV (cfPWV) in just 4 months from baseline measurement and a three-fold increase compared to the control group. Similarly, Drafts et al. (2013) reported a rapid increase in arterial stiffness in the first month of the monitoring period with a 51% increase over the course of the full 6 months after correcting for baseline blood pressure. Importantly, these ranges of arterial stiffness increase are similar to that have been reported in aging populations and those with atherosclerosis[34, 54], highlighting the potential clinical implications. Contrary to a majority of the identified studies, Mizia-Stec et al. (2013) found no differences in cfPWV from baseline to 6 months following the last anthracycline treatment. However, half of the study participants were on cardiovascular related medications (36% beta blockers, 19% angiotensin converting enzyme inhibitors, 10% calcium channel blockers) or supplemented with Tamoxifen (58% of patients), all of which are known to have positive vascular effects which

could have neutralized detrimental vascular effects from anthracycline administration[3,21,61,68]. It is worth noting that acute anthracycline cardiotoxicity in the cardiomyocytes is resolved shortly after discontinuation of the drug and there is an asymptomatic period before latent overt cardiotoxicity[56,58]. It is reasonable to hypothesize this is occurring in the vasculature, but more data is needed to determine if there is a latency period before overt vascular toxicity.

It is important to note the high variability in magnitude of acute increase in arterial stiffness among the identified studies. Similar ages of patients and treatment paradigms suggest that additional factors may contribute to the magnitude of stiffening that occurs with anthracycline chemotherapy. While unknown at this time, these factors may include patient's baseline cardiovascular health, use of combination therapy, simultaneous treatment with cardiovascular medications, and measurement modality. Future work is needed to elucidate what underlying factors contribute to large increases in arterial stiffness with anthracycline chemotherapy. Physiologically, these acute changes could be due to numerous factors including endothelial dysfunction, altered smooth muscle tone, and changes in the extracellular matrix regulated by factors such as catabolic matrix metalloproteases (MMPs)[77]. Importantly, Bai et al. (2004) demonstrated in a pre-clinical model an increase in aortic MMPs within days of doxorubicin administration, thus highlighting the potential for significant vascular remodeling during and in the months following treatment[4].

In addition to acute changes in arterial stiffness, most long-term effects of arterial health have been reported in childhood cancer survivors. Our search included four studies in adults, adolescents, and children who were treated with anthracycline chemotherapy as young children, all four reported significant increases in arterial stiffness when compared to age matched controls with a follow-up time ranging from 1-20 years. Herceg-Cavrak et al. (2011) reported a 13%

increase in aortic PWV in children and adolescents (range 6-20 years old) treated with anthracycline chemotherapy compared to healthy sex, age, matched controls with an average follow up time of 2 years following chemotherapy administration. Conversely, Krystal et al. (2015), reported no differences in cfPWV between 51 age and sex matched controls and 68 adolescent childhood cancer survivors with an average follow-up time of 7 years from end of treatment. However, in a subgroup analysis, patients >18 years old had a 10% increase in cfPWV compared to >18-year-old controls, suggesting that older childhood cancer survivors develop chronic changes in arterial stiffness 5-10 years following treatment. Finally, and most notably, Jenei et al. (2012) reported a 3-fold increase in β -Stiffness with a 10-year follow-up period in adolescent childhood cancer survivors when compared to age and sex matched controls, further indicating that alterations in vascular integrity persist years to decades following anthracycline chemotherapy. Use of radiation therapy is commonly prescribed in treatment of breast cancer and has been shown to increase arterial stiffness in cancer survivors[45]. While it is feasible patients with prior history of radiotherapy could have augmented the changes seen in our analysis, only 17% of patients receiving primary anthracycline chemotherapy had a history of radiotherapy.

Anti-angiogenic tyrosine kinase inhibitors

One study included in our analysis assessed arterial stiffness in patients receiving vascular endothelial growth factor tyrosine kinase inhibitors[1]. Alivon et al. (2015) reported an acute increase in PWV of 11% in the first 7-10 days of therapy administration and statistically significant increases up through the second visit, however, further significance was not observed in either the third or fourth visit. The authors suggested the lack of continued significance may

be attributed to the development of hypertension (systolic blood pressure >140 and/or diastolic blood pressure >90mmHg) in 49% of patients treated with anti-angiogenic drugs; thus, 30% of patients were prescribed calcium channel blockers to control blood pressure. Regardless, other cardiovascular measures such as carotid stiffness assessed by ultrasound remained significant throughout the study with an overall increase of 13% from baseline to the 4th visit. Similarly, patients receiving anti-angiogenic tyrosine kinase inhibitors had a 9% increase in PWV 6 weeks into treatment[67]. These findings suggest anti-angiogenic tyrosine kinase inhibitors cause acute changes in arterial integrity leading to greater arterial stiffness; however, our search did not provide any insight on long term effects of anti-angiogenic tyrosine kinase inhibitors and association of arterial stiffness.

Alkylating agents

Two studies examined the association of alkylating agents and arterial stiffness[55,72]. Willemse et al. (2014) reported no change in aortic PWV with measurements at baseline, 3 months, and 9 months follow up which could be attributed to a small sample size (n=19). In contrast, Sekijima and colleagues (2011; n=43 reported a 10% increase in brachial-ankle PWV from baseline to 12 months post treatment as well as changes in other cardiovascular measures. This suggests that arterial stiffness persists chronically and is prevalent up to a year post treatment with alkylating agents.

Meta-analysis

Two separate meta-analyses were conducted to determine if increases in arterial stiffness was associated with exposure to anticancer therapy. We separately examined the association over

time in patients from pre-treatment baseline to follow-up after treatment and between controls and patient groups with anti-cancer therapy exposure.

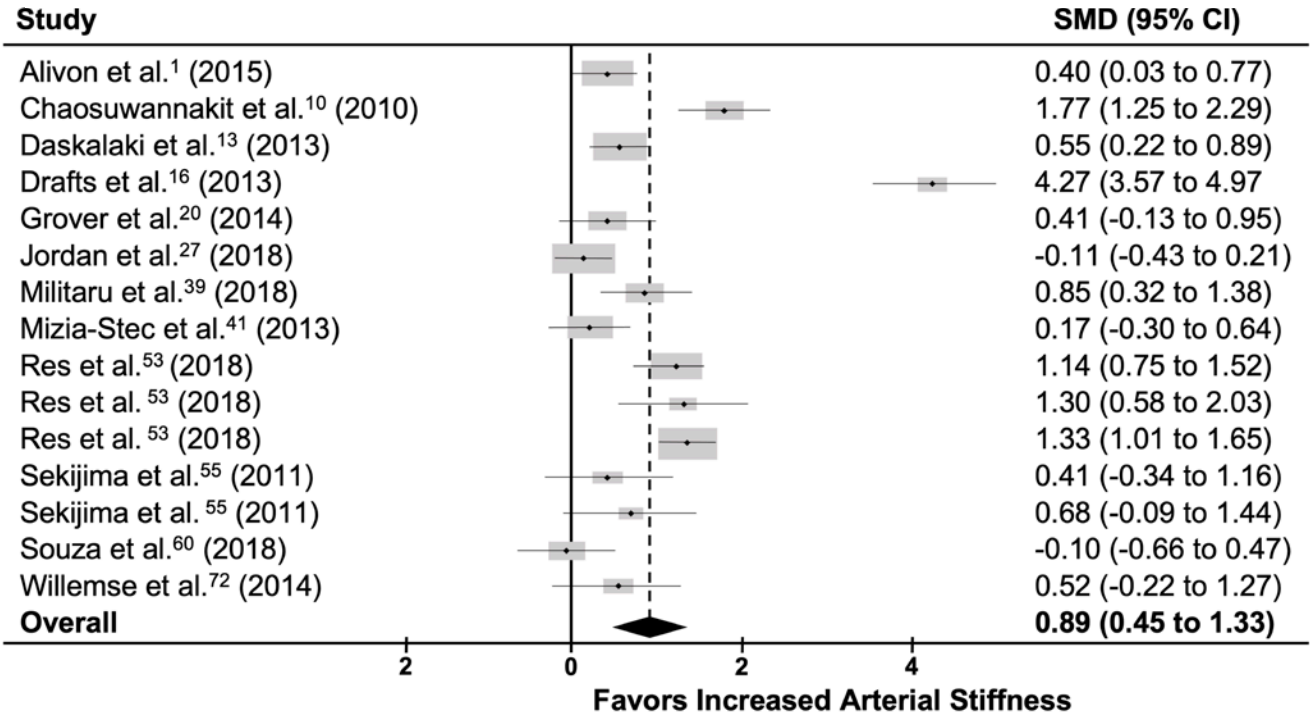
The first analysis included twelve longitudinal studies that examined cancer patients receiving anticancer therapy from pre-treatment baseline to follow-up either during or after completion of treatment (**Table 2-1**)[1,10,13,16,20,27,39,41,53,55,60,72]. The results revealed a statistically significant increase in arterial stiffness following anticancer therapy exposure in cancer patients. Heterogeneity was confirmed with a statistically significant ($P \leq 0.001$) Q statistic (180.99, 305.25) and I^2 (92%, 96%) in both SMD and MD analyses, respectively. The random effects meta-analysis revealed a significant increase in arterial stiffness after anticancer therapy in cancer patients. This increase was seen in the months following chemotherapy compared to baseline values before the start of treatment (standardized mean difference [SMD]=0.890, 95% confidence intervals [CI] = 0.448-1.332, $z= 3.95$, $p \leq 0.0001$; **Figure 2-3**)[1,10,13,16,20,27,39,41,53,55,60,72] (mean difference [MD]=1.505, 95% CI = 0.789-2.221, $z= 4.12$, $p \leq 0.0001$; **Figure 2-4**)[1,10,16,20,39,41,53,55,60,72].

Table 2-1 Baseline to follow-up

Study	Modality	Primary Chemotherapy	Cancer Type	Population (Sample Size, Age in years)	%Weight (SMD, MD)	Follow-Up Duration (mo)	Results (Baseline vs. Follow-up)	Risk of Bias Score (max of 9)
Daskalaki et al [13] (2014)	AoD	Anthracycline	Lymphoma	N=70, 44 ± 19	7.1%, N/A	>3 months	2.48 ± 0.2 vs. 2.36 ± 0.23**	9
Jordan et al.[27] (2018)	AoD	Anthracycline	Breast, Leukemia, Lymphoma, Sarcoma	N=76, 51 ± 12	7.2%, N/A	6 months	1.68 ± 1.6 vs. 1.86 ± 1.6	8
Sekijima et al.[55] (2011)	PWV	Alkylating Agent	Ovarian	N=14, 57 ± 13	6.1%, 4.8%	12 months	14.67 ± 2.88 vs. 16.00 ± 3.44**	9
	PWV	Alkylating Agent	Endometrial	N=14, 57 ± 8	6.1%, 6.5%	12 months	15.09 ± 2.03 vs. 16.67 ± 2.45*	
Willemse et al.[72] (2014)	PWV	Alkylating Agent	Testicular	N=19, 20-54	6.1%, 9.5%	9 months	4.6 ± 0.7 vs. 5.0 ± 0.8	8
Chaosuwannakit et al.[10] (2010)	PWV	Anthracycline	Breast, Leukemia, Lymphoma	N=40, 52 ± 11	6.7%, 6.6%	4 months	6.9 ± 2.3 vs. 13.5 ± 4.7‡	8
Drafts et al.[16] (2013)	PWV	Anthracycline	Breast, Lymphoma, Leukemia	N=53, 50 ± 2	6.3%, 9.9%	6 months	6.7 ± 0.5 vs. 10.1 ± 1†	8
Grover et al.[20] (2014)	PWV	Anthracycline	Breast	N=27, 54 ± 11	6.7% 4.1%	4 months	6.8 ± 3.2 vs. 8.9 ± 6.4*	8
Militaru et al.[39] (2018)	PWV	Anthracycline	Leukemia	N=30, 47 ± 13	6.7%, 9.5%	6 months	7.03 ± 1.07 vs. 7.97 ± 1.12†	9
Mizia-Stec et al.[41] (2013)	PWV	Anthracycline	Breast	N=35, 50 ± 9	6.9%, 1.8%	9-12 months	16.7 ± 11.8 vs. 14.9 ± 8.4	7
Souza et al.[60] (2018)	PWV	Anthracycline	Breast	N=24, 52 ± 9	6.6%, 9.2%	>3 months	7.61 ± 1.21 vs. 7.49 ± 49	9
Alivon et al.[1] (2015)	PWV	Antiangiogenic Tyrosine Kinase Inhibitor	Renal, Liver, Thyroid, Melanoma, Sarcoma	N=57, 59 ± 15	7.1%, 8.4%	7-10 days	10 ± 2.3 vs. 11.1 ± 3.1**	8
Res et al.[53] (2018)	PWV	Antiangiogenic Tyrosine Kinase Inhibitor	Kidney	N=60, 58 ± 10	7.0%, 9.9%	N/A	7.3 ± 0.7 vs. 8.1 ± 0.7‡	8
			Gastrointestinal	N=18, 67 ± 7	6.2%, 9.8% 7.2%, 10.0%	N/A	7.4 ± 0.6 vs. 8.2 ± 0.6‡	
			Bowel	N=93, 65 ± 11		N/A	7.6 ± 0.6 vs. 8.4 ± 0.6‡	

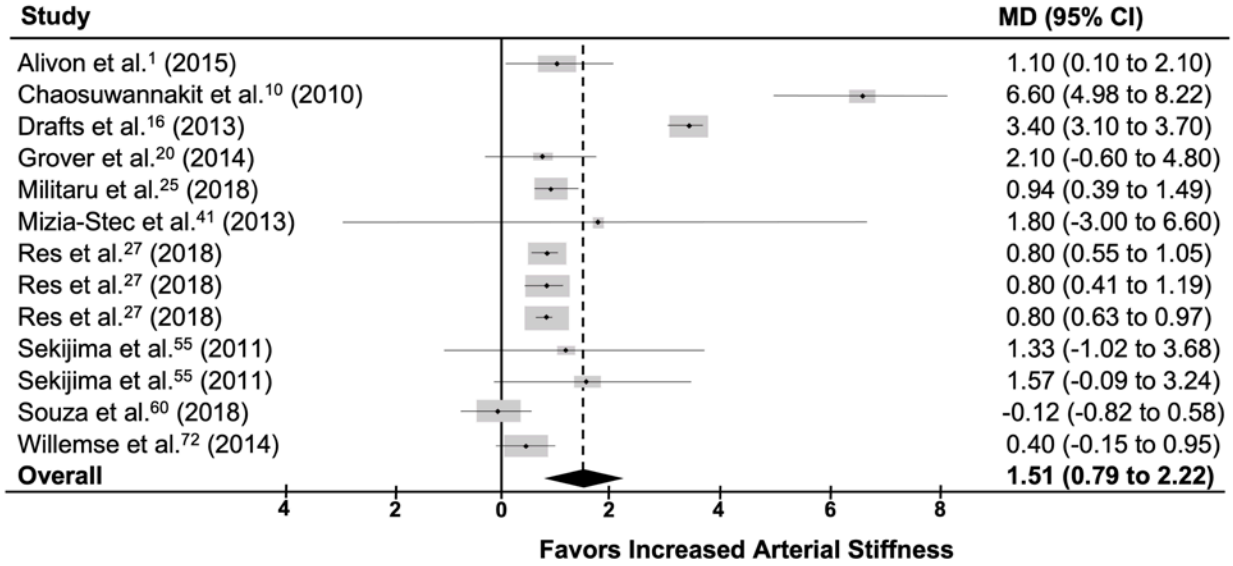
Abbreviations: PWV, pulse wave velocity (m/s); AoD, aortic distensibility ($mmHg^{-1}$); %W, weight of study in analysis
*Indicates significant increases in arterial stiffness (p<.05)
**Indicates significant increases in arterial stiffness (p<.01)
† Indicates significant increases in arterial stiffness (p<.001)
‡Indicates significant increases in arterial stiffness (p<.0001)

Figure 2-3 Standard mean difference results from longitudinal studies



Forest plot illustrating the effect size for each of the 12 longitudinal studies reporting arterial stiffness with anticancer therapy. Overall effect favored greater arterial stiffness following anticancer treatment compared with pretreatment (SMD, 0.890; 95% CI, 0.447-1.332; z=3.95; P≤0.0001)[1,14,15,24-32]. SMD indicates standard mean difference.

Figure 2-4 Mean difference results from longitudinal studies



Forest plot illustrating the effect size for each of the 10 longitudinal studies reporting arterial stiffness with anticancer chemotherapy. Overall effect favored greater arterial stiffness following anticancer treatment compared to pre-treatment. (mean difference [MD] = 1.505, 95% CI = 0.789-2.221, z= 4.12, P≤0.0001)[1,10,16,20,39,41,53,55,60,72]

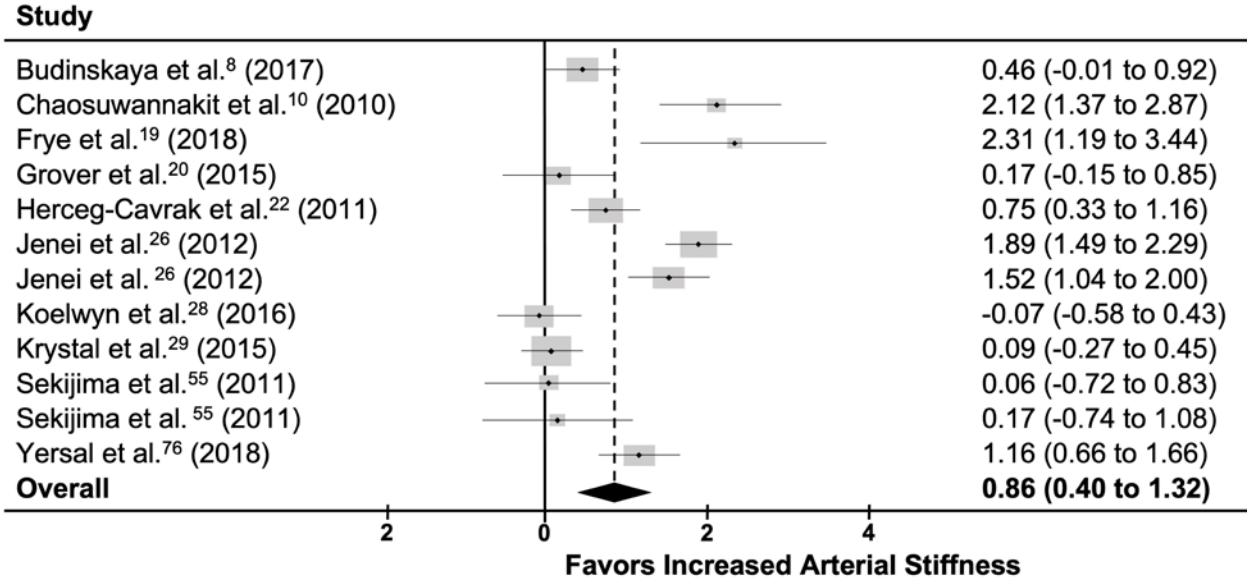
The second analysis included ten cross-sectional studies that examined differences in arterial stiffness between cancer patients with a history of anticancer therapy and age, sex, cardiovascular risk factor matched control subjects (**Table2-2**)[8,10,19,20,22,26,28,29,55,76]. The results revealed a statistically significant increase in arterial stiffness in the cancer patient group with prior anticancer therapy exposure. Heterogeneity of the analysis was confirmed with a statistically significant ($p \leq 0.001$) Q statistic (94.59, 132.74) and I^2 (88.4%, 94.0%) for SMD and MD analyses, respectively. The random effects meta-analysis revealed arterial stiffness was significantly greater in cancer survivors treated with anticancer therapy than with healthy controls ([SMD] = 0.860, 95% CI= 0.402-1.318, z= 3.68, p= 0.0002; **Figure 2-5**) [8,10,19,20,22,26,28,29,55,76] ([MD] = 1.437, 95% [CI] = 0.426-2.448, z= 2.79, p= 0.0052; **Figure 2-6**) [8,10,20,22,28,29,55,76].

Table 2-2 Patient versus control

Study	Modality	Primary Chemotherapy	Cancer Type	Patient Population (Sample Size, %W)	Patient Age (yrs)	Controls (Sample Size, %W)	Control Age (yrs)	Results (Patient vs. Control)	Risk of Bias Score (max of 9)
Frye et al.[19] (2018)	ß Stiffness Index	Anthracycline	Breast, Lymphoma, Pancreatic, Prostate	N=11, 6.2%	56 ± 2	N=11, 6.2%	57 ± 4	8 ± 0.8 vs. 6.3 ± 0.6*	8
Jenei et al.[26] (2012)	ß Stiffness Index	Alkylating Agent	Leukemia, Lymphoma	N=29, 8.9%	14 ± 5	N=72, 8.9%	15 ± 5	4.12 ± 2.32 vs. 2.08 ± 0.6**	8
	ß Stiffness Index	Anthracycline	Leukemia, Lymphoma	N=67, 9.2%	15 ± 4	N=72, 9.2%	15 ± 5	6.45 ± 3.25 vs. 2.08 ± 0.6**	
Sekijima et al.[55] (2011)	PWV	Alkylating Agent	Ovarian	N=14, 7.7%	57 ± 13	N=12, 7.7%	55 ± 11	16.0 ± 3.44 vs. 15.26 ± 2.24**	9
	PWV	Alkylating Agent	Endometrial	N=14, 7.1%	57 ± 8	N=7, 7.1%	57 ± 5	16.7 ± 2.44 vs. 16.18 ± 3.56*	
Budinskaya et al.[8] (2017)	PWV	Anthracycline	Leukemia, Lymphoma	N=21, 9.0%	19-24	N=122, 9.0%	19-24	7.4 ± 1.08 vs. 6.98 ± 0.88*	4
Chaosuwannakit et al.[10] (2010)	PWV	Anthracycline	Breast, Lymphoma, Leukemia	N=40, 7.8%	52 ± 11	N=13, 7.8%	53 ± 11	13.5 ± 4.7 vs. 4.6 ± 0.9‡	8
Grover et al.[20] (2015)	PWV	Anthracycline	Breast	N=27, 8.1%	54 ± 11	N=12, 8.1%	54 ± 13	8.9 ± 6.4 vs. 7.9 ± 4.0*	8
Herceg-Cavrak et al.[22] (2011)	PWV	Anthracycline	Lymphoma, Sarcomas	N=53, 9.1%	14 ± 4	N=45, 9.1%	12 ± 3	6.24 ± 1.34 vs. 5.42 ± 0.69†	5
Koelwyn et al.[28] (2016)	PWV	Anthracycline	Breast	N=30, 8.8%	61 ± 7	N=30, 8.8%	62 ± 8	7.75 ± 1.78 vs. 7.78 ± 1.47	7
Krystal et al.[29] (2015)	PWV	Anthracycline	Lymphoma, Leukemia, Sarcomas	N=68, 9.3%	17 ± 6	N=51, 9.3%	19 ± 6	5.74 ± 1.1 vs. 5.65 ± 1.88	7
Yersal et al.[76] (2018)	PWV	Anthracycline	Breast	N=45, 8.8%	53 ± 9	N=30, 8.8%	50 ± 11	7.3 ± 1.2 vs. 5.8 ± 1.4†	4

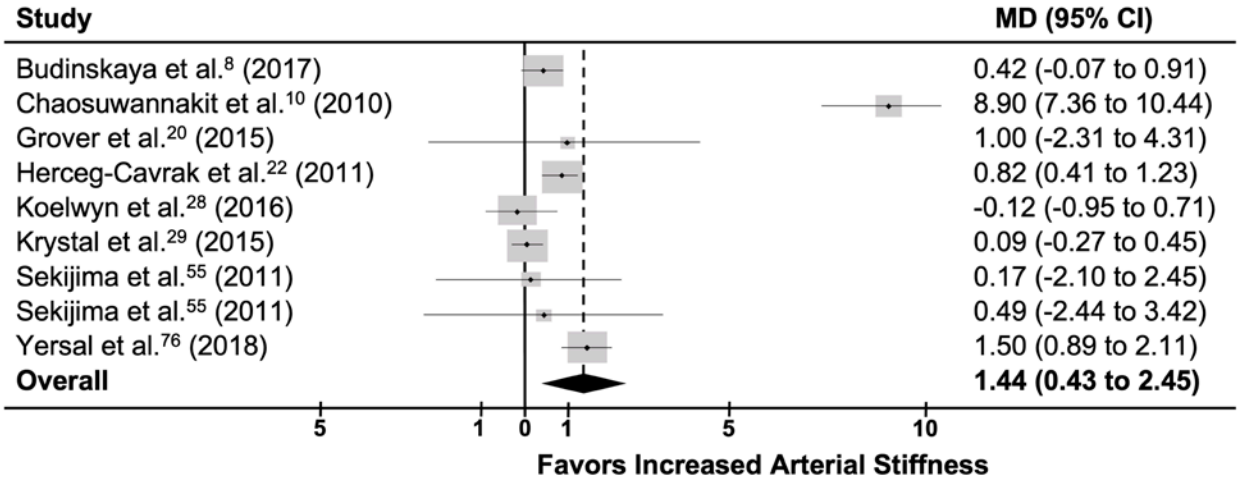
Abbreviations: PWV, pulse wave velocity (m/s); ß Stiffness Index (U)
*Indicates significant increases in arterial stiffness (p<.05)
**Indicates significant increases in arterial stiffness (p<.01)
† Indicates significant increases in arterial stiffness (p<.001)
‡Indicates significant increases in arterial stiffness (p<.0001)

Figure 2-5 Standard mean difference results from cross sectional studies



Forest plot illustrating the effect size for each of the 10 cross-sectional studies reporting arterial stiffness with anticancer chemotherapy. Overall effect favored greater arterial stiffness following anticancer treatment compared with matched healthy control participants (standardized mean difference, 0.860; 95% CI, 0.402-1.318; z= 3.68; P= 0.0002).[2,30-38]

Figure 2-6 Mean difference results from cross sectional studies



Forest plot illustrating the effect size of the 8 cross-sectional studies reporting arterial stiffness with anticancer chemotherapy. Overall effect favored greater arterial stiffness following anticancer treatment compared to healthy matched control participants. (mean difference [MD]= 1.437, 95% CI= 0.426-2.448, z= 2.79, P=0.0052).[8,10,20,22,28,29,55,76]

Table 2-3 outlines the subgroup analyses of several different treatment effect modifiers within the studies. Treatment modifiers included type of chemotherapy consisting of anthracycline groups and non-anthracycline groups (tyrosine kinase inhibitors, alkylating agents) and time points of <6 months, 6-12 months, and >12 months of exposure to anti-cancer therapy. We sorted the cancer patient groups and control groups from all 19 studies into the appropriate treatment modifier groups and time modifier groups. A statistically significant difference in arterial stiffness was found between both chemotherapy treatment modifiers and each time point versus the corresponding control group (i.e., anthracycline vs. control, non-anthracycline vs. control, <6months vs. control, 6-12 months vs. control, >12 months vs. control). There were no statistically significant differences in arterial stiffness found between studies at different time points (<6months vs. 6-12 months, <6months vs. >12 months, 6-12 months vs. >12 months). However, a significant difference in arterial stiffness was observed between the chemotherapy modifier groups of anthracycline vs. non-anthracycline comparison groups ([SMD] =0.20, 95% CI= 0.001-0.41 p= 0.048). Forest plots for the time point and drug comparisons against control groups can be found in **Figure 2-7** [1, 8, 10, 13, 16, 19, 20, 22, 26-29, 39, 41, 53, 55, 60, 72, 76].

Table 2-3 Treatment effect modifiers

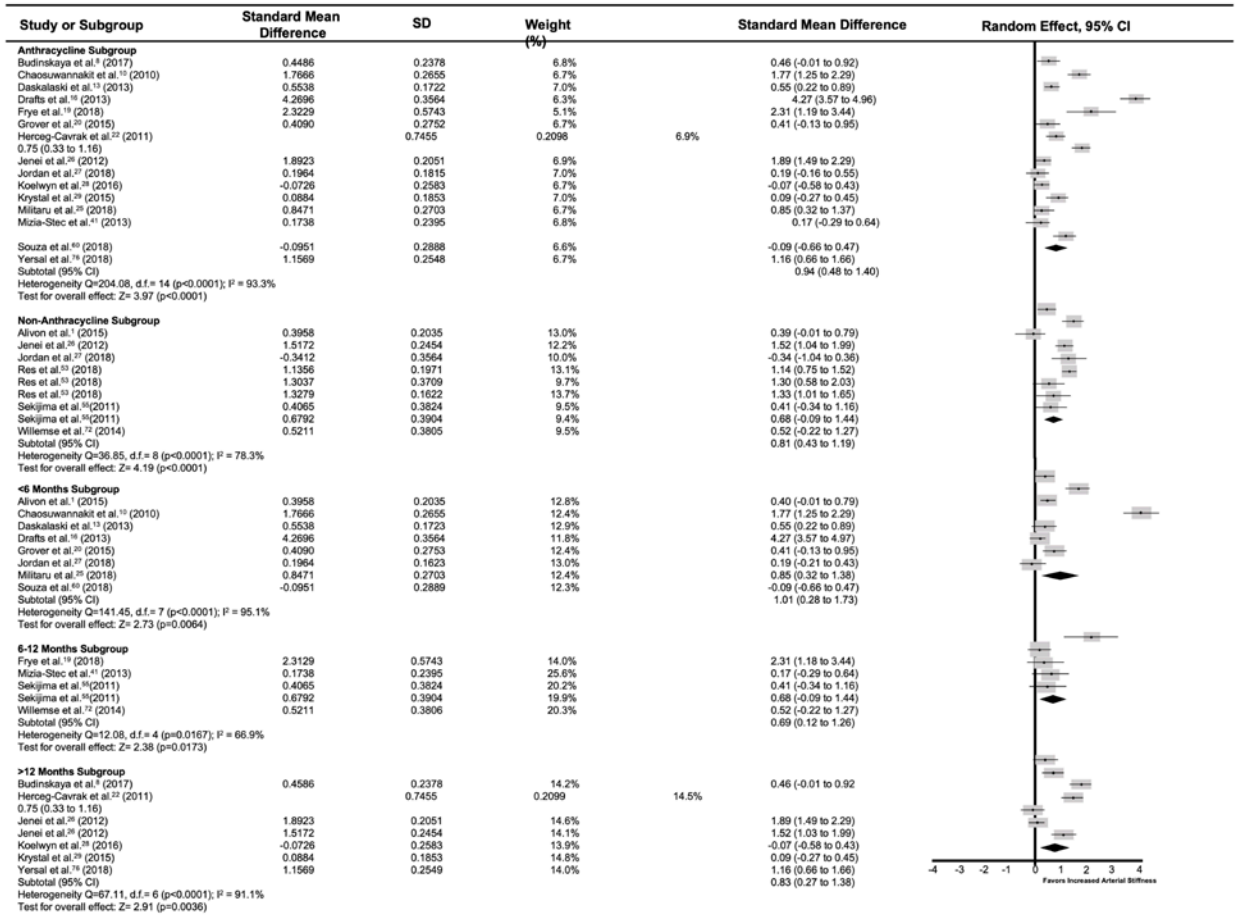
Treatment Modifier	No. of Studies	No. of Patients by Arm		SMD			
				Between Patient and Control Arms*		Between Modifier Subgroups †	
		Patient	Control	Mean (95% CI), direction	*P*	Mean (95% CI), direction	*P*
Time							
<6 months	8	373	366	1.01 (0.28-1.73)	.0064	-0.17 (-0.52-0.17), <6 months *v* 6-12 months	0.33
6-12 months	4	87	90	0.69 (0.12-1.26)	.0173	0.30 (-0.04-0.65), 6-12 months *v* >12 months	0.09
>12 months	6	313	422	0.83 (0.27-1.38)	.0036	0.13 (-0.09-0.36), <6 months *v* >12 months	0.25
Chemotherapy							
Anthracycline	15	635	701	.94 (0.48-1.40)	<.0001	0.20 (0.001-0.41), anthracycline *v*	0.04
Non-Anthracycline	6	310	349	0.81 (0.43-1.19)	< .0001	non-anthracycline	

Abbreviations: SMD, standard mean difference

*Represents the SMD between patient and modifier subgroup (eg, patient *v* control <6 months into treatment, anthracycline group *v* control).

† Represents the SMD between modifier subgroups (eg. anthracycline *v* non-anthracycline groups, <6months *v* 6-12 months).

Figure 2-7 Standard mean difference results from subgroup analyses



Forest plots illustrating the effect size for each subgroup analysis separated by time point and drug class. Overall effect for each analysis favored greater arterial stiffness with each drug class and all time points after treatment when compared to healthy control participants (Anthracycline subgroup vs. control, standard mean difference [SMD] = 0.94, 95% [CI] = 0.48-1.40, z = 3.97, P<0.0001; Non-anthracycline subgroup vs. control, [SMD] = 0.81, 95% [CI] = 0.43-1.19, z = 4.19, p<0.0001; <6months of treatment vs. control, [SMD] = 1.01, 95% [CI] = 0.28-1.73, z = 2.73, p=0.00064; 6-12 months treatment vs. control, [SMD] = 0.69, 95% [CI] = 0.12-1.26, z = 2.38, p=0.0173; >12 months treatment vs. control, [SMD] = 0.83, 95% [CI] = 0.27-1.38, z = 2.91, p=0.0036)[1,8,10,13,16,19,20,22,26-29,39,41,53,55,60,72,76]

Sensitivity analysis

To ensure reliability of the present meta-analyses with our high scores of heterogeneity, we performed a sensitivity analysis to evaluate the robustness of our SMD and MD. One by one removal of studies revealed significance in a random effect model was maintained through the entire analysis. Sensitivity analysis showed that the SMD and MD did not vary substantially with the exclusion of any one study.

Discussion

The present systematic review and meta-analysis represent the most recent and updated work summarizing the evidence for increases in arterial stiffness in cancer patients receiving anticancer therapy, which has previously been hypothesized as one of several major contributing factors for the increased risk of premature CVD in this population[45,69]. Overall, the meta-analysis determined that cancer patients after anticancer therapy have a significantly increased arterial stiffness. Additionally, subgroup analyses revealed arterial stiffness is increased at all follow up time points and in response to both anthracycline and non-anthracycline treatment groups. This is the first systematic review and meta-analysis to demonstrate this significant relationship between increased arterial stiffness and treatment with anticancer therapy. The clinical implications of these findings are several-fold. First, these findings expand our understanding of the effects of anticancer therapy on the cardiovascular system beyond the heart, by demonstrating that increases in arterial stiffness are detectable early after treatment and persists years into survivorship. This is significant given that a small increase in arterial stiffness in the general population increase the risk of CVD by more than 10%[70]. Second, the results support the use of arterial stiffness as part of a targeted vascular imaging strategy, that, based on its known association with CVD outcomes, can be used for patient risk stratification, identification of early cardiovascular injury during treatment, and detect long-term cardiovascular injury into survivorship.

The present study showed that anticancer therapy is associated with an increase in arterial stiffness, supporting the concept that anticancer therapy-induced cardiotoxicity extends beyond the left ventricle with direct vascular damage[18,64]. Several recent reviews have highlighted the importance of arterial stiffness in the evaluation of cardiovascular health in the general and non-

cancer patient populations, particularly for the prediction of all-cause cardiovascular outcomes[30]. Both local and regional assessments of arterial stiffness are significantly associated with an increased risk of developing various adverse cardiovascular outcomes[7,32]. Beyond its predictive capabilities, arterial stiffness has been shown to be directly associated with left ventricular dysfunction, left ventricular hypertrophy, and heart failure over time[45,47]. Stiffening of large arteries causes early return of peripheral reflection waves which augments late systolic pressure rather than early diastolic pressure; this limits coronary perfusion and increases myocardial oxygen demand[25]. Thus, the overall importance of arterial stiffness as it directly relates to both overall cardiovascular health and changes in left ventricular mechanics has made it a parameter of interest that provides clinical insight beyond traditional risk factors such as aging, Systematic COronary Risk Evaluation (SCORE), and Framingham risk score[5,33,40] and may provide a clinical tool for the monitoring of late developing cardiovascular outcomes.

In our literature search, we came across various methods of measuring arterial stiffness, including both local and regional measurements of arterial stiffness, and measures of compliance, distensibility, and elasticity. In the present study, we included measures of regional stiffness (PWV) and local measurements (AoD, β stiffness index), all of which have been shown to be associated with the manifestation of CVD[74]. PWV is a direct measure of stiffness which records the speed of the pulse wave as it travels down the arterial tree, thus encompassing both large arteries and small muscular arteries[35] and is considered the gold standard for measuring arterial stiffness[33,73]. β stiffness index and AoD also provide a direct measure of arterial stiffness by measuring changes in local pressure and arterial diameter in areas that are likely to develop atherosclerotic lesions[47]. While there is some potential for variability between local and regional measurements and within those that are pressure/volume related, six studies[1,10,20,26,41,53] included

multiple measurements of arterial stiffness. Notably, Alivon et al.[1]reported significant differences in local measures of carotid β stiffness index, carotid distensibility, and regional carotid-femoral PWV over the course of treatment. These values remained significant after adjustment for blood pressure and adds to the rigor and reproducibility of these measurements with this specific population.

Exact pathophysiological mechanisms for increased arterial stiffness following anti-cancer chemotherapy are currently not known; however, we speculate that many of the same mechanisms contributing to arterial stiffness in response to aging and various types of CVD[31,46] are also occurring in cancer patients receiving systemic anticancer therapy. Both normal aging and CVD progression are associated with vascular matrix remodeling and endothelial dysregulation of vascular smooth muscle tone as a result of increases in oxygen free radicals and overexpression of inflammatory cytokines[15,31,44]. Importantly, anthracyclines, tyrosine kinase inhibitors, and alkylating treatments have all been shown to directly or indirectly promote an intracellular oxidant to antioxidant imbalance, thereby eliciting oxidative stress[12,57,59]. Within the vascular endothelium, nitric oxide control of vascular smooth muscle is decreased in response to elevations in oxidative stress[38,71]. Additionally, oxidative stress causes intracellular damage to the endothelium and vascular smooth muscle layers through DNA damage, lipid peroxidation, and alteration of key cellular signaling pathways. These changes induce inflammation, necrosis, and apoptosis if damage is significant enough[48,63]. Together, oxidative injury coupled with increased inflammatory cytokines also leads to an abnormal production of collagen and depressed production of normal elastin. Such alterations in the balance of these vascular structural proteins causes loss of elasticity and arterial stiffening[77]. These mechanistic

possibilities will require further investigation to determine whether they are relevant in the context of chemotherapy associated arterial stiffening.

It is also well established that arterial blood pressure can significantly impact measurements of arterial stiffness and must be considered with interpretation of the changes in arterial stiffness reported in the present analysis[66]. Importantly, Drafts et al. (2013) demonstrated that patients with a higher systolic pressure at baseline had a faster increase in arterial stiffness, assessed via PWV, compared to those with lower pressures[16]. This is a critical finding that highlights the integrative nature of arterial pressure and changes in stiffness and the importance of considering both physiological outcomes in the cancer patient receiving anti-cancer therapy. However, in the present analysis, several studies corrected for blood pressure[1,8,13,29], and all studies but two studies reported no change in arterial pressure with therapy[28,76]. In addition, the risk of treatment-induced hypertension is primarily limited to drugs inhibiting the vascular endothelial growth factor signaling pathway[23,75], of which was used in only two of the studies included in the analysis[1,53]. Of those, Alivon et al. (2014) adjusted for changes in pressure and Res et al. (2018) report no changes in pressure. While this does not exclude the possible confounding effects of small changes in pressure on the changes in stiffness observed, it does suggest that other factors may be at play. Future prospective investigations are needed to further evaluate the relationship between changes in arterial stiffness as it relates pressure in those treated for cancer and their impact on clinical outcomes.

Clinical perspective

Increased arterial stiffness is relevant for patient prognosis, as greater arterial stiffness is associated with all-cause mortality and fatal/non-fatal cardiovascular outcomes (e.g., myocardial

infarction, stroke, revascularization, hypertension, and heart failure) and is thus increasingly used in CVD risk stratification models[17,32,37,40,70]. In our meta-analysis, anticancer therapy was associated with greater arterial stiffness compared to both pre-treatment baseline and untreated controls. Importantly, the findings from our MD analysis have extensive clinical impact. Our analysis revealed a 1.5 m/s increase in PWV across treatment in patients (**Figure 2-4**) and a 1.4 m/s increase in PWV in cancer survivors with a history of anticancer therapy when compared to cancer-free controls (**Figure 2-6**). This is clinically significant because every 1m/s increase in PWV has been reported to equate to an age, sex, and risk factor adjusted 14%, 15%, and 15% increased risk in cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively[70], which is consistent with the reported increased CVD risk in this population[69]. These findings fill a serious gap in knowledge needed for the development of evidence-based guidelines for the surveillance of vascular damage[2,6,9]. Like how direct cardiomyocyte damage and decreased cardiac function led to the development of clinical guidelines to direct surveillance of cardiac damage via various imaging strategies[2], the present study, coupled with reports of direct vascular damage, support the need for specific vascular monitoring. An important outcome of this study is that arterial stiffness, which is a simple, non-invasive, cost-efficient, and reproducible measurement, is an approach that should be considered as part of recommended care in those at-risk patients receiving cardiotoxic anticancer therapies. Cancer patients receiving cardiotoxic therapies are innately considered a high-risk group as many patients diagnosed with cancer have subclinical or overt clinical CVD. Measuring arterial stiffness prior to initiation of treatment can serve as a cumulative index of vascular health as well as an assessment of risk for the development of cardiotoxicity, both during and following

treatment, that goes beyond those provided by measurements of left ventricular ejection fraction alone.

Previous works have investigated potential therapeutic interventions to restore arterial elasticity in ageing populations and decrease stiffness in patient populations. Increased carotid artery distensibility and decreased β stiffness has been reported in middle/older aged men and women following moderate and high intensity aerobic exercise interventions[14,43,65] and antioxidant supplementation of vitamin C and E, and inorganic nitrates[50,51] have been shown to decrease PWV in hypertensive populations and older adults with increased CVD risk. Pharmacological agents such as angiotensin converting enzyme inhibitors, statins, and angiotensin receptor blockers have been demonstrated to decrease arterial stiffness in hypertension and end stage renal disease[3,21,68,71]. These decreases are hypothesized to be due to decreased levels of oxidative stress and inflammatory cytokine production, enhanced nitric oxide bioavailability, and decreased blood pressure. Further studies are needed to investigate the therapeutic effects of exercise, antioxidant, and cardiovascular medications to determine the effects on anticancer therapy associated increases in arterial stiffness in cancer survivors.

Study limitations

There were four main limitations of the present meta-analysis and systematic review. First, as discussed above, potential methodological limitations include dependence on blood pressure and age. Only four of the included studies[1,8,13,29] were adjusted for systolic blood pressure, sex, and body mass index; however, most of the studies included age, cardiovascular risk factor, and sex matched controls or patients who served as their own controls from start of treatment to follow-up. However, there were only two studies that reported a significant difference in blood pressure

between controls and patient groups[28,76]. In the other seventeen studies, there were no significant differences in blood pressure between patients and controls and longitudinally between baseline and follow-up periods in cancer patients as they received treatment. Therefore, blood pressure, while a critical confounding factor in determining arterial stiffness, appeared to have a minor role in the reported increases in arterial stiffness of the present analysis. Secondly, we could not control for variable drug combination and dosage between and within studies. Third, there are the potential factors such as obesity, hypertension, and use of medications which could have influenced arterial stiffness outside of anticancer therapy, although most studies measured changes over time which would eliminate this potential limitation. Regardless, our analysis showed significant increases in arterial stiffness in various methods of measuring arterial stiffness and in patients on different combinations of anticancer drugs translating the potential use of arterial stiffness in clinical practice for a wider population than just those receiving known cardiotoxic chemotherapies. Lastly, we recognize some statistical limitations exist with using SMD in weighting studies, limitations in standardizing different modalities that measure arterial stiffness, the possibility of upweighting some individual studies, and high levels of heterogeneity. However, our sensitivity analyses-maintained significance even with removing higher weighted studies. We also acknowledge the multi-testing burden presented with our analyses since three studies contained both longitudinal and cross-sectional data.

Conclusions

The results of the present meta-analysis show an associated increase in arterial stiffness in patients receiving anticancer therapy when compared to healthy, age, and sex matched controls, and from baseline prior to treatment when compared over time during treatment or after

completion of treatment. Local and regional arterial stiffness measurements have independent predictive ability in all-cause mortality and cardiovascular events in various patient populations that share similar cardiovascular risk factors as cancer patients receiving cardiotoxic anticancer therapy. These findings support the need to measure vascular health outside of monitoring changes in left ventricular function in this population through course of treatment and in the survivorship phase to monitor/prevent the onset of overt CVD.

References

1. Alivon M, Giroux J, Briet M, Goldwasser F, Laurent S and Boutouyrie P. Large artery stiffness and hypertension after antiangiogenic drugs: influence on cancer progression. J Hypertens. 2015;33:1310-7.

2. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, Dent S, Douglas PS, Durand JB, Ewer M, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35:893-911.

3. Asmar RG, London GM, O'Rourke ME, Safar ME, Coordinators RP and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. Hypertension. 2001;38:922-6.

4. Bai P, Mabley JG, Liaudet L, Virag L, Szabo C and Pacher P. Matrix metalloproteinase activation is an early event in doxorubicin-induced cardiotoxicity. Oncol Rep. 2004;11:505-8.

5. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014;63:636-646.

6. Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, Skopicki H, Lenihan DJ, Gheorghiade M, Lyon AR, et al. Cancer Therapy-Related Cardiac Dysfunction and Heart Failure: Part 1: Definitions, Pathophysiology, Risk Factors, and Imaging. Circ Heart Fail. 2016;9:e002661.

7. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P and Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension. 2002;39:10-5.

8. Budinskaya K, Puchnerova V, Svacinova J, Novak J, Hrstkova H, Novakova M, Pekarova A, Pekar M and Novakova Z. Non-invasive assessment of vascular system function and damage induced by anthracycline treatment in the pediatric cancer survivors. Physiol Res. 2017;66:S553-S560.

9. Campia U, Moslehi JJ, Amiri-Kordestani L, Barac A, Beckman JA, Chism DD, Cohen P, Groarke JD, Herrmann J, Reilly CM, et al. Cardio-Oncology: Vascular and Metabolic Perspectives: A Scientific Statement From the American Heart Association. Circulation. 2019;139:e579-e602.

10. Chaosuwannakit N, D'Agostino R, Jr., Hamilton CA, Lane KS, Ntim WO, Lawrence J, Melin SA, Ellis LR, Torti FM, Little WC, et al. Aortic stiffness increases upon receipt of anthracycline chemotherapy. J Clin Oncol. 2010;28:166-72.

11. Chirinos JA, Segers P, Hughes T and Townsend R. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;74:1237-1263.

12. Conklin KA. Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness. Integr Cancer Ther. 2004;3:294-300.

13. Daskalaki M, Makris T, Vassilakopoulos T, Moyssakis I, Siakantaris M, Angelopoulou M, Papadogiannis D, Vaiopoulos G and Pangalis G. Effects of anthracyclines on aortic distensibility in patients with lymphomas: a prospective study. Hellenic J Cardiol. 2014;55:191-6.

14. DeVan AE and Seals DR. Vascular health in the ageing athlete. Exp Physiol. 2012;97:305-10.

15. Donato AJ, Black AD, Jablonski KL, Gano LB and Seals DR. Aging is associated with greater nuclear NF kappa B, reduced I kappa B alpha, and increased expression of proinflammatory cytokines in vascular endothelial cells of healthy humans. Aging Cell. 2008;7:805-12.

16. Drafts BC, Twomley KM, D'Agostino R, Jr., Lawrence J, Avis N, Ellis LR, Thohan V, Jordan J, Melin SA, Torti FM, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging. 2013;6:877-85.

17. Duprez DA and Cohn JN. Arterial stiffness as a risk factor for coronary atherosclerosis. Curr Atheroscler Rep. 2007;9:139-44.

18. Duquaine D, Hirsch GA, Chakrabarti A, Han Z, Kehrer C, Brook R, Joseph J, Schott A, Kalyanaraman B, Vasquez-Vivar J, et al. Rapid-onset endothelial dysfunction with adriamycin: evidence for a dysfunctional nitric oxide synthase. Vasc Med. 2003;8:101-7.

19. Frye JN, Sutterfield SL, Caldwell JT, Behnke BJ, Copp SW, Banister HR and Ade CJ. Vascular and autonomic changes in adult cancer patients receiving anticancer chemotherapy. J Appl Physiol (1985). 2018;125:198-204.

20. Grover S, Lou PW, Bradbrook C, Cheong K, Kotasek D, Leong DP, Koczwara B and Selvanayagam JB. Early and late changes in markers of aortic stiffness with breast cancer therapy. Intern Med J. 2015;45:140-7.

21. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME and London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation. 2001;103:987-92.

22. Herceg-Cavrak V, Ahel V, Batinica M, Matec L and Kardos D. Increased arterial stiffness in children treated with anthracyclines for malignant disease. Coll Antropol. 2011;35:389-95.

23. Herrmann J, Yang EH, Iliescu CA, Cilingiroglu M, Charitakis K, Hakeem A, Toutouzas K, Leesar MA, Grines CL and Marmagkiolis K. Vascular Toxicities of Cancer Therapies: The Old and the New--An Evolving Avenue. Circulation. 2016;133:1272-89.

24. Higgins JPT GS. The standardized mean difference Cochrane Handbook for Systematic Reviews of Interventions
The Cochrane Collaboration 2011(1): 9.2.3.2.

25. Ikonomidis I, Lekakis J, Papadopoulos C, Triantafyllidi H, Paraskevaidis I, Georgoula G, Tzortzis S, Revela I and Kremastinos DT. Incremental value of pulse wave velocity in the determination of coronary microcirculatory dysfunction in never-treated patients with essential hypertension. Am J Hypertens. 2008;21:806-13.

26. Jenei Z, Bardi E, Magyar MT, Horvath A, Paragh G and Kiss C. Anthracycline causes impaired vascular endothelial function and aortic stiffness in long term survivors of childhood cancer. Pathol Oncol Res. 2013;19:375-83.

27. Jordan JH, Castellino SM, Melendez GC, Klepin HD, Ellis LR, Lamar Z, Vasu S, Kitzman DW, Ntim WO, Brubaker PH, et al. Left Ventricular Mass Change After Anthracycline Chemotherapy. Circ Heart Fail. 2018;11:e004560.

28. Koelwyn GJ, Lewis NC, Ellard SL, Jones LW, Gelinas JC, Rolf JD, Melzer B, Thomas SM, Douglas PS, Khouri MG, et al. Ventricular-Arterial Coupling in Breast Cancer Patients After Treatment With Anthracycline-Containing Adjuvant Chemotherapy. Oncologist. 2016;21:141-9.

29. Krystal JI, Reppucci M, Mayr T, Fish JD and Sethna C. Arterial stiffness in childhood cancer survivors. Pediatr Blood Cancer. 2015;62:1832-7.

30. Kullo IJ and Malik AR. Arterial ultrasonography and tonometry as adjuncts to cardiovascular risk stratification. J Am Coll Cardiol. 2007;49:1413-26.

31. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. Circulation. 2003;107:490-7.

32. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P and Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37:1236-41.

33. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588-605.

34. Liu CY, Chen D, Bluemke DA, Wu CO, Teixido-Tura G, Chugh A, Vasu S, Lima JA and Hundley WG. Evolution of aortic wall thickness and stiffness with atherosclerosis: long-term follow up from the multi-ethnic study of atherosclerosis. Hypertension. 2015;65:1015-9.

35. London GM and Pannier B. Arterial functions: how to interpret the complex physiology. Nephrol Dial Transplant. 2010;25:3815-23.

36. Mackenzie IS, Wilkinson IB and Cockcroft JR. Assessment of arterial stiffness in clinical practice. QJM. 2002;95:67-74.

37. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006;113:657-63.

38. McAllister RM and Laughlin MH. Vascular nitric oxide: effects of physical activity, importance for health. Essays Biochem. 2006;42:119-31.

39. Militaru A, Avram A, Cimpean AM, Iurciuc M, Matusz P, Lighezan D and Militaru M. The Assessment of Left Ventricle Function and Subclinical Atherosclerosis in Patients with Acute Myeloid Leukemia. In Vivo. 2018;32:1599-1607.

40. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D and Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation. 2010;121:505-11.

41. Mizia-Stec K, Goscinska A, Mizia M, Haberka M, Chmiel A, Poborski W and Gasior Z. Anthracycline chemotherapy impairs the structure and diastolic function of the left ventricle and induces negative arterial remodelling. Kardiol Pol. 2013;71:681-90.

42. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA and Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

43. Moreau KL, Donato AJ, Seals DR, DeSouza CA and Tanaka H. Regular exercise, hormone replacement therapy and the age-related decline in carotid arterial compliance in healthy women. Cardiovasc Res. 2003;57:861-8.

44. Moreau KL, Gavin KM, Plum AE and Seals DR. Oxidative stress explains differences in large elastic artery compliance between sedentary and habitually exercising postmenopausal women. Menopause. 2006;13:951-8.

45. Mozos I, Borzak G, Caraba A and Mihaescu R. Arterial stiffness in hematologic malignancies. Onco Targets Ther. 2017;10:1381-1388.

46. O'Rourke MF and Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol. 2007;50:1-13.

47. Oliver JJ and Webb DJ. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arterioscler Thromb Vasc Biol. 2003;23:554-66.

48. Pacher P and Szabo C. Role of peroxynitrite in the pathogenesis of cardiovascular complications of diabetes. Curr Opin Pharmacol. 2006;6:136-41.

49. Pannier BM, Avolio AP, Hoeks A, Mancia G and Takazawa K. Methods and devices for measuring arterial compliance in humans. Am J Hypertens. 2002;15:743-53.

50. Plantinga Y, Ghiadoni L, Magagna A, Giannarelli C, Franzoni F, Taddei S and Salvetti A. Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. Am J Hypertens. 2007;20:392-7.

51. Rammos C, Hendgen-Cotta UB, Sobierajski J, Bernard A, Kelm M and Rassaf T. Dietary nitrate reverses vascular dysfunction in older adults with moderately increased cardiovascular risk. J Am Coll Cardiol. 2014;63:1584-5.

52. Rao G, Lopez-Jimenez F, Boyd J, D'Amico F, Durant NH, Hlatky MA, Howard G, Kirley K, Masi C, Powell-Wiley TM, et al. Methodological Standards for Meta-Analyses and Qualitative Systematic Reviews of Cardiac Prevention and Treatment Studies: A Scientific Statement From the American Heart Association. Circulation. 2017;136:e172-e194.

53. Res E, Kyvelou SM, Vlachopoulos C, Manousou K, Tousoulis D, Stefanadis C and Pektasides D. Metastatic malignancies and the effect on arterial stiffness and blood pressure levels: the possible role of chemotherapy. Onco Targets Ther. 2018;11:6785-6793.

54. Rogers WJ, Hu YL, Coast D, Vido DA, Kramer CM, Pyeritz RE and Reichek N. Age-associated changes in regional aortic pulse wave velocity. J Am Coll Cardiol. 2001;38:1123-9.

55. Sekijima T, Tanabe A, Maruoka R, Fujishiro N, Yu S, Fujiwara S, Yuguchi H, Yamashita Y, Terai Y and Ohmichi M. Impact of platinum-based chemotherapy on the progression of atherosclerosis. Climacteric. 2011;14:31-40.

56. Shan K, Lincoff AM and Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med. 1996;125:47-58.

57. Sies H. Oxidative stress: oxidants and antioxidants. Exp Physiol. 1997;82:291-5.

58. Simunek T, Sterba M, Popelova O, Adamcova M, Hrdina R and Gersl V. Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. Pharmacol Rep. 2009;61:154-71.

59. Soultati A, Mountzios G, Avgerinou C, Papaxoinis G, Pectasides D, Dimopoulos MA and Papadimitriou C. Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications. Cancer Treat Rev. 2012;38:473-83.

60. Souza CA, Simoes R, Borges KBG, Oliveira AN, Zogeib JB, Alves B, Malachias MVB, Drummond-Lage AP and Rezende BA. Arterial Stiffness Use for Early Monitoring of Cardiovascular Adverse Events due to Anthracycline Chemotherapy in Breast Cancer Patients. A Pilot Study. Arq Bras Cardiol. 2018;111:721-728.

61. Stamatelopoulos KS, Lekakis JP, Poulakaki NA, Papamichael CM, Venetsanou K, Aznaouridis K, Protogerou AD, Papaioannou TG, Kumar S and Stamatelopoulos SF. Tamoxifen

improves endothelial function and reduces carotid intima-media thickness in postmenopausal women. Am Heart J. 2004;147:1093-9.

62. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-5.

63. Stocker R and Keaney JF, Jr. Role of oxidative modifications in atherosclerosis. Physiol Rev. 2004;84:1381-478.

64. Sutterfield SL, Caldwell JT, Post HK, Lovoy GM, Banister HR and Ade CJ. Lower cutaneous microvascular reactivity in adult cancer patients receiving chemotherapy. J Appl Physiol (1985). 2018;125:1141-1149.

65. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA and Seals DR. Aging, habitual exercise, and dynamic arterial compliance. Circulation. 2000;102:1270-5.

66. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015;66:698-722.

67. Vallerio P, Stucchi M, Moreo A, Ricotta R, Pozzi M, Giupponi L, Cazzaniga M, Meani P, Varrenti M, Facchetti R, et al. 8C.04: POSSIBLE ROLE OF ARTERIAL FUNCTION IN CANCER TREATMENT TARGETING VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR ONCOLOGIC RESPONSE. Journal of Hypertension. 2015;33:e111.

68. Van Bortel LM, Struijker-Boudier HA and Safar ME. Pulse pressure, arterial stiffness, and drug treatment of hypertension. Hypertension. 2001;38:914-21.

69. Vasiliadis I, Kolovou G and Mikhailidis DP. Cardiotoxicity and cancer therapy. Angiology. 2014;65:369-71.

70. Vlachopoulos C, Aznaouridis K and Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55:1318-27.

71. Wilkinson IB, Franklin SS and Cockcroft JR. Nitric oxide and the regulation of large artery stiffness: from physiology to pharmacology. Hypertension. 2004;44:112-6.

72. Willemse PM, van der Meer RW, Burggraaf J, van Elderen SG, de Kam ML, de Roos A, Lamb HJ and Osanto S. Abdominal visceral and subcutaneous fat increase, insulin resistance and hyperlipidemia in testicular cancer patients treated with cisplatin-based chemotherapy. Acta Oncol. 2014;53:351-60.

73. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement D, Coca A, De Simone G, Dominiczak A, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2018;36:2284-2309.

74. Wohlfahrt P, Krajcoviechova A, Seidlerova J, Mayer O, Bruthans J, Filipovsky J, Laurent S and Cifkova R. Arterial stiffness parameters: how do they differ? Atherosclerosis. 2013;231:359-64.

75. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, Durand JB, Gibbs H, Zafarmand AA and Ewer MS. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation. 2004;109:3122-31.

76. Yersal O, Eryilmaz U, Akdam H, Meydan N and Barutca S. Arterial Stiffness in Breast Cancer Patients Treated with Anthracycline and Trastuzumab-Based Regimens. Cardiol Res Pract. 2018;2018:5352914.

77. Zieman SJ, Melenovsky V and Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25:932-43.

Chapter 3 - Arterial stiffness is associated with all-cause and cardiovascular mortality in cancer patients: insights from NHANES III

Abstract

Background: Cancer survivors are at greater risk for cardiovascular disease (CVD) than second malignancy, resulting in a decreased quality of life and increased cost of care. Additional knowledge of CVD prevention by identifying possible risk factors has clinical relevance. Our main objective was to determine the relevance of a clinical index of arterial stiffness, pulse pressure, in predicting CVD mortality in cancer patients, with a second objective to examine its relationship with cancer mortality. **Methods**: We retrospectively analyzed 781 cancer patients from Third National Health and Nutrition Examination Survey and Linked Mortality File, including demographic, anthropometric, blood pressure, and cause of death. Kaplan-Meier survival curve and Cox hazard regression analyses were performed to assess the relationship between pulse pressure and all-cause, cardiovascular, and cancer mortality. **Results**: During a mean follow-up time of 8.1 years, 603 deaths, 257 cancer and 151 CVD, occurred. In unadjusted models, the risk of all-cause, CVD, and cancer mortality were 3.8-fold, 5.3-fold, and 1.6-fold higher, respectively, for pulse pressure ≥70 mmHg compared to <50 mmHg. Adjusted analyses revealed a higher CVD mortality in cancer patients <65 years with a pulse pressure 60-70 mmHg (adjusted hazard ratio, 5.26; 95%CI, 1.12-24.78) and ≥70 mmHg (adjusted hazard ratio, 5.17; 95%CI, 1.1-25.1) when compared to pulse pressure of <50mmHg. Pulse pressure was not associated with risk of all-cause, CVD, or cancer in those ≥65 years. **Conclusion**: Pulse pressure, an index of arterial stiffness, is predictive of CVD mortality in cancer patients. Our findings

support non-invasive office-setting measurements of arterial stiffness to identify high risk patients.

Introduction

Over the last half century improvements in cancer treatments and technological advancements have led to an overall decline in cancer-related mortality, with more patients surviving cancer and living long enough to develop a secondary chronic disease. Recent studies, across a spectrum of cancer types, have demonstrated that many patients who survive their cancer diagnosis have a higher risk of death from cardiovascular disease (CVD) compared to the general population, with reports of a greater risk of CVD death than secondary malignancy[1,2]. This increased chronic disease burden not only diminishes quality of life but is also a significant driver of the escalated cost of care in cancer survivorship[3]. Thus, advancing our understanding of the predictors of CVD in the nearly 17 million cancer survivors, representing approximately 5% of the population in the United States, is fundamentally important in improving cardio-oncology care for this population[4]. In an effort to mitigate risk of CVD in current cancer patients and survivors, current cardio-oncology guidelines are directed towards monitoring overt structural changes in left ventricular function for the detection of cardiovascular toxicity[5,6]. However, there is increasing evidence by our group and others that adverse vascular changes, specifically increases in arterial stiffness, manifest into cancer survivorship and can occur independent of cardiac dysfunction[7–11]. Because arterial stiffness is an established surrogate endpoint for CVD and is a strong predictor of future major adverse cardiovascular events and all-cause mortality in non-cancer patients and otherwise healthy populations[12–14], it has the potential to provide predictive utility in those previously diagnosed with cancer. Importantly, several recent reviews have also highlighted the shared biological mechanisms mediating cancer and cardiovascular disease risk[15–17]. In this context, arterial stiffness, which is a well-known predictor of mortality in the general population[12–14], may also serve as a unique risk-stratification tool for cancer

outcomes. While, both traditional and non-traditional cardiovascular disease risk factors have been associated with an increased risk for incident cancer[16–19], there remains a paucity as it relates to arterial stiffness. Therefore, given the complex mortality risks in those following cancer diagnosis, evaluation of additional potential predictors, like arterial stiffness, for both disease entities in this population is essential. Therefore, the first goal of this investigation was to evaluate whether pulse pressure, a clinical index of arterial stiffness[20,21], is a significant predictor of CVD mortality. Since cancer and CVD share several common biological mechanisms[15] and underlying CVD increases cancer risk[17], the second goal was to examine the influence of pulse pressure as a predictor of cancer mortality. Identification of these relationships could assist in stratifying mortality risk in cancer populations during routine visits in the clinic without additional imaging procedures

Methods

Study design and population

Data were obtained from the Third National Health and Nutrition Examination Survey (NHANES III) which spanned from 1988 to 1994 and was collected by the US National Center for Health Statistics. NHANES III was conducted using a stratified, multistage, and cluster sampling design to obtain a randomized representative sample of the noninstitutionalized civilian U.S. population. The survey included in-depth, in-person interviews, physical examination, physiological measurements, laboratory assessments, and health history questionnaire. The methodology of the NHANES III, as well as the data, are publicly available and can be accessed online (https://www.cdc.gov/nchs/nhanes/). The original NHANES III sample size included ~33,994 individuals. The inclusion criteria for our study consisted of participants ≥17 years old with a history of a physician diagnosed cancer. Cancer types included bladder, breast, cervical, colorectal, prostate, uterine, bone, brain/neurological, esophageal, gallbladder, and Hodgkin's disease for a final sample size of 781 subjects. We did not exclude any participants based on location or type of cancer. NHANES III was reviewed and approved by the NCHS Institutional Review Board. Our initial analysis examined pulse pressure as a predictor of cardiovascular, cancer, and all-cause mortality in all cancer patients. We performed a secondary analysis after dividing the cohort into two groups based on age.

Arterial pulse pressure

Serial brachial blood pressure measurements were taken in triplicate in the seated position after 5 min of rest with the arm rested on a table and positioned at heart level. To calculate mean pulse

pressure, we calculated the algebraic mean systolic and diastolic blood pressure foreach participant and then calculated the difference between the systolic and diastolic pressures[23].

Outcome variables

The primary outcome variables of the study were cardiovascular, cancer, and all-cause mortality, obtained from the NHANES III Linked Mortality File, collected by the National Center for Health Statistics through December 31st, 2011. All mortality outcomes were based on the NHANES III Linked Mortality file (ICD-10; 13 underlying causes of death) and were linked with the National Death Index (NDI). Pertinent to this study, cancer (ICD-10 codes: C00–C97) and cardiovascular (ICD codes: I00–I78) related deaths were coded by NDI. Follow-up for each person was calculated as the difference between the time from the NHANES III examination date and the last known date alive or censored from the NHANES III mortality file.

Covariate assessment

Covariates included in the multivariate models were identified based on their clinical relevance and current use in CVD risk stratification[21,23,24]. These included age (years), sex (male or female), race (specified as black or nonblack), total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertensive medications, history of diabetes mellitus, and smoking status (each as binary variables). Information for age, sex, race, use of hypertension medication, diabetes status, and smoking status were self-reported using standardized questionnaires during interview and were coded as dichotomous “yes/no” variables in the NHANES database. Race/ethnicity were classified dichotomously as non-Hispanic white/Mexican American/Other and non-Hispanic Black[21].

Serum total cholesterol and high density-lipoprotein (HDL) cholesterol was collected and analyzed as previously described[25].

Statistical analysis

Continuous data are presented as mean ± SD. Categorical data are presented as counts and percentages. Kaplan–Meier plots were used to show the difference in time to event by pulse pressure quartile and statistically compared with the log-rank test. Cox proportional hazard regression analysis was used to compare the risk of cardiovascular, cancer, and all-cause mortality with pulse pressure as a continuous variable and across pulse pressure quartiles. For the analyses in younger and older patient cohorts, pulse pressure was binned into four categories: $PP_1<50$; $50 \leq PP_2 > 60$; $60 \leq PP_3 >70$; $70 \leq PP_4$, similar to previous investigations[26]. In the younger and older cohorts, the assumption of linearity was violated and therefore required categorization. All primary analyses were also performed without pulse pressure, using only the above defined CVD risk factors. The predicted performance of the models with and without pulse pressure were evaluated by concordance index (C index) and the likelihood ratio χ^2 statistic[27]. A C index of 0.5 indicates a random predictor, while 1.0 indicates a perfect predictor. Statistical analyses were conducted using survival package in publicly available R software (version 3.5)[28]. All significance tests were two-sided using $p < 0.05$ as the level of statistical significance.

Results

Baseline demographics and subject characteristics are outlined in **Table 3-1**. A total of 781 adults (307 men, 474 women) with a history of a cancer diagnosis were included in the analysis, with an average follow-up of 8.1 years. During the follow-up period, there were 603 deaths (77% of the participants) including 257 cancer related deaths (43%) and 151 cardiovascular related deaths (25%). The total follow-up duration was 18 years and 136 total deaths occurred in that period [103 cancer related deaths (75%) and 22 cardiovascular related deaths (16%)]. The ≥65 year old sub cohort consisted of 480 subjects (227 men, 253 women) with an average follow-up time of 8 years and 467 total deaths [154 cancer related deaths (33%) and 129 cardiovascular related deaths (28%)]. Baseline demographics and subject characteristics based on pulse pressure levels are shown in **Table 3-1**. The four indexes of arterial blood pressure (systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP)) were positively and significantly correlated with each other as determined via product moment (Pearson) simple correlations. The correlation coefficients of pulse pressure with other blood pressure parameters were $r = 0.4$ ($P < 0.0001$) with MAP, $r = 0.85$ ($P < 0.0001$) with SBP, and $r = -0.14$ ($P < 0.0001$) with DBP.

Table 3-1 Baseline cardiovascular risk factors by pulse pressure category in participants with cancer, NHANES III 1988-1994

	PP1	PP2	PP3	PP4
		Entire Cancer Cohort, n =781		
Systolic blood pressure, mmHg	116.09 ± 12.27	129.38 ± 10.06	138.96 ± 12.31	159.10 ± 19.96
Diastolic blood pressure, mmHg	76.53 ± 9.89	75.47 ± 9.76	74.62± 11.96	73.17 ± 14.84
Age, y	52.91 ± 17.10	65.07 ± 15.85	71.35 ± 12.44	75.85 ± 9.66
Total cholesterol, mg/dL	216.56 ± 40.01	223.21 ± 41.57	212.20 ± 45.65	218.67 ± 41.20
HDL cholesterol, mg/dL	52.90 ± 14.81	52.35 ± 41.57	50.25 ± 14.08	50.71 ± 14.19
Race, % black	25%	15%	12%	8%
Sex, % women	67%	61%	54%	58%
Diabetes, %	6%	12%	14%	14%
HTN meds, %	82%	83%	88%	88%
Cigarette smokers, %	40%	25%	24%	12%
		Young Cohort (<65 years), n=301		
Systolic blood pressure, mmHg	115.11 ± 11.73	128.85 ± 10.16	141.17 ± 15.15	158.53 ± 23.44
Diastolic blood pressure, mmHg	76.78 ± 9.15	75.16 ± 9.40	77.19 ± 14.00	77.16 ± 18.15
Age, y	44.69 ± 12.12	50.50 ± 13.27	54.95 ± 9.67	55.32 ± 12.81
Total cholesterol, mg/dL	211.75 ± 37.37	219.79 ± 39.86	207.33 ± 36.36	233.74 ± 45.02
HDL cholesterol, mg/dL	53.42 ± 14.31	50.93 ± 11.25	49.85 ± 13.60	56.05 ± 12.64
Race, % black	27%	4%	26%	21%
Sex, % women	76%	70%	64%	79%
Diabetes, %	6%	10%	15%	16%
HTN meds, %	74%	78%	87%	84%
Cigarette smokers, %	49%	44%	51%	32%
		Old Cohort (≥ 65 years), n =480		
Systolic blood pressure, mmHg	144.67 ± 54.67	129.76 ± 10.03	138.19 ± 11.14	159.16 ± 19.67
Diastolic blood pressure, mmHg	75.89 ± 11.61	75.70 ± 10.05	73.73 ± 11.10	72.79 ± 14.49
Age, y	73.81 ± 7.25	75.48 ± 6.68	77.01 ± 7.13	77.79 ± 6.60
Total cholesterol, mg/dL	228.81 ± 44.01	225.53 ± 42.81	213.88 ± 48.47	217.25 ± 40.66
HDL cholesterol, mg/dL	52.90 ± 14.81	52.35 ± 12.52	50.23 ± 14.08	50.71 ± 14.19
Race, % black	21%	12%	5%	7%
Sex, % women	57%	55%	50%	56%
Diabetes, %	7%	13%	14%	14%
HTN meds, %	93%	87%	88%	89%
Cigarette smokers, %	16%	11%	15%	10%

Data are presented as mean ± standard deviation.

Associations of pulse pressure with cardiovascular mortality

The unadjusted Cox analysis revealed that in the entire cancer cohort, pulse pressure was a significant determinant of cardiovascular mortality with a hazard ratio of 1.03 (95% confidence interval, 1.02–1.03) for every 10mmHg increase ($P < 0.001$). Moreover, Kaplan Meier curve analysis revealed significant differences in cardiovascular survival probabilities between pulse pressure categories for the entire cancer cohort ($P < 0.0001$) (**Fig. 3-1A**), such that each level of elevated pulse pressure category was significantly predictive of mortality (**Table 3-2**). In younger cancer survivors a significant association between pulse pressure levels (PP_2, PP_3, and PP_4) and cardiovascular mortality was observed ($P = 0.00025$) (**Table 3-3**) (**Figure 3-2**).

The overall predictive model that included pulse pressure and the traditional cardiovascular risk factors was significant (C index = 0.86, $\chi^2 = 38.45$, $P < 0.0001$). In this model, a pulse pressure of 60–70 mmHg (PP_3) showed significant increase in the risk for cardiovascular mortality, with highest pulse pressure category [(>70 mmHg (PP_4)] approaching significance ($P < 0.1$). Compared to the model containing only risk factors, the modeling including pulse pressure was incrementally more predictive of cardiovascular mortality. In the older cohort of cancer survivors pulse pressure was not predictive of cardiovascular mortality in univariate or multivariate analysis (**Table 3-3**).

Figure 3-1 Kaplan-Meier survival curve analysis

Kaplan-Meier curve analysis of **A**) cardiovascular, **B**) cancer, and **C**) all-cause mortality in the entire cancer cohort across pulse pressure level. CV indicates cardiovascular mortality.

Table 3-2 Association of pulse pressure with cardiovascular, all-cause and cancer mortality on unadjusted analysis in participants with cancer, NHANES III 1988-1994

	Unadjusted	p Value
Outcome	HR (95% CI)	
Cardiovascular Mortality		
PP_1	-	
PP_2	2.05 (1.21-3.49)	0.007
PP_3	3.15 (1.88-5.28)	<0.001
PP_4	5.34 (3.34-8.44)	<0.001
All-Cause Mortality		
PP_1	-	
PP_2	2.27 (1.78-2.92)	<0.001
PP_3	3.11 (2.43-3.98)	<0.001
PP_4	3.78 (3.01-4.76)	<0.001
Cancer Mortality		
PP_1	-	
PP_2	1.52 (1.09-2.12)	0.014
PP_3	1.85 (1.31-2.63)	0.0005
PP_4	1.60 (1.13-2.26)	0.008

HR = Hazard Ratio, CI = confidence interval

Table 3-3 Association of pulse pressure with cardiovascular, all-cause, and cancer mortality on unadjusted and multivariate adjusted analysis in participants with cancer, stratified by age; NHANES III 1988-1994

	Younger Cohort (< 65 years)		*Older Cohort (≥ 65 years)*	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Outcome	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cardiovascular Mortality				
PP_1	-	-	-	-
PP_2	0.94 (0.25-3.50)	0.88 (0.21-3.69)	1.08 (0.59-1.99)	0.82 (0.44-1.54)
PP_3	5.65 (2.08-15.39)***	5.26 (1.12-24.78)**	0.87 (0.47-1.58)	0.57 (0.29-1.10)*
PP_4	4.85 (1.29-18.31)**	7.28 (0.73-72.18)*	1.37 (0.81-2.31)	0.88 (0.44-1.77)
All-Cause Mortality				
PP_1	-	-	-	-
PP_2	1.78 (1.18-2.70)***	1.31 (0.82-2.07)	1.29 (0.94-1.78)	1.12 (0.80-1.56)
PP_3	3.16 (2.01-4.98)***	1.65 (0.90-3.02)	1.16 (0.85-1.59)	0.97 (0.69-1.37)
PP_4	2.86 (1.59-5.15)***	1.71 (0.69-4.27)	1.28 (0.96-1.70)*	1.14 (0.78-1.67)
Cancer Mortality				
PP_1	-	-	-	-
PP_2	1.28 (0.80-2.06)	1.22 (0.72-2.06)	1.04 (0.63-1.73)	1.09 (0.65-1.86)
PP_3	1.87 (1.03-3.39)**	1.49 (0.69-3.17)	0.95 (0.58-1.55)	1.11 (0.63-1.94)
PP_4	1.52 (0.69-3.34)	1.53 (0.52-4.45)	0.74 (0.46-1.18)	1.06 (0.55-2.05)

Multivariate model adjusted for age (years), sex (male or female), race (specified as black or nonblack), total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertensive medications, history of diabetes mellitus, and smoking status (each as binary variables).

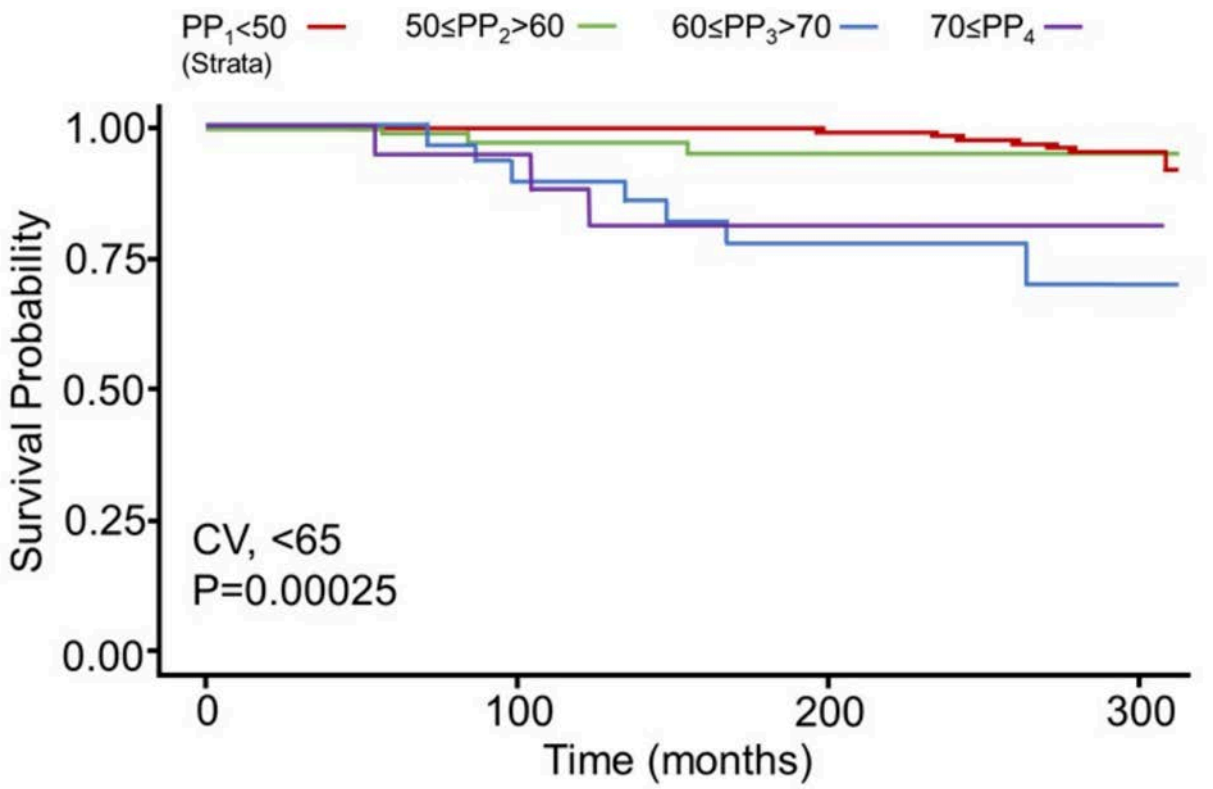
HR = Hazard Ratio, CI = confidence interval

* P<0.1

** P<0.05

*** P<0.01

Figure 3-2 Kaplan-Meier cardiovascular survival <65 years old



Kaplan–Meier survival analysis curves for different levels of pulse pressure: $PP_1<50$; $50 \leq PP_2 >60$; $60 \leq PP_3 >70$; $70 \leq PP_4$ in the <65-year-old Cohort for Cardiovascular disease.

Associations of pulse pressure with cancer mortality

Similar to cardiovascular mortality analyses, the unadjusted Cox analysis revealed that in the entire cohort, pulse pressure was a significant determinant for cancer mortality with a hazard ratio of 1.02 (95% confidence interval, 1.01 – 1.02, $P < 0.001$). In addition, statistically significant differences were found in the Kaplan-Meier curve analyses between different pulse pressure levels and cancer survival probabilities in the entire cancer cohort analysis (**Fig. 3-1B**), $P = 0.0024$). Univariate Cox regression analysis, but not adjusted, suggest that compared to the reference PP1, the risk of cancer mortality were 1.52-fold, 1.85-fold, and 1.60-fold higher for those patients with elevated pulse pressures in PP_2, PP_3, and PP_4 groups, respectively (**Table 3-2**). In younger cancer survivors a significant association between 60 to 70 mmHg (PP_3) and cancer mortality was observed (**Table 3-3**) (**Fig. 3-3**). However, on multivariate analysis in both <65 year and ≥65 years cohorts this relationship was no longer significant (**Table 3-3**).

Figure 3-3 Cancer mortality analysis <65 years old

<65-year-old Cohort, Cancer Mortality Analysis. Panel A. Kaplan–Meier Survival analysis curves for different levels of pulse pressure: $PP_1<50$; $50 \leq PP_2 >60$; $60 \leq PP_3 >70$; $70 \leq PP_4$. Panel B. Univariate Cox Regression Analysis.

Associations of pulse pressure with all-cause mortality

Arterial pulse pressure was associated with all-cause mortality (unadjusted HR: 1.01 (95% CI: 1.001 - 1.02, P = 0.03). However, this only equated to a <1% increased risk for every 10mmHg increase in pulse pressure. Kaplan-Meier curve analyses revealed statistically significant differences in all-cause survival probabilities between different pulse pressure levels in the entire cohort (P<0.0001) (**Fig. 3-1C**). Across the entire cohort, compared to the reference (PP_1), the risk of all-cause mortality were 2.27-fold, 3.11-fold, and 3.78-fold higher for cancer patients with an arterial pulse pressure 50–60 mmHg (PP_2), 60–70 mmHg (PP_3), and ≥70 mmHg (PP^4), respectively (**Table 3-2**). All-cause mortality was significantly associated with elevated pulse pressures in the younger cancer survivors across all categories (**Table 3- 3**). In the fully adjusted analyses, pulse pressure was no longer a significant predictor for all-cause mortality. However, the combination of pulse pressure and these risk factors revealed slightly better model for predicting all-cause mortality (C index = 0.77, $\chi 2 = 126.8$) compared to only the traditional CVD risk factors alone (C index = 0.76, $\chi^2 = 124.0$). In the older cohort, there were no differences in all-cause survival probabilities between the different levels of pulse pressure (P = 0.32). Cox regression analysis revealed pulse pressure was not independently predictive of all-cause mortality in the univariate analysis or the multivariate analyses. The model including pulse pressure with CVD risk factors as a whole was a significant predictor of all-cause mortality (C index = 0.65, $\chi^2 = 128.5$, P < 0.0001), but did not appear to improve upon the model consisting of only traditional risk factors.

Discussion

This study is the first to demonstrate the association of pulse pressure, a clinical index of arterial stiffness[20,21], with CVD mortality in a large cancer cohort. Specifically, after dividing the cohort by age, we found in those less than 65 years old, a higher pulse pressure conferred an increased risk of all-cause and CVD-related mortality after controlling for multiple traditional CVD risk factors. Moreover, an increased arterial pulse pressure was also independently predictive of cancer mortality, highlighting the role of arterial stiffness as a potential common risk factor for both CVD and cancer. A critical innovative aspect of these findings includes the applicability to patients; specifically, the relative ease in which pulse pressure measures are obtained in the office setting, make it a valuable tool for straightforward assessment of CVD mortality risk upon adjustment for traditional risk factors. Several investigations to date have demonstrated a relationship between CVD outcomes and elevated arterial pulse pressure. In 1991 Domanski and colleagues evaluated the role of arterial pulse pressure in predicting CVD outcomes in the general population using the NHANES I dataset. Their study revealed that every 10 mmHg increase in pulse pressure was associated with a 26% and 10% increased risk of cardiovascular death in individuals aged 25–45 years and 46–77 years old, respectively[21]. Similarly, Liu et al.[29] evaluated the relationship between pulse pressure and mortality in younger (i.e. <65 years) cancer and CVD free individuals and found that elevated pulse pressure was a predictor of both all-cause and cardiovascular mortality. Moreover, several reports support the premise that arterial pulse pressure provides prognostic information in specific populations including patients with type II diabetes, heart failure, and chronic kidney disease[21, 30-32]. None of these early works, however, focused on patients with a history of cancer specifically, even though they are at a higher risk for CVD compared with the general population[1,2,33].

There is a growing body of evidence suggesting a biological link between cancer and cardiovascular disease[15]. Reasons for this include shared risk factors such as inflammation, smoking, obesity, hypertension, diabetes, diet, and physical inactivity[15,16,34]. Findings from a community based retrospective cohort study consisting of 36,236 cancer survivors support this notion. In a study conducted by Armenian et al.1, cancer survivors were found to be more likely to have cardiovascular risk factors than cancer-free controls; additionally, cancer survivors with two or more CVD risk factors were more likely to develop CVD over time[1]. Most importantly, their analysis revealed cancer survivors who developed CVD had worse 8-year survival outcomes when compared to CVD free cancer survivors, independent of age, sex, cancer stage, and CVD risk factors. In another retrospective population-based study, Strongman and colleagues reported findings similar to Armenian et al.[33] with cancer survivors in this cohort were more likely to have baseline CVD risk factors and previous CVD when compared to cancer-free controls. Additionally, cancer survivors were also found to be at an increased risk of CVD than the general population and this association persisted after adjustment for shared risk factors for cancer and CVD. Findings from both of these studies indicate an increased prevalence of CVD related risk factors in cancer survivors when compared to cancer free controls, along with support for the notion that presence of CVD results in worsened outcomes in cancer survivors, further providing evidence for a shared biological link between cardiovascular disease and cancer..

To date, most studies evaluating the relationship between CVD risk and cancer have focused on the direct cardiotoxic effects, such as decreases in left ventricular function, following treatment with anti-cancer therapies including doxorubicin, trastuzumab, 5-fluorouracil, and androgen deprivation therapy[35–38]. Traditional therapies such as anthracyclines have been

associated with a dose-dependent cardiotoxicity resulting in irreversible structural myocardial damage over time that manifests as decreased left ventricular mass and wall thickness, eventually leading to dilated cardiomyopathy and synchronous heart failure[39]. Characterization of this relationship has led to surveillance strategies in the cardio-oncology field that are centered around monitoring changes in left ventricular ejection fraction during and immediately after treatment[40]. However, it has come to light that vascular changes are occurring in this patient population that manifest as endothelial dysfunction, coronary vasospasm, and increased arterial stiffness[41–43]; and importantly, these changes often precede structural alterations in the myocardium[9,10]. Recently, our group performed an in-depth meta-analysis to demonstrate significant increases in arterial stiffness after exposure to anticancer therapies during cancer treatment and into survivorship, highlighting the vascular toxicity associated with many chemotherapy agents[7]. This coupled with the findings of the current study highlight arterial stiffness as a possible treatable risk factor for the prevention of CVD following cancer treatment.

Mechanistically increases in pulse pressure, via increases in arterial stiffness, increase the risk for cardiovascular events through alterations in the Windkessel effect. In health, each cardiac contraction sends energy waves across the periphery that are reflected back to the myocardium during early diastole to increase diastolic coronary perfusion, without increasing cardiac afterload. With increases in stiffness, the wave reflection returns to the myocardium during late systole and augments systolic pressure[44]. Coupled together, these factors augment total systolic ventricular load, decrease coronary perfusion pressure, and lead to an imbalance of myocardial oxygen delivery and demand[45,46].

Study strengths and limitations

Strengths of this study include the relatively large study population that consisted of a broad range of cancer types in both men and women. A second key strength is multiple adjustment analyses for competing risk factors, thus preventing the overestimation of the 'real' effect of pulse pressure on each outcome of interest. Furthermore, by evaluating subcohorts defined by age, the relationship between arterial pulse pressure and each outcome was specific to younger and older cancer populations, which have known differences in CVD risk[2,47]. Lastly, the use of pulse pressure to evaluate arterial stiffness versus other more costly and time-consuming techniques allows for easier translation of this work into the cardio-oncology clinic. Limitations of this study however must be taken into consideration. Specifically, with the NHANES III database, we were only able to utilize a snapshot in time of pulse pressure and we were not able to track these changes over time leading to the study endpoint. Further, our study does not have treatment information on the patients examined in this analysis. Because of this limitation, we cannot determine whether specific treatments or the diagnosis of cancer itself could have led to higher pulse pressure in this population.

Conclusions

In a large study of cancer patients from the NHANES III database, arterial pulse pressure adds valuable clinical information for CVD stratification. Given that pulse pressure is a readily available measurement in the office setting, our study supports the use of pulse pressure as a clinical tool to identify cancer patients and survivors who are at an enhanced risk of cardiovascular mortality. Future studies are warranted to examine whether this association is due to cancer treatments or the shared risk factors between cancer and cardiovascular disease.

Clinical perspectives

In cancer patients increases in arterial stiffness, assessed via arterial pulse pressure, are associated with an increased risk of cardiovascular and cancer mortality

References

1. Armenian SH, Xu L, Ky B et al. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. J Clin Oncol 2016;34:1122-30.

2. Sturgeon KM, Deng L, Bluethmann SM et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J 2019;40:3889-3897.

3. Rim SH, Guy GP, Jr., Yabroff KR, McGraw KA, Ekwueme DU. The impact of chronic conditions on the economic burden of cancer survivorship: a systematic review. Expert Rev Pharmacoecon Outcomes Res 2016;16:579-589.

4. Miller KD, Nogueira L, Mariotto AB et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 2019;69:363-385.

5. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc 2014;89:1287-306.

6. Plana JC, Thavendiranathan P, Bucciarelli-Ducci C, Lancellotti P. Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient. JACC Cardiovasc Imaging 2018;11:1173-1186.

7. Parr SK, Liang J, Schadler KL, Gilchrist SC, Steele CC, Ade CJ. Anticancer Therapy-Related Increases in Arterial Stiffness: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2020;9:e015598.

8. Frye JN, Sutterfield SL, Caldwell JT et al. Vascular and autonomic changes in adult cancer patients receiving anticancer chemotherapy. J Appl Physiol (1985) 2018;125:198-204.

9. Sekijima T, Tanabe A, Maruoka R et al. Impact of platinum-based chemotherapy on the progression of atherosclerosis. Climacteric 2011;14:31-40.

10. Chaosuwannakit N, D'Agostino R, Jr., Hamilton CA et al. Aortic stiffness increases upon receipt of anthracycline chemotherapy. J Clin Oncol 2010;28:166-72.

11. Krystal JI, Reppucci M, Mayr T, Fish JD, Sethna C. Arterial stiffness in childhood cancer survivors. Pediatr Blood Cancer 2015;62:1832-7.

12. Ben-Shlomo Y, Spears M, Boustred C et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014;63:636-646.

13. Laurent S, Boutouyrie P, Asmar R et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236-41.

14. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318-27.

15. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation 2016;133:1104-14.

16. Johnson CB, Davis MK, Law A, Sulpher J. Shared Risk Factors for Cardiovascular Disease and Cancer: Implications for Preventive Health and Clinical Care in Oncology Patients. Can J Cardiol 2016;32:900-7.

17. Klooster CCvt, Ridker PM, Cook NR et al. Prediction of Lifetime and 10-Year Risk of Cancer in Individual Patients With Established Cardiovascular Disease. JACC: CardioOncology 2020;2:400-410.

18. Handy CE, Desai CS, Dardari ZA et al. The Association of Coronary Artery Calcium With Noncardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis. JACC Cardiovasc Imaging 2016;9:568-576.

19. Eyre H, Kahn R, Robertson RM et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Stroke 2004;35:1999-2010.

20. Said MA, Eppinga RN, Lipsic E, Verweij N, van der Harst P. Relationship of Arterial Stiffness Index and Pulse Pressure With Cardiovascular Disease and Mortality. J Am Heart Assoc 2018;7.

21. Domanski M, Norman J, Wolz M, Mitchell G, Pfeffer M. Cardiovascular risk assessment using pulse pressure in the first national health and nutrition examination survey (NHANES I). Hypertension 2001;38:793-7.

22. Surveillance E, and End Results (SEER) Program SEER*Stat Database: Populations-Total U.S. (1969-2018). In: Adjustment> KR, editor: National Cancer Institute 2019.

23. Benetos A, Safar M, Rudnichi A et al. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 1997;30:1410-5.

24. Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH. Pulse pressure and mortality in older people. Arch Intern Med 2000;160:2765-72.

25. Wu CK, Lin JW, Caffrey JL, Chang MH, Hwang JJ, Lin YS. Cystatin C and long-term mortality among subjects with normal creatinine-based estimated glomerular filtration rates: NHANES III (Third National Health and Nutrition Examination Survey). J Am Coll Cardiol 2010;56:1930-6.

26. Goff DC, Jr., Lloyd-Jones DM, Bennett G et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S49-73.

27. Harrell F. Regression Modeling Strategies. 1 ed. New York: Springer-Verlag New York, 2001.

28. Team RC. R: A language and environment for statistical computing. . 2013.

29. Liu D, Qin P, Liu L et al. Association of pulse pressure with all-cause and cause-specific mortality. J Hum Hypertens 2020.

30. Karras A, Haymann JP, Bozec E et al. Large artery stiffening and remodeling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease. Hypertension 2012;60:1451-7.

31. Mitchell GF, Moye LA, Braunwald E et al. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. Circulation 1997;96:4254-60.

32. Schram MT, Kostense PJ, Van Dijk RA et al. Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. J Hypertens 2002;20:1743-51.

33. Strongman H, Gadd S, Matthews A et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. Lancet 2019;394:1041-1054.

34. Li J, Lee DH, Hu J et al. Dietary Inflammatory Potential and Risk of Cardiovascular Disease Among Men and Women in the U.S. J Am Coll Cardiol 2020;76:2181-2193.

35. Hamo CE, Bloom MW, Cardinale D et al. Cancer Therapy-Related Cardiac Dysfunction and Heart Failure: Part 2: Prevention, Treatment, Guidelines, and Future Directions. Circ Heart Fail 2016;9:e002843.

36. Kanar BG, Ozben B, Sunbul M et al. Androgen-deprivation therapy impairs left ventricle functions in prostate cancer patients. Int Urol Nephrol 2019;51:1107-1112.

37. Perez IE, Taveras Alam S, Hernandez GA, Sancassani R. Cancer Therapy-Related Cardiac Dysfunction: An Overview for the Clinician. Clin Med Insights Cardiol 2019;13:1179546819866445.

38. Volkova M, Russell R, 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev 2011;7:214-20.

39. Armenian SH, Lacchetti C, Barac A et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 2017;35:893-911.

40. Sutterfield SL, Caldwell JT, Post HK, Lovoy GM, Banister HR, Ade CJ. Lower cutaneous microvascular reactivity in adult cancer patients receiving chemotherapy. J Appl Physiol (1985) 2018;125:1141-1149.

41. Chong JH, Ghosh AK. Coronary Artery Vasospasm Induced by 5-fluorouracil: Proposed Mechanisms, Existing Management Options and Future Directions. Interv Cardiol 2019;14:89-94.

42. Soultati A, Mountzios G, Avgerinou C et al. Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications. Cancer Treat Rev 2012;38:473-83.

43. Kelly RP, Tunin R, Kass DA. Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. Circ Res 1992;71:490-502.

44. Recchia FA, Senzaki H, Saeki A, Byrne BJ, Kass DA. Pulse pressure-related changes in coronary flow in vivo are modulated by nitric oxide and adenosine. Circ Res 1996;79:849-56.

45. Saeki A, Recchia F, Kass DA. systolic flow augmentation in hearts ejecting into a model of stiff aging vasculature. Influence on myocardial perfusion-demand balance. Circ Res 1995;76:132-41.

46. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res 2011;13:R64.

Chapter 4 - Is Doppler derived aortic arch pulse wave velocity related to the gold standard carotid-femoral pulse wave velocity? Implications for monitoring large artery stiffness in the clinic

Abstract

Introduction. Aortic stiffness is an independent predictor of all-cause mortality and cardiovascular events in the general population and in those with chronic cardiovascular disease; however, incorporating traditional monitoring methods into routine clinical practice remains unfeasible. The gold standard, carotid-femoral pulse wave velocity (cfPWV), poses methodological and physiological challenges as it is difficult to perform in the clinic and the measured path length bypasses the most distensible vessel, the proximal aorta. Therefore, we propose a modified method, aortic arch pulse wave velocity (aaPWV) assessed during standard transthoracic echocardiography, encompassing the proximal aorta. **Methods**. We recruited 74 volunteers (44.2±15.8y, range 19-69y, 75% female) for this study. Both aaPWV and cfPWV were measured using the wave-foot method with a commercial Logic S8 Ultrasound system (GE Healthcare) with synchronous electrocardiography. cfPWV was calculated by determining the distance between the two sites and dividing by transit time between the two vessels. aaPWV was calculated by determining the distance sites and dividing by transit time, starting at the level of the aortic valve and ending at the descending aorta. **Results**. Our findings reveal a remarkable intraclass correlation coefficient with excellent agreement within (0.94) and between sonographers (0.95) for aaPWV. Pearson correlation determined a significant relationship between the two methods ($r=0.32$; $P<0.01$) while paired t-tests showed significant differences between measures (aaPWV: 5.81±2.2m/s vs. cfPWV: 6.84±1.9m/s; $P<0.01$). **Conclusion**. The

findings from this study suggest aaPWV could be a more feasible method to measure large artery stiffness in routinely in the clinic, as it has ICC excellent scores. Future studies are needed to determine if aaPWV is similarly predictive of adverse cardiovascular outcomes.

Introduction

Large artery stiffening is a consequence of aging and a critical factor in the pathogenesis of major cardiovascular events. Stiffening of the vascular wall relates to the resistance to pressure-induced deformation, which is determined by structural and functional components[1]. Contributions of elastin and collagen in the aortic wall play a prominent role in determining large artery stiffness, given that elastin pools are determined early in life and become fragmented through the lifespan, which places more load on stiffer collagen fibers, thus resulting in a stiffer vessel[2]. Pro-inflammatory pathological states can increase the rate of elastin degradation and influence functional components of the arterial wall, leading to a faster rate of stiffening than what is seen with aging alone[3,4]. Physiologically, this has consequences as the elastic aorta acts as a buffer to ventricular ejection, facilitates steady blood flow to the periphery, and minimizes excessive pulsatile pressure within the peripheral microcirculation. Additionally, elevated aortic stiffness adversely affects the heart by increasing afterload through reductions in the Windkessel effect[3,5,6]. Thus, uncoupling of this process contributes to many pathological cardiovascular conditions, as elevated aortic stiffness is associated with heart failure, stroke, diabetes, chronic kidney disease, and fatal cardiovascular events[7-11].

The in vivo gold standard assessment of large artery stiffness is pulse wave velocity (PWV), which is measured between the carotid and femoral sites (cfPWV). It is determined by dividing the distance travelled by the time delay of pressure or velocity waveforms from the respective sites[12]. It is implied that a faster pulse wave velocity through the segments indicates a stiffer vessel[1]. Incorporation of cfPWV into risk prediction models has been shown to improve prognostic capacity even when accounting for traditional cardiovascular risk factors[13]. Although this information has been available for almost a decade, implementing this method into regular

clinical practice remains a significant challenge. Various societies have taken conflicting stances on clinical applications of measuring arterial stiffness, including this recent statement from the 2018 European Society of Cardiology and European Society of Hypertension Guidelines for the management of Hypertension stating, “The additive value of PWV above and beyond traditional risk factors, including SCORE and the Framingham risk score, has been suggested in some studies. However, routine use of pulse wave velocity measurement is not practical and is not recommended for routine practice”[14]. Some of the key challenges include mild patient discomfort with exposure of the inguinal region during femoral artery imaging. Patients are also liable for the cost of the test since reimbursement codes are tailored towards diagnostics for non-invasive vascular studies, rather than tests that add to risk stratification for cardiovascular disease[15]. Additionally, this test could likely require an office visit separate from routine imaging and would be performed by a vascular-specific sonographer or someone with dedicated tonometry training.

To address these problems, a growing number of studies have utilized magnetic resonance imaging (MRI) to measure aortic arch pulse wave velocity (aaPWV), a regional assessment of stiffness beginning at the proximal aorta and ending at the descending aorta. Notably, investigations using the Multi-Ethnic Study of Atherosclerosis (MESA) cohort reported an association between aaPWV and incident cardiovascular events in middle-aged adults[16]. In the same cohort higher aaPWV was associated with left ventricular concentric remodeling and worsened systolic function in both sexes, but worsened diastolic function in only women[17]. An essential methodological and physiological component of measuring aaPWV is that it includes the proximal portion of the aorta, which is missed in the cfPWV vascular path[12]. MRI-derived aaPWV also allows for more reliable path length measurement than cfPWV, which can be

heavily influenced by erroneous body surface measurements and isn't sensitive to vessel tortuosity with aging[18]. However, despite the advantages of this approach, it remains challenging to incorporate regular MRI monitoring of aaPWV into clinical practice with the time and cost associated with image acquisition and post-processing[19]. Therefore, our primary aim was to propose a new method to measure aaPWV using standard views obtained during a routine transthoracic echocardiography scan. This approach would eliminate the need for a separate office visit and could be performed simultaneously with traditional cardiac measurements. Incorporating stiffness assessments into echocardiography scans may also reduce the burden of additional time for image acquisition and may not require additional insurance coding. We hypothesize aortic arch pulse wave velocity (aaPWV) will demonstrate a high intraclass correlation coefficient (ICC) and show a significant association with age. Furthermore, considering differences in the specific vascular structures assessed, we hypothesize that while aaPWV will be correlated with carotid-femoral pulse wave velocity (cfPWV), the two measurements will exhibit significant differences. Lastly, in a sub-analysis, we expect aaPWV to be elevated in participants with cardiovascular disease risk factors or known cardiovascular disease, compared to matched healthy controls.

Methods

Participants

Seventy-four participants (44.2±15.8y, range 19-69y, 75% female) actively volunteered for this study by responding to general advertisements. Inclusion criteria required participants to be 18-85 years old, with each participants providing a comprehensive health history. The Institutional Review Board of Kansas State University approved this study (IRB #10924), ensuring compliance with the ethical standards outlined in the Declaration of Helsinki. Each participant provided consent prior to commencing the study. Participants completed each test in a temperature-controlled laboratory maintained at 20-22 degrees Celsius. The study procedures were conducted over the course of a single day visit to the laboratory.

Experimental measures

Participants laid supine on a table in a rested state for the duration of the experiment unless positioned on their left side for cardiac imaging. Brachial blood pressure was measured in the left arm by an automated blood pressure monitor (HEM-907XL, OMRON Healthcare, Kyoto, Japan) after resting for 10 minutes.

cfPWV measurements

Pulsed Doppler ultrasound (Logic S8, GE Healthcare) equipped with a linear array probe (9L-D probe, 2.4-10.0 MHz) was used to image the carotid and femoral arteries separately. The participants were instructed to turn their heads 45° to the right and the left common carotid artery was located with B-mode at the supraclavicular level, 1-2 cm below the bifurcation. 3-5 cardiac cycles of pulse wave Doppler were recorded with simultaneous ECG for analysis at a sweep

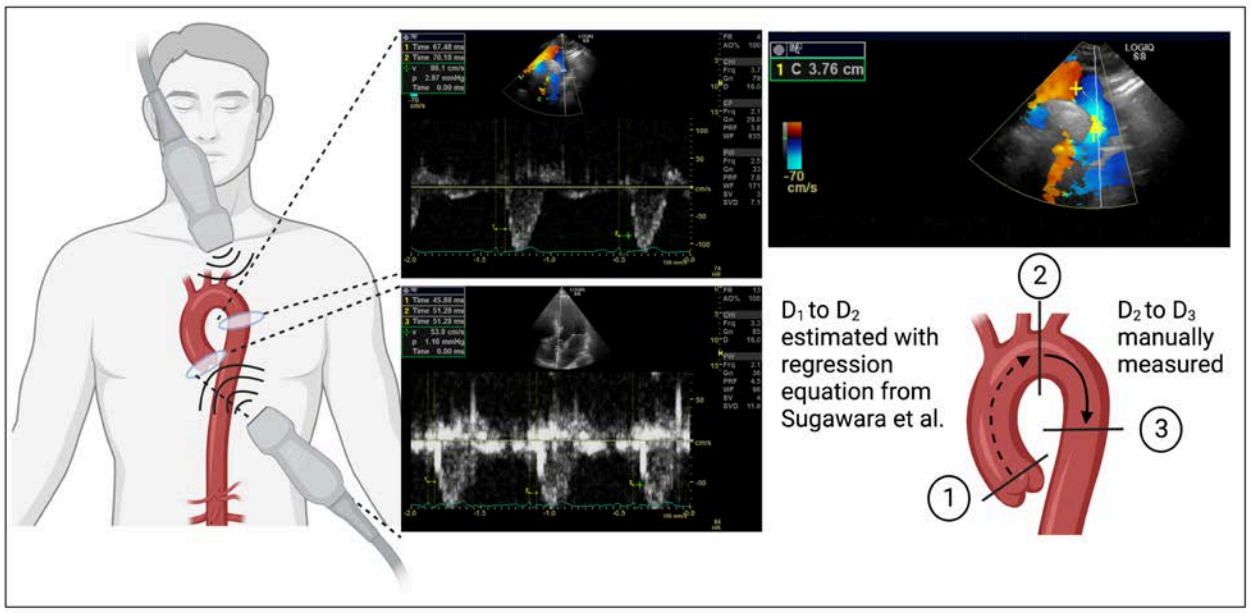
speed of at least 100mm/sec. This process was repeated for image acquisition of the ipsilateral common femoral artery in the inguinal region. Time delay was determined by identifying the time interval between the peak of the R wave to the upstroke of the Doppler velocity waveform at each site, as previously described[12]. Distance was determined as the distance between the two sites. cfPWV was calculated as the distance divided by transit time, reported in units of meters per second.

aaPWV measurements

The same ultrasound machine equipped with a standard cardiac probe (M5S probe, 1.9 to 3.8-MHz) was used to obtain separate images of the aortic valve and the descending aorta for determination of aaPWV (Figure 1). The aortic valve was located in the apical 5-chamber view. 3-5 cycles of pulse wave Doppler were recorded with simultaneous ECG for analysis at a sweep speed of at least 100mm/sec. The same process was repeated for collection of the descending aortic waveforms in a suprasternal view. Briefly, the cardiac probe was placed on the suprasternal notch and the aortic arch was identified using both B-mode and color flow. Pulse wave Doppler images were captured at the start of the descending aorta, 1cm below the left subclavian artery. For analysis, time was determined using the wave foot method starting at the peak of the R wave to the upstroke of the descending aortic velocity waveform. Distance between sites was determined using the sum of a validated age-adjusted regression equation and manual measurement. The distance from the sinus of Valsalva to the apex of the aortic arch was estimated using a regression equation previously published[20]. The remaining distance was manually traced using an open-spline curve from the arch's apex to the velocity sampling point within the descending aorta for each subject. The arch's apex was identified with color flow as

the demarcation point where color flow switched from blue to red, indicating that flow was no longer moving towards the probe in the aortic arch and instead flowed away from the probe in the descending aorta as seen in **Figure 4-1**. The total acquisition and post-processing time was <5 minutes.

Figure 4-1 Transthoracic echocardiography derived aortic arch pulse wave velocity



Transit time was determined using the wave-foot method starting at the peak of the R-wave and the foot of the waveform. Distance from the Sinus of Valsalva (D_1) to the apex of the aortic arch (D_2) was estimated with an age-related regression equation D= (0.9) * (age) + 26.1. Distance from D_2 to D_3 was manually traced through the lumen, starting at the Doppler sampling point to the apex of the aortic arch. The apex of the aortic arch was identified with color flow as the demarcation point in ascending to descending flow, as seen above. Total distance was the sum of the two measures. Made with biorender.com

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows (Ver. 27; IBM, Armonk, NY) and R software (version 4.1.3) with packages lpSolve and irr. ICC for aaPWV was performed to determine agreement within and between different observers. For ICC, the following scale was used: <0.5, 0.5-0.75, 0.75-0.9, and >0.9 were considered poor, moderate, good, and excellent agreement, respectively[21]. Bland-Altman plots were used to assess the limits of agreement between different observers when measuring aaPWV. Normality was assessed via quantile-quantile (Q-Q) plots and from the results of the Shapiro-Wilk tests. Data was natural log transformed due to right-skewness in the data. Univariate linear regression analyses were used to evaluate the individual relationships between PWV measures or systolic blood pressure. Multiple linear regression was used to adjust the relationship between measures of PWV and age, accounting for sex and systolic blood pressure. The correlation between aaPWV and cfPWV was assessed using Pearson's Correlation Coefficient following natural log transformation. Paired comparisons between cfPWV and aaPWV were made by paired t-test or the non-parametric Wilcoxon Signed-Rank test where appropriate. A sub-analysis was performed to determine if aaPWV differed between participants with risk factors (including hypertension, smoking, hypercholesterolemia, and diabetes) or known CVD and risk-free controls using Student's t-test or the Mann–Whitney test. Participants with CVD were age-, sex-, and BMI-matched to CVD-free healthy controls. Statistical significance was set a priori at $P \leq 0.05$. Data are reported as mean ± SD.

Results

Baseline characteristics of the 74 participants can be found in **Table 4-1**.

Table 4-1 Characteristics of the study population

Table 1

Number of participants	N=74
Age, years	44±16
Female, %	N=56, 76%
Height, m	1.7±0.1
Weight, kg	78.6±16.6
BMI, kg/m^2	27.1±5.8
cfPWV, m/s	6.8±1.8
aaPWV, m/s	5.8±2.2
SBP, mmHg	119.2±13.7
DBP, mmHg	71.6±11.9
MAP, mmHg	87.3±11.2
HR, bpm	67.6±9.4
Type II diabetes, %	N=1, 1%
Hypertension, %	N=15, 20%
Hypercholesterolemia, %	N=11, 15%
Known CVD, %	N=4, 5%

Abbreviations. cfPWV= carotid-femoral pulse wave velocity (m/s), aaPWV= aortic arch pulse wave velocity (m/s).

Intraclass correlation coefficient and linear regression

The intraclass correlation coefficient revealed excellent agreement within and between raters (0.94 and 0.95 respectively; a rating >0.9 indicates excellent agreement). Mean bias for the Bland-Altman analysis comparing aaPWV between raters was 0.05 (95% limits of agreement -1.82 to +1.93). Univariate linear regression revealed a significant relationship between PWV measures and age (aaPWV: r=0.25, SEE=0.36, P=0.03; cfPWV: r=0.75, SEE=0.17, P<0.001) and PWV measures and systolic blood pressure (aaPWV: r=0.23, SEE=0.37, P=0.04; cfPWV: r=0.48, SEE=0.22, P<0.001) for each method. Specifically, aaPWV and cfPWV increased 0.6% and 1.2% respectively, with every year of age. We further performed multivariable linear regression and found age remained associated with cfPWV when controlling for sex and systolic blood pressure (age; P<0.001), but the association was lost in aaPWV (age; P=0.15).

Relationship between aaPWV and cfPWV

Pearson's Correlation revealed the two methods were moderately, positively associated (r=0.32; P<0.01). When comparing mean values across the entire data set, our analysis revealed aaPWV was lower than cfPWV (aaPWV: 5.81±2.2m/s vs. cfPWV: 6.84±1.9m/s; P<0.01) (**Figure 4-2**).

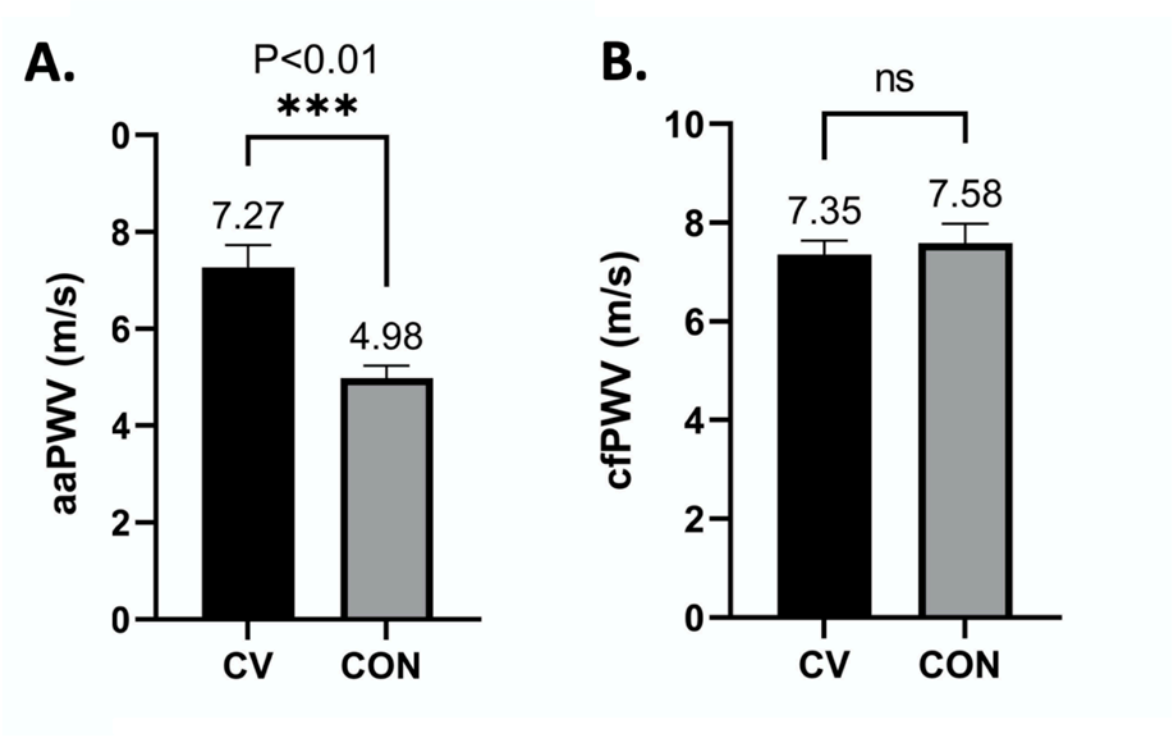
Figure 4-2 Differences in aaPWV and cfPWV

Differences in aaPWV and cfPWV across the entire cohort. Significant differences were detected between aaPWV and cfPWV (5.81±2.2m/s vs. 6.84±1.9m/s; $P<0.01$)

Influence of CV risk factors on aaPWV and cfPWV

We separated the data by individuals with risk factors or known CVD (n=29; CV) with age-, sex-, and BMI- matched controls (n=25; CON); those with risk factors/known CVD had an elevated aaPWV (CV: 7.27±2.5m/s vs. CON: 4.98±1.3m/s; P<0.01) (**Figure 4-3A**) but cfPWV was not different between groups (CV: 7.35±1.51m/s vs. CON: 7.58±1.9m/s; P=0.37) (**Figure 4-3B**). Additionally, when comparing aaPWV (7.27±2.5m/s) and cfPWV(7.35±1.5m/s) within the risk factor/CVD group, our analysis revealed no difference between the measures (P=0.89) (**Figure 4-4**).

Figure 4-3 Differences in pulse wave velocity stratified by cardiovascular risk factors



A, Differences in aortic arch pulse wave velocity in controls and participants with cardiovascular risk factors **B,** Differences in carotid-femoral pulse wave velocity in controls and participants with cardiovascular risk factors.

Figure 4-4 Differences in aaPWV and cfPWV in individuals with CV risk factors

No differences were found between aaPWV and cfPWV in individuals with cardiovascular risk factors.

Discussion

This study assessed the reliability of aaPWV measurements obtained via transthoracic echocardiography, how aaPWV relates to age and known CVD, and how it compares to cfPWV. The findings of the present study suggest that echocardiography derived aaPWV demonstrates excellent intra and inter-observer agreement and has favorable variability between measures. Moreover, participants with known CVD had a greater aaPWV than healthy controls. When compared to cfPWV, aaPWV was significantly lower, but the two measures maintained a significant and positive correlation. Discrepancies exist between the measures, but overall, our data suggest that aaPWV is a reliable measurement of large artery stiffness with significant clinical implications. Thus, echocardiography derived aaPWV could be useful for assessing aortic stiffness in the clinical setting.

Clinical significance of aortic stiffness

There is a critical need to incorporate monitoring of large artery stiffness in regular practice. Increases in aortic stiffness have been postulated to precede the development of hypertension[22], contribute to the etiology of heart failure with preserved ejection fraction[23], and have been independently associated with numerous conditions such as left ventricular hypertrophy[17], diastolic dysfunction[24,25], cognitive decline[26], and end-organ damage in low impedance, high flow organs like the brain and kidney[27]. Additionally, aortic stiffness is a strong independent predictor of cardiovascular events (i.e., coronary heart disease, stroke) even after accounting for traditional risk factors[13,28,29]. A meta-analysis from Ben-Shlomo et al.[13] has highlighted that adding aortic stiffness into cardiovascular risk prediction models improved long-term risk

classification by up to 13%, which makes a strong case for monitoring large artery stiffness in high-risk individuals.

Cardiac consequences of aortic stiffness

The physiological basis for the relationship between increased arterial stiffness and the cardiac outcomes discussed above may be attributable to the ventricular-vascular coupling present in health and becomes uncoupled with pathological conditions. Data from animal models, clinical, and large-population human studies have shown independent associations between increased large artery stiffness indices and left ventricular mass, fibrosis, and reductions in global longitudinal strain. In health, optimal ventricular-vascular coupling allows for efficient passive filling of the heart and augmentation of diastolic coronary perfusion pressure[30,31]. The proximal aorta acts as a spring that compresses longitudinally with systolic ejection and contributes to early filling by recoiling early in diastole while the ventricle is untwisting and displace the atrioventricular plane to facilitate passive filling[32]. In healthy states, with each left ventricular ejection a forward pressure wave is sent through the aorta that is reflected at branching points within the cardiovascular system, returning to the heart during diastole and augmenting coronary perfusion pressure. With a stiffened aorta, the spring function becomes impaired, limiting early diastolic filling and increasing the left atrium's active filling contributions[33]. The pressure wave will also travel through the system at a greater rate and arrive back at the heart during mid-to-late systole, which increases late systolic load and leads to a greater rate of diastolic pressure decay, thereby reducing coronary perfusion pressure[34]. This uncoupling has been hypothesized to undermine reductions in diastolic function seen with aging, especially in women[6,24,33]. Data from animal models, clinical, and large-population human studies have shown independent

associations between increased large artery stiffness indices and left ventricular mass, fibrosis, and reductions in global longitudinal strain.[3,5,27,33,35]

Systemic vascular consequences of aortic stiffness

With each ventricular contraction, a pulsatile load is imposed on the peripheral cardiovascular system that that is gradually buffered by an impedance gradient. The impedance gradient represents resistance to pulsatile flow and has an inverse relationship with blood vessel diameter so that it begins in the proximal elastic aortic segment and impedance is greatest at distal muscular arteries. This gradient is crucial for maintaining steady blood flow to the periphery and reflecting pulsatile energy at sites of impedance mismatch[36,37]. With increased large artery stiffness, the impedance gradient is reduced, systolic pressure will be augmented as the pulse travels faster through the periphery and greater pulsatility will transmit into the microcirculation[36,37]. This pulsatility is particularly problematic in organs that require high blood flow to meet metabolic demands but offer low resistance to flow. With excessive pulsatility in these organs, the vulnerable capillary beds are exposed to higher pressure levels and can disrupt the vessel-tissue interface through barrier leakage and fluid accumulation[27]. As such, target organ damage to the brain and kidney is associated with increased arterial stiffness-mediated increases in pulsatility resulting in white matter hyperintensities, covert brain infarcts, reduced glomerular filtration rate, and albuminuria; all of which are reflective of end-organ microvascular damage[27,38,39].

Differences between measurements

While we report both an association and differences between the two measurements, this is similar to comparing MRI-derived aaPWV and tonometry-derived cfPWV[40]. Physiologically, this was not entirely unexpected given the increasing gradient of large artery stiffness when moving from the proximal aorta to the more muscular peripheral vessels like the carotid and femoral arteries. For example, when considering the elastin:collagen ratio in the arterial wall, the proximal aorta contains 60% elastin and 40% collagen compared to the femoral and carotid arteries, which both contain 25% elastin and 75% collagen[41]. Younger individuals have a lower aaPWV than cfPWV, but previous studies have suggested this relationship changes with comorbidities, as elastin fragmentation accumulates across the life span, and the two velocities become more similar[6,27,42,43]. This was reflected in our sub-analysis of individuals with CVD risk factors/known CV, where no differences were detected between aaPWV and cfPWV within subjects, but the CV group presented with a greater aaPWV when compared to matched controls.

Additionally, differences in local vascular structure and function along these vessel segments with aging should be considered when comparing the two methods. cfPWV increases at a rate of 0.52±0.4m/s per decade before the age of 50 years old, and the rate of increase accelerates afterwards to 2.05±0.3m/s per decade[6,44]. When we consider the anatomical length traveled when measuring cfPWV, this includes the carotid artery, thoracic descending aorta, abdominal aorta, and the aorto-iliac bifurcation, but does not account for the proximal aorta. With aging, there are heterogenous increases in PWV along the descending and abdominal aortic segments, as documented in MRI studies[43-45]. It is reasonable to hypothesize that changes in cfPWV with aging are a reflection of increasing stiffness along the thoracic and abdominal segments, as well as possible impacts by changes in local stiffness of the carotid and femoral

arteries[46]. Several studies have shown an age-related increase in carotid stiffness, while the same relationship has not been unequivocally demonstrated with the femoral artery[47-49]. Aging-driven differences in local stiffening properties could also explain the variability in the predictive ability of local pulse wave velocity measures[46]. Local indices of both carotid stiffness and femoral stiffness have been associated with cardiovascular events and all-cause mortality[50]. However, when examining these local stiffness measures on specific outcomes, carotid stiffness is independently associated with incident stroke, but local femoral stiffness has not been independently associated with specific outcomes[51,52].

Age-related remodeling also occurs in the ascending aorta and the aortic arch. A study by Hickson et al. (2010)[44] highlighted the age-associated changes in aortic segment morphology as assessed by MRI. They reported the ascending aorta increased in diameter and length by 0.96mm and 8mm per decade, respectively, and reported pulse wave velocity increases through the aortic arch at a rate of 0.3m/s per decade which is substantially less than the rate of increase reported with cfPWV[44]. These differences in local properties and age-associated remodeling could help explain the differences between our two methods. Like cfPWV and local carotid stiffness, indices of regional (aortic arch) and local proximal aortic stiffness have been related to all-cause mortality and cardiovascular events. Findings from the MESA have reported regional aaPWV and local proximal aortic stiffness, assessed with MRI, to be significant predictors of CVD in middle-aged adults independent of traditional cardiovascular risk factors[16,53].

Previous studies utilizing doppler to measure aortic stiffness

We are not the first group to attempt to measure aortic stiffness with echocardiography. Bonapace et al.[54] measured thoracic aortic pulse wave velocity (taPWV) (i.e., from the distal

descending aorta to abdominal aorta) in a cohort of patients with heart failure with reduced ejection fraction over 5 years and found that taPWV was an independent predictor of hospitalization and death. This method has promising clinical application given that the images were obtained from standard transthoracic echocardiographic windows. However, this approach still does not encompass the proximal aorta, but is a measure of abdominal aortic stiffness which remains susceptible to vessel tortuosity with age[45]. Aortic arch pulse wave velocity (i.e., from the ascending aorta at the level of the right pulmonary artery to the descending aorta) obtained from the suprasternal view has also been measured in patients with different heart failure phenotypes (reduced or preserved ejection fraction), dilated cardiomyopathy, and end-stage renal disease populations[55-58]. This measurement is associated with left ventricular mass and diastolic filling in end-stage renal disease populations[55] and left ventricular systolic and diastolic function in multiple phenotypes of dilated cardiomyopathy[56,57]. Additionally Pugliese et al. used this alongside left ventricular longitudinal strain to calculate an index of ventricular-arterial coupling in patients with different heart failure phenotypes[58]. While all three of the aforementioned studies assessing aortic arch pulse wave velocity offer clinical utility, this method has a few limitations. The first includes challenges in obtaining a clear window of the aortic arch with proper visualization of the right pulmonary artery as a reference point and a clear Doppler signal. In our experience, obtaining a clear signal in clinical populations can be difficult to determine the precise timing of the ascending aortic upstroke, which is crucial for determining pulse wave velocity over such short distances[59]. Another limitation of this method is the potential influence of vortical or helical flow in the ascending aorta, as suggested by Chirinos et al.[59] and others[60], which influences the profile of the velocity waveform, and thus assessment of timing. The latter

limitation adds strength to our proposed measurement since our initial sampling site is at the level of the aortic valve level in the apical 5-chamber view.

Clinical feasibility

Our proposed measurement of aaPWV offers clinical utility and feasibility as it is obtained from standard echocardiographic views. Additionally, any routine echocardiography assessment will obtain aortic valve pulsed Doppler waveforms. The only additional image that would need to be obtained is a velocity waveform in the descending aorta using the suprasternal view, which takes <30s by a trained sonographer, and is often a part of standard practice. Even in the hands of novice sonographers in our lab, it took less than less 5 minutes combined to obtain the appropriate images and complete data analysis, which also adds to practical implementation in research settings. Additionally, this eliminates the need to use tonometry equipment which can be costly and takes time to train individuals on how to use them. Relevant to the time demands in clinical practice, post-processing took an average of 3 minutes to manually analyze 3-5 cardiac cycles between the two views.

Methodical considerations and limitations

Our method of aaPWV will allow for serial measurements to be taken longitudinally to monitor changes in proximal aortic stiffness which is supported by excellent within- and between-observer agreement. However, our study does have limitations to be taken into consideration. Even though our cohort has a diverse age range, it primarily contains women, which may not be reflective of the general population as it has been reported sex differences exist in arterial aging[61]. Secondly, we could not simultaneously sample velocities at the aortic valve and in the

descending aorta. Due to this limitation, there could be some inherent differences in timing between the two sites. However, this method would be required in the clinical setting where often only a single ultrasound system and sonographer are available. Lastly, we used a regression equation[20] to estimate the distance of the ascending aorta to the peak of the apex of the aortic arch. We acknowledge this distance could be under or overestimated in our subjects, but this is also a methodological limitation to cfPWV[12,18]. In the case of accounting for tortuosity in our distance measurements, we manually measured the length of the descending aorta, which has been suggested to be prone to this type of remodeling with age and in the presence of risk factors[45]. However, our proposed method of aaPWV may not be appropriate if subjects are known to have ascending aorta or aortic root geometry abnormalities.

Conclusion

The current findings indicate our echocardiography derived measure of aortic arch stiffness is related to the gold standard cfPWV, and that aaPWV is increased in individuals with cardiovascular risk factors or disease. aaPWV shows excellent rating within and between raters and could be easily incorporated into clinical practice. Future studies are warranted to determine if this method is predictive of cardiovascular or all-cause mortality outcomes in general or clinical populations.

References

1. Chirinos JA. Arterial stiffness: basic concepts and measurement techniques. J Cardiovasc Transl Res. 2012;5:243-255. doi: 10.1007/s12265-012-9359-6

2. Ott CE, Grunhagen J, Jager M, Horbelt D, Schwill S, Kallenbach K, Guo G, Manke T, Knaus P, Mundlos S, et al. MicroRNAs differentially expressed in postnatal aortic development downregulate elastin via 3' UTR and coding-sequence binding sites. PLoS One. 2011;6:e16250. doi: 10.1371/journal.pone.0016250

3. Chirinos JA, Segers P, Hughes T, Townsend R. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;74:1237-1263. doi: 10.1016/j.jacc.2019.07.012

4. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25:932-943. doi: 10.1161/01.ATV.0000160548.78317.29

5. Zamani P, Bluemke DA, Jacobs DR, Jr., Duprez DA, Kronmal R, Lilly SM, Ferrari VA, Townsend RR, Lima JA, Budoff M, et al. Resistive and pulsatile arterial load as predictors of left ventricular mass and geometry: the multi-ethnic study of atherosclerosis. Hypertension. 2015;65:85-92. doi: 10.1161/HYPERTENSIONAHA.114.04333

6. Mitchell GF. Arterial Stiffness in Aging: Does It Have a Place in Clinical Practice?: Recent Advances in Hypertension. Hypertension. 2021;77:768-780. doi: 10.1161/HYPERTENSIONAHA.120.14515

7. Cooper LL, Woodard T, Sigurdsson S, van Buchem MA, Torjesen AA, Inker LA, Aspelund T, Eiriksdottir G, Harris TB, Gudnason V, et al. Cerebrovascular Damage Mediates

Relations Between Aortic Stiffness and Memory. Hypertension. 2016;67:176-182. doi: 10.1161/HYPERTENSIONAHA.115.06398

8. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006;113:657-663. doi: 10.1161/CIRCULATIONAHA.105.555235

9. Tsao CW, Lyass A, Larson MG, Levy D, Hamburg NM, Vita JA, Benjamin EJ, Mitchell GF, Vasan RS. Relation of Central Arterial Stiffness to Incident Heart Failure in the Community. J Am Heart Assoc. 2015;4. doi: 10.1161/JAHA.115.002189

10. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. Am J Kidney Dis. 2005;45:494-501. doi: 10.1053/j.ajkd.2004.11.011

11. Smulyan H, Lieber A, Safar ME. Hypertension, Diabetes Type II, and Their Association: Role of Arterial Stiffness. Am J Hypertens. 2016;29:5-13. doi: 10.1093/ajh/hpv107

12. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588-2605. doi: 10.1093/eurheartj/ehl254

13. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014;63:636-646. doi: 10.1016/j.jacc.2013.09.063

14. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021-3104. doi: 10.1093/eurheartj/ehy339

15. Services CfMM. Billing and Coding: Non-Invasive Vascular Studies CMS.gov. 2022. Accessed 6/25/23.

16. Ohyama Y, Ambale-Venkatesh B, Noda C, Kim JY, Tanami Y, Teixido-Tura G, Chugh AR, Redheuil A, Liu CY, Wu CO, et al. Aortic Arch Pulse Wave Velocity Assessed by Magnetic Resonance Imaging as a Predictor of Incident Cardiovascular Events: The MESA (Multi-Ethnic Study of Atherosclerosis). Hypertension. 2017;70:524-530. doi: 10.1161/HYPERTENSIONAHA.116.08749

17. Ohyama Y, Ambale-Venkatesh B, Noda C, Chugh AR, Teixido-Tura G, Kim JY, Donekal S, Yoneyama K, Gjesdal O, Redheuil A, et al. Association of Aortic Stiffness With Left Ventricular Remodeling and Reduced Left Ventricular Function Measured by Magnetic Resonance Imaging: The Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2016;9. doi: 10.1161/CIRCIMAGING.115.004426

18. Sugawara J, Hayashi K, Tanaka H. Arterial Path Length for Arterial Stiffness: Methodological Consideration. Am J Hypertens. 2016;29:1237-1244. doi: 10.1093/ajh/hpw075

19. Ohyama Y, Redheuil A, Kachenoura N, Ambale Venkatesh B, Lima JAC. Imaging Insights on the Aorta in Aging. Circ Cardiovasc Imaging. 2018;11:e005617. doi: 10.1161/CIRCIMAGING.117.005617

20. Sugawara J, Hayashi K, Yokoi T, Tanaka H. Age-associated elongation of the ascending aorta in adults. JACC Cardiovasc Imaging. 2008;1:739-748. doi: 10.1016/j.jcmg.2008.06.010

21. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15:155-163. doi: 10.1016/j.jcm.2016.02.012

22. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012;308:875-881. doi: 10.1001/2012.jama.10503

23. Ali D, Tran P, Ennis S, Powell R, McGuire S, McGregor G, Kimani PK, Weickert MO, Miller MA, Cappuccio FP, et al. Rising arterial stiffness with accumulating comorbidities associates with heart failure with preserved ejection fraction. ESC Heart Fail. 2023. doi: 10.1002/ehf2.14422

24. Russo C, Jin Z, Palmieri V, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Arterial stiffness and wave reflection: sex differences and relationship with left ventricular diastolic function. Hypertension. 2012;60:362-368. doi: 10.1161/HYPERTENSIONAHA.112.191148

25. Weber T, O'Rourke MF, Ammer M, Kvas E, Punzengruber C, Eber B. Arterial stiffness and arterial wave reflections are associated with systolic and diastolic function in patients with normal ejection fraction. Am J Hypertens. 2008;21:1194-1202. doi: 10.1038/ajh.2008.277

26. Meyer ML, Palta P, Tanaka H, Deal JA, Wright J, Knopman DS, Griswold ME, Mosley TH, Heiss G. Association of Central Arterial Stiffness and Pressure Pulsatility with Mild Cognitive Impairment and Dementia: The Atherosclerosis Risk in Communities Study-Neurocognitive Study (ARIC-NCS). J Alzheimers Dis. 2017;57:195-204. doi: 10.3233/JAD-161041

27. Vasan RS, Short MI, Niiranen TJ, Xanthakis V, DeCarli C, Cheng S, Seshadri S, Mitchell GF. Interrelations Between Arterial Stiffness, Target Organ Damage, and Cardiovascular Disease Outcomes. J Am Heart Assoc. 2019;8:e012141. doi: 10.1161/JAHA.119.012141

28. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55:1318-1327. doi: 10.1016/j.jacc.2009.10.061

29. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation. 2005;111:3384-3390. doi: 10.1161/CIRCULATIONAHA.104.483628

30. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y. Coronary circulation in dogs with an experimental decrease in aortic compliance. J Am Coll Cardiol. 1993;21:1497-1506. doi: 10.1016/0735-1097(93)90330-4

31. Pierce GL, Coutinho TA, DuBose LE, Donato AJ. Is It Good to Have a Stiff Aorta with Aging? Causes and Consequences. Physiology (Bethesda). 2022;37:154-173. doi: 10.1152/physiol.00035.2021

32. Carlsson M, Ugander M, Mosen H, Buhre T, Arheden H. Atrioventricular plane displacement is the major contributor to left ventricular pumping in healthy adults, athletes, and patients with dilated cardiomyopathy. Am J Physiol Heart Circ Physiol. 2007;292:H1452-1459. doi: 10.1152/ajpheart.01148.2006

33. Bell V, McCabe EL, Larson MG, Rong J, Merz AA, Osypiuk E, Lehman BT, Stantchev P, Aragam J, Benjamin EJ, et al. Relations Between Aortic Stiffness and Left Ventricular

Mechanical Function in the Community. J Am Heart Assoc. 2017;6. doi: 10.1161/JAHA.116.004903

34. Chemla D, Nitenberg A, Teboul JL, Richard C, Monnet X, le Clesiau H, Valensi P, Brahimi M. Subendocardial viability ratio estimated by arterial tonometry: a critical evaluation in elderly hypertensive patients with increased aortic stiffness. Clin Exp Pharmacol Physiol. 2008;35:909-915. doi: 10.1111/j.1440-1681.2008.04927.x

35. Kobayashi S, Yano M, Kohno M, Obayashi M, Hisamatsu Y, Ryoke T, Ohkusa T, Yamakawa K, Matsuzaki M. Influence of aortic impedance on the development of pressure-overload left ventricular hypertrophy in rats. Circulation. 1996;94:3362-3368. doi: 10.1161/01.cir.94.12.3362

36. Haidar MA, van Buchem MA, Sigurdsson S, Gotal JD, Gudnason V, Launer LJ, Mitchell GF. Wave Reflection at the Origin of a First-Generation Branch Artery and Target Organ Protection: The AGES-Reykjavik Study. Hypertension. 2021;77:1169-1177. doi: 10.1161/HYPERTENSIONAHA.120.16696

37. Mitchell GF. Aortic stiffness, pressure and flow pulsatility, and target organ damage. J Appl Physiol (1985). 2018;125:1871-1880. doi: 10.1152/japplphysiol.00108.2018

38. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension. 2008;52:1120-1126. doi: 10.1161/HYPERTENSIONAHA.108.119024

39. Woodard T, Sigurdsson S, Gotal JD, Torjesen AA, Inker LA, Aspelund T, Eiriksdottir G, Gudnason V, Harris TB, Launer LJ, et al. Mediation analysis of aortic stiffness and renal microvascular function. J Am Soc Nephrol. 2015;26:1181-1187. doi: 10.1681/ASN.2014050450

40. Joly L, Perret-Guillaume C, Kearney-Schwartz A, Salvi P, Mandry D, Marie PY, Karcher G, Rossignol P, Zannad F, Benetos A. Pulse wave velocity assessment by external noninvasive devices and phase-contrast magnetic resonance imaging in the obese. Hypertension. 2009;54:421-426. doi: 10.1161/HYPERTENSIONAHA.109.133645

41. Wilmer W. Nichols MFOR, Charalambos Vlachopoulos McDonald's Blood Flow in Arteries Theoretical, Experimental, and Clinical Principles. Sixth Edition Sixth ed. London Hodder Arnold 2011.

42. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M, Salerno M, Teague SD, Valsangiacomo-Buechel E, van der Geest RJ, et al. Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. J Cardiovasc Magn Reson. 2020;22:87. doi: 10.1186/s12968-020-00683-3

43. Rogers WJ, Hu YL, Coast D, Vido DA, Kramer CM, Pyeritz RE, Reichek N. Age-associated changes in regional aortic pulse wave velocity. J Am Coll Cardiol. 2001;38:1123-1129. doi: 10.1016/s0735-1097(01)01504-2

44. Hickson SS, Butlin M, Graves M, Taviani V, Avolio AP, McEniery CM, Wilkinson IB. The relationship of age with regional aortic stiffness and diameter. JACC Cardiovasc Imaging. 2010;3:1247-1255. doi: 10.1016/j.jcmg.2010.09.016

45. Adriaans BP, Heuts S, Gerretsen S, Cheriex EC, Vos R, Natour E, Maessen JG, Sardari Nia P, Crijns H, Wildberger JE, et al. Aortic elongation part I: the normal aortic ageing process. Heart. 2018;104:1772-1777. doi: 10.1136/heartjnl-2017-312866

46. Paini A, Boutouyrie P, Calvet D, Tropeano AI, Laloux B, Laurent S. Carotid and aortic stiffness: determinants of discrepancies. Hypertension. 2006;47:371-376. doi: 10.1161/01.HYP.0000202052.25238.68

47. Vermeersch SJ, Rietzschel ER, De Buyzere ML, De Bacquer D, De Backer G, Van Bortel LM, Gillebert TC, Verdonck PR, Segers P. Age and gender related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population. J Hypertens. 2008;26:1411-1419. doi: 10.1097/HJH.0b013e3282ffac00

48. Benetos A, Laurent S, Hoeks AP, Boutouyrie PH, Safar ME. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. Arterioscler Thromb. 1993;13:90-97. doi: 10.1161/01.atv.13.1.90

49. Boutouyrie P, Laurent S, Benetos A, Girerd XJ, Hoeks AP, Safar ME. Opposing effects of ageing on distal and proximal large arteries in hypertensives. J Hypertens Suppl. 1992;10:S87-91.

50. van Sloten TT, Schram MT, van den Hurk K, Dekker JM, Nijpels G, Henry RM, Stehouwer CD. Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality: the Hoorn study. J Am Coll Cardiol. 2014;63:1739-1747. doi: 10.1016/j.jacc.2013.12.041

51. van Sloten TT, Sedaghat S, Laurent S, London GM, Pannier B, Ikram MA, Kavousi M, Mattace-Raso F, Franco OH, Boutouyrie P, et al. Carotid stiffness is associated with incident stroke: a systematic review and individual participant data meta-analysis. J Am Coll Cardiol. 2015;66:2116-2125. doi: 10.1016/j.jacc.2015.08.888

52. Pewowaruk RJ, Korcarz C, Tedla Y, Burke G, Greenland P, Wu C, Gepner AD. Carotid Artery Stiffness Mechanisms Associated With Cardiovascular Disease Events and Incident Hypertension: the Multi-Ethnic Study of Atherosclerosis (MESA). Hypertension. 2022;79:659-666. doi: 10.1161/HYPERTENSIONAHA.121.18772

53. Redheuil A, Wu CO, Kachenoura N, Ohyama Y, Yan RT, Bertoni AG, Hundley GW, Duprez DA, Jacobs DR, Jr., Daniels LB, et al. Proximal aortic distensibility is an independent predictor of all-cause mortality and incident CV events: the MESA study. J Am Coll Cardiol. 2014;64:2619-2629. doi: 10.1016/j.jacc.2014.09.060

54. Bonapace S, Rossi A, Cicoira M, Targher G, Valbusa F, Benetos A, Vassanelli C. Increased aortic pulse wave velocity as measured by echocardiography is strongly associated with poor prognosis in patients with heart failure. J Am Soc Echocardiogr. 2013;26:714-720. doi: 10.1016/j.echo.2013.03.022

55. Patrianakos AP, Parthenakis FI, Karakitsos D, De Groot E, Skalidis EA, Nyktari E, Daphnis E, Vardas PE. Relation of proximal aorta stiffness to left ventricular diastolic function in patients with end-stage renal disease. J Am Soc Echocardiogr. 2007;20:314-323. doi: 10.1016/j.echo.2006.08.034

56. Patrianakos AP, Parthenakis FI, Karakitsos D, Nyktari E, Vardas PE. Proximal aortic stiffness is related to left ventricular function and exercise capacity in patients with dilated cardiomyopathy. Eur J Echocardiogr. 2009;10:425-432. doi: 10.1093/ejechocard/jen304

57. Patrianakos AP, Parthenakis FI, Nyktari E, Malliaraki N, Karakitsos DN, Vardas PE. Central aortic stiffness in patients with nonischemic dilated cardiomyopathy: relationship with neurohumoral activation. J Card Fail. 2009;15:665-672. doi: 10.1016/j.cardfail.2009.03.007

58. Pugliese NR, Balletti A, Armenia S, De Biase N, Faita F, Mengozzi A, Paneni F, Ruschitzka F, Virdis A, Ghiadoni L, et al. Ventricular-Arterial Coupling Derived From Proximal Aortic Stiffness and Aerobic Capacity Across the Heart Failure Spectrum. JACC Cardiovasc Imaging. 2022;15:1545-1559. doi: 10.1016/j.jcmg.2022.03.024

59. Chirinos JA. Echocardiographic Assessment of Large Artery Stiffness. J Am Soc Echocardiogr. 2016;29:1117-1121. doi: 10.1016/j.echo.2016.09.004

60. Bensalah MZ, Bollache E, Kachenoura N, Giron A, De Cesare A, Macron L, Lefort M, Redheuil A, Mousseaux E. Geometry is a major determinant of flow reversal in proximal aorta. Am J Physiol Heart Circ Physiol. 2014;306:H1408-1416. doi: 10.1152/ajpheart.00647.2013

61. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. J Am Coll Cardiol. 2013;61:96-103. doi: 10.1016/j.jacc.2012.08.997

Conclusions

To conclude this dissertation, there are two primary take aways. First a significant relationship exists with arterial stiffness and various chemotherapy regimens and the development of adverse long-term outcomes. We first established arterial stiffness is increasing pre to post treatment in a diverse group of cancer patients after exposure to chemotherapy. In our mean difference analysis, pulse wave velocity increased 1.5m/s which is clinically meaningful given that for every 1m/s increase in pulse wave velocity equates to a 15% increase in cardiovascular mortality[1]. In the second investigation, we determined that increased levels of pulse pressure, a clinical index of arterial stiffness, was predictive of cardiovascular and all-cause mortality, especially in younger cancer patients. This was consistent with data in the literature highlighting arterial stiffness has independent predictive ability for cardiovascular events in the general population, especially in younger, high-risk individuals. The findings from these studies suggest a need to implement additional vascular monitoring strategies into the clinic, and we attempted to address this need with Chapter 4. Our next investigation determined transthoracic echocardiography derived aortic arch stiffness was related to the gold standard carotid-femoral pulse wave velocity and presented with excellent ratings between and within observers. Future directions will examine whether this measurement can be implemented in clinical settings and whether this measure is associated with adverse cardiac outcomes.

Taken together, our data suggests changes in arterial stiffness can be additive to risk stratification in cardio-oncology and we provide a potential method to monitor changes in the clinic. We feel this represents an integrative approach to gain a picture of the global cardiovascular system to monitor cardiovascular health in cancer patients through the cancer care continuum.

References

1. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55:1318-1327. doi: 10.1016/j.jacc.2009.10.061