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Special Issue from Queen Elizabeth University Hospital and Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland

Guest Editors:
Sandosh Padmanabhan, Linsay McCallum

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Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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Editorial

Special Issue 2 from Queen Elizabeth University Hospital and Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland

Linsay McCallum[1,2], Sandosh Padmanabhan[1,2]

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The second special issue brings together another collection of up-to-date articles from Glasgow academic clinicians and their collaborators featuring a wide range of review topics and clinical cases from pediatric and adult hypertension practice.

The hot topic of climate change features in a systematic review from Clements *et al.*[1] appraising 46 articles, examining the relationship between short-term exposure to particulate matter and gaseous pollutants as well as the long-term impacts. We cover special populations in four reviews – Lucas-Herald[2] explores the challenge of assessing cardiovascular risk in children and young people and examines the role of non-invasive vascular phenotyping assessments, Casey *et al.*[3] reviewed the pathogenesis, association with cardiovascular disease, and the need for postpartum cardiovascular risk reduction, McGettrick *et al.*[4] described the pathophysiology of pulmonary hypertension as a result of chronic pulmonary thromboembolic disease and review the use of MR imaging as an adjunct to echocardiography, right heart catheterization and CT, and Shields *et al.*[5] reviewed the relationship between inflammatory bowel disease (IBD) and cardiovascular disease and examined the associated increased cardiovascular risk seen in individuals with IBD and discussed the potential role of TNF antagonism for risk reduction. Clinical evidence and guidelines feature in a comprehensive systematic review by Alsanosi *et al.*[6] on the comparative efficacy of the different antihypertensive drug classes as monotherapy.

This issue features an interesting and unique case report from Crowe *et al.*[7] offering clinical learning pearls on intravitreal VEGF inhibitor complications.

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Review Article

Comparative Efficacy of Antihypertensive Drug Classes – A Systematic Review and Network Meta-analyses (Review)

Safaa Alsanosi[1,2], Panniyammakal Jeemon[2,3], Nur Aishah Binti Che Roos[2], Mohammed Alsieni[2], Linsay McCallum[2], Anna Dominiczak[2], Sandosh Padmanabhan[2]

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Abstract

Multiple systematic reviews have demonstrated no significant differences between blood pressure (BP)-lowering drug classes on protection against major cardiovascular events. However, there is a paucity of similar data on the comparative efficacy of different antihypertensive drug classes on BP lowering. Published randomized controlled trials were reviewed from MEDLINE, EMBASE, Web of Science, and Cochrane for trials. We included randomized controlled trials of antihypertensive agents, with at least 100 participants and with a minimum follow-up of 1-year. Two authors independently selected the included trials, evaluated the risk of bias, and retrieved the data on BP response. Meta-analyses were performed to summarize the pooled standardized mean differences (SMD) of BP between treatment arms. A network meta-analysis was also completed to compare the BP response of all possible pairs of antihypertensive agents (classes of drugs). We identified 66 trials, with 163,491 participants. Calcium channel blockers (CCBs) were superior to angiotensin-converting enzyme inhibitors (ACEIs) in lowering systolic BP (pooled SMD of −0.09 mmHg, $P = 0.006$, high quality based on Grading of Recommendations, Assessment, Development and Evaluation) and diastolic BP (−0.15 mmHg, $P = 0.0002$, high quality). Diuretics (DIs) were superior to ACEIs (−0.11 mmHg, $P < 0.00001$, moderate quality) and CCB (−0.10 mmHg, $P = 0.0001$, moderate quality) in lowering systolic BP. Network meta-analysis involving 94 pairwise comparisons showed DIs lowered BP greater than any other antihypertensive agents except angiotensin II receptor blockers which had a similar effect.

Key words: Antihypertensive agent, blood pressure response, hypertension, meta-analyses, monotherapy

Introduction

Despite declines in age-standardized mortality rates in the past three decades, globally cardiovascular disease (CVD) is the leading cause of death.[1] Hypertension (HTN) is responsible for majority of the deaths due to CVD[2] and is one of the main entry points of initiating drug therapy to achieve global CVD risk reduction.[3] Regardless of the availability of effective therapies in blood pressure (BP) reduction[4] and the growing evidence of benefits of antihypertensive therapies on mortality reduction,[5] the treatment and control rates of HTN remain inadequate.[6]

Multiple clinical guidelines are produced by national and international HTN societies and used to assist in therapeutic drug choices but initial drug class choice is currently based on age and ethnicity. Intensive BP control in clinical trials demonstrate further reduction of CVD risk and all-cause mortality,[7] leading to a lower BP threshold being adopted for diagnosis or treatment target in different guidelines. However, achieving ideal BP goals are indeed challenging for both physicians and patients in real-life settings and this is reflected in the poor control rates in all the regions of the world.[8] Whereas there are abundant data through large systematic reviews on the comparative efficacy of BP-lowering drug classes on protection against major cardiovascular events, there is a paucity of information on class-specific BP-lowering effects.[9,10] Evidence on the comparative efficacy of

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different classes of drugs in reducing BP may help physicians select appropriate BP-lowering drugs and communicate more effectively with patients on their queries about different drugs. We conducted a systematic review and network meta-analyses of randomized controlled trials (RCTs) to identify the drug class-specific effect of antihypertensive monotherapy on BP response. We have included all the main classes of antihypertensive agents, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics (DIs), and beta-blockers (BBs).

Methods

Literature search

Comprehensive electronic searches of MEDLINE, EMBASE, Web of Science, and Cochrane (the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews) were conducted for the published trials [Online Supplement, Table S1]. Cross-references of all retrieved manuscripts were also checked to identify additional trials. The author (S.A) conducted the initial screening (including titles and abstracts) of potentially eligible article. Data were extracted independently by two of the reviewers (M.A. and A.C.) using a standardized spreadsheet (Microsoft Excel 2010). A third investigator (SP) served as a tiebreaker, independently reviewing articles to resolve the disagreement between the other two investigators.

Statistical analysis

Study participants were analyzed in the groups to which they were randomized, regardless of adherence to allotted treatment (intention to treat analyses). Standardized mean difference (SMD) of the average BP reduction was used to pool the effect size. For delta, BP response was calculated by subtracting the baseline value at randomization from the value reported at the end of the trial or at the last time point during treatment. Pooled SMD was calculated by choosing the random effects (REs) model in the Review Manager 4.2.1 software. Heterogeneity was estimated by both χ^2 test and I^2 statistics. When there was a significant statistical heterogeneity (χ^2 $P < 0.05$ or I^2 statistics of above 60%), sensitivity analysis was conducted by substituting alternate decisions, and the cause of heterogeneity (methodological or clinical) was investigated with reference to the characteristics of the studies included in the meta-analysis. Study-specific effect sizes of the standard pairwise meta-analysis model along with 95% CIs were shown in forest plots. Multiple classes of antihypertensive agents were simultaneously compared (all possible pairwise comparisons) using RE network meta-analysis. Correlation of effect sizes was accounted in multi-arm trials. Summary mean differences were presented in forest plots. Network meta-analyses were fitted in a frequentist framework using R (netmeta package). In addition, we ranked the classes of antihypertensive agents based on frequentist analogue of surface under cumulative ranking curve (SUCRA).

Results

Studies included in the meta-analyses

The initial literature search identified 10,577 publications. After excluding duplicates, there were 5568 records. In total, 168 articles were identified as potentially eligible studies, based on abstract review. After full-text review of the 168 eligible studies, 102 RCTs were excluded (in nine studies, participants had HTN; however, baseline BP was not specified). Protocol for dis or continuation of background BP-lowering drugs before randomization was not pre-specified in 10 studies, whereas protocol for supplemental drugs after randomization was not pre-specified in 14 studies. In four cross-over studies, there was no washout period between treatment groups. Mean, duration or measurement protocol for BP response was not specified in 43 studies. In total, 31 studies included individuals without HTN; 16 studies had <70% of participants with HTN, and 15 studies not specified the percentage of participants with HTN). In the end, 66 RCTs, with a total of 163,491 participants, were considered appropriate for inclusion in the meta-analysis [Figure 1].

Risk of bias in the included studies

Most of the included RCTs (n = 43) did not address how treatment randomization occurred or how allocation of treatment was concealed (n = 53) and therefore had an unclear risk of selection bias [Figure 2]. Random sequence generation was addressed in 23 studies (AASK, 2002; ALLHAT, 2002; CASE-J, 2008; CONVINCE, 2003; Derosa, 2013; Derosa, 2014; ELSA, 2002; FACET, 1998; HYVET, 2008; HYVET-P, 2003; IDNT, 2001; INVEST, 2003; James, 2002; JMIC-B, 2004; LAARS, 2002; LIFE, 2002; MIDAS, 1996; PATS, 1995; RACE, 1995; SHELL, 2003; SYST-EUR, 1997; UKPDS, 1998; and VALUE, 2004). Allocation concealment was addressed in 13 studies (ALLHAT, 2002; CONVINCE, 2003; Derosa, 2013; Derosa, 2014; HYVET, 2008; IDNT, 2001; INVEST, 2003; JMIC-B, 2004; LAARS, 2002; PATS, 1995; RACE, 1995; SYST-EUR, 1997; and UKPDS, 1998), whereas in the other studies, the information provided was insufficient to assess risk of bias and was considered unclear.

Five studies did not describe the double blinding strategy with sufficient details (LOTHAR, 2006; SHELL, 2003; VHAS, 1998; Wu, 2004; and Yang, 2015). There were eight open-label studies (CASE-J, 2008; CONVINCE, 2003; FACET, 1998; HYVET, 2008; HYVET-P, 2003; INVEST, 2003; NORDIL, 2000; and UKPDS, 1998).

The risk of attrition bias was minimum, and all studies followed intention to treat analyses. Another source of bias attributable to addition of multiple BP lowering agents on top of the randomized treatment was present in 13 (AASK, 2002; ALLHAT, 2002; CONVINCE, 2003; FACET, 1998; HYVET, 2008; IDNT, 2001; INSIGHT, 2000; INVEST, 2003; LIFE, 2002; NORDIL, 2000; UKPDS, 1998; VALUE, 2004; and VHAS, 1998) of the 66 studies.

The baseline BP represented in the pooled population covered a wide range, from mild to moderate HTN, with the

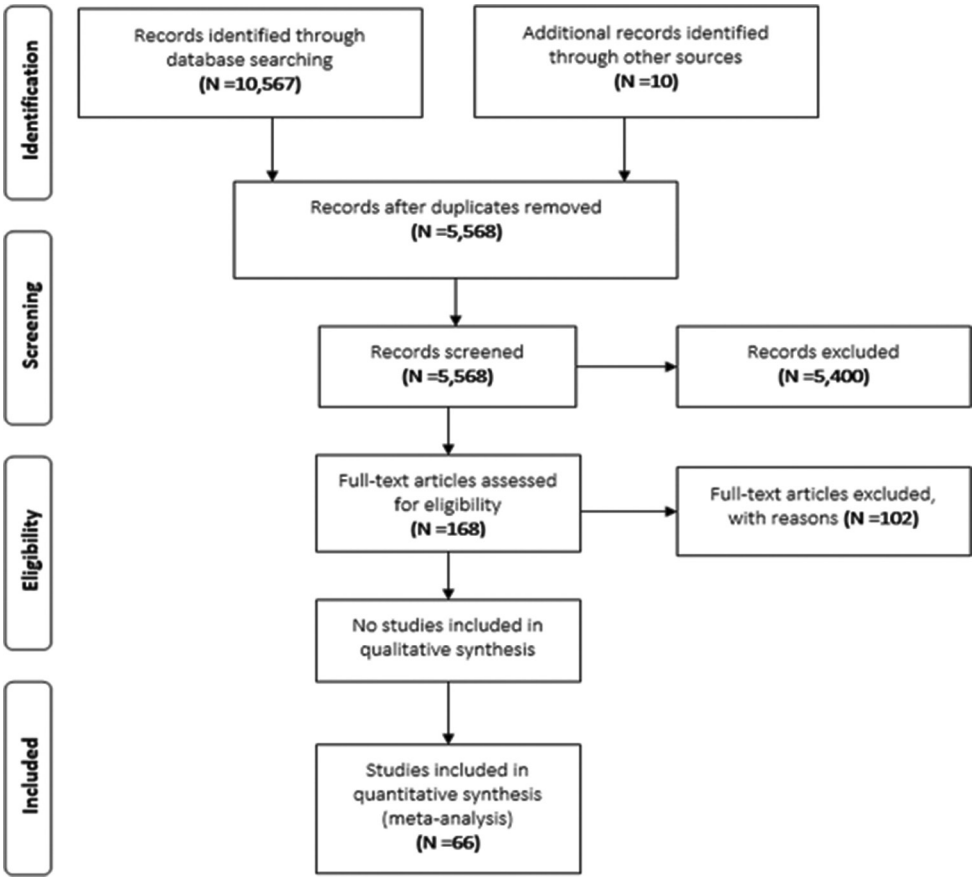

Figure 1: Flow diagram describing selection of trials for meta-analysis

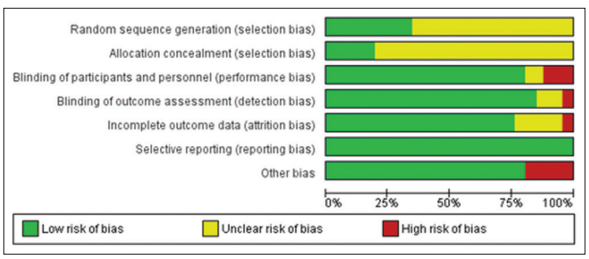

Figure 2: Risk of bias graph: Review authors' judgments about each risk of bias item, presented as % across all included studies

mean of BP 160/96 mmHg. Overall, 14 trials were undertaken in patients with isolated systolic HTN, nine in patients with type 2 diabetes mellitus, seven in patients with coronary heart disease, and four in patients with chronic kidney disease (CKD). Monotherapy was used as the first line of approach in all included studies. However, more than 1 BP-lowering agents were required to achieve the BP goal in 13 of the 66 studies. In total, 14,523 participants were randomized to ACEIs (30 RCTs), 19,838 to ARBs (30 RCTs), 56,998 to CCBs (38 RCTs), 40,333 to DIs (19 RCTs), and 33,418 to BBs (17 RCTs). Overall, CCBs were the most frequently prescribed antihypertensive agents for HTN (24.8%), followed by ARBs (21.5%) and ACEIs (20.15), DIs (13.4%), and BBs (11.4%) [Online Supplement, Table S4].

BP response in trials comparing CCBs and ACEIs

In total, 14 trials were included in the meta-analysis comparing the BP response of CCBs and ACEIs [Figures 3 and 4]. The pooled SMD in the RE model was −0.12 mmHg, 95% CI (−0.20, −0.03) and −0.15 mmHg, 95% CI (−0.22, −0.07) for SBP and DBP, respectively (I^2 = 69% and 56 %; χ^2 P = 0.007 and P < 0.0001, for SBP and DBP, respectively). The FACET, 1998, trial was methodologically weaker than other studies as drugs were administered under open labels. Sensitivity analyses after excluding the above-mentioned study resulted in a SMD of −0.09, 95% CI (−0.15, −0.03) and −0.15 (−0.23, −0.07) for SBP and DBP, respectively (I^2 = 37% and 59%; χ^2 P = 0.006 and P = 0.0002 for SBP and DBP; respectively, [Online Supplement, Figure S2]). The overall quality evidence was rated as high using the GRADE criteria [Online Supplement, Table S5].

BP response in trials comparing ACEIs and ARBs

In total, 10 trials were included in the meta-analysis comparing the BP response of ACEIs and ARBs [Figures 3 and 4]. In the RE model, the pooled SMD was 0.30 mmHg, 95% CI (−0.12, 0.72) and −0.18 mmHg, 95% CI (−0.32, −0.04) for SBP and DBP, respectively ([I^2 = 97% and 71% for SBP and DBP; respectively; χ^2 P = 0.16 and P = 0.01]). The Ruilope, 2001, trial was clinically

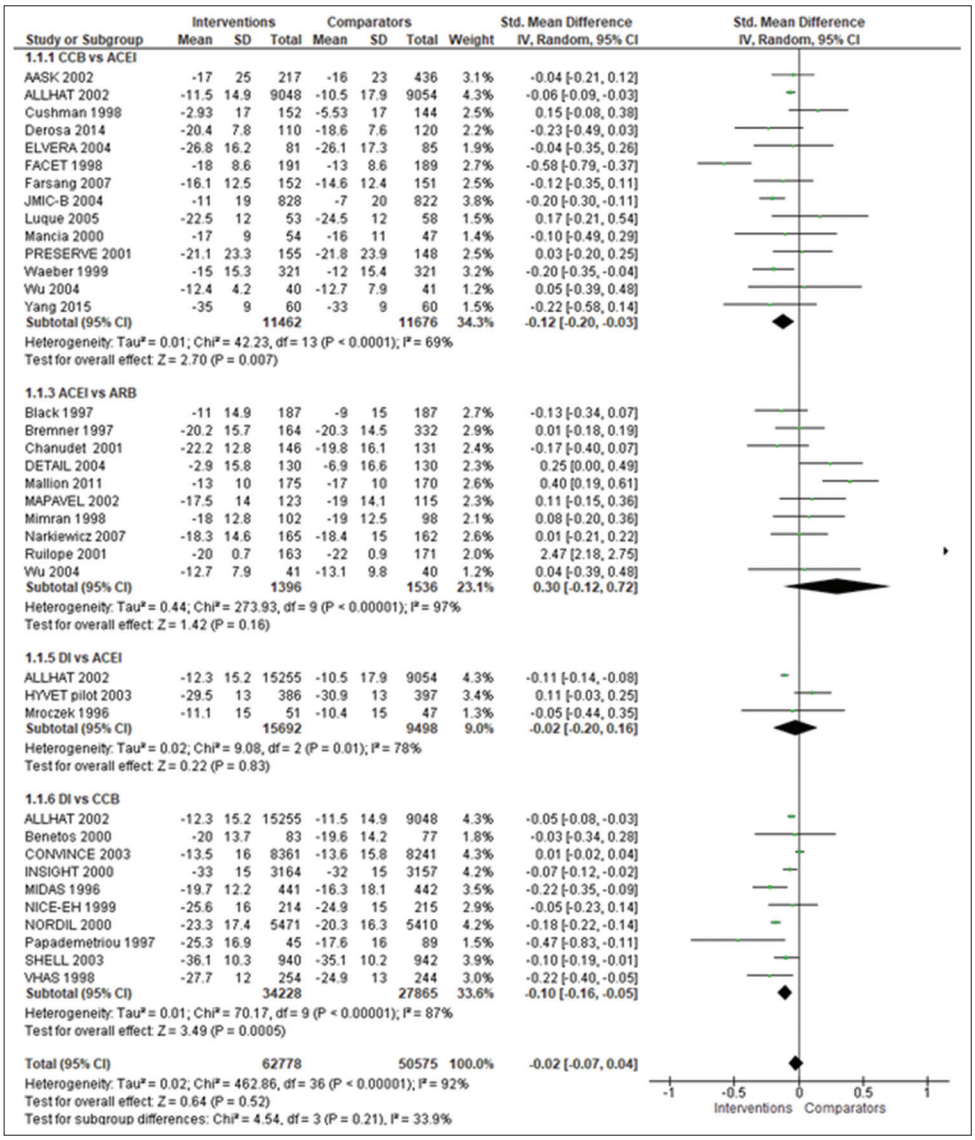

Figure 3: Forest plot of antihypertensive agents' comparison (SMD): BP response, outcome (RE model): SBP reduction. Both in diagrammatic and numerical format (mmHg, 95% CI). The overall effect represents the pooled estimate of mean net change in SBP response

different from other studies as patients with isolated systolic HTN were included in this study. Sensitivity analyses after excluding the above-mentioned study resulted in a SMD of 0.06, 95% CI (−0.06, 0.19) and −0.13, 95% CI (−0.24, −0.02) for SBP and DBP, respectively (I^2=59% and 46%; χ^2 P = 0.31 and P = 0.02, for SBP and DBP, respectively Online Supplement, Figure S2). The overall quality evidence was rated as high using the GRADE criteria [Online Supplement, Table S5].

BP response in trials comparing DIs and ACEIs

In total, three trials were included in the meta-analysis comparing the BP response of DIs and ACEIs [Figures 3 and 4]. In the RE model, the pooled SMD was −0.02 mmHg, 95% CI (−0.20, 0.16) and 0.01 mmHg, 95% CI (−0.02, 0.03) for SBP and DBP, respectively (I^2 = 78% and 0%, χ^2 P = 0.83 and P = 0.49, for SBP and DBP, respectively). The HYVET pilot 2003 was methodologically different from other studies as drugs were administered under open labels. Sensitivity analyses after excluding the above-mentioned study resulted in a SMD of −0.11, 95% CI (−0.14, −0.08) and 0.01 (−0.02, 0.04) for SBP and DBP, respectively (I^2 = 0% and 0%; χ^2 P < 0.00001 and P = 0.49, for SBP and DBP, respectively; Online Supplement, Figure S2). The overall quality of evidence was rated as moderate using the GRADE criteria [Online Supplement, Table S5].

BP response in trials comparing DIs and CCBs

In total, 10 trials were included in the meta-analysis comparing the BP response of DIs and CCBs [Figures 3 and 4]. In the RE

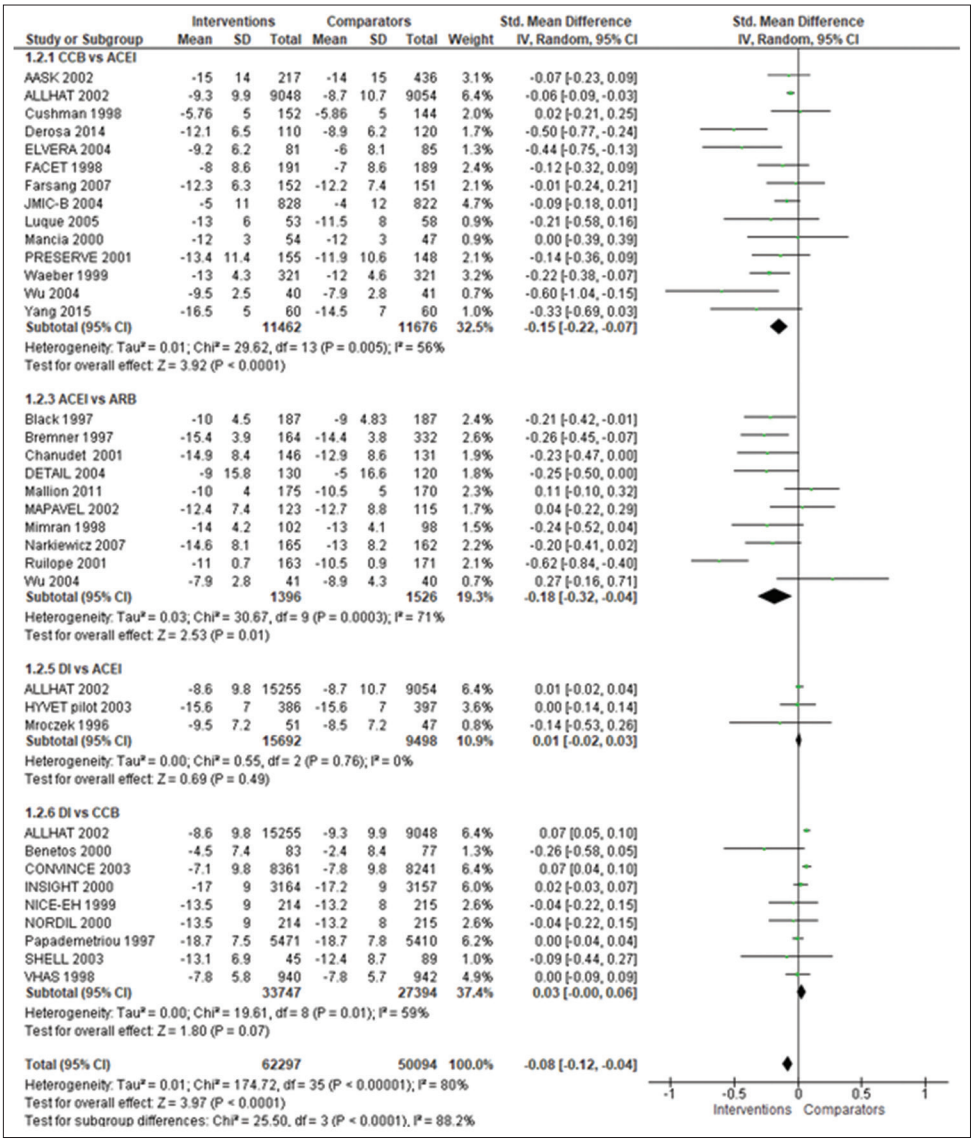

Figure 4: Forest plot of antihypertensive agents' comparison (SMD): BP response, outcome (RE model): DBP reduction. Both in diagrammatic and numerical format (mmHg, 95% CI). The overall effect represents the pooled estimate of mean net change in DBP response

model, the pooled SMD was −0.10 mmHg, 95% CI (−0.16, −0.05) and 0.03 mmHg, 95% CI (0.00, 0.06) for SBP and DBP, respectively (I^2 = 87% and 59%; χ^2 P = 0.0005 and P = 0.07, for SBP and DBP, respectively). The CONVINCE, 2003, and NORDIL, 2000, trials were methodologically different from other studies as drugs were administered under open labels. Sensitivity analyses after excluding the above-mentioned studies resulted in a SMD of −0.10, 95% CI (−0.15, −0.05) and 0.02 (−0.02, 0.07) for SBP and DBP, respectively (I^2 = 52% and 45%; χ^2 P = 0.0001 and P = 0.34, for SBP and DBP, respectively; Online Supplement, Figure S2). The overall quality of evidence was rated as moderate quality using the GRADE criteria [Online Supplement, Table S5].

BP response in trials comparing antihypertensive agents and placebos

In placebo-controlled trials, all classes of antihypertensive drugs show significant reduction in BP as compared to placebo [Online Supplement, Figures S3 and S4].

Network meta-analysis

In the network meta-analyses, DIs ranked first in SBP response (P score of 0.90, 0.89, 0.60, 0.41, 0.20, and 0.00 for DIs, ARBs, CCBs, BBs, ACEIs, and placebo, respectively), based on frequentist analogue of SUCRA. However, in terms of DBP response, CCBs topped the table with highest reduction followed by BBs, DIs,

ACEI, and ARBs. In all possible 94 pairs of comparisons [Figure 5a], ACEIs, BBs, and even CCBs fared worse than DIs in terms of SBP response [Figure 5b1]. In addition, ARBs did not differ from DIs in terms of SBP response. However, in terms of DBP response, CCBs fared better than ARBs and ACEIs [Figure 5b2].

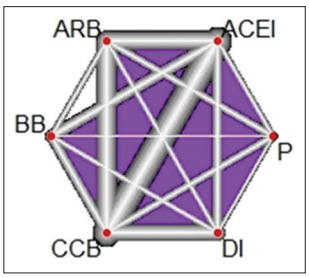

Figure 5A: Network diagram showing the strength of all possible pairs of comparison in terms of their sample size. The thickness of lines between treatment groups indicate total pooled sample size in the comparison

Discussion

In our systematic review and meta-analyses, we demonstrate that not all antihypertensive drugs are equal in reducing BP. The network meta-analyses conducted as part of the study, facilitated comparisons across all different possible pairs of commonly used antihypertensive classes of drugs. The results clearly show that DIs and ARBs are superior choices in achieving better reduction in systolic BP as compared to other classes of drugs. The quality of evidence across studies has been graded as "moderate" to "high" based on the GRADE criteria.

Despite having reasonably good direct evidence on the superiority of DIs over ACEIs, CCBs, and BBs in terms of SBP response,

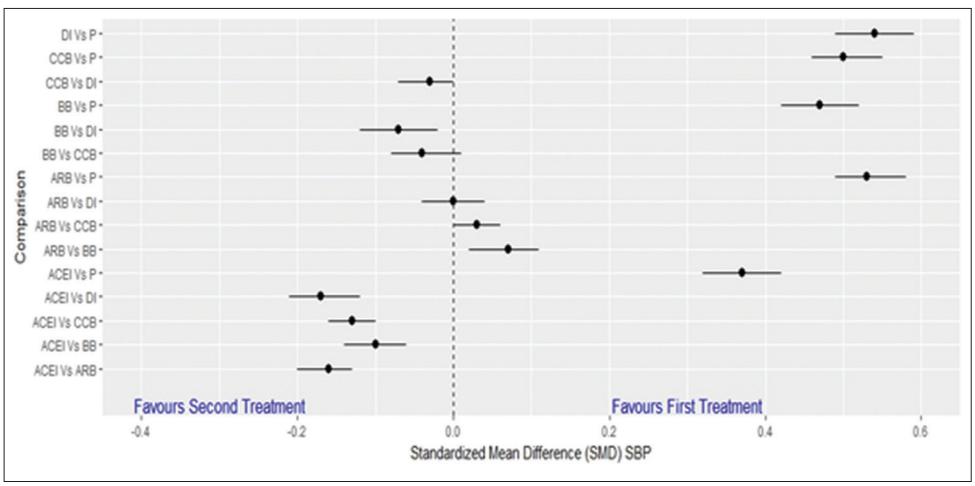

Figure 5B1: Forest plot of SBP response in the network meta-analyses of all possible pairs of comparisons

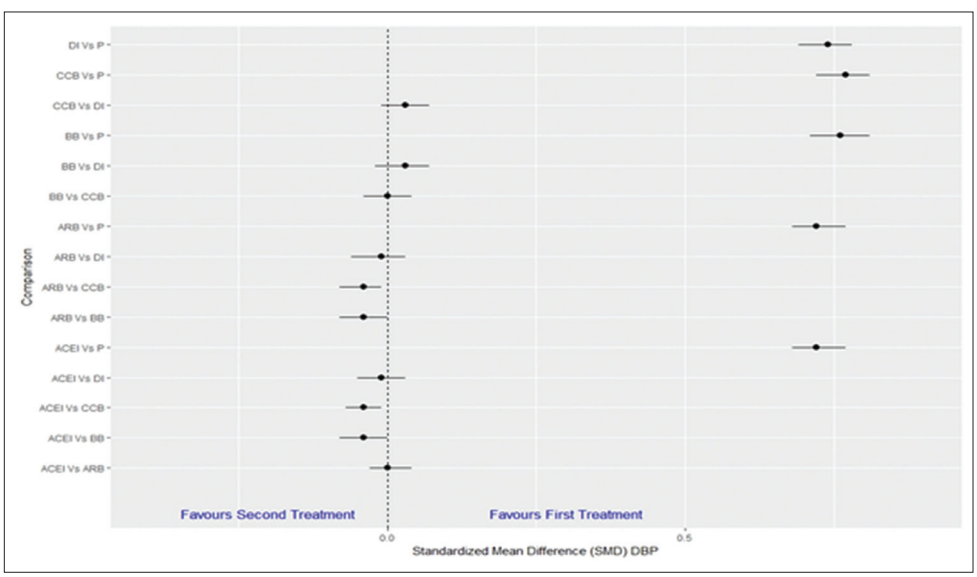

Figure 5B2: Forest plot of DBP response in the network meta-analyses of all possible pairs of comparisons

they are not the preferred choice of first-line antihypertensive classes of drugs. Overall, CCBs are the most frequently prescribed antihypertensive agents for HTN in our systematic review (24.8%), followed by ARBs (21.5%) and ACEIs (20.15), DIs (13.4%), and BBs (11.4%). Higher preference of ACEIs and CCBs over DIs is, however, not justified by data in terms of BP response. Although the Joint National Council (JNC 8)[11] guidelines recommend the use of diuretic as first-line antihypertensive agents, the European Society of HTN[12] or American Diabetes Association[13] or the World Health Organization-International Society of HTN[14] guidelines do not recommend diuretic as first-line agents. DIs are off-patent drugs and are available in generic form at relatively cheap prices in most of the countries. Ideally, all patients should be offered DIs immediately if their BP is not under control with their first-line treatment.

Although ARBs show similar SBP reduction as compared to DIs, there are only a few trials directly comparing ARBs versus DIs. The number of participants is also limited in all the studies directly comparing ARBs versus DIs. In addition, the evidence coming from indirect comparisons is always inferior to evidence from head to head and direct comparisons.[15] In contrast to the SBP response, DBP response was better in CCBs as compared to ARBs and ACEIs. The differences in DBP response were very small in most of the other direct comparisons. In addition, available evidence also suggest that SBP should be the primary target of antihypertensive therapy.[16,17]

Although the effect size of the observed BP reduction across classes of antihypertensive agents is only marginally different at the individual level, it has the potential to avert several undesirable cardiovascular events at the population level. For example, at the population level, an average of 2 mmHg reduction in SBP is sufficient to avert nearly 10% of mortality attributable to CVD.[18] We demonstrate that in hypertensive population, physicians can achieve similar additional reduction by carefully choosing the classes of antihypertensive therapy. However, better reduction in BP alone should not be the only criterion for choosing appropriate therapies. In a recent network meta-analysis, the efficacy of both ARBs and ACEIs was comparable in terms of survival and major renal outcomes in patients with diabetes.[19] However, in patients with CKD, ACEIs showed consistently higher probabilities of reducing kidney failure, cardiovascular, and all-cause death.[20] We could not perform a subgroup analysis to independently assess the BP response in hypertensive patients with other comorbidities.

Strengths and Limitations of this Study

Our study has several strengths. We did a comprehensive review covering all potential and accessible sources of information and carefully evaluated risk of bias and quality of all individual studies included in the meta-analyses. Furthermore, we have also evaluated the quality of pooled evidence based on the GRADE criteria. The baseline BP was different across studies, and therefore, we used SMD for pooling BP response data.

Our study has some limitations. The degree of heterogeneity in most of the primary comparisons was significant. The sequential administration of additional drugs following the first-line randomized therapy in some of the included studies may have resulted in biased estimates of the BP response. The previous systematic reviews (Wright, 1999)[21] and (Wright, 2000)[22] restricted the analyses to studies where supplementary BP-lowering agents were administered to <1/2 of patients. We tried to address the heterogeneity by conducting sensitivity analyses based on careful critical evaluation of methodological differences, biases, and other study quality parameters in individual studies included in the meta-analyses. The effect sizes in our sensitivity analyses even after excluding the methodologically diverse studies were, however, comparable to the primary analyses. We have analyzed the major five drug classes used in HTN and have not differentiated subclasses within each major categories. Conclusion

Our network meta-analysis compares the BP response of all possible pairs of different classes of antihypertensive drugs in the management of HTN. Better BP response in DIs and ARBs makes them the preferred choices to achieve target systolic BP. The results of the present network meta-analysis will influence evidence-based decision-making in prescription and enable more effective communication of the relative efficacies of different drug classes on BP.

Clinical Significance

BP response measurements in clinical studies, mainly RCTs, may guide physicians to estimate the expected BP reduction for each BP-lowering agent. Consequently, they can set their management plans in terms of determining the likely duration to achieve the target BP and the need for using additional BP-lowering agents besides first-line agents.

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Review Article

Inflammatory Bowel Disease and Cardiovascular Disease (Review)

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Abstract

Inflammatory bowel diseases (IBDs) are immune-mediated inflammatory conditions causing inflammation of the gastrointestinal tract. A range of medical treatment options are used to treat IBD-related inflammation including biologic tumor necrosis factor (TNF) antagonists. IBD prevalence is growing with patients increasingly older and more comorbid. Globally, cardiovascular diseases remain the leading cause of morbidity and mortality. IBD patients are at higher risk of cardiovascular disease, but this does not appear to be conferred by traditional risk factors such as hyperlipidemia and obesity. Appreciation of the relationship between IBD, cardiovascular disease, and inflammation is, therefore, of clinical importance. TNF-α is a key pro-inflammatory cytokine in the development of IBD-related inflammation, hypertension, and cardiovascular disease. Data suggest that commonly prescribed TNF antagonists may mitigate the increased cardiovascular risk in IBD patients. It is unclear if this is a direct effect of TNF antagonism or reflects better control of inflammation. Future research should focus on an improved understanding of the cardiovascular impact of IBD-related inflammation, the risk of adverse outcomes, and the potential effects of IBD treatment on cardiovascular risk profiles. This knowledge should allow better risk stratification when selecting treatment options, contributing to our goal of personalizing the approach to IBD treatment.

Key words: Inflammatory bowel disease, cardiovascular disease, tumor necrosis factor antagonists

Introduction

The inflammatory bowel diseases (IBDs), Crohn's disease, and ulcerative colitis are chronic inflammatory conditions of the intestinal tract. The exact etiology of IBD is unclear but considered to be multifactorial involving environmental and dietary triggers in an individual with a susceptible genetic profile and immune system.[1] Symptoms vary, but often include diarrhoea, abdominal pain, and fatigue. Medical management options have expanded to include biologic drugs for moderate-to-severe disease, significantly improving outcomes and quality of life for IBD patients.[2] The most commonly used biologics for IBD are the tumor necrosis factor (TNF) antagonists infliximab and adalimumab. The prevalence of IBD has grown globally.[3] With evolving and improving pharmacological management, and an aging population, it is predicted that the prevalence of IBD will continue to grow,[4] with the highest prevalence currently seen in the most developed nations.[5] The global burden of cardiovascular disease remains very high, necessitating a good understanding of its impact and interaction with other disease states and their treatment.[6] Gastroenterologists are increasingly caring for an older and more comorbid patient group, making treatment selection more challenging. Here, we discuss current evidence for the relationship between cardiovascular disease, IBD, and chronic inflammation, and review the role of TNF antagonists.

The clinical trajectory of IBD varies, often unpredictably, from mild disease with infrequent symptomatic exacerbations, to more severe phenotypes with significant, treatment refractory symptoms. Conditions resulting in chronic, persistent states of inflammation, as well as diseases characterized by discrete and self-limiting episodes of inflammation, may precipitate vascular

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endothelial dysfunction and a resultant rise in arterial stiffness; a recognized risk factor for cardiovascular disease and cause of elevated systolic blood pressure.[7] Changes in endothelial function as a result of inflammation can arise through a number of mechanisms; primarily the presence of inflammatory cytokines, resulting in oxidative stress and the relaxation, or hyperplasia, of vascular smooth muscle cells. Cardiovascular disease is thought to be more prevalent within the IBD population, but traditional risk factors for cardiovascular disease, for example, obesity and hyperlipidemia, are not.[8] Some studies have suggested that the observed increased risk of cardiovascular disease in individuals with IBD is not related to disease severity.[9] As such, in individuals with chronic inflammatory conditions such as IBD, there may not simply be a direct relationship between increased risk of cardiovascular disease and burden of inflammation.[10]

TNF-α is a key pro-inflammatory cytokine involved in the development and ongoing activity of IBD. It's role in activating the adaptive and innate immune system can lead to both acute and chronic states of inflammation.[11] As such, antagonism of TNF-α using monoclonal antibodies is a primary target in IBD treatment.[12] The expression of TNF-α has also been identified as a contributor to hypertension and cardiovascular disease by increased oxidative stress, triggered by the activation of polymorphonuclear leukocyte NADPH oxidase.[13,14] Inhibition of TNF-α has been shown to improve endothelial function[15] and markers of vascular function such as common carotid intima–media thickness and flow-mediated vasodilation.[16] Alongside this, it has been shown to have a positive blood pressure-lowering impact.[14]

Despite these theoretical benefits, the evidence for the association between TNF-α inhibition, inflammation, and cardiovascular disease risk in IBD is limited. A 2017 nationwide French study of 178,360 patients with IBD supported the hypothesis that there is increased risk of cardiovascular disease in this population. However, treatment with a TNF antagonist appeared to mitigate this risk as better cardiovascular outcomes was observed in this subgroup of patients. This improvement only reached statistical significance when dual therapy with a thiopurine was used.[17] Higher levels of serum infliximab and better IBD treatment outcomes are seen for patients treated with combination azathioprine and infliximab therapy compared to infliximab monotherapy.[18] This suggests that the lower risk of cardiovascular disease seen in the French cohort above could relate to thiopurine treatment, higher infliximab levels, or better control of inflammation. However, the relative contribution or any or all of these effects remains unclear. In addition, a long-term follow-up study of 145 IBD patients demonstrated a deterioration in cardiovascular risk over time, but this risk was reduced by treatment with an anti-TNF-α therapy to control IBD symptoms.[19]

An interesting observation was made in a 2019 abstract examining the prevalence of hypertension in a Greek population of IBD patients. This study showed that in the 29.9% of patients with hypertension, the use of an antihypertensive, particularly an angiotensin receptor blocker, was independently associated with a milder IBD phenotype.[20] Recent evidence suggests that angiotensin II has a role in driving colonic mucosal inflammation,[21] with a 2020 study highlighting the renin angiotensin system as a potential, novel therapeutic target in IBD treatment.[22]

However, a wider body of evidence exists looking at cardiovascular risk, TNF antagonists, and chronic inflammation for rheumatology and dermatology conditions. While the phenotype of disease and patient populations are different to IBD, the common issue is acute and chronic inflammation, with TNF antagonists providing a core treatment option. A 2015 meta-analysis of 6321 patients from 11 studies demonstrated a significantly increased risk of developing hypertension in patients with rheumatoid arthritis.[10] A small study of 16 infliximab-treated, rheumatoid arthritis patients showed a significant drop in morning ambulatory blood pressure following the initiation of infliximab therapy. This finding was associated with a reduction in norepinephrine, but was independent of changes in disease activity.[23] Similarly, a 2011 study of 23 rheumatoid arthritis patients treated with the TNF antagonists adalimumab, etanercept, or infliximab and 17 control patients treated only with a disease-modifying antirheumatic drug (DMARD), demonstrated reduced systolic blood pressure, and improved endothelial function in the TNF antagonist group versus DMARD group.[24] A more recent double-blind, placebo-controlled, randomized, crossover trial of 10 patients with rheumatoid arthritis evaluated the immediate impact of a single infusion of infliximab. Following a single infusion of infliximab, a significant reduction in mean blood pressure was seen, but with no change to endothelial function as measured by flow-mediated vasodilation.[25]

Another 2015 meta-analysis, this time of 34 studies examined the cardiovascular risk in patients with rheumatoid, arthritis, psoriatic arthritis, and psoriasis. This analysis suggested an overall reduction in cardiovascular events, including myocardial infarction, heart failure, and ischemic stroke, in patients treated with TNF-α antagonists.[26] Large biologics registries have also proved a useful source of information. In 2013, the British Society for Rheumatology's Biologics Registry was used to review the ischemic stroke risk in rheumatoid arthritis patients. This study of more than 14,000 patients demonstrated no increased risk of stroke in TNF antagonist treated, compared to DMARD-treated patients.[27] More recently, a large study of patients with spondyloarthropathy also demonstrated a rise in cardiovascular events in these patients, which was counteracted by the use of TNF antagonist medicines as treatment.[28]

Patients with heart failure have been observed to have elevated levels of plasma TNF-α. The clinical significance of this finding is not fully elucidated but TNF-α is understood to affect the function of beta-adrenergic receptors and produce a negative inotropic effect on myocardiocyte activity.[29] In contrast to the positive effect of TNF antagonists on blood pressure discussed above, these medicines have been shown to worsen heart failure. The 2003 ATTACH trial investigated infliximab as a treatment for moderate-to-severe heart failure; no clinical benefit was

derived, but it was associated with a deterioration in heart failure, particularly at higher doses.[30] Reassuringly, treatment of IBD with infliximab in clinical trials was not associated with the development of new heart failure or cardiovascular complications,[31] but initiation in patients with moderate-to-severe heart failure in contraindicated in clinical practice.

Conclusion

In summary, the current evidence indicates that there is an overlap in some of the physiological mechanisms involved in the development of acute and chronic inflammatory diseases such as IBD and cardiovascular disease. Although the evidence based is limited, increased rates of cardiovascular disease and poorer cardiovascular outcomes are observed in individuals with IBD. Commonly prescribed TNF antagonists may mitigate this increased cardiovascular risk. It is unclear if this is a direct effect of TNF antagonism or reflects better control of inflammation. With an aging and increasingly comorbid IBD population, future research should focus on an improved understanding of the cardiovascular impact of IBD-related inflammation, the risk of adverse outcomes, and the potential effects of IBD treatment on cardiovascular risk profiles. This knowledge should allow better risk stratification when selecting treatment options, contributing to our goal of personalising the approach to IBD treatment.

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Review Article

A Systematic Review of the Association between Air Pollution and Cardiovascular Parameters: Blood Pressure, Arterial Stiffness, and Endothelial Function. (Review)

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Abstract

Exposure to air pollution is hypothesized to influence blood pressure, arterial stiffness, and endothelial function, all independent predictors of cardiovascular disease. Systematic literature search for articles reporting exposure to particulate matter (PM) or gaseous pollutants (carbon monoxide, ozone, sulfur dioxide, nitrogen oxide, and nitrogen dioxide) on blood pressure, arterial stiffness, and endothelial function. Short-term exposures studies presented heterogeneous results: 17 of 31 papers supported a rise in blood pressure after exposure to PM, and five of 13 studies of gaseous pollutants; impaired endothelial function in response to PM (six of 11 papers) and gaseous pollutants (three of six studies); and arterial stiffness after PM exposure in three of six studies. Blood pressure data from long-term air pollution studies were more consistent: Seven of nine PM and five of six gaseous exposure studies reported blood pressure elevation. Three studies reported arterial stiffness, with heterogeneous results. A single study was identified reporting PM impaired dilatation. This supports an association between long-term exposure to certain gaseous pollutants, particularly sulfur dioxide (SO_2), and PM with increased blood pressure, arterial stiffness, and possibly endothelial dysfunction. Acute exposure can impair endothelial function and may affect blood pressure, but not measures of vascular stiffness. The implication for researchers is that acute versus long-term air pollution conveys different patterns of confounding on these cardiovascular measures. Regarding population-based prevention strategies, data support air quality as potentially a modifiable risk factor in the development of cardiovascular diseases.

Key words: Air pollution, blood pressure, particulate matter, vascular endothelium, vascular stiffness

Introduction

Cardiovascular disease represents a significant contribution to the global burden of chronic disease, with annual mortality reaching 18.6 million in 2019.[1] The causes of cardiovascular disease are a complex interaction between genetic and environmental risk factors over an extended period of time. These include obesity, hypertension, hyperlipidemia, and diabetes mellitus, but there is increasing evidence that air pollution may be an additional environmental risk factor, with epidemiological studies demonstrating increased cardiovascular morbidity and mortality.[2,3]

Due to continuing industrialization in many parts of the world, high use of private vehicles and failure to divest from fossil fuels, air quality continues to decline in many parts of the world. Indeed, the Global burden of disease study estimates that mortality from air pollution increased by 5.8% between 2007 and 2017, with 5 million deaths caused by air pollution in 2017.[4] Some models forecast that the contribution of outdoor air pollution to premature mortality will double by 2050.[5] Air pollution is a heterogeneous mixture of gaseous pollutants, volatile, semi-volatile, and particulate matter (PM). Although many gaseous pollutants can have serious health effects such as ozone (O_3), carbon monoxide (CO) and nitrogen oxides (NO),

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the largest body of epidemiological evidence supports PM as having the strongest association with health problems.[6]

PM is subdivided into coarse, fine and ultrafine, collectively termed PM_{10} meaning particulate diameter <10 μm. Fine particles ($PM_{2.5}$) have diameter <2.5 μm, and ultrafine particles ($PM_{0.1}$) with diameter <100 nm. Size is important as it influences how easily they form aggregates of material that can readily deposit in the lungs and affects their inflammatory properties.[7] Outdoor air quality depends on a range of covariant factors including meteorological conditions, industrial activity, time of day and traffic. Hence, estimates of air pollution exposure in epidemiological models are limited by spatial and temporal variation in pollutant concentrations and must adjust for many covariates.[8]

Methodologically, air pollution exposure has been studied short-term, measuring acute effects of changes in pollutant concentrations over hours or days, or long-term exposure over several years. Contrasting attitudes regarding exposure reflect uncertainty of the biological mechanisms linking air pollution and cardiovascular disease, with various direct or indirect inflammatory, and endocrine pathways being proposed.[9]

Assessing cardiovascular health and predicting risk of cardiovascular disease can be aided by measurement of known risk factors such as blood pressure, and surrogate markers of arterial function, in particular endothelial function and arterial stiffness.[10] Arterial stiffness can be quantified using validated techniques such as pulse wave velocity (PWV) - the speed at which arterial pressure waves transmit representing stiffness of the arterial tree, and Pulse wave analysis (PWA) or "Augmentation index (AIx)," based on the morphology of reflected pulse wave as an indicator of arterial stiffness. Flow-mediated dilatation (FMD) and Peripheral artery tonometry (PAT) both assess for endothelial function with methods involving arterial occlusion and measuring the vascular response.

Our aim was to systematically review the available evidence to provide a comprehensive assessment of the association between air pollution exposure and cardiovascular risk parameters. This data informs health-care professionals and academics when considering air quality as a contributory or confounding factor in cardiovascular research, and policy decision makers tasked with prevention of cardiovascular diseases.

Methods

Protocol

The systematic review was written following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] A review protocol was developed, including eligibility criteria, databases searched, and the search terms.

Eligibility criteria

Studies had to meet pre-determined criteria to be included: published in a peer-reviewed journal; cross-sectional studies, case-control studies, case-crossover studies, time series, cohort studies, or panel studies; measured effect of long-term exposure ≥30 days or short-term exposure <30 days; at least ten subjects and conducted in humans; measured exposure to PM PM_{10} or $PM_{2.5}$ or gaseous pollutants CO, O_3, SO_2, NO, and nitrogen dioxide (NO_2). Outcome measures had to be validated tools, including FMD and PAT as measures of endothelial function; PWV, PWA, and AIx adjusted to 75 bpm (AI at 75) as measures of arterial stiffness; and blood pressure based on office, 24 h ambulatory, or standardized technique home readings.

Publications that were excluded from this systemic review: Case reports, editorials, comments, news items and letters; studies conducted in animals; duplicate reports; only measured exposure to pollutant not stated in eligibility criteria; measured outcome on cardiovascular health by methods other than endothelial function, arterial stiffness, and blood pressure; and measured exposure to indoor sources of air pollution.

Information sources

A comprehensive literature review was conducted using the databases Scopus and PubMed for publications between 2000 and July 2021 in the English language. The literature search of the databases was carried out on July 13, 2021, with an additional citation search on July 23, 2021.

The search terms were combined with Boolean operators "AND" and "OR" and asterisk "*": "(air pollution OR PM_{10} OR $PM_{2.5}$ OR PM OR particul* OR particle* OR CO OR O_3 OR SO_2 OR NO OR NO_2) AND (FMD OR FMD OR PWV OR PWV OR blood pressure OR hypertension OR hypertensive OR hypertens* OR endotheli* OR arterial stiffness)".

Study selection

Duplicates were removed from the initial records using software, then one reviewer read through titles and abstract of each remaining study to determine if they met the eligibility criteria and exclude those that although mention search terms did not meet the parameters of the eligibility criteria. Perusal of the remaining studies determined eligibility for inclusion in the review, Figure 1.

Data collection and analysis

Data items collated from eligible studies included study design, population characteristics, duration of exposure and follow-up, pollutants measured, and cardiovascular health parameter(s). Wherever possible the standard deviation, 95% confidence interval and *P* value were extracted from the study to quantify effect size. Meta-analysis was intended; however, outcome data were found to be inadequate for undertaking a valid assessment.

Risk of bias (ROB) assessment

The ROB of cross-sectional, case-control, case-crossover, cohort, and panel studies were analyzed using the Newcastle-Ottawa quality assessment tool adapted for use with cross-sectional studies [Table S1].[12] For randomized blinded trials, the revised Cochrane ROB tool (RoB 2) was used [Table S2].[13]

Table S1: Scores based on modified Newcastle-Ottawa scale measuring the risk of bias for non-randomised clinical trials, cohort studies, cross-sectional studies

Study	Selection	Comparability	Outcome	Total
Shan *et al*. 2014	****	*	**	7/10
Liu *et al*. 2018	***	*	***	7/10
Wu *et al*. 2016	**	*	***	6/10
Liu *et al*. 2014	**	*	***	6/10
Zhao *et al*. 2020	***	*	*	5/10
Fang *et al*. 2008	***	**	*	6/10
Briet *et al*. 2007	***	**	**	7/10
Cole *et al*. 2018	***	**	*	6/10
Gong *et al*. 2003	***	*	*	5/10
Adamopoulos *et al*. 2010	****	**	***	9/10
Jiang *et al*. 2016	*****	**	***	10/10
Krishnan *et al*. 2012	*****	**	***	10/10
Kumarathasan *et al*. 2018	***	**	***	8/10
Mehta *et al*. 2014	***	**	***	8/10
Lenters *et al*. 2010	****	**	*	7/10
Weichenthal *et al*. 2014	****	*	*	6/10
Chen *et al*. 2015	***	**	*	6/10
Babisch *et al*. 2014	***	**	*	6/10
Coogan *et al*. 2012	****	**	**	8/10
Dong *et al*. 2013	****	*	**	7/10
Foraster *et al*. 2014	****	**	**	8/10
Lin *et al*. 2017	****	**	***	9/10

Results

Literature search and study selection

The initial search strategy identified 4500 published articles that contained potentially relevant information. An additional 14 articles were retrieved through searching of citations. Duplicates were removed before the screening process. The titles and abstracts of the remaining 4512 articles were screened. One of the remaining 67 papers could not be retrieved, leaving 66 articles assessed in detail for eligibility. Perusal of the full text excluded 20 articles for the reasons listed in Figure 1, resulting in 46 articles being included in this review.

Study characteristics

The characteristics, design, and principal findings of the included studies are summarized in supplemental Tables S3 and S4. Of the 46 studies, 36 focused on short-term and ten reported long-term exposure to air pollution. Study design was cross-sectional in nine studies, three were panel studies, two were cohort studies, and 32 were crossover studies. Crossover designs were most frequently adopted for short-term exposure studies, and cross-sectional designs for long-term exposure studies. The included studies were conducted in 12 countries across, Asia, Europe, and America, with the sample size ranging from 12 to 27,752.

Several approaches were adopted by the studies in this review to account for the uncertainty regarding spatial and temporal variation in pollutant concentrations. The most common approach of long-term exposure studies was land-use regression modeling.[14-19] Other methods included spatio-temporal modeling;[20] satellite-derived column aerosol optical depth to estimate $PM_{2.5}$ concentrations;[21,22] and closest monitoring sites.[23,24] Short-term exposure methodologies included purpose-designed exposure chambers;[25] indoor filtration units to measure acute response to filtered versus unfiltered air; ambient exposure with high versus low pollution environs, and particulate filtering respirators. Pollutant concentrations were mainly measured using purpose designed monitors at the relevant locations. A small number of studies (14%) utilized personal exposure monitors.

Descriptive results

Short-term exposure

PM

The relationship of PM with blood pressure, endothelial function, and arterial stiffness was investigated by 31 observational studies (details in Table S3). Twelve studies included in this review found a statistically significant association between PM and blood pressure.[26-37] Elevations of up to 12 mmHg in SBP were demonstrated in a double-blind randomized cross-over trial (145 ± 4 mmHg diesel fume exposure, vs. filtered air 133 ± 3 mmHg, p=0.012).[36] This trial was an outlier however, with the remainder demonstrating much smaller changes in blood pressure, Table S3. Methods of reporting were too heterogeneous to allow meta-analysis. Two of the 12 employed ambulatory blood pressure measurements,[27-29] the remainder were "in-office" blood pressure. Adjustment for confounders was common; design details and outcome data are listed in Table S3.[26-37] In half of these studies, only the association with systolic, but not diastolic blood pressure (DBP) achieved statistical significance.[28,29,32,34,36,37] Eleven studies in contrast found no association between PM exposure and blood pressure.[38-48] Most of these studies (8 of 11) did report an acute rise in blood pressure following exposure to PM; however, statistical significance was not sustained following adjustment for confounding variables.[38-43,45,46] Considering methodology as a source of data variability; 89% of exposure chamber studies reported an association,[28,30,32-37] conversely, 78% of air filtration studies concluded no association.[39,42-47] Aggregated, there does appear to be evidence of short-term effects of PM on blood pressure, though the effect size does not appear to be large. Strength of the evidence is limited by heterogeneous methodology and the large number of variables determining air pollution exposure.

Table S2: Scores based on revised Cochrane risk of bias tool (RoB 2) measuring the risk of bias for blinded randomised clinical trials, randomized single, and double-blinded crossover studies

Study	Domain 1. Randomization process	Domain 2. Deviations from intended interventions	Domain 3. Mising outcome data	Domain 4. Measurement of the outcome	Domain 5. Selection of the reported result	Domain 6. Overall Bias
Cui *et al*. 2018	L	SC	L	SC	L	SOME CONCERNS
Rich *et al*. 2018	L	SC	L	L	L	LOW RISK OF BIAS
Barath *et al*. 2010	L	L	L	L	L	LOW RISK OF BIAS
Bellavia *et al*. 2013	L	SC	L	L	L	LOW RISK OF BIAS
Brook *et al*. 2002	L	SC	L	SC	L	LOW RISK OF BIAS
Brook *et al*. 2009	L	L	L	L	L	LOW RISK OF BIAS
Brook *et al*. 2014	L	L	L	L	L	LOW RISK OF BIAS
Chen *et al*. 2015	L	L	L	L	L	LOW RISK OF BIAS
Cosselman *et al*. 2012	L	L	L	L	L	LOW RISK OF BIAS
Langrish *et al*. 2010	L	SC	L	L	L	LOW RISK OF BIAS
Fakhri *et al*. 2009	L	SC	L	SC	L	SOME CONCERNS
Frampton *et al*. 2015	L	L	L	SC	L	LOW RISK OF BIAS
Kajbafzadeh *et al*. 2015	L	SC	L	SC	L	SOME CONCERNS
Karottki *et al*. 2013	L	L	L	L	L	LOW RISK OF BIAS
Mills *et al*. 2011	L	L	L	SC	L	LOW RISK OF BIAS
Morishita *et al*. 2015	L	L	L	L	L	LOW RISK OF BIAS
Morishita *et al*. 2018	L	L	L	L	L	LOW RISK OF BIAS
Padró-Martínez *et al*. 2015	L	SC	L	L	L	LOW RISK OF BIAS
Törnqvist *et al*. 2007	L	L	L	L	L	LOW RISK OF BIAS
Allen *et al*. 2011	L	SC	L	SC	L	SOME CONCERNS
Shi *et al*. 2017	L	SC	L	SC	L	SOME CONCERNS
Tank *et al*. 2011	L	L	L	L	L	LOW RISK OF BIAS
Weichenthal *et al*. 2019	L	L	L	L	L	LOW RISK OF BIAS
Arjomandi *et al*. 2015	L	SC	L	L	L	LOW RISK OF BIAS

Endothelial dysfunction was linked to PM exposure in six studies. This included exposure studies,[35,36,49] an air filtration study,[50] a high- and low-pollution bicycle route crossover-trial,[51] and a cross-sectional study.[26] Five studies conversely concluded no association between PM exposure and endothelial function.[33,47,52-54] Such divergent results may indicate an exposure interaction; one such proposed interaction is between PM and gaseous pollutants, though even here authors disagree on directionality: Briet *et al*. 2007[53] reporting PM exaggerates dilatory response of small arteries to ischemia, contradicting evidence of particular matter-induced lower serum NO levels[26] and reduced vasodilation.[36,49] The method used to measure endothelial function (reactive hyperemic index [RHI] from PAT, and FMD) did not appear affect the outcome.

Three studies found an association between arterial stiffness and PM exposure, all adjusted for confounding variables. Two were panel studies and one was cross-sectional, sample size ranging from 26 to 371.[26,55,56] Three smaller sample size studies (n = 25–70), all adjusted for confounding variables, did not demonstrate a statistically significant association.[33,38,46] Contrasting outcomes may relate to methodology, the three studies reporting an association were all based on AIx,[26,55,56] with carotid-femoral PWV (cfPWV)[38,46] and PWA[33] not demonstrating significant change with exposure. AIx and PWV are not interchangeable as measures of arterial function; AIx is an index of pressure wave reflection and is affected by vasoactive substances that do not produce parallel changes in PWV.[57] Many of the studies included multiple outcome measures of BP, endothelial function and arterial stiffness, Table S3. For example, Jiang *et al*.[26] reported participants who lived within 50 m of a major road compared with those lived more than 200 m away had higher average personal $PM_{2.5}$ (111.1 vs. 68.2 μg/m^3), 4.3-fold higher AIx ($P < 0.05$), 1.6-fold higher SBP ($P < 0.05$), 1.9-fold higher DBP ($P < 0.01$), and 4.6-fold lower NO production ($P < 0.01$). Data would suggest that air pollution is a confounding factor that should be taken into consideration when measuring AIx, but not PWV.

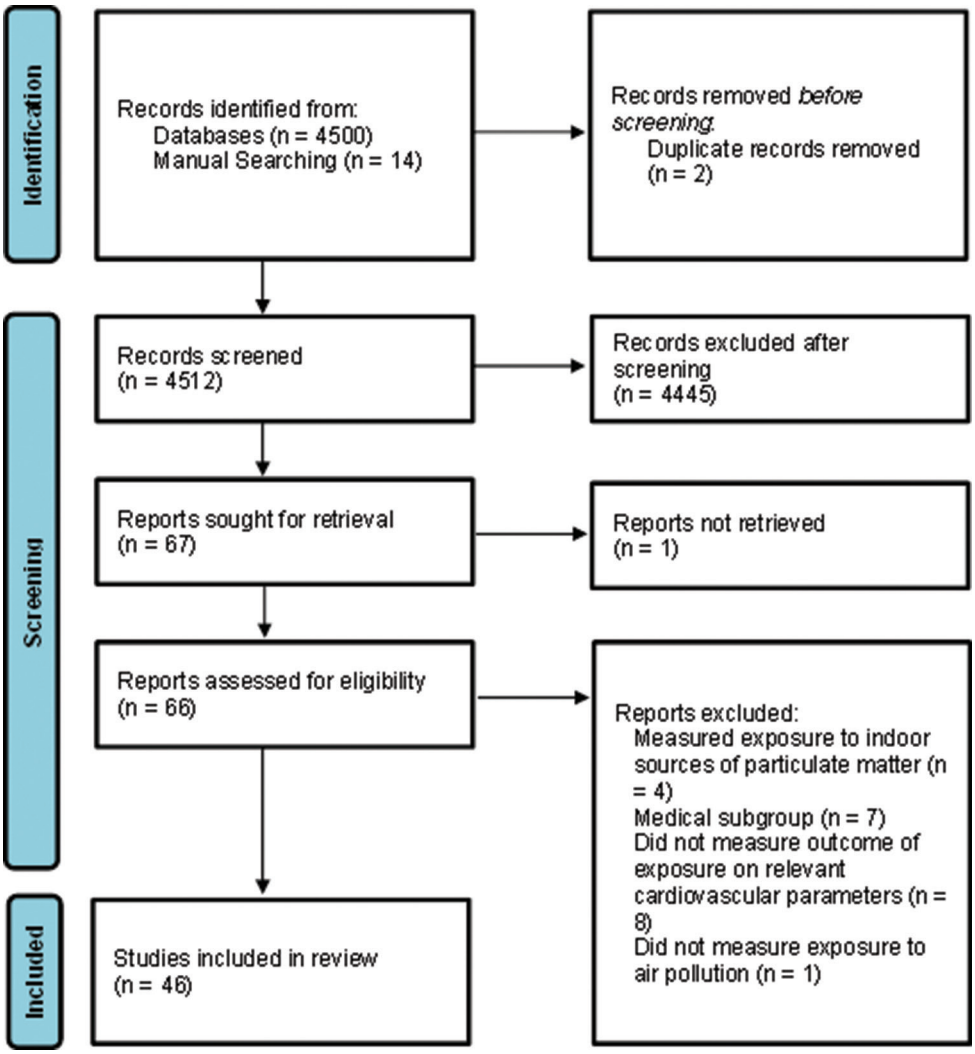

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection process

Gaseous pollutants

The relationship between gaseous pollutants with blood pressure and endothelial function was investigated by 13 crossover studies [Table S3]. There were no articles reporting the association between short-term exposure to gaseous pollutants with arterial stiffness.

A minority (three of eight) studies reported an association between O_3 and blood pressure,[30,35,51] five demonstrating no association.[46,47,58-60] Two of the studies only demonstrated an association when exposed to $PM_{2.5}$ 150 μg/m^3 in combination with O_3 120 ppb, but not O_3 in isolation.[30,35] Only two studies investigated exposure to NO_X, one air filtration study and one diesel exposure study; both reporting no statistically significant effect on blood pressure.[46,48] Of gaseous pollutant exposure studies concluding no association, three did not assess O_3 or NO_X exposure specifically, but rather filtered air versus unfiltered air[46,47] or diesel exhaust[48] that was measured to confirm higher O_3 or NO_X concentration.

Six studies in this review investigated the association between gaseous pollutants and endothelial function. Two found an association between endothelial dysfunction as measured by FMD and exposure to CO or NO_x, Breit *et al.* also reported a reduction in FMD with SO_2 exposure, but not supported by Liu *et al.*[41,53] Both studies had similar designs, both used fixed site air quality monitors to measure exposure at either two different locations or two different times. Although, both studies found an association between endothelial dysfunction and NO_X, only NO demonstrated a statistically significant association for Breit *et al.*, only NO_2 for Liu *et al.*, and neither NO or NO_2 reached statistical significance for Langrish *et al.*,[61] who did differ in their use of an exposure chamber rather than fixed site air quality monitors. Only one study found an association between O_3 with endothelial dysfunction[35] with three studies reporting no association after adjustment for confounding variables.[47,59,62] Most studies used FMD to measure endothelial function,[35,41,53,59] but one study measured response to vasodilators[61] and one used RHI.[62]

Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Cross-Sectional					
Shan *et al*. 2014	7/10	Sichuan Province; *n*=25 Age range: 38–85 Mean age: 59 Sex: male 0% female 100% Smoking status: Never smoked Inclusion criteria: Not pregnant, never smoked, used biomass fuel for cooking Adjusted for age, waist circumference, daily salt intake with statistical methods	Average 24 h exposure to $PM_{2.5}$ using personal exposure monitors with a d_{50} of $_{2.5}$ µm at 1.8 lpm (±10%) and a greased impaction surface.	Brachial artery and central SBP and DBP with 3 measurements using mean of final 2 measurements. cfPWV up to 3 readings in supine position	Difference between high $PM_{2.5}$ (>58 µg/m^3) and low $PM_{2.5}$ (<58 µg/m^3): Brachial SBP (95% CI) = 4.6 (−7.8, 16.9) *P*=0.4 Brachial DBP (95% CI) = −1.2 (−7.3, 4.9), *P*=0.54 Central SBP (95% CI) = 3.1 (−8.4, 14.5), *P*=0.53 Central DBP (95% CI) = −1.0 (−7.3, 5.3), *P*=0.61 cfPWV (95% CI) = −0.1 (−0.9, 0.7). *P*=0.97
Jiang *et al*. 2016	10/10	Urban Shanghai, China, *n*=371 Age range: 45–79 Mean age: 56.5±10.3 Sex: male 139 female 232 Smoking status: 14.8% smoker Adjusted for age, gender, BMI, educational status, smoking status, history diseases, and medication use	Categorsied by residential distance from major road. Personal $PM_{2.5}$ exposure measured with AM510, with plastic tube inlet port close to patients mouth to estimate $PM_{2.5}$ exposure	AIx, SBP, DBP, NO production in serum	Participants who lived within 50 m of a major road compared with those lived more than 200 m away had higher average personal $PM_{2.5}$ (111.1 vs. 68.2 µg/m^3) and 4.3×higher AIx (*P*<0.05), 1.6×higher SBP (*P*<0.05), 1.9×higher DBP (*P*<0.01), 4.6×lower NO production (*P*<0.01)
Panel Study					
Mehta *et al*. 2014	8/10	Participants of Normative Aging Study in Massachusetts, USA; *n*=370 Age range: 21–80 Mean age: 78.0±6.2 Sex: male 100% female 0% Smoking status: 1.9% smoker, 65.7% ex-smoker Adjusted for: Age, BMI, HDL, years of education, race, alcohol intake, smoking status, diabetes status, , seasonality, weekend of examination, average temperature, relative humidity	$PM_{2.5}$: Ambient $PM_{2.5}$ concentrations from local monitoring station. Short-term exposure windows of 4 h, 24 h, and 3, 7, 14 days preceding each examination.	AIx; mixed effects regression model as continuous functions of moving averages of air pollution exposure.	% change in AIx for 3.6-µg/m^3 increase in $PM_{2.5}$ (95% CI): 0.8% higher AIx (0.2–1.4) (*P*<0.05) Concluded that data support an association between exposure to air pollution and vascular function.
Fang *et al*. 2008	6/10	Construction workers regularly exposed to welding fumes; *n*=26 Age range: 24–64 Mean age: 41.2±11.7 Sex: male 100% female 0% Smoking status: 39% smoker Adjusted for age, smoking and smoking by time interaction	Exposure to $PM_{2.5}$ Gravimetric particle samplers in workers breathing zones.	AIx; measured radial artery pulse wave pressure forms with high fidelity micro manometer, before work, after work and following morning.	Increase in afternoon AIx (95% CI): 2.8% (−1.4, 7.0). Decrease in next morning AIx: −2.4% (−6.9, 2.2). Authors conclude welding fume exposure increases same day and decreases next morning augmentation index.
Randomized Crossover					
Liu *et al*. 2018	7/10	Elderly residents of Peking, China, *n*=35 Mean age: 66.26±7.71 Sex: male 20 female 15 Smoking status: smokers excluded Exclusion criteria: smoker Adjusted for age, gender, BMI, air filtration (yes vs. no) and time of day with statistical methods	$PM_{2.5}$: 4-week observational intervention - 2-weeks with filter and consecutive 2-weeks without. Air pollution monitoring devices measured 12 h real-time indoor and outdoor $PM_{2.5}$	12 h daytime ambulatory BP measurement, measured SBP and DBP every 30 min.	% increase in SBP per 10 µg/m^3 increase in indoor $PM_{2.5}$ (95% CI): 0.39 (0.03–0.75) (*P*<0.05) % increase in DBP per 10 µg/m^3 increase in indoor $PM_{2.5}$ (95% CI): 0.57 (0.05–1.10) (*P*<0.05). Concluded that short-term indoor air filtration intervention can be of cardiovascular benefits in elderly living with high pollution episodes.

(Contd...)

Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Zhao *et al*. 2020	5/10	Peking University students, China, *n*=29 Age range: 18–25 Mean age: 21.8±2.1 Sex: male 16 female 13 Inclusion criteria: non-smoker, no history of CVD, BMI<30 Adjusted for sex, age, BMI, indoor temperature, indoor humidity	$PM_{2.5}$: Aerosol spectrometer was used to monitor real-time indoor $PM_{2.5}$ during active filtration and sham filtration	SBP and DBP measured from upper arm. 3 measurements, mean of last 2 used.	No statistically significant effect on $PM_{2.5}$ on SBP or DBP. Hypothesised that $PM_{2.5}$ could still affect health through systematic oxidative stress, platelet activation and respiratory inflammation.
Gong *et al*. 2003	5/10	Los Angeles, USA, *n*=12 Age range: 18–45 Mean age: 28±10 Sex: male 6 female 6 Inclusion criteria: healthy, non-smoker, non-asthmatic	$PM_{2.5}$: Exposure laboratory single person exposure chamber delivered air to chamber containing 8×outdoor $PM_{2.5}$ concentration	Measured BP, heart rate and heart rate variability	DBP showed no significant differences. SBP (baseline 120 mmHg) increased marginally at 4 h relative to filtered air, slope –0.30 mmHg/(μg/m^3), *P*=0.02. Concluded that $PM_{2.5}$ exposure elicits inflammation and heart rate variability consistent with systemic rather than respiratory effects.
Cole *et al*. 2018	6/10	Cyclists in downtown Vancouver, Canada, *n*=38 Age range: 20–39 Mean age: 29±5.6 Sex: male 28 female 10 Inclusion criteria: healthy, non-smoker, not taking medication for respiratory disease or CVD, no exposed to passive tobacco smoke Adjusted for route differences, pollutant exposure, BMI, age, sex	PM_1, $PM_{2.5}$ and PM_{10}: Exposure to low pollution residential route and high pollution downtown route. Ultrafine particle counter mounted onto wire panier measuring particle number concentration at 1 s intervals. GRIMM dust monitors measured PM10, $PM_{2.5}$ and PM1 at 6 s intervals	RHI measured 1 h before beginning cycle route and 15 min after completing route.	Mean difference downtown (pre-post change in RHI) vs residential (pre-post change) (95% CI): −0.39 (−0.77–0.017). Association between route and RHI were independent of pollutant exposure, suggesting other confounders.
Weichenthal *et al*. 2014	6/10	Montreal females (Canada); *n*=53 Age range 18–44 Mean age: 25±6.0 Sex: male 0 female 53 Smoking status: all non-smokers; 13.3% 2nd hand smoke exposure Adjusted for: caffeine/alcohol consumption, age, race, BMI, recent illness, or second hand smoke exposure in the past 24-h	$PM_{2.5}$ and $PM_{0.1}$, O_3: 3 separate days 2 h high traffic routes, low traffic routes, indoor cycling. 5 day washout period between 3 visits. Personal air pollution exposure measured with instruments mounted onto the bicycle. Harvard impacts measure $PM_{2.5}$ and $PM_{0.1}$ concentration. Ogawa sampling bags measured O_3 concentration.	Measured SBP, DBP and RHI Evaluated before and 3 h after each 2 h exercise period. 3 BP measurements average of 2 closest values.	$PM_{0.1}$ exposure was associated with a 4.91% (95% CI: −9.31, −0.512) decrease in RHI 24 ppb increase in O_3 exposure corresponded to a 2.49% (95% CI: 0.141, 4.84) increase in SBP and a 3.26% (95% CI: 0.0117, 6.51) increase in DBP 3-h after exposure. Exposure to traffic pollution may contribute to acute changes in blood pressure, autonomic and micro-vascular function in women
Kumarathasan *et al*. 2018	8/10	Residents with adjacent steel mill; Canada *n*=52 Age range: 18–34 Medium age: 23.0 Sex: male 24 female 28 Smoking status: smokers were excluded Adjusted for: date of exposure, carry-over effect, age, sex, body mass index (BMI), ambient air pressure, humidity and temperature.	$PM_{2.5}$, SO_2, NO_X, O_3: fixed site ambient air quality monitor measured pollutant concentration hourly. Participant spend 5×8 h days adjacent to Steel plant and 5×8 h days on college campus or in air filtered. 9-day washout period	Measured SBP, DBP, heart rate	College site vs Steel plant change SBP (mmHg) (95% CI): – 0.4733 (−3.1738–2.2272) (*P*=NS). College site versus Steel plant change DBP (mmHg) (95% CI): −0.1021 (−2.2438–2.0396) (*P*=NS). Conclude that air pollutants in the proximity of steel mill site can influence inflammatory and vascular mechanisms.

(Contd...)

Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Liu *et al*. 2014	6/10	Ontario, Canada from University campuses; *n*=61 Age range: 18–34 Medium age: 22±1.6 Sex: male 28 female 33 Exclusion criteria: smoker, occupational exposure to Iron and Steel industry, history of CVD or Respiratory disease, diabetes, exercise limiting disorders, pregnancy or breastfeeding Adjusted for sex, temperature, humidity	Steel plant in proximity; randomized cross over study with fixed site air quality monitor at two sites Measured exposure to $PM_{2.5}$, NO_2, CO and SO_2	SBP and DBP were calculated from 6 consecutive readings, mean of last 5 used. FMD subject supine scanned basal brachial artery diameter following 5 min of cuff occlusion	Resting and post-exercise BP were not significantly different between two sites. % change in FMD for IQR increase in NO2 (95% CI) = −0.14% (−0.31, 0.02) (P<0.1), % change in FMD for IQR increase in CO (95% CI) = −0.02% (−0.03, −0.00) (P<0.05). Conclude NO2 and CO inversely associated with FMD.
Briet *et al*. 2007	7/10	France, *n*=40 Age range: 18–35 Sex: male 100% female 0% Inclusion criteria: non-smoker, no passive smoke exposure, normal creatinine and cholesterol levels, no proteinuria, normotensive. Adjusted for R53R/R53H genotype, diet, subject factor, visit, and air temperature	Measured exposure to NO, NO_2, SO_2, CO, PM_{10}, $PM_{2.5}$ Air pollution data extracted from AIRPARIF, Paris air pollution monitoring network, used monitoring station closest to HEGP hospital	Measured endothelium dependent FMD of brachial artery in response to 5 min hand ischemia.	Correlation between SO2 with FMD: P<0.001 Correlation between NO with FMD: P<0.01 Correlation between CO with FMD: P<0.05 Correlation NO_2, $PM_{2.5}$, PM_{10} with FMD: P=NS. SO_2 levels explained 19% of the variance of FMD. An increase in gaseous pollutants, 2 weeks apart, was significantly associated with a decreased FMD. Endothelial function was impaired by ordinary levels of urban pollution in healthy young males.
Randomized Single-blind Crossover					
Shi *et al*. 2017	Some Concerns	Healthy college students, Shanghai, China; *n*=24 Mean age: 23 Sex: male 13 female 11 Smoking status: smokers were excluded Adjusted for: age, sex, body mass index, $PM_{2.5}$ concentration, 48-h mean temperature, and 48-h mean humidity.	$PM_{2.5}$: Randomized; wore N95 disposable particulate filtering respirators for 48 h alternating with 3-week washout period. $PM_{2.5}$ was continuously monitored indoors and outdoors using personal aerosol monitors.	Heart rate variability and ABPM BP measured every 15 min during day and 30 min at night)	Mean % change in SBP: −2.7 (−5.2, −0.1) (P=0.049) Mean % change in DBP: −0.5 ($-_{2.5}$, 1.5) (P=0.622) Concluded that short-term wearing of particulate-filtering respirators may reduce BP.
Kajbafzadeh *et al*. 2015	Some Concerns	Residents of Vancouver, Canada, *n*=68 Age range: 19–72 Mean age: 43.8±12.8 Sex: male 32 female 36 Exclusion Criteria: pregnant women, recent surgery, diabetes, heart disease, hypertension, metabolic syndrome, asthma, COPD, or Raynaud's syndrome, use of anti-inflammatory medication Adjusted for average indoor temperature and relative humidity	$PM_{2.5}$: 7 days with filtration device followed by 7 days with placebo filtration device. Indoor and outdoor $PM_{2.5}$ concentration was measured.	RHI at the end of each 7-day period	Mean RHI non-filtration±SD: 2.1±0.6 Mean RHI with air filtration±SD: 2.1±0.6 P=0.71 Concluded no relationship between $PM_{2.5}$ exposure and endothelial function.

(Contd...)

Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Allen *et al*. 2011	Some Concerns	Canada, *n*=45 Age range: 20–63 Mean age: 43.0±9.9 Sex: male 21 female 24 Smoking status: smokers were excluded Inclusion criteria: healthy, non-smoking, non-smoking households Adjusted for: age, sex, BMI, temperature	$PM_{2.5}$: Each home was monitored for 2 consecutive 7 day periods during filtration and placebo filtration. During exposure $PM_{2.5}$ filter samples were collected indoor and outdoors to calculate $PM_{2.5}$ mass concentration.	Measured microvascular endothelial function with RHI	RHI unfiltered air±SD: 2.06±0.63, RHI filtered air±SD: 2.28±0.72 (*P*=0.03) Increases in RHI during filtration HEPA filtration was associated with a 9.4% (95% CI, 0.9–18%) increase in RHI.
Fakhri *et al*. 2009	Some Concerns	Canada, *n*=50 Age range: 19–48 Mean age: 27.08±7.13 Sex: male 24 female 26 Inclusion criteria: healthy, non-smoker, no history of CVD or CVD risk factors Adjusted for age, sex, asthmatic status	$PM_{2.5}$, O_3: 4×2 h exposures to sham filtered air, $PM_{2.5}$ 150 μg/m^3, O_3 120 ppb, $PM_{2.5}$ and O_3 Exposures were separated by 2 weeks. $PM_{2.5}$ and O_3 concentrations were continuously monitored. Human exposure chamber used.	Measured heart rate variability and BP: SBP and DBP were measured every 30 mins throughout 2 h exposure.	Change in DBP after $PM_{2.5}$ and O_3 exposure (mmHg)±SE: 1.97±1.21 (*P*=0.02). Change in SBP after $PM_{2.5}$ and O_3 exposure (mmHg)±SE: 0.90±2.00 (*P*=0.48).
Randomised Double-blind Crossover					
Padró-Martínez *et al*. 2015	Low Risk of Bias	Residents living within 200 m of Massachusetts State highway, USA; *n*=20 Mean age: 53.6±9.2 Sex: male 4 female 16 Inclusion criteria: healthy, non-smoking, not allow smoking in home, lived 200 m form Massachusetts state highway Adjusted for: time activity, subjects served as own control	$PM_{2.5}$: 21-day period for each exposure to filtered air and unfiltered air. Particle counter and filtration units were installed in each living room.	Measured SBP and DBP	Difference in SBP unfiltered vs filtered air (mmHg) (95% CI): 8.19 (−0.991, 17.4) (*P*=NS) Difference in DBP unfiltered vs filtered air (mmHg) (95% CI): 4.23 (−3.89, 12.4) (*P*=NS) Concluded no evidence that the filtration improved BP
Morishita *et al*. 2018	Low Risk of Bias	Reducing air pollution in Detroit intervention study: participants living in a low income residential building for senior citizens; USA; *n*=40 Mean age: 67±8 Sex: male 25 female 15 Inclusion criteria: healthy, non-smoking, not receiving supplementary oxygen, Adjusted for: outdoor $PM_{2.5}$ exposure	$PM_{2.5}$: 3 day period for each intervention unfiltered air, low efficiency filtration, high efficiency filtration. Participant wore personal air monitors. Daily $PM_{2.5}$ samples were collected at each participant's residence both indoor and outdoor.	Measured SBP and DBP of Brachial artery,	Mean decrease SBP using high efficiency filtration mmHg (95% CI): 2.9 (−6.2–0.5) (*P*=0.75). Mean decrease DBP using high efficiency filtration mmHg (95% CI): 0.8 (−2.8–1.2) (*P*=0.14). Concluded: short-term use of portable air filtration systems reduced personal $PM_{2.5}$ exposures and may reduce SBP.
Karottki *et al*. 2013	Low Risk of Bias	Elderly residents of Copenhagen, Denmark, *n*=48 Age range: 51–81 Mean age: 67±6.5 Sex: male 22 female 26 Exclusion criteria: smokers Adjusted for: baseline level, BMI, age, and gender	$PM_{2.5}$: exposure to particle filtered and sham filtered indoor air over 14-day period each exposure. Particle number concentrations of $PM_{2.5}$ were continually monitored every 16 s	Measured BP	No effect of air filtration on BP (data not reported)

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Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Weichenthal *et al*. 2013	Low Risk of Bias	First nations reserve, Canada. *n*=37; age range 11–64; mean age: 32. Sex: male 47% female 53%. Smoking status: 64% current smokers. Adjusted for: outdoor temperature, indoor CO2 concentration, air filtration, and mean number of cigarettes smoked.	PM_{10}, $PM_{2.5}$, PM_1: Air filter placed in each home. 1 week filtered air, 1 week unfiltered air with 1 week washout period. Weekly average PM_{10}, $PM_{2.5}$, PM_1 was determined with cascade impactors.	DBP, SBP, RHI: collected at start and end of each exposure period. BP measurements in duplicate. Participant was seated in quiet dimly lit room.	Change after exposure to $PM_{2.5}$ (95% CI): SBP −0.54 (−5.5, 4.5), *P*=NS; DBP 1.8 (−1.7, 5.3) *P*=NS; RHI −0.085 (−0.34, 0.17), *P*=NS. Concluded: air pollutants not strongly associated with cardiovascular parameters.
Chen *et al*. 2015	Low Risk of Bias	College students in Shanghai, China, *n*=35 Age range: 18–35 Mean age: 23±2 Sex: male 10 female 25 Inclusion criteria: healthy, non-smoker, no cardiopulmonary disease Adjusted for age, sex, BMI, indoor temperature, and indoor relative humidity.	$PM_{2.5}$: air purifier in room for 48 h, 2-week washout period, then sham purifier in room for 48 h. Measured indoor and outdoor $PM_{2.5}$ using personal aerosol monitor 1 m away from air purifier and outdoor monitor on rooftop.	BP measured 3 consecutive readings, mean of final 2 measurements to obtain SBP and DBP.	% change SBP (95% CI): −2.7% (−5.1, −0.4). % change DBP (95% CI): −4.8% (−8.5, −1.2). Concluded: cardiopulmonary benefits of indoor air purification among healthy adults living in urban areas with severe particulate air pollution.
Cui *et al*. 2018	Some Concerns	Medical and nursing students, China; *n*=70 Age range: 19–26 Mean age: 22±1.6 Sex: male 29 female 41 Smoking status: smokers were excluded Adjusted for filtration duration, temperature and relative humidity	$PM_{2.5}$, O_3, NO_2: Two indoor air filtration sessions. Measured exposure before, during and after air filtration.	SBP and DBP at start and end of filtration session. cfPWV average value of 3 consecutive measurements	% change between true and sham filtration: PWV 0.39% (−2.36, 3.15) (*P*=0.78). SBP −0.13% (−2.06, 1.79) (*P*=0.89). DBP 2.67% (−0.01, 5.34) (*P*=0.06) Concluded: changes in PWV and BP not significantly different from sham filtration.
Bellavia *et al*. 2013	Low Risk of Bias	Canada; *n*=15 Age range: 18–60 Mean age: 27.7±8.06 Sex: male 8 female 7 Exclusion criteria: fasting total cholesterol >6.2 mmol/L, fasting glucose >7 mmol/L hypertension, pregnancy or lactation, ECG abnormalities	PM_{10} and $PM_{2.5}$: 3 exposures in random order, volunteers and study personal were blinded. Human exposure facility.	BP measured when seated 10 min before and 5 min after exposure.	Post exposure to $PM_{2.5}$ difference in SBP relative to control: $_{2.5}$3 mmHg (*P*=0.001). Post exposure to PM_{10} difference in SBP relative to control: 1.56 mmHg (*P*=0.03). Post-exposure differences in DBP were not statistically significant. Concluded that PM elevates BP.
Brook *et al*. 2014	Low Risk of Bias	USA, *n*=32 Age range: 18–46 Mean age: 25.9±6.6 Sex: male 16 female 16 Inclusion criteria: healthy, non-smoker, without CVD or risk factors eg hypertension, hyperlipidemia, diabetes; not taking medication that may affect vascular function	PM_{10} and filtered air: PM_{10} generated by a system that concentrates ambient course particles. PM_{10} mass levels continuously monitored during exposure using personal DataRAM. Human exposure chamber used.	Measured endothelium dependant FMD from brachial artery, PWV, AIx, RHI and brachial artery BP	SBP (mean difference = 0.32 mmHg; 95% CI: 0.05, 0.58; *P*=0.021) and DBP (0.27 (0.003, 0.53); *P*=0.05) linearly increased per 10 min of exposure during the inhalation of $PM_{10.}$ FMD, AIx, PWV were not significantly altered by exposure to PM_{10}. Reported inhalation of coarse PM was associated with a rapid elevation in BP and heart rate during exposure.

(Contd...)

Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Morishita *et al*. 2015	Low Risk of Bias	USA, *n*=32 Age range: 18–46 Mean age: 25.9±6.6 Sex: male 16 female 16 Inclusion criteria: healthy, non-smoking, without CVD, BP <140/90 mmHg, fasting glucose <126 mg/dl, not taking medications that may alter outcomes. Unadjusted data.	2 h long exposure to $PM_{2.5}$-10 vs filtered air, 1–3 week washout period. Virtual impact or system generated $PM_{2.5}$-10. Filtered air generated with high efficiency PM filter.	Left upper arm BP and heart rate measured every 10 min	Report concentration–response associations between $PM_{2.5}$-10 exposure and SBP, but not DBP. Particulate composition was not an important determinant of these responses. Values not reported.
Brook *et al*. 2002	Low Risk of Bias	Canada, *n*=25 Age range: 18–50 Mean age: 34.9±10 Sex: male 15 female 10 Inclusion criteria: healthy, non-smoker. Exclusion criteria: CVD; fasting glucose ≥126 mg/dL, total cholesterol ≥240 mg/dL, hypertension.	Measured exposure to concentrated ambient $PM_{2.5}$ O_3, vs filtered air 2 h inhalation to $PM_{2.5}$ and O_3 in human exposure facility to $PM_{2.5}$ = 150 μg/m^3 and O_3 = 120 ppb	Measured endothelium dependant FMD, SBP and SBP	% change FMD polluted air vs filtered air: +0.29±4.11% vs −0.03±6.63%, (*P*=0.88), % change SBP polluted air vs filtered air: +0.4±8.6% vs +0.8±10.3%, (*P*=0.61), % change DBP polluted air vs filtered air: +0.9±7.2% vs −0.4±7.3%, (*P*=0.77) FMD and BP responses did not significantly differ between the exposure types.
Brook *et al*. 2009	Low Risk of Bias	Canada, *n*=31 Age range: 18–50 Mean age: 27±8 Sex: male 16 female 15 Smoking status: smokers excluded Inclusion criteria: healthy, non-smoker, without CVD or CVD risk factors, not taking medications Exclusion criteria: fasting glucose ≥126 mg/dL, fasting total cholesterol ≥240 mg/dL	Measured exposure to concentrated ambient $PM_{2.5}$ O_3, filtered air 2 h inhalation to $PM_{2.5}$ and O_3 in human exposure facility or virtual impact system to $PM_{2.5}$ = 150 μg/m^3 and O_3 = 120 ppb. $PM_{2.5}$ level monitored using tapered element oscillating microbalance during exposure.	Measured endothelium dependent FMD SBP and SBP calculated from mean of 3 supine measurements.	% change FMD 24 h after exposure to $PM_{2.5}$ and O_3: 8.8±4.2 (*P*=0.016); $PM_{2.5}$ alone: 5.8±5.3 (*P*<0.05). Change in DBP after exposure to $PM_{2.5}$ and O_3: 0.89±0.22 (*P*=0.01); $PM_{2.5}$ alone: 0.71±0.21 (*P*=0.002), Concluded: immediately post-exposure, FMD not significantly impaired (data not shown), but decreased 24 h post-exposure. DBP increased linearly during $PM_{2.5}$ containing exposures.
Frampton *et al*. 2015	Low Risk of Bias	USA, *n*=12. Age range: 18–40 Mean age: 27.3±4.2 Sex: male 7 female 5 Inclusion criteria: healthy, non-smoker, no pulmonary disease or CVD, normal spirometry, normal ECG, not pregnant, not using anti-inflammatory drugs, no respiratory infections	Measured exposure (3 h) to 100 ppb O_3, 200 ppb O_3, and filtered air. Washout: 2 weeks between exposures.	Measured vascular endothelial function with RHI using peripheral artery tonometry.	No significant effect of O_3 on RHI. Figures not shown.
Tank *et al*. 2011	Low Risk of Bias	Germany, *n*=14. Age range 22–47 Mean age: 33.7±9.5 Sex: male 11 female 3 Inclusion criteria: healthy, forced expiratory volume in 1st s >80%. Exclusion criteria: respiratory tract infections, medication, hormone replacement therapy	Measured exposure (3 h) to 100 ppb O_3, 250 ppb O_3, and filtered air. Washout: 2 weeks between exposures. O_3 concentration was monitored	Measured brachial artery BP After overnight fast in the morning.	Resting SBP (clean air: 121±3 mmHg; ozone: 121±2 mmHg), DBP (clean air: 71±2 mmHg; ozone: 71±2 mmHg). *P* value not reported No significant effect for BP.

(Contd...)

Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Rich *et al.* 2018	Low Risk of Bias	Multicentre Ozone Study in oldEr Subjects (MOSES); USA; *n*=87 Age range: 55–70 Mean age: 59.9±4.5 Sex: male 35 female 52 Inclusion criteria: healthy non-smoker, normal resting ECG, normal spirometry Adjusted for filtration duration, temperature and relative humidity	Exposure to O_3 in ventilated climate-controlled chambers.	SBP and DBP FMD	% change SBP pre-post exposure (95% CI): −1.3% (−3.7, 1.2) *P*=0.950, % change DBP: -0.1% (−1.2, 1.0) (*P*=0.816), % change FMD pre-post exposure (95% CI): −0.1% (−1.1, 0.9) (*P*=0.637) No statistically significant effect of Ozone on SBP and DBP, slight increase in FMD wasn't statistically significant.
Arjomandi *et al.* 2015	Low Risk of Bias	USA, *n*=26; Age range: 18–50 Mean age: 31.8±7.6 Sex: male 13 female 13 Smoking status: non-smokers Inclusion criteria: ability to perform exercise, healthy, no recreational drug use Adjusted for age and smoking	O_3 Exposure in ventilated chambers for 4 h with subjects exercising for 30 min. Exposed to 0, 100, 200 ppb O_3. 3-week washout period between exposures.	BP and heart rate measured at 0 h, 4 h, 24 h with subjects placed in supine position	Data not provided. Concluded: no significant trends between the changes in BP and heart rate with level of ozone exposure from 0 h to either 4 h or 24 h.
Langrish *et al.* 2010	Low Risk of Bias	Sweden, *n*=10; all male Age range: 22–28 Medium age: 24 Inclusion criteria: male, healthy, no respiratory infections, non-smoker, no current illness, no regular medications, normal lung function	NO_2, NO: NO_2 or filtered air in exposure chamber. Monitored for NOX using oxides of Nitrogen analyser. NOX concentration maintained at 4 ppm	Measured endothelial function with forearm blood flow following infusion with endothelium dependant and independent vasodilators	No difference in vascular response to any vasodilator following NOX exposure.
Barath *et al.* 2010	Low Risk of Bias	Sweden; *n*=18 Age range: 21–30 Mean age: 27 Sex: male 100% female 0% Smoking status: smokers were excluded inclusion criteria: healthy, non-smoking, free from respiratory tract infection	PM_{10}, NO and NO_2: exposure chamber with diesel exhaust generated by diesel engine. Standard glass fiber sampling and tapered element microbalance to measure PM_{10}. Chemiluminescence to measure NO and NO_2	Measured forearm blood flow using the fusion of vasodilators into brachial artery, BP and heart rate	SBP filtered air vs exhaust (mmHg)±SD: 142±3.2 versus 142±2.7 (*P*=NS), DBP filtered air vs exhaust±SD: 68±2.9 vs 68±1.8 (*P*=NS) Concluded: no differences on resting heart rate, BP, or forearm blood flow after diesel exposure.
Mills *et al.* 2011	Low Risk of Bias	UK, *n*=16; Age range: 18–32 Sex: male 100% female 0% Smoking status: smokers were excluded Exclusion criteria: taking regular medication, chronic health conditions, occupational exposure to air pollution	PM: Purpose built exposure chamber. Air was continuously monitored for NOx, CO, SO_2, O_3, PM concentrations. Diesel exhaust from diesel engine.	Measured SBP, DBP, and endothelial function: forearm blood flow following infusion with endothelium dependent and independent vasodilators	SBP following diesel exhaust inhalation±SD: 145± 4, versus filtered air 133± 3 (*P*=0.012) DBP± SD: 69±8 vs 69± 8 (*P*=NS) Infusion response diesel versus filtered: bradykinin (*P*=0.005), acetylcholine (*P*=0.008), and sodium nitroprusside (*P*<0.001) Concluded: Reduced vasodilation following exposure to diesel exhaust.

(Contd...)

Table S3: Evidence table of studies investigating association between short-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Reference	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Cosselman *et al*. 2012	Low Risk of Bias	USA, *n*=31; Age range: 18–49 Mean age: 28±8.6 Sex: male 22 female 9 Exclusion criteria: smoker, hypertension, other chronic medical conditions, pregnancy. Adjusted for diesel exhaust exposure, metabolic syndrome, sex	$PM_{2.5}$: Diesel exhaust fumes generated to maintain $PM_{2.5}$ concentration at 200 μg/m^3. $PM_{2.5}$ measured with tapered element oscillating microbalance and adjusted.	Measured resting BP and heart rate during exposure at 5, 30, 60, 90, 110 min from exposure start and 3 h, 5 h, 7 h, 24 h after exposure	No significant effect on heart rate or DBP, but a rapid, increase in SBP in young non-smokers: Mean SBP increased, peaking 30 to 60 min after exposure 3.8 mmHg (95% CI 0.4–8.0) at 30 min, 5.1 mmHg (95% CI 0.7–9.5) at 60 min
Törnqvist *et al*. 2007	Low Risk of Bias	UK, *n*=15 Age range: 18–38 Mean age: 26 Sex: male 15 female 0 Smoking status: smokers were excluded Inclusion criteria: healthy, non-smoking, ,	PM: Exposed to filtered ambient air or diesel exhaust at 300 150 μg/m^3 for 1 h in exposure chamber. 2 week washout period	Measured response to various endothelium dependant and independent vasodilators Vascular measurements 2-4h and 24 h after exposure.	After exposure to diesel exhaust, endothelium-dependent vasodilatation was reduced with acetylcholine (*P*=0.01), bradykinin reduction did not reach significance (*P*=0.08). No effect on endothelium-independent vasodilatation: Sodium nitroprusside and Verapamil.

Long-term exposure

PM

The relationship between long-term exposure to PM with blood pressure was investigated by five observational studies [Table S4]. All studies defined hypertension as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg, or physician diagnosis with use of antihypertensive medication,[63] and all found an association.[14,16,18,22,23] Endothelial function was not widely reported, with only one study identified. This concluded an inverse association, that is, elevated long-term (but not short-term) $PM_{2.5}$ concentrations impaired endothelial function as measured by FMD, independent of other cardiovascular risk factors.[20]

The association between arterial stiffness and long-term PM exposure was investigated by three studies. Wu *et al.*[17] reported an increase in arterial stiffness measured with brachial-ankle PWV (baPWV) when exposed to $PM_{2.5}$, but not when exposed to NO_2. In contrast, Lenters *et al.*[15] using cfPWV found an association with NO_2 and SO_2, but not $PM_{2.5}$. Adamopoulos *et al.*[24] also used cfPWV to measure arterial stiffness, and failed to find an association with long-term PM_{10} exposure.

Gaseous pollutants

The relationship between long-term exposure to gaseous pollutants with blood pressure and arterial stiffness was investigated by six observational studies; no articles reported the association with endothelial function; and four studies investigated the association with blood pressure [Table S4].

Dong *et al.*[23] using data from the nearest monitoring site found a positive association between O_3 and SO_2 exposure (but not NO_2) with odds of hypertension. Three other studies that used land-use regression models did conclude an association between NO_X exposure and increased blood pressure.[16,18,19] The association of arterial stiffness with gaseous pollutant exposure was investigated by two studies. Lenters *et al.*[15] found a positive association between SO_2 and NO_2 with arterial stiffness, in contrast Wu *et al.*[17] found no association. Considering the discrepancy, both studies used similar methods (PWV and land-use regression models), thus the long-term effect of gaseous pollutants on arterial stiffness remains unclear.

Risk of bias across the studies

Modified Newcastle-Ottawa scale applied to the cross-sectional studies gave scores between 5/10 and 10/10, and the revised Cochrane risk of bias tool (RoB 2) gave "some concerns" to "low risk of bias" for the randomized trials; detailed information regarding each study is reported in the supplemental data [Tables S1 and S2]. Potential sources of bias affecting the quality of the included studies included representativeness of the sample, lack of justification of sample size, and failure to control or adjust for exposure uncertainties or confounding variables, selection bias.

Discussion

Long-term exposure studies consistently report an association between air pollution and elevated blood pressure. These have largely been cross-sectional from which one cannot infer causation; however, one cohort study measuring exposure to $PM_{2.5}$ and NO_X over 10 years also supported a temporal association with air pollution.[18] Arterial stiffness and endothelial function were reported less frequently, but the majority of the studies supported an association. Data [Table S4] support the hypothesis that longer exposures to air pollution represent cumulative biological effects.

Table S4: Evidence Table of studies investigating association between long-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness

Author, Title, Country	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Cross-Sectional					
Krishnan *et al*. 2012	10/10	MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution); USA; *n*=3040 Age range: 45–84 Mean age: 61.2±9.9 Sex: male 1545 female 1495 Smoking status: smokers were excluded Inclusion: free from cardiovascular disease Adjusted for multiple factors	$PM_{2.5}$: Long term exposure hierarchical spatio-temporal model using EPA air quality monitoring stations used to predict exposure at home locations for year 2000. Short term exposure control site air quality monitoring station on day of examination and 2 days prior	Measured FMD	For every 3-μg/m^3 increase in the annual average $PM_{2.5}$ FMD % ↓ by 0.3% (0.6, 0.03) (*P*=0.03). Short-term $PM_{2.5}$ concentrations were associated with a small ↓ in FMD% 0.1% (0.2, 0.04) *P*=NS. Concluded: inverse association between long-term $PM_{2.5}$ concentrations and FMD, independent of cardiovascular risk factors.
Babisch *et al*. 2014	5/10	KORA-survey 2000; Germany; *n*=4166 Age range: 25–74 Mean age: 74.8±6.4 Sex: male 2046 female 2120 946 smoker, 132 occasional, 1305 ex-smoker Adjusted for: age, sex, smoking, alcohol intake, BMI, physical activity, socio-economic status.	$PM_{2.5}$: annual average $PM_{2.5}$ concentration at residential address from land use regression modeling using data from 20 monitoring sites 2008 to 2009.	Hypertension: 3 BP measurements. SBP ≥140 and/ or DBP ≥90 mm Hg or physician diagnosed with use of antihypertensive medication.	OR of hypertension: 1.15 (95% CI 1.02, 1.30) per 1 μg/m^3 ↑ increase in $PM_{2.5}$
Lin *et al*. 2017	9/10	Chinese respondents to WHO's SAGE study Hypertensive: *n*= 7777 Normotensive: *n*= 4888 Age range: ≥50 Mean age: 63 Sex: male 5895 female 6770 Smoking: 8417 none, 1655 0–8 cigs/day, 2588 >8 cigs/day.	$PM_{2.5}$: Van Donkelaar *et al*. method to estimate average $PM_{2.5}$ exposure in each participant communities. Used data from 3 years preceding the Survey.	Hypertension: SBP ≥140 and/or DBP ≥90 mmHg or physician diagnosed with use of antihypertensive medication. BP measured in triplicate.	OR of hypertension: 1.14 (95% CI 1.07, 1.22) per 10 μg/m3 ↑ in $PM_{2.5}$
Lenters *et al*. 2010	7/10	Young adults; Netherlands, *n*=745 Age range: 45–84 Mean age: 28.4±0.9 Sex: male 47% female 53% 31% smoker, 14% former smoker Adjusted for: age, sex, mean BP, PWV analysis, BMI, pack-years smoking, alcohol, socio-economic status, diabetes.	NO_2, $PM_{2.5}$, SO_2: Regression models were developed using land use data and population density. Long term exposure characterized as the sum of regional, urban and local traffic. NO_2, $PM_{2.5}$ and SO_2 from air monitoring sites were averaged for the year 2000.	Measured carotid artery intima media thickness, cfPWV, AIx.	cfPWV: 4.9% ↑ (95% CI 1.2, 8.7)/20-μg/m NO2. AIx: 37.6% ↑ (2.2, 72.9)/25-μg/m^3 ↑ NO_2 *P*<0.04. cfPWV: 5.26% ↑ (0.09, 10.43)/5-μg/m^3↑ SO2. Concluded: association between gaseous pollutant exposure and arterial stiffness; but not $PM_{2.5}$ which showed a weak association with PWV after adjustment for covariates.

(Contd...)

Table S4: Evidence Table of studies investigating association between long-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Author, Title, Country	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Chen *et al*. 2015	6/10	Taiwan elderly health screening programme 2009 *n*=27752; Mean age: 74.8±6.4 Sex: male 14414 female 13338 Smoking status: 6.7% smoker, 93.3% ex-smoker Inclusion criteria: age >65, BP 120–60 to 190–90 mmHg Adjusted for: sex, age, BMI, smoking, alcohol, education, BP, diabetes, traffic proximity	NO_2, PM_{10}, $PM_{2.5}$, NOx: Land use regression to model annual average concentration for each participant using 40 monitoring sites. One-year exposures.	Hypertension: SBP ≥140 and/or DBP ≥90 mm Hg or physician diagnosed with antihypertensive medication use. BP performed seated, 1 measurement taken.	PM10, $PM_{2.5}$–10, and NOx were associated with higher DBP (but not $PM_{2.5}$) in generalised linear models: mmHg (95% CI) – PM10 (10 μg/m^3) 0.77 (0.46, 1.09); $PM_{2.5}$–10 (5 μg/m^3) 0.46 (0.29, 0.63); $PM_{2.5}$ (5 μg/m^3) –0.05 (–0.20, 0.11); NOx (20 μg/m^3) 0.41 (0.23, 0.59) None of the air pollutants was associated with SBP.
Dong *et al*. 2013	7/10	Communities <1 km from monitoring site, China *n*=24845; Age range: 18–74; Mean age: 46±13 Sex: male 12661 female 12184 Smoking status: approx. 1/3 smokers Adjusted for: age, race, education, income, smoke, drink, exercise, diet, sugar, family history of hypertension, and district.	PM10, SO_2, NO_2, O_3 concentrations were obtained from monitoring stations. Calculated 3-year average concentrations between 2006 and 2008	Hypertension: SBP ≥140 and/or DBP ≥90 mm Hg or physician diagnosed with antihypertensive medication use. BP was measured 3 times	OR of hypertension: A) 1.12 (95% CI 1.08, 1.16) per 19 μg/m^3 ↑ in PM_{10}. B) 1.11 (1.04, 1.18) per 20 μg/m^3 ↑ in SO_2. C) 1.13 (1.06, 1.20) per 22 μg/m^3 ↑ in O_3. D) 1.09 (1.00, 1.20) per 9 μg/m^3 ↑ in NO_2
Foraster *et al*. 2014	8/10	Population based Cohort of REGICOR study; Spain Hypertensive: *n*= 704, non-hypertensive: *n*= 1222 Age range: 36–82 Mean age: 56±18 Sex: male 876 female 1050 Smoking status: 406 smoker, 539 former smoker Adjusted for: age, sex, education, diet, exercise, alcohol, smoking, BMI, diabetes, deprivation, daily temperature, and indoor railway noise.	NO_2: outdoor levels at each subjects address with land use regression models using data from outdoor monitoring sites.	Hypertension: SBP ≥140 and/or DBP ≥90 mm Hg, or physiciandiagnosedwith use of antihypertensive medication. BP measured in duplicate.	OR of hypertension: 1.16 (95% CI 0.99, 1.36) per 10 μg/m^3 ↑ in NO_2. Concluded: association between long-term exposure to NO_2/traffic-related air pollution and hypertension.

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Table S4: Evidence Table of studies investigating association between long-term exposure to air pollution and blood pressure, endothelial dysfunction, and arterial stiffness *(Continued)*

Author, Title, Country	Quality Rating	Population Characteristics	Air Pollution Measurement	Cardio-Vascular Measurement	Principal Findings
Panel Study					
Wu *et al*. 2016	6/10	Residents of a Metropolitan area of Taiwan, *n*=89 Age range: 18–79 Mean age: 43.7; Sex: male 35 female 54 Exclusion criteria: incomplete health outcome data. Adjusted for sex, age, body mass index, waist, SBP.	$PM_{2.5}$ and NO_2: Outdoor air pollutants measured at air quality monitoring stations. Indoor air pollution sampled within a finance office in Taipei using personal dust and chemiluminescence methods. Land use regression modeling to estimate exposure levels.	baPWV 2 examinations, 8 months apart.	Increase in baPWV: 2.4% (95% CI 0.8, 4.0) per 10 μg/m^3 increase in $PM_{2.5}$ concentration (1 day lag), *P*<0.05. Increase in baPWV: 1.9% (95% CI–0.3, 4.1) per 10 ppb increase in NO_2 concentration (1-day lag) *P*=NS. Concluded: $PM_{2.5}$ increases baPWV as a measure of arterial stiffness, no significant association for NO_2.
Cohort Study					
Adamopoulos *et al*. 2010	9/10	Hypertension Outpatients in Athens, Greece; *n*=1222 Mean age: 51±13; Sex: male 649 female 573 42.1% smokers Inclusion criteria: hypertension outpatient clinics	PM10: Ambient PM10 obtained from 7 air quality monitoring station in Athens. Mean daily and mean 5-day values were calculated.	Cohort Study Length: 3 years Measure BP, cfPWV	Change in cfPWV: −1.99 m/s (95% CI −4.19, 0.19) per 43.4 μg/m^3, *P*=NS. Change in SBP: 0.26 mmHg (−2.02– $_{2.5}$4) per 43.4 mg/m^3, *P*=NS. Multiple-linear regression analysis revealed no significant associations between environmental variables and arterial stiffness.
Coogan *et al*. 2012	8/10	Black Women's Health Study; USA; *n*=4204 Age range: 21–69; all female Smoking tertiles: non-smoker, <25, ≥25 cigs/day Inclusion criteria: age 21–69, black, female Adjusted for: age, BMI, income, number of people in the household, smoking, alcohol, physical activity, socioeconomic status.	$PM_{2.5}$ and NOx: 23 state and local monitoring stations used to calculate long term mean $PM_{2.5}$ at ZIP code area. Land use regression models to estimate mean annual NOx based on 183 measurement sites in LA.	10 year follow up. SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or physician diagnosed with use of antihypertensive medication.	Incidence Rate Ratio (IRR) for hypertension with a 10 μg/m^3 increase in $PM_{2.5}$ (95% CI): 1.48 (0.95–2.31). IRR for hypertension for a interquartile range increase in NOX (95% CI):1.14 (1.03–1.25) Concluded: exposure to traffic-related pollutants, may increase the risk of hypertension.

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PWV: Pulse wave velocity, baPWV: Brachial-ankle pulse wave velocity, cfPWV: Carotid-femoral pulse wave velocity, FMD: Flow mediated dilatation, RHI: Reactive hyperemic index, AIx: Augmentation index, CVD: Cardiovascular disease, BMI: Body Mass Index, SD: Standard deviation, CI: Confidence interval, OR: Odds ratio, NS: Not significant, ABPM: Ambulatory blood pressure measurement, PM10: Coarse particulate matter diameter is <10 μm, $PM_{2.5}$: Fine particulate matter diameter $<_{2.5}$ μm, CO: Carbon monoxide , O_3: Ozone , SO_2: Sulfur dioxide, NO: Nitrogen oxide, NO_2: Nitrogen dioxide, NOX: Nitrogen oxide and/or nitrogen dioxide, USA: United States of America. All BP reported in mmHg, all PWV reported in m/s

Although a greater number of studies have reported short-term exposure, they proffer conflicting conclusions, likely in part reflecting heterogeneity in pollutant, design, and methodologies. In summary, data on blood pressure outcomes were mixed; there was no association with arterial stiffness techniques, but evidential support that endothelial function is impaired after exposure to both PM and gaseous air pollution. This fits with the hypothesis that endothelial dysfunction occurs earlier in the natural history of arterial disease and hypertension, with arterial stiffening indicating more established pathology. Endothelial effects were rapid, but also transient,[64] such that timing of outcome measures becomes a key methodological aspect.

For example, Cosselman *et al.*,[37] report SBP (although still elevated) had reduced towards baseline over 24 h following the exposure. However, most short-term exposure studies did not measure the aftereffects of exposures beyond 1–2 h, so duration of acute effects of air pollution exposure and relation to longer-term cardiovascular dysfunction remains unclear.

PM is a complex mixture ammonium, sulfate, nitrate, elemental carbon matter, organic carbon matter, sodium, and silicon.[65] The effects of these individual components were modeled by Krall *et al.* with time series data from 72 communities in USA; reporting that only silicon and sodium were associated with an increase in mortality.[66] This was reinforced by Dai *et al.*, using a city season specific Poisson regression model for 75 cities; they estimated $PM_{2.5}$ effects on approximately 4.5 million deaths for all causes. This epidemiological data suggested that silicon, calcium, and sulfate were associated with increased all-cause mortality,[67] but not carbon or nitrate exposure. Furthermore, despite reports that exposure to ultrafine carbon particles alters peripheral blood leukocyte distribution and expression of adhesion molecules,[68] they have no consistent effects on systemic vascular function.[69] This suggests the with regard to vascular function, the effects of carbon are smaller than other major components of PM, and highlights that the composition of pollutants is a determinant of the health consequences, as well as a factor contributing to the inconsistency in the results of short-term exposure studies.[36]

The adverse effects of diesel exhaust exposure persist even after the removal of PM,[70] indicating that gaseous pollutants also have a role in mediating the negative effects of air pollution. SO_2 was the only gaseous pollutant consistently associated with increase blood pressure and endothelial dysfunction from the studies included in this review. Increased oxidative stress caused by exposure to SO_2 may also lead to impaired bioavailability of NO contributing toward endothelial dysfunction.[71] Spirometry and venous sampling on military recruits with identical daily activities has also demonstrated that SO_2 and PM have a pro-inflammatory effect, elevating numbers of circulating polymorphonuclear leukocytes and release of white blood cells from the bone marrow. This may be stimulated by alveolar macrophages as they phagocytose fine particulates,[72] the final result of systemic inflammation being endothelial damage.

Other groups have previously performed systematic review investigating the association between air pollution and blood pressure,[73,74] or arterial stiffness[75] all concluding with varying degrees of certainty that there was an association. To the best of our knowledge, this is the first to look at endothelial function and the first to aggregate evidence on a range of cardiovascular risk parameters. However, this review is only as robust as the original data, for example, all the long-term studies included are observational, mainly cross-sectional studies and none of the studies investigated the effect of reducing exposure to air pollution to ascertain reversibility, nor measured the persistence of any acute changes beyond 24 h. Future studies should focus on investigating these aspects. There was high heterogeneity between trials in the concentration of pollutants, duration of exposure, measurement of outcome and the population sampled with highly variable inclusion and exclusion criteria. This is likely the most important factor in the inconsistent results reported by this review and makes comparability between trials difficult.

Conclusion

The results of this systematic review support the hypothesis of an association between long-term exposure to certain gaseous pollutants (particularly SO_2) and PM with increased blood pressure, arterial stiffness, and possibly endothelial dysfunction. Conversely, acute exposure demonstrates evidence of association with endothelial function and may effect blood pressure, but not measures of vascular stiffness. This carries implications for cardiovascular research, as a source of confounding or bias, but also inferences for public health policy and population-based prevention strategies, as air quality is potentially a modifiable risk factor in the development of cardiovascular disease.

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Review Article

Non-invasive Clinical Vascular Phenotyping in Children with Hypertension (Review)

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Abstract

Cardiovascular risk factors such as hypertension and obesity are rising in young children. Children with untreated hypertension are at high risk of cardiovascular complications and target organ damage later in life. As such, there is a need to identify feasible and reproducible techniques for vascular phenotyping of children and young people with hypertension and other chronic diseases. This will allow for the determination of which children are most at risk of early vascular dysfunction and for consideration of strategies to mitigate this risk. This narrative review describes current approaches to non-invasive clinical vascular phenotyping in the pediatric setting, with a particular focus on the assessment of endothelial function, through flow-mediated dilatation, venous occlusion plethysmography, and measurement of reactive hyperemia; identification of atherosclerosis through intima–media thickness measurements; and assessment of arterial stiffness through pulse wave analysis.

Key words: Blood pressure, carotid intima–media thickness test, flow-mediated dilatation, pediatric, pulse wave velocity

Introduction

The fetal origins of disease hypothesis was first proposed by Barker and colleagues in the 1980s and suggested that cardiovascular diseases (CVDs) originate through adaptations made by the fetus when it is compromised in some way *in utero* so that typical embryological development does not occur or there are imbalances in nutrient supply to the fetus or growth of the fetus.[1] Barker's landmark studies focused on the realization that infants born low birth weight had increased risk of ischemic heart disease later in life. This theory has since been corroborated by multiple studies which have shown associations between adverse fetal conditions and CVD. It appears that maternofetal stressors may result in epigenetic changes, leading to alterations in the sympathetic nervous system, renin-angiotensin system, and hypothalamic pituitary axis, with consequent modification to kidney, heart, and blood vessel function.[2] As such, over time the hypothesis has progressed to be called the Developmental Origins of Health and Disease model.

CVD remains the leading cause of death worldwide, representing over 30% of all deaths and 45% of non-communicable deaths.[3] Cardiovascular risk factors such as hypertension, obesity, and atherogenic lipid profiles are rising in young children, with this rise being attributed to pregnancy complications, genetic inheritance, and environmental risk factors in the early years. Children with untreated hypertension are at high risk of cardiovascular complications and target organ damage later in life.[4] Treatment of pediatric hypertension reduces the risk of atherosclerosis in adulthood, but there is some evidence to suggest that currently accepted thresholds for the definition of hypertension in children, do not take into account that the risk of target organ damage may be increased even at lower blood pressure (BP) levels.[4]

Given the association between early life influences and adult disease, it is essential to consider how to assess cardiovascular risk in children and young people using other non-invasive techniques, as this may lead to opportunities for risk mitigation and reduction in the public health burden of CVD in adulthood, as well as critical insights into the pathophysiology behind disease development. For example, a 20-year longitudinal study

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of children born preterm, demonstrated that the predominant underlying vascular phenotype in adult life differed according to maternal BP during pregnancy, suggesting that different risk stratification techniques would be required for these individuals to prevent future CVD.[5]

With an increasing focus on the vascular effects of childhood diseases, an abundance of research has studied non-invasive and acceptable methods to measure vascular function clinically in young people. New initiatives, including the Youth Vascular Consortium, have also recently been established to develop reference ranges for the most commonly used non-invasive vascular phenotyping techniques, on young people between the ages of 5 and 40 years.[6] The current reference ranges tend to be either from a single center or limited by small sample size, so collaborations such as these will ensure that these reference data are generalizable to the wider population. This narrative review will focus on these more commonly used methods for clinical vascular phenotyping, to assess vascular endothelial function, vascular remodeling, and arterial stiffness, and how they could be used to determine a clinical vascular phenotype in children. Although to date, there is insufficient evidence to support routine clinical use of the above methods in pediatric hypertension, large cohort studies, including work with the Avon Longitudinal Study of Parents and Children group, have shown that all of the techniques considered in this review are both feasible and reproducible in children and young people.[7] A summary of the techniques is given in Table 1.

Assessment of Vascular Endothelial Function

Flow-mediated dilatation

First described in a cohort of patients aged 8–57 years,[8] flow-mediated dilatation (FMD) is a technique which has been used as a surrogate marker of vascular health for nearly 30 years. FMD is determined by the change in brachial artery diameter caused by releasing a lower arm cuff that has been inflated to suprasystolic pressure for 5 min, with artery diameter being measured through ultrasound.[9] Cuff release triggers an endothelium-dependent nitric oxide (NO) response, which has been shown to be indicative of future vascular risk, as confirmed by meta-analysis, demonstrating a strong inverse relationship between FMD and increased cardiovascular risk.[9] This can be done manually using a traditional ultrasound machine and apparatus to keep the ultrasound probe in place above the brachial artery for the duration of the procedure or through a semi-automated device which uses B-Mode ultrasound to simultaneously capture longitudinal and cross-sectional views of the brachial artery.[10]

Several factors may influence endothelial function and as such recommendations in adults advise undertaking FMD on fasted participants, who have not undertaken strenuous exercise in the previous 24 h or taken any caffeine, tobacco, or drugs which may affect vascular status.[11] These issues are less likely to be prevalent in younger children, but must be considered in the assessment of adolescents. The use of nitroglycerin to assess endothelium-independent vasodilatation is also recommended in adults, but is not common practice in the pediatric setting. Repeated measures should be taken at the same time of the day to prevent potential diurnal variation and the readings should be undertaken on participants who are in the supine position and relaxed and through skilled operators. The technique can be technically difficult in children as they have to lie supine with their arm outstretched and under the ultrasound probe for 5 min without moving. The procedure cannot be reliably repeated immediately after an attempt because there may be some residual NO response.

Reference ranges for FMD have not yet been described in children. Observational studies have, however, shown sex differences in FMD in young children and adolescents, with males having lower median (range) FMD at 7.62% (7.33, 7.91) compared to age-matched females (8.31% [7.95, 8.66] ($P < 0.001$) and larger baseline artery diameter (2.96 mm [95% CI:2.92–3.00] vs. 3.24 mm [3.19–3.28]).[12] In addition, FMD declined with age throughout the cohort of 978 children (54% males, median age (range) 12.2 (6, 18) years), with more significant reduction post-puberty in males.[12] In adults, lower FMD levels are associated with vascular dysfunction.[8]

In disease states, FMD has been measured to date in children with type 1 diabetes, obesity, metabolic syndrome, rheumatic diseases, sickle cell diseases, Kawasaki disease, nephrotic syndrome, and moyamoya disease and lifestyle modifications and statin treatment have reported improved endothelial function as measured by FMD in children.[13]

Venous occlusion plethysmography

Although FMD is now considered to be the gold standard of the assessment of endothelial function, venous occlusion plethysmography is a technique which has been used to describe

Table 1: Summary of commonly used techniques for non-invasive vascular phenotyping in children

Focus of vascular assessment	Method	Vascular bed
Endothelial function	Flow mediated dilatation	Brachial artery
	Reactive hyperemia	Finger microcirculation
	Venous occlusion plethysmography	Forearm circulation
Atherosclerosis and vascular remodeling	Intima–media thickness	Carotid artery
		Aorta
Arterial stiffness	Pulse wave velocity	Carotid-femoral
Cardiac and vascular structure and function	Cardiac magnetic resonance imagining	Heart

vascular physiology since the early 20th century. In brief, this technique measures local vascular tone in response to an ischemic challenge by interrupting venous return from the area of study through cuff inflation below diastolic pressure, allowing for arterial inflow and venous emptying.[14] This can be done on two limbs at the same time and it can be combined with intra-arterial drug administration, if an invasive procedure will be tolerated by the child. A wrist cuff may be rapidly inflated above normal systolic pressure approximately 60 s before taking any measurements to exclude the effects of the hand's arteriovenous shunts from analysis. With increasing availability of ultrasound however, the set up for plethysmography can be more difficult and time consuming, as well as intimidating and difficult to tolerate for children. The procedure requires adherence to strict protocols, as factors such as cuff inflation time can significantly alter results. Although venous occlusion plethysmography has been demonstrated to be predictive of cardiovascular events in adults, variations in body habitus, forearm size, and blood flow mean that this technique is better suited for longitudinal studies measuring differences in blood flow in single patients, rather than comparison of distinct patient groups.

Reactive hyperemia index (RHI)

Measurement of RHI, through endothelial peripheral arterial tonometry (PAT), has potential to be useful in assessing endothelial function in a pediatric population because of its ease of use and automated analysis, reducing the effects of operator dependency and difficulty with engaging children in staying stationery for sufficient time to obtain accurate results. PAT is another plethysmographic method, which measures post-occlusive volume changes at the fingertip after an arterial occlusion of the upper arm of 5 min, through a thimble-shaped finger cap that applies pressure at the distal phalanx of the index fingers.[15] A close relationship between RHI and coronary dysfunction is described in adults, with reduced RHI values (typically <1.67) being used to define endothelial dysfunction in CVD and cerebrovascular disease.[15] RHI measurements have been found to be feasible and reproducible in both adolescents and school-aged children. There is increasing interest in this technique in children and to date, it has been described in children with acute lymphoblastic leukemia, obesity, juvenile dermatomyositis, and type 1 diabetes, although reference ranges have not yet been reported, and as such, it remains a research tool only. In addition, due to the disposable fingertip probes currently required for this technique, it is substantially more expensive than other non-invasive measures of endothelial function.

Assessment of Early Atherosclerosis and Vascular Remodeling

The pathological basis for CVD is arterial damage in the form of thickening and stiffness of the arteries. Atherosclerosis causes characteristic focal lesions in the intima of large and medium-sized arteries and can be identified through measurement of intima–media thickness (IMT).[16] In adults, carotid IMT (CIMT) is measured in the common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA) as standard. The carotid bulb and ICA are difficult to visualize in young children, however, so common practice is to measure only the CCA until late adolescence, albeit more advanced plaque formation usually occurs in the other 2 sites.[13,16]

IMT is closely related to BP, therefore in the general pediatric population correlates with age-related rises in BP, as well as height and body mass index (BMI).[17] IMT increases with age by approximately 0.003–0.004 mm per year in adolescence and 0.012–0.017 mm per year in adulthood (mean CIMT).[18] The morphological basis of IMT thickening is vascular smooth muscle cell hypertrophy and thickening of the extracellular matrix. In adults, CIMT varies with sex and ethnicity but these differences have not been identified in children as yet.[13]

In adults, increased CIMT is closely correlated with cardiovascular risk.[19-21] In children and adolescents, CIMT is increased in primary hypertension, end-stage renal disease, coarctation of the aorta, poorly controlled type 1 diabetes, and obesity. Fatty atherosclerotic streaks have been seen in children as young as 1 year.[22] Approximately 40% of children have some evidence of lipid deposition by the age of 16 years[23] and longitudinal studies have demonstrated that increased CIMT in childhood is likely to persist into adulthood.[13] Reference ranges for CIMT in children are available.[24]

Aortic IMT

Due to the anatomy of young children, CIMT measurements can be technically challenging. Therefore, when autopsy studies reported that initial atherosclerotic lesions are seen in the abdominal aorta rather than the carotid artery,[25] interest in aortic IMT (AIMT) developed, with early studies demonstrating this to be a feasible technique in children, correlating well with CIMT.[13] AIMT can be measured in fetuses and infants, enabling investigation of vascular remodeling from early in development. IMT increases can be observed in the aortas of human fetuses in response to the physiological rise in BP as gestation increases.[26] In addition, growth-restricted fetuses have been shown to have evidence of intimal–medial thickening detected in the abdominal aorta, identified on ultrasound as well as histological assessment of elastin structure, macrophage infiltration, and endothelial cell activation compared to non-growth-restricted fetuses.[27] The extent of fatty streaks in the abdominal aorta seems to correlate with the coronary arteries, suggesting that aortic atherosclerosis can be used as a proxy for coronary atherosclerosis.[28] Of note, although AIMT and CIMT are well correlated into adulthood, differences in AIMT were identified in younger children than CIMT, suggesting that it may be a more sensitive technique to identify vascular remodeling in younger populations.[29]

On a practical level, AIMT remains a research tool, with no available reference ranges. Detailed protocols have been published, however,[18] and it is an accepted and useful measure of early subclinical atherosclerosis, given that it is well tolerated,

with measurements only minimally affected by infant or environmental factors.[30]

Assessment of Arterial Stiffness

Arterial stiffness depends in part on smooth muscle tone. The shape of the arterial pressure waveform can, therefore, provide an objective assessment of arterial stiffness through pulse wave analysis.[31] Using an oscillometric device, measurements of pulse pressure (PP), central augmented pressure (AP), and augmentation index (AIx) are generated automatically. The central AP is the difference between the maximum systolic peak on the aortic pulse wave and the time to the reflected wave, as shown in Figure 1. The AIx is the AP/PP. The AIx is usually corrected to a heart rate of 75 as per previous studies (AIx 75).[13]

Pulse wave velocity (PWV) is regarded as a simple, robust, and reproducible way to measure arterial stiffness, with stiffer blood vessels resulting in a faster travel time and resultant higher PWV. It measures the speed of the pressure pulse, generated by ventricular ejection according to the geometric and elastic properties of the arterial wall, and is defined by the Moens–Korteweg equation, where E is Young's modulus of the arterial wall; h is wall thickness; p is blood density; and R is the arterial radius at the end of diastole: [13]

$$PWV = \sqrt{(Eh / 2pR)}$$

Carotid-femoral PWV is considered to be the gold standard assessment of arterial stiffness[32] and has been validated in children using applanation tonometry. Reference ranges are available, according to the age and height of the young person in different populations.[33,34] It is, however, subject to variation according to the accuracy of carotid-femoral distance measurements and differences in pressure application.

Studies have demonstrated that hypertension in childhood leads to increased PWV in adulthood.[35] Increased PWV has been reported in children with hypertension, diabetes, congenital heart disease, and obesity and may also adversely affect cognition in both adults and children.[35] Major predictors for PWV in childhood include sex, height, weight, BMI, diastolic BP, and heart rate demonstrating a need to consider ways to improve the modifiable risk factors such as BMI, BP, and HR early in life.[36]

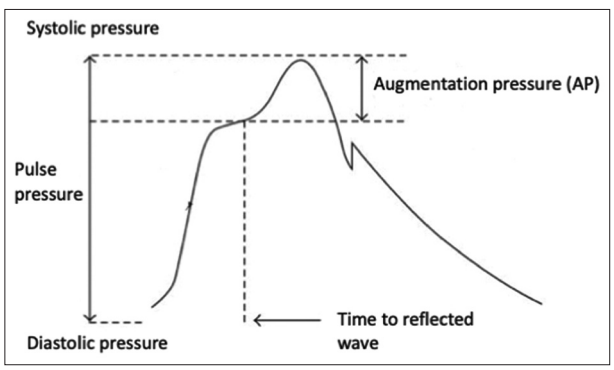

Figure 1: Pulse wave form as measured by pulse wave velocity

Cardiac Magnetic Resonance Imaging (MRI)

Cardiac MRI offers promise as an integrated approach to the assessment of both vascular and cardiac functions. Systemic vascular resistance, arterial stiffness, aortic flow, left ventricular mass and volumes, cardiac timings, and myocardial velocities can all be measured in a single sitting. Studies to date have examined MRI parameters in children with both renovascular hypertension and essential hypertension, and identified differences in the physiology between the two groups.[37] Cardiac MRI is also used routinely in clinical practice for girls with Turner syndrome and associated hypertension, to guide management.[38] However, it is an expensive procedure and requires access to state-of-the art MRI facilities, as well as expertise in analyzing and reporting the scans. In addition, MRI scans usually require general anesthetic in children between the ages of 6 months and 8 years, due to difficulty with image quality with any motion. As such, its utility in younger children is limited.

Circulating Cardiovascular Biomarkers

The identification of circulating cardiovascular biomarkers which can be identified non-invasively, through urine or saliva, will be of significant benefit in the pediatric setting for the assessment of vascular function. Hypertension is associated with endothelial dysfunction, inflammation, and oxidative stress and biomarkers such as endothelin-1, interleukin-6, C-reactive protein, and 8-hydroxy-deguanosine have all been measured successfully in the urine of children, with evidence of increased levels in children with hypertension and obesity.[39] In addition, miRNAs are short, non-coding RNAs, which act as post-transcriptional regulators by modifying target gene expression and may reflect molecular changes, which can be measured readily in urine and correlate well with other markers of cardiometabolic health in children.[40] Urinary metabolomics, therefore, offer the opportunity to identify relevant biomarkers on a large scale, with the benefit of urine samples being much easier and acceptable to obtain from pediatric patients compared to serum. Future studies should aim to determine whether these can be used in the clinical setting to guide risk stratification of children with hypertension.

Future Directions

Each of the tools considered in this review remains primarily for research purposes, with insufficient evidence to date to justify their routine clinical use. There is a need to focus future work on pooling international study data to confirm appropriate reference ranges for these techniques and to consider whether any of these methods could be used as a gold standard to identify subclinical vascular risk in at-risk patient groups, such as those with childhood-onset hypertension. The overall aim should be to reduce this risk in children, so as to prevent some of the significant CVD seen in adulthood. Longitudinal studies assessing the change in vascular parameters with age are also required.

Conclusions

Non-invasive vascular phenotyping is an area of increasing interest in pediatrics. Atherosclerosis has a long subclinical course, from the fetal period, where initial functional and structural arterial changes can be identified through to adulthood, where advanced atherosclerotic lesions result in cardiovascular morbidity and mortality. There has been some debate regarding the responsibility of pediatricians to prevent adult disease, but differences in endothelial function and arterial stiffness can be measured accurately in young children. As such, the methods described in this review should be considered in studies assessing vascular risk in the pediatric setting. Each technique has its own challenges within the pediatric population and may need to be adapted to ensure tolerability for the age and stage of the child being assessed.

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Review Article

Contemporary Imaging in Chronic Pulmonary Thromboembolic Disease

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Abstract

Pulmonary hypertension is the end result of rarefaction of functioning blood vessels within the lung. This can be caused by a number of pathologies, but in the case of chronic thromboembolic pulmonary hypertension, occlusion of the blood vessel is usually initiated by acute thrombus, which, over time changes to chronic fibrous plaque which has a limited response to medical therapy. The most effective treatment options involve mechanical solutions in the form of surgery or balloon pulmonary angioplasty. Treatments are most effective when introduced early in the disease process. In order that patients may benefit from these treatments, an effective diagnostic pathway is essential. Echocardiogram remains the most effective screening tool in the diagnosis of pulmonary hypertension. Right heart catheterization is the gold standard tool for the assessment of pulmonary hemodynamics. Cardiac magnetic resonance (CMR) imaging is an evolving tool that can be used to evaluate the right ventricular function. It is the gold standard in evaluating right ventricular function and has lower interobserver variability than echocardiography. Despite being a more expensive and less available tool, CMR has the ability to accurately assess blood flow within the pulmonary vasculature, which can enable early detection of disease and response to therapy. Cardiac magnetic resonance imaging is now recognized as an essential component of the imaging armamentarium to assess pulmonary vascular disease.

Key words: Conventional medical therapy, pulmonary hypertension, right ventricle

Introduction

Pulmonary hypertension refers to a constellation of conditions defined by an elevated pulmonary arterial pressure. It is usually a progressive disease, associated with a poor prognosis at 5 years and a high associated symptom burden.[1] The etiologies of pulmonary hypertension have been divided into 5 groups as defined by the 2018 National Institute for Health and Care Excellence (NICE) classification. The disorder may be idiopathic or complicate a number of medical conditions, including connective tissue disease and the majority of cardiovascular and respiratory diseases. It may also be the result of occlusive pulmonary emboli, in the form of chronic thromboembolic pulmonary hypertension (CTEPH), classed as Group IV in the 2018 NICE classification of pulmonary hypertension.[2] This is defined by a mean pulmonary arterial pressure obtained at right heart catheterization (RHC) above 25 mmHg and a pulmonary capillary wedge pressure of <15 mmg along with at least one persistent perfusion defect seen on imaging (V/Q scanning or pulmonary angiography) after 3 months of anticoagulation. This often occurs as a complication following acute pulmonary embolus and is said to occur in 2–4% of cases.[3]

There are a number of treatment options which are available for patients with CTEPH. This includes surgical clearance (pulmonary thromboendarterectomy), percutaneous procedures (balloon pulmonary angioplasty [BPA]), and medical therapy. The treatment offered depends on the anatomical location of the thromboembolic disease and whether it is proximal pulmonary artery (PA) (surgically operable) or distal disease (BPA and medical therapies available).

In order for patients to benefit from these well-established treatments, an appropriate diagnosis is required.

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Echocardiography [Figure 1] remains the main screening investigation for pulmonary hypertension, mainly because it is inexpensive, widely available, and convenient to perform. The presence of a tricuspid regurgitation jet is used to estimate right ventricular systolic pressure but can over or underestimate pressure and is not present in up to 30% of patients.[4] The gold standard diagnostic investigation remains RHC,[5] in conjunction with a number of imaging modalities, such as computer tomography pulmonary angiography (CTPA), cardiac magnetic resonance (CMR) imaging and magnetic resonance pulmonary angiography (MRPA). RHC is an invasive investigation, which carries some associated risks and discomfort for patients but allows direct measurement of the pressure within the main PA, in addition to pulmonary vascular resistance and cardiac output. Ideally there would be an accurate non-invasive investigation, which would reliably provide the diagnosis without exposing patients to such risk.

The use of CMR has been increasing in pulmonary arterial hypertension in recent years due to increased availability, improved acquisition times and ease of use.[6] CMR has several advantages over echocardiography, including improved assessment of left and right ventricular mass, volume and ejection fraction, and is the gold standard for structural and functional assessment of the right ventricle (RV).[7]

Pathophysiology of Chronic Thromboembolic Disease (CTED)

Present evidence suggests that the development of CTEPH follows an acute thromboembolic event and in the majority of cases of CTEPH a history of acute VTE can be elicited.[8] The presence of acute thrombus induces an inflammatory response within the vessel lumen which organizes the thrombus, before spontaneously lysing it using endogenous fibrinolytic system. Over time, there is usually complete resolution of the thrombus,

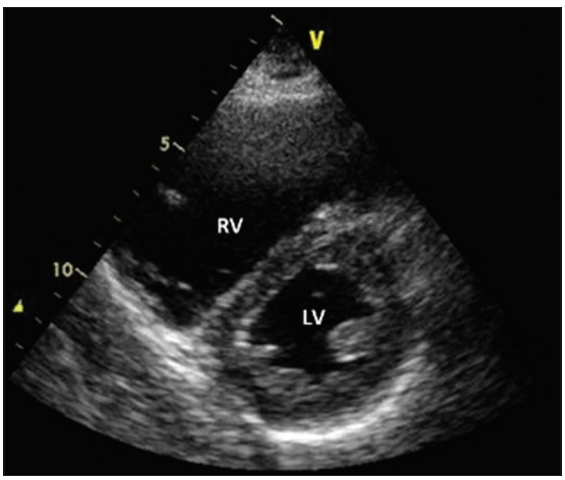

Figure 1: Echocardiography image of parasternal short axis demonstrating a dilated right ventricle and compression of the interventricular septum toward the left ventricle

restoring normal blood flow. However, in some cases, the clot is not completely lysed and instead, the thrombus material changes to a fibrous plaque, containing macrophages and lymphocytes,[9,10] leading to permanent pulmonary vascular occlusion. This vascular occlusion leads to increased pulmonary vascular resistance and increased pulmonary arterial pressure leading to the condition of CTEPH. CTEPH can also cause remodeling of the small distal pulmonary arterioles, in addition to chronic stenosis of larger more central vessels. Clinically, it leads to impaired exercise capacity and can proceed to right heart failure and premature death.[11] The management of CTEPH is well validated:[12] there is a potential cure for CTEPH in the form of surgery. Pulmonary endarterectomy has been shown to cure, or at least substantially reduce the pressure within the pulmonary vasculature and RV in those with central disease.[12] For those with more distal disease, or those with persisting pulmonary vascular obstruction following surgery, there is an option for BPA, which has been shown to improve pulmonary vascular hemodynamics and functional state.[13]

CTED is a term currently employed for those patients in whom following acute pulmonary embolus there remains chronic vascular obstruction and exercise intolerance, without evidence of pulmonary hypertension at rest. It has been shown that these patients can have a functional limitation when tested with cardiopulmonary exercise testing[11,14,15] and rarely successful treatment with PEA has been performed.[16] It should be recognized that CTED represents a spectrum of conditions characterized by as few as a single residual obstruction versus, on the other extreme, enough disease to lead to elevated pulmonary vascular resistance and the development of pulmonary hypertension. Differentiating between these conditions in patients is important since it dictates the individuals' treatment strategies.

Magnetic resonance imaging (MRI) is now central to the investigation of patients with thrombotic pulmonary vascular disease. This manuscript will cover some of the advances in imaging techniques that help in the evaluation of patients with thrombotic pulmonary vascular disease.

Physics of MRI

MRI was discovered by Paul Lauterbur and Peter Mansfield in the 1940s. It uses the natural magnetic properties of the body to produce images. The human body is composed mainly of water, which is principally made from the hydrogen ion (H_2O). Under normal circumstances, H_2O have two poles, north and south, and spin on their axes, which are randomly aligned. When exposed to a magnetic field, such as in an MRI scanner, the protons axes then align. The uniform position of the ions then creates a magnetic vector along the axis of the MRI scanner. The vector is created by an electromagnetic wave and represents the instantaneous magnetic field strength and direction at any point in which the wave is propagating.[17] The magnet in the MRI scanner can act upon the positively charged H_2O, with radiofrequency pulses,

causing the ions to spin. The direction of the pulses can change the direction of the spins, allowing the build-up of layers of detail. The frequency of atomic nuclei rotation is dependent on the strength of the magnetic field to which they are exposed.[17] This can be changed using a series of electric coils and can be done for different parts of the body with different sections of the body resonating as different frequencies are applied.

As the radiofrequency is turned off, the vector returns to its resting state with proton axes randomly aligned, this in itself causes a radio wave to be emitted. This is the signal used to create the MRI images. There are coils used around the region of the body that is being imaged to optimize the detection of that emitted signal. These signals are plotted and with multiple signals, images are developed.[18] Multiple radio wave pulses can be used to highlight particular tissues or abnormalities. Tissue differentiation is seen as different tissues, such as water and fat, have different relaxation times once the radio waves are turned off. This relaxation time can be measured. T1 relaxation is the time taken for the vector to return to its normal resting state and T2 is the time taken for the axial spin to return to baseline.[19]

Clinical Role of CMR Imaging

Despite echocardiography being a valuable first line investigation, there are some weaknesses and a more comprehensive evaluation is merited when there is diagnostic uncertainty. CMR is the gold standard imaging modality for assessing the right ventricular structure such as size and function. As pulmonary hypertension progresses and the PA is unable to accommodate the full cardiac output, the RV begins to maladapt to the pressure changes with progressive dilatation. CMR can characterize these morphological and functional changes over time. As pressure increases, the interventricular septum shifts towards the left ventricle (LV) during late systole and, in severe cases, the septum bows towards the LV as RV and PA pressures exceed systemic pressure.[20] There are a number of specific imaging techniques which can be used in MRI that can characterize the RV with increasing accuracy and utility.

Cine MRI images are obtained by repeatedly imaging an area of interest over a period of time. In CMR, this is achieved by acquisition of images at multiple time points during the cardiac cycle, synchronized with the electrocardiogram. These images can be arranged such that the blood flow within the heart can be seen during a cardiac cycle. From this, both RV and LV end-diastolic and end-systolic volumes can be measured and hence ejection fraction and stroke volume can then be calculated[7] along with accurate determination of ventricular dimensions and muscle masses [Figure 2]. In pulmonary hypertension, these are both seen to increase. Factors such including RV: LV ratio >1 and RV wall thickness >4 mm are suggestive of the presence of PH.[21] A further advantage of the high-level tissue characterization and multi-planar images that can be obtained from CMR is the ability to assess for and quantify intracardiac shunting. In addition, a hot topic in contemporary pulmonary vascular research is the determination of risk for the individual patient using risk scores. CMR is proving to be increasingly useful in risk stratifying the likelihood of clinical deterioration. Higher RV volume and reduced RV ejection fraction are predictive of worse outcomes.[22]

Phase contrast imaging [Figure 3] is an MRI technique that can be used to visualize moving fluid. Proton spins moving in the same direction as the magnetic field gradient develop a phase shift that is proportional to the spin velocities. In a pulse sequence, bipolar gradients are used to encode spin velocities. Moving spins in fluid will experience a different magnitude of the second gradients compared to the first because of the spatial position. This information can be used to determine the velocity of the fluid. This technique can be applied to the PA to assess cardiac output.[23] Blood velocity can be calculated, which has been shown to strongly correlate with PA pressures and pulmonary vascular resistance.

However, despite the many strengths of cardiac MRI in the evaluation of the RV, there is as yet no reliable way of using it to measure the PA pressure. Therefore, the "gold standard" investigation for pulmonary arterial pressure remains RHC. This is the most accurate way of measuring pressure and can estimate RV function by the assessment of the right atrial pressure and right ventricular end diastolic pressure. These represent a measure of preload, PA pressure, pulmonary vascular resistance and stroke volume, to measure contractility.

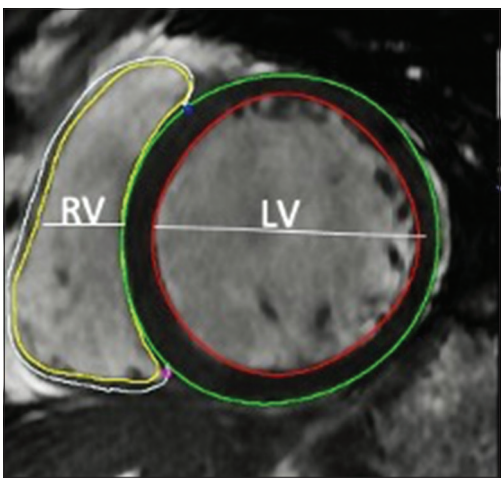

Figure 2: Short axis CMR images of the right ventricle and left ventricle in a healthy individual

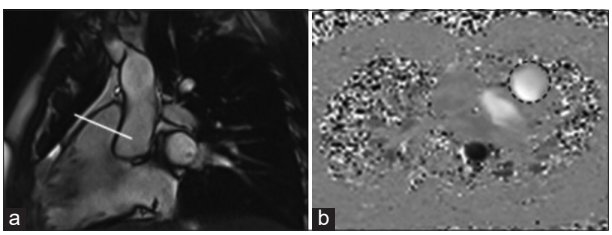

Figure 3: Steady State Free Precession cine sequence used to identify the location of the pulmonary valve (a) and phase imaging (b) of the blood flow across the valve

Flow Mapping

Phase contrast measurements of blood flow through the great vessels can be used to calculate the cardiac output, shunt fractions and regurgitant flow over the valves. It is a phase-sensitive method that can calculate velocity of blood flow from the detected signals in vessel lumen. Flow is measured by obtaining thin, cross-sectional images of the vessels that are sensitized to through-plane velocity during a single cardiac cycle, usually 3 mm or less. An oblique slice is obtained to intersect the vessel [Figure 3]. The lumen is covered by a set of pixels by drawing a region of interest (ROI) around the blood pool. If a ROI is drawn around each slice in the cardiac cycle, the cardiac output can be calculated. The flow through each pixel is calculated and multiplied by the number of pixels covering the area of the vessel.[24] This gives an accurate estimate of cardiac output and can be therefore used to determine the functionality of the RV.

Flow velocity can also be measured. This is done by applying a flow-encoding gradient along the direction of the imaging pulse sequence after the excitation. This generates a flow curve and can be used to determine if there is significant valve regurgitation and allows quantification of intracardiac shunts. In addition, vessel compliance can be evaluated using this technique. Measuring the change in vessel area in cross section during the cardiac cycle can be used to calculate the distensibility, which is reduced when there is high pressure in the vessel.[24] These measures again have been used to evaluate the function of the RV and has prognostic use with regards to pulmonary hypertension.

Although phase contrast measurements are the most accurate way of measuring the cardiac outputs on CMR, there are some issues that may introduce inaccuracies to the measurements. Regions of interest around the vessel lumen need to be accurately drawn, otherwise signals will only partially be from flowing magnetization and tissue will be used as part of the flow calculation. This can lead to underestimation of the blood flow. Changes in flow velocity using a 2-dimensional acquisition can lead to ghosting artifacts. This can occur during respiration. As such, there can be replication of blood vessels along the direction of the phase-encoded signal. Using signal averaging during non-breath-hold can reduce the risk of these flow variables.[25]

Tissue Tracking

Regional wall abnormalities can impact upon ventricular function and influence clinical outcomes. Regional ventricular function can be measured using both CMR and echocardiography. However, the latter can be complicated by poor image quality using subcostal views. CMR provides higher quality images and is able to provide biventricular imaging. This imaging can be done using a number of techniques, including myocardial tagging, phase contrast velocity imaging, displacement encoding, strain encoding and feature tracking (CMR-FT). The exact methodology employed is dependent on the software package used for analysis.[26]

CMR-FT is a useful technique because, unlike the other techniques, it can be applied to the short axis stack acquired during standard CMR protocols, whereas other techniques tend to require specific tissue tracking image acquisition in addition to the standard protocol. Tracking methods identify a small window on one image and search for a comparable image on the subsequent frame. The displacement detected on serial images represents the local tissue displacement. In cardiac tissue tracking, the window is required to be at least 8 × 8 pixels. Much larger images leads to degradation of the quality and any smaller may mean that the tissue displacement is beyond the limits of some of the images, and therefore does not detect the tissue movement. The resolution of the images is important. If this is too low, the larger displacement leads to larger search areas and images become less comparable. If too high, frame to frame displacements are too small, such that the pixels are difficult to identify. The sequences detect movement inward and outward, during systole and diastole. It is easier to track tissues moving apart, and, as such, the sequence begins near end-systole and tracks the tissue during diastole. Initially, tracking was designed for 2-dimensional images, but has now been developed for 3-dimensional volumetric regions, such that radial, longitudinal and circumferential tracking of the RV wall can be performed.[26]

Dimensional Flow

This is an exciting novel measurement technique which is in its infancy in its application to pulmonary vascular medicine. Blood flow in the cardiac chambers and great blood vessels is multidimensional and multidirectional. Whilst CMR can measure cardiac chamber volumes, and therefore calculate cardiac output using the difference between volumes measured at end diastole and end-systole, there are some inaccuracies in using this method, with the inclusion of papillary muscles and trabeculations, leading to interobserver variability. A more accurate and comprehensive way of measuring intracardiac flow and cardiac output is using velocity encoded phase contrast imaging and is now recognized to be the gold standard for these measurements.[27] Using these methods, a shunt fraction can be calculated in the presence of intracardiac abnormalities. Furthermore, it allows the estimation of peak blood flow velocity and the effects of turbulent blood flow on the vessel wall. The measurement encodes flow in all three special directions for the duration of the cardiac cycle. This had previously been performed using 2D cine CMR but 4D flow has been shown to have improved reproducibility compared with 2D.[28]

4D CMR includes phase-contrast MR with blood flow encoded in all spatial dimensions in addition to the dimension of time. It allows for the visualization of the multidirectional blood flow throughout the pulmonary circulation [Figure 4]. It has been shown that the 4D flow appearances are altered in those with pulmonary hypertension and it has been used to assess for hemodynamic changes.[29] Abnormal flow patterns,

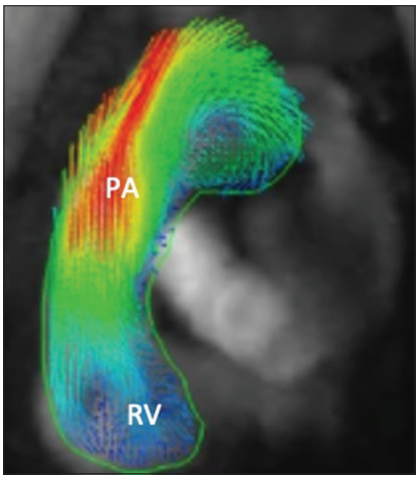

Figure 4: Flow mapping of blood travelling from right ventricle to pulmonary artery. Color mapping represents the flow velocity ranging from highest in red (55 cm/s) to the slowest in blue (0 cm/s)

mainly in the form of vortex formation, are associated with raised intrapulmonary pressures. The persistence time of the vortex has been demonstrated to correlate with mean PA pressure, making it an attractive tool not only in the diagnosis of pulmonary hypertension, but in monitoring response to treatment.

Wall sheer stress can also be evaluated using 4D flow. This is the frictional force along the inner wall of the artery, caused by viscous drag. At a pathophysiological level, a reduction in wall sheer stress in the systemic circulation is thought to lead to endothelial cell dysfunction because higher wall sheer stress increases endothelial nitric oxide release.[30] In pulmonary hypertension, wall sheer stress has been demonstrated to be reduced. As such, it can be said that reduction in sheer stress does lead to reduced endothelial cell health, possibly leading to further vascular remodeling. Wall sheer stress assessment remains a technique used only in research studies, but there is an increasing body of evidence to support its use and it may become a clinical parameter in due course.[30] Pulmonary vascular resistance and clinical indices are currently the main methods by which response to therapy is measured. However, having another objective measurement would lead to a more holistic evaluation of an individual's response to therapy.

MRPA

MRPA has the benefit of being able to identify the presence of acute or chronic pulmonary embolus, without using ionizing radiation. Performed using gadolinium contrast, MRPA has sensitivity of 78% and specificity of 99%[31] for the presence of acute pulmonary thromboembolism, which makes it an attractive option for routine diagnostic use. However, acquiring technically optimal images is more challenging than other modalities used to image the pulmonary vasculature. Longer breath-hold times and acquisition times limits the routine use of MRPA. In the PIOPED III study, up to 25% of studies were shown to be technically inadequate[31] due to poor arterial opacification, breathing artefact and wrap-around artefact. As such, although pulmonary embolus can be diagnosed using MRPA, the absence of it does not exclude its presence to the same degree as CTPA.

Given that widespread use of MRPA appears not to be possible, it is important to ensure the correct population is chosen for its use. Examples for the use of MRPA include: (1) those with a low to intermediate probability for the presence of pulmonary thromboembolism; (2) patients who are intolerant of iodine-based contrast agents, and; (3) females of childbearing age who are at higher risk of the effects of ionizing radiation. Using MRPA in those who are claustrophobic, who are unable to hold their breath and have a high probability of venous thromboembolism the diagnostic yield is likely to be low and require a second imaging modality.[32]

In current UK practice, MRPA is not a part of the routine diagnostic pathway for the diagnosis of acute pulmonary embolism. Its role lies mainly in the multi-modality evaluation of those with CTED and pulmonary hypertension and assessing the potential to benefit from surgical intervention. Defects seen in CTEPH on MRPA are similar to that seen on CTPA, such as intraluminal bands, narrowing or obstructed vessels, central thrombus and bronchial arterial hypertrophy. MRPA is used as a "road map" for surgeons performing pulmonary endarterectomy.[33] It has the advantage over conventional angiography of being non-invasive, as well as allowing evaluation of the RV in the same investigation. Whilst this has not replaced RHC, it has the ability to evaluate patients in response to therapy, both medical and surgical.[34]

Whilst MRPA has limitations for routine use for the diagnosis of acute and chronic pulmonary thromboembolism, this is an evolving technology. With its lack of exposure to ionizing radiation and strong sensitivity and specificity, there are strengths that make it an attractive option for common usage if the evolution of technology can reduce costs improve image acquisition.

Conclusions

CTED is a complex disease which represents a significant burden for patients following acute VTE. The recognition of this disease is important as it can be associated with significant morbidity and mortality for patients and if detected early enough there are potential curative options available for management. Imaging plays a critical role in this process in determining the diagnosis, risk stratification and management strategies. Cardiac MRI is now recognized as an essential component of the imaging armamentarium to assess pulmonary vascular disease. There are a number of emerging MRI-facilitated techniques for determining key functional and structural parameters of the RV which can guide the clinician in making the best decisions for the care of their patients. This includes MR-pulmonary angiography which can identify key anatomical occlusions in the pulmonary vascular tree.

It is clear that over the next 5 years that cardiac MRI will become central to the diagnosis and management of patients with CTED.

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Review Article

Pre-eclampsia and Long-Term Cardiovascular Disease Consequences (Review)

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Abstract

Pre-eclampsia (PE) is a hypertensive disorder of pregnancy that leads to multisystem maternal endothelial dysfunction. PE affects 3–5% of all pregnancies and is responsible for over 70,000 maternal deaths and 500,000 fetal deaths worldwide every year. The incidence of pre-eclampsia continues to increase worldwide year on year, while due to increased recognition and early intervention, the rates of maternal death from PE are falling.[1] Large strides have also been made in the understanding of pre-eclampsia in recent years through pre-clinical and clinical research. However, our understanding of the pathophysiology and the heterogeneity of PE remains incomplete. PE is now recognized as a disorder beyond pregnancy with long-term consequences with an increased risk of future cardiovascular disease which is now well documented in this cohort. As the incidence of PE increases, this will place an ever-growing burden on health-care systems worldwide. PE must, therefore, be recognized as requiring continued care outside of pregnancy and structures and systems must be put in place worldwide to enable this.

Key words: Cardiovascular disease, hypertension, pre-eclampsia, pregnancy, risk factors

Introduction

Pre-eclampsia (PE) is a leading cause of maternal and neonatal morbidity and mortality worldwide affecting 3–5% of all pregnancies.[1-3] The classification of PE from the International Society for the Study of Hypertension in Pregnancy recognizes PE as a multisystem disorder.[4] PE is defined as systolic blood pressure at ≥140 mmHg and/or diastolic blood pressure at ≥90 mmHg, on at least two occasions measured 4 h apart, in previously normotensive women and is accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation: 1. Proteinuria; 2. Evidence of other maternal organ dysfunction, including acute kidney injury; liver involvement; neurological complications; or hematological complications; or 3. Uteroplacental dysfunction.[4]

Pathogenesis

Although the severe seizures of eclampsia have been described as early as 400 BC by Hippocrates and a wealth of research has been carried out, the etiology and full pathogenesis of PE remain unknown.[5] PE was initially thought of purely as a disease of placentation characterized histologically by abnormal shallow trophoblastic invasion of myometrial spiral arteries, leading to uteroplacental hypoperfusion.[6] Advances in science have elucidated the important role of oxidative stress, inflammation, secondary endothelial dysfunction, and the balance of angiogenic and antiangiogenic factors in the pathophysiology of PE.[7,8] These discoveries have led to the identification of many important biomarkers with a role in PE being identified such as placental growth factor, soluble fms-like tyrosine kinase-1, placental protein 13, a disintegrin and metalloprotease 12, and pappalysin.[9] However, despite vast amounts of in depth study in this area, we still do not fully understand PE pathogenesis.

Early (<34 weeks gestation) and late (>34 weeks gestation) onset PE are increasingly acknowledged as potentially having different pathophysiological processes, leading to a common presentation.[7] Early-onset pre-eclampsia is associated with abnormal early placentation, subsequent placental hypoperfusion, and fetal growth restriction.[10,11] Late PE placental studies have

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not conclusively shown these findings and it is not as strongly associated with fetal growth restriction.[7,10] It has, therefore, been proposed that in late PE, placental dysfunction may be due to placental failure to deal with the increase in trophoblast growth in later gestation, resulting in syncytiotrophoblast stress rather than abnormal early placentation.[10]

Previously, PE was seen as purely a disease of the placenta and delivery of the placenta to be curative. It is now well established that PE can occur days to weeks postpartum.[12] In a single-center study of a tertiary center in Pittsburgh over 4.5 years, 0.5% of delivered women returned with new-onset postpartum PE.[13] This postpartum PE may represent another subtype of PE in which the placenta does not contribute a central pathogenic role or may indicate that the placenta is not the primordial candidate in PE pathogenesis.[7] Much is still to be learned about postpartum PE and how this subtype fits into the PE pathogenesis narrative.

The potential differing etiology of PE and heterogeneity of the subtypes within the condition adds to the complexity of the challenge to understand PE pathogenesis. However, analysis and detailed study of PE subtypes may also provide opportunities to discover new insights.

Cardiovascular disease (CVD) and PE share common risk factors such as obesity, diabetes, chronic kidney disease, and hypertension.[14,15] Along with the knowledge that a history of PE increases risk of future CVD, this has led to the theory that women with PE may be unmasking underlying subclinical CVD.[16-18] The theory that pregnancy is a stress test for the cardiovascular system, in which PE demonstrates suboptimal cardiovascular adaptation to pregnancy, is yet to be fully proven.[14,16,19] If proven, how different subsets of PE would interact with this theory, remains to be elucidated. However, whether pre-existing or causative it is now well established is that a history of PE increases risk of CVD in later life.

CVD Risk

The National Institute for Health and Care Excellence guidance advises a history of PE increases the risk of major adverse cardiovascular event approximately 1.5–3 times, stroke approximately 2–3 times, cardiovascular mortality approximately 2 times, and hypertension approximately 2–5 times, when compared to the background risk in women who had normotensive pregnancies.[20]

These findings have been based on a wealth of data and have been demonstrated worldwide in large cohorts. A study of a Norwegian cohort with 626,272 births showed that women who had pre-eclampsia had a 1.2-fold higher long-term risk of CVD mortality (confidence interval [CI] 1.02–1.37) than those without pre-eclampsia.[21] In a recent large systematic review of 83 studies containing 28,993,438 patients, a history of PE has been shown to be associated with approximately 75% (95% ICI, 1.46–2.06) higher risk of CVD-related mortality compared to woman with no history of pre-eclampsia.[22]

A study of the Child Health and Development Studies Pregnancy Cohort in San Francisco investigating pregnancy complications subsequent CVD risk followed over 14,000 women for over 50 years follow-up.[23] PE was the pregnancy complication associated with the highest risk of CVD mortality in this cohort. Early pre-eclampsia (heart rate [HR] 3.6 CI 1.04–12.19) was associated with a higher risk of CVD than late pre-eclampsia (HR 2.0 CI 1.18–3.46).[23] A large meta-analysis of 38 studies containing over 3,488,000 women, of whom 198,252 had PE supported this, showing women with a history of early PE had a markedly increased risk of CVD compared to those with late PE (risk ratio [RR] 7.71, 95% CI 4.40–13.52 vs. RR 2.16, 95% CI 1.86–2.52).[24] This indicates that specific subsets of women with PE are in even higher risk categories for future CVD.

The Cardiovascular Health After Maternal Placental Syndromes (CHAMPS) population-based cohort study looked at 1.03 million women in Ontario Canada.[25] The pre-eclampsia group containing 36,982 women showed an increased risk of premature CVD (HR 2.1 CI 1.8–2.4) with an average age of just 38 years at their first cardiovascular event.[25] A meta-analysis of >258,000 women with pre-eclampsia showed that the pre-eclampsia was independently associated with a 4-fold increased risk of future heart failure (RR, 4.19; 95% confidence interval [CI], 2.09–8.38), and a 2-fold increase in coronary heart disease (RR, 2.50; 95% CI, 1.43–4.37), CVD death (RR, 2.21; 95% CI, 1.83–2.66), and stroke (RR, 1.81; 95% CI, 1.29–2.55).[16] The risk for developing stroke, heart failure, and ischemic heart disease in this analysis supported the CHAMPS finding of early onset with highest risk at 1–10 years postpartum.[16]

Postpartum Risk Reduction

This early onset of CVD, along with the burden of disease risk associated with pre-eclampsia, provides us with a window of opportunity postpartum in which intensification of primary preventative measures and future monitoring may reduce adverse cardiovascular outcomes.

This clearly identified at-risk group, however, does not have a uniform follow-up guideline in place currently. The American Heart Association and National Institute for Health and Care Excellence guidelines advise to perform a first cardiovascular follow-up 6–8 weeks postpartum.[15,26] The American College of Obstetricians and Gynaecologists, European Society of Cardiology/European Society of Hypertension, and American Stroke Association guidelines advise cardiovascular follow-up 6–12 months postpartum.[27-30] The early onset of CVD in this cohort indicates that screening and intervention introduced in the early postpartum period may be of benefit.

Follow-up guidelines after initial follow-up also vary, the periods range from annually to every 5 years by the primary care team. The lack of uniform follow-up along with clear guidance on the exact screening needed in the subsequent postpartum years may lead to valuable opportunities for initiation of preventive

measures being missed. This is something that must be tackled by guidance bodies internationally.

Raising awareness among health professionals of the increased future risk associated with PE is paramount but this awareness must be conveyed to those women in the population at risk. Much of cardiovascular prevention relies on lifestyle modification, working within a multidisciplinary team and empowering this cohort to engage with their health outside of the critical period of pregnancy may be the most valuable tool to reduce risk. Due to the early onset of cardiovascular risk seen and the short proximity to the postpartum period, women in this cohort are likely to have many competing priorities and their future cardiovascular risk may not be apparent to them or a priority. It is, therefore, necessary we aid in the dissemination of knowledge to this population and provide strategies and tools to help them tackle this.

The provision of uniform guidance on follow-up and cardiovascular screening, along with a dedicated services and structure to reduce the future risk in this cohort, provides an opportunity to improve women's health and acts on the large body of research we have gained about PE's long-term consequences.

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Case Report

Intravitreal Anti Vascular Endothelial Growth Factor-Driven Deterioration in Proteinuria, Renal Function, and Hypertension in the Context of Diabetic Nephropathy: A Case Report (Case Report)

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Abstract

Background: Diabetic retinopathy and nephropathy are microvascular complications of diabetes mellitus that often occur concomitantly. Anti vascular endothelial growth factor (VEGF) therapy is the mainstay of treatment for proliferative diabetic retinopathy and although oral and intravenous anti-VEGF therapies have been linked with adverse renal outcomes and hypertension, such associations with intravitreal anti-VEGF agents are less well established. **Case Description:** A case is presented of worsening hypertension, proteinuria, and renal function of a 62-year-old patient with presumed diabetic nephropathy who was referred to renal services with declining proteinuria and edema after being commenced on intravitreal anti-VEGF. **Discussion:** Intravitreal anti-VEGF agents have a significant amount of systemic absorption and cases of worsening proteinuria, hypertension, and estimated glomerular filtration rate have been previously reported. There is a significant clinical overlap with the natural history of diabetic nephropathy and the epidemiology of this association is poorly understood. It is not clear what modifiable factors exist to minimize the development of this syndrome of worsening proteinuria, hypertension, and renal function. **Conclusion:** A heightened awareness of the potential for intravitreal anti-VEGF agents to lead to worsening proteinuria, hypertension, and renal function is required. Further study is needed to understand the potential modifiable factors to mitigate the adverse effects of these agents that have a key role in treating diabetic retinopathy.

Key words: Diabetes, hypertension, nephropathy, retinopathy, vascular endothelial growth factor

Introduction

Diabetes mellitus is associated with significant macrovascular and microvascular systemic complications, and patients frequently exhibit coexistent vascular disease in multiple territories.[1] Diabetic retinopathy is the most common complication of diabetes mellitus. Hyperglycemia-induced microvascular damage results in retinal ischemia/hypoxia, leading to the upregulation of angiogenesis signaling protein vascular endothelial growth factor (VEGF), and consequent pathological neo-vascularization.[2] The mainstay of therapy in patients with proliferative diabetic retinopathy and macular edema is intravitreal anti-VEGF which targets the inappropriate blood vessel proliferation which threatens sight.[2]

The adverse systemic effects of oral and intravenous anti-VEGF agents have been well established in their widespread use in oncology as anti-neoplastic agents; this includes new or worsening proteinuria, renal dysfunction, and hypertension.[3] The association with intravitreal anti-VEGF agents and these adverse effects is less well established but has been previously described.[4-6] Considering the established clinical association between diabetic retinopathy and nephropathy, and therefore the widespread use of anti-VEGF agents in a population already vulnerable to kidney insults, the exploration of this relationship deserves further consideration.

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Case Report

A 62-year-old female, with a medical history of hypothyroidism, hypertension, and type 2 diabetes mellitus, was referred to renal services due to significant peripheral edema, nephrotic range proteinuria (urinary protein creatinine ratio 373 mg/mmol) with relatively preserved renal function (estimated glomerular filtration rate [eGFR] 92.3 ml/min), and serum albumin (35 g/L). She had been diagnosed with diabetes mellitus 6 months previously after severe non-proliferative retinopathy in both eyes and macular edema of the left eye had been noted during a routine eye examination. The extent of her eye disease suggested her diabetes mellitus had been present for a significant time, and her hemoglobin A1c (HBA1c) was 93 mmol/mol at time of diagnosis. She was hypertensive at 176/87 mmHg. Her medications included levothyroxine, metformin, furosemide, and ramipril.

A glomerulopathy screen confirmed negative/normal antinuclear antibody, antineutrophil cytoplasmic antibodies, anti-phospholipase A2 receptor antibody, rheumatoid factor, complement factors, blood-borne virus serology, and no evidence of elevated immunoglobulin or serum paraprotein. A renal ultrasound revealed right kidney 13 cm, left kidney 12.4 cm with no hydronephrosis nor calculi, and normal cortical thickness and echogenicity bilaterally.

Diabetic nephropathy was felt the most likely underlying reason for her proteinuria and her ramipril was uptitrated, furosemide increased for control of peripheral edema, and amlodipine added for blood pressure control. At this point, her HBA1c had improved to 56 mmol/mol.

On return visits to the renal clinic, her peripheral edema continued to deteriorate. An N-terminal pro-brain natriuretic peptide level was undertaken and found elevated at 1256 pg/ml. She, therefore, underwent echocardiography which revealed an estimated ejection fraction of 60–65% with undilated ventricles, Grade II diastolic dysfunction, mild-moderate left atrial dilatation, and estimated mild pulmonary hypertension (37 mmHg). Her hypertension remained poorly controlled. At this stage, her bisoprolol was uptitrated further, amlodipine stopped and canagliflozin commenced.

Her diuretic requirements improved with the introduction of canagliflozin but her blood pressure remained elevated and doxazosin was added to her antihypertensive regime. Her eGFR showed significant decline over 20 months, but stabilized at an eGFR ~20 ml/min.

Her case notes were re-reviewed given the difficulty controlling her peripheral edema and hypertension. It was noted that 6 months before her referral to renal services, she had been commenced on ranibizumab (Lucentis) injections, a humanized monoclonal antibody to VEGF, by ophthalmology due to the appearances of her ocular examination, which had not appeared on her primary care repeat prescription.

The patient's proteinuria and eGFR are displayed graphically in Figures 1 and 2. She continues to receive anti-VEGF therapy. Over the graphically displayed period, she received nine ranibizumab injections and 17 aflibercept (a soluble decoy receptor that binds to VEGF) injections to her left eye and seven ranibizumab injections and 16 aflibercept injections to her right eye.

Discussion

In this case, the progression of hypertension and peripheral edema coinciding with the initiation of intravitreal VEGF inhibition, led to the suspicion of VEGF blockade exacerbating existing proteinuric chronic kidney disease. The clinical overlap between diabetic nephropathy and adverse renal outcomes from anti-VEGF therapy is considerable and presents a diagnostic challenge given the widespread use of these agents in this patient population.

The use of systemic anti-VEGF agents in oncology settings has been clearly associated with adverse renal outcomes including new or worsening proteinuria, decline in GFR, and irreversible glomerular injury with a variety of pathologies reported on kidney biopsy (focal segmental glomerulosclerosis, minimal change, and membranous).[3] The amount of proteinuria appears linked with the duration of the anti-VEGF therapy.[3] In addition, these agents have been associated with worsening hypertension and thrombotic microangiopathy, and increased cardiovascular-associated mortality.[5]

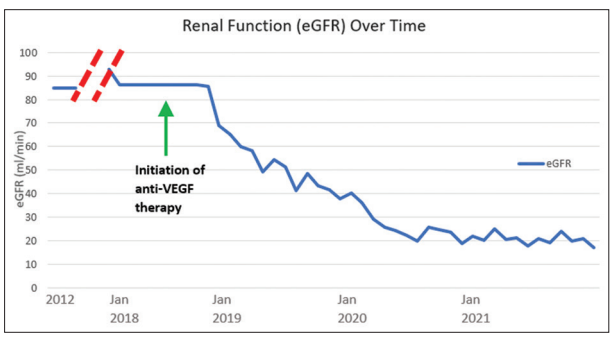

Figure 1: Case patient's trend in renal function using chronic kidney disease-EPI estimated glomerular filtration rate. Baseline renal function in 2012 before regular blood testing from 2018 onwards. Timing of anti vascular endothelial growth factor therapy indication on graph with arrow

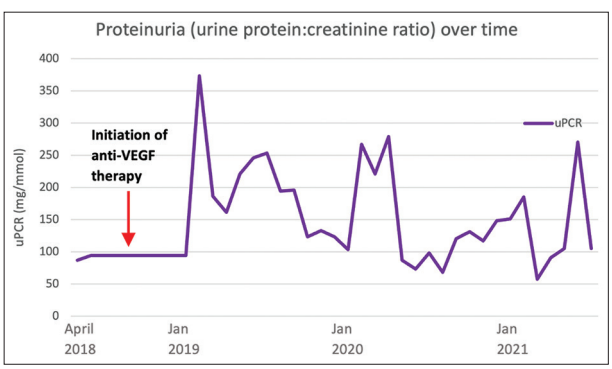

Figure 2: Trend in case patient's level of proteinuria over time. Arrow indicates timing of commencement of anti vascular endothelial growth factor therapy

VEGF signaling plays an important role in the maintenance of the healthy structure of the kidney podocyte through organization of the actin cytoskeleton.[3,5] Disruption of this signaling can lead a loss of endothelial fenestrations, podocyte effacement, and the clinical presentation of nephrotic syndrome.[2,5] VEGF signaling is also required for the functioning of the renal endothelium and is involved in nitric oxide production and vasodilation. Inhibition of this signaling results in an increase in potent vasoconstrictor endothelin-1 and inhibition of nitric oxide production.[3,5] Endothelial dysfunction results in hypertension, thrombotic microangiopathy, and dysregulation of the clotting cascade.[3] Declining renal function is related to these underlying pathological mechanisms driving glomerular disease and hypertension.

Although intravitreal anti-VEGF therapy has not previously been associated with these systemic adverse effects, several case reports have described the clinical syndrome of worsening proteinuria, hypertension, and renal function following its initiation, and many have correlated with renal biopsy pathology reports.[4-6] This has included case reports of patients with no diagnosis of diabetes mellitus/diabetic nephropathy.[6] Withdrawal of intravitreal anti-VEGF treatment has been associated with improvement in renal function and proteinuria.[6] Shye *et al.* estimated a 14% risk of worsening of hypertension and 14–45% risk of proteinuria worsening through analysis of available limited data, which compares to an estimated risk of 23.6% of worsening hypertension and 21–63% of worsening proteinuria for intravenous agents.[5]

However, population studies have thus far failed to find a significant relationship between intravitreal anti-VEGF therapy and the development of these adverse outcomes. Glassman *et al* (2018)[7] undertook a randomized clinical trial comparing intravitreal anti-VEGF agents without control and did not find a significant worsening of category measurement of proteinuria nor hypertension for 660 participants over a 2-year follow-up period. O'Neil *et al.* (2019)[8] did not find a significant association with intravitreal anti-VEGF exposure and declining eGFR or worsening albuminuria in 85 patients over a 2.5-year follow-up period, although acknowledged a longer follow-up of more participants was likely required to power a study designed to capture low-frequency systemic events. Therefore, the true incidence of glomerular disease due to intravitreal VEGF inhibition is unknown, and there is a need for further epidemiologic study to determine this and the subgroups of patients that are at particular risk. This requires transparent recording of medication administration out with a patient's primary care prescription record.

Intravitreal anti-VEGF agents are typically given on a monthly basis. The drug levels with intravitreal injection are 100–200 times lower than with systemic therapy.[5] Nonetheless, ophthalmic administration of anti-VEGF agents can result in detectable serum levels which are high enough to suppress more than 50% of intravascular VEGF levels.[9] Injection in one eye can have therapeutic benefits for the other given the systemic absorption.[4] The modulating factors for the variation in systemic absorption of VEGF inhibitors are unknown. The association between number of anti-VEGF injections and development of adverse effects has not been demonstrated. Ranibizumab has a shorter half-life and lower systemic absorption compared with the other anti-VEGF and possibly associated with less severe VEGF inhibition.[9] Confirmation of VEGF inhibition/measurement of drug levels has not featured in studies assessing adverse outcomes of intravitreal anti-VEGF, which is possibly a contributor to the conflicting results of studies.

Further study of the optimal dosage and frequency of these injections to minimize the development of systemic complications is required, as complete withdrawal of these agents may not be possible due to the lack of alternative options for preserving sight. Focal laser as an adjuvant treatment can significantly reduce the frequency of anti-VEGF injections.[2] Increasing evidence that other inflammatory pathways and retinal neurodegeneration are implicated as independent pathogenesis pathways in diabetic retinopathy may provide alternative therapeutic avenues.[2]

Conclusion and Clinical Significance

The clinical syndrome of anti-VEGF-induced worsening eGFR, proteinuria, and hypertension overlaps with the natural progression of diabetic nephropathy, and this clinical presentation represents significant diagnostic challenge. Given the widespread use of these agents in patients with diabetic retinopathy who have concomitant nephropathy, there needs to be a heighted awareness to changes in proteinuria and blood pressure after the initiation of these treatments. Epidemiological research is required to assess the prevalence of adverse reactions to anti-VEGF in this vulnerable patient group. Anti-VEGF agents are often necessary to maintain sight, and therefore, quality of life for patients and identification of patient factors which increase susceptibility for adverse renal events and hypertension are welcomed to develop strategies for renal protection, and help patients make informed choices regarding the risks of these therapies.

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