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Changes in arterial stiffness indices during a single hemodialysis session in end-stage renal disease population -- A systematic review and meta-analysis protocol

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ABSTRACT

Introduction: End-stage renal disease patients are at higher risk of cardiovascular morbidity and mortality, a risk mediated in part by increased aortic stiffness. Arterial stiffness is assessed at different anatomical locations (central elastic or peripheral muscular arteries) using a variety of mechanical biomarkers. However, little is known on the robustness of each of these mechanical biomarkers following a hemodynamic stress caused by a single hemodialysis session.

Methods and analysis: A systematic review has been designed and reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols. A targeted search strategy applicable in key databases (PubMed, Embase, the Cochrane Library, Web of Science and grey literature) is constructed to search articles and reviews from inception to October 16th 2020. Only articles of studies conducted with adults under chronic hemodialysis for kidney failure, with repeated measures of arterial stiffness metrics (pulse wave velocity, augmentation index, arterial distensibility or stiffness) following a before-and-after design surrounding a hemodialysis session will be selected. The screening process, data extraction and assessment of risk bias (ROBINS-I tool) will be done by two independent pairs of reviewers. Meta-analysis will enable adjustments for potential confounders and subgroup analyses will be performed to discriminate changes in arterial stiffness metrics from elastic, muscular or global arterial territories.

Ethics and dissemination: This study does not require ethical approval. Findings will be submitted for publication to relevant peer-reviewed journals and will be presented at profession-specific conferences.

Prospero registration number: Under Prospero editorial review for acceptance since October 12, 2020.

Keywords: hemodialysis, end-stage renal disease, arterial stiffness, pulse wave velocity, PWV, pulse wave analysis, augmentation index, central pulse pressure, distensibility, arterial compliance.

ARTICLE SUMMARY

Strengths and limitations

- Selection of before-and-after design studies will enable a better comprehension of the effect of hemodynamic stress that occurs during hemodialysis session on arterial mechanical properties.
- Subgroup analysis according to site of blood vessels (central elastic vs. peripheral muscular) is a relevant approach to explain discrepancies of arterial stiffness changes during hemodialysis, as large elastic and medium-sized muscular arteries may behave differently during excess liquid removal and sympathetic activation.
- Meta-regression will help assessing the extent of the impact of potential clinical and hemodynamic confounders on the different arterial stiffness indices during a hemodialysis session
- Implementing well-validated scales for the assessment of risk of bias and certainty of evidence will minimize misinterpretation.
- Potential diversity and heterogeneity of arterial stiffness markers may limit quantitative analyses.

INTRODUCTION

Hemodialysis (HD) is the most common treatment for patients with end-stage renal disease (ESRD). Its intermittent regimen, usually thrice weekly, leads to inexorable retention of solutes, toxins, and excess volume during the interdialytic period (2-3 days), which are partially corrected during the subsequent HD (i.e. usually 4 hours). Despite its vital role, HD is not a physiological treatment. A high ultrafiltration rate during this short period reduces intravascular blood volume leading to a decrease in blood pressure and coronary flow, hypoperfusion of vital vascular beds, and reflex activation of sympathetic nervous system which causes tachycardia [1]. Moreover, during HD, the dialysis membrane is a site where blood has substantial contact with non-biological material, activating white blood cells and their downstream biological reactions which involve activation of complement alternative pathway [2]. In addition, electrolyte composition of dialysis solution may alter cardiovascular response through the acute changes in serum calcium and magnesium concentrations [3].

Patients with chronic kidney disease are at increased risk of aortic stiffness through various biological processes [4]. Aortic stiffness is a non-traditional mechanical biomarker of cardiovascular morbidity and mortality [5], which increases cardiac workload and pulse pressure transmission along the arterial tree. Classically, aortic stiffness is evaluated non-invasively by measuring or estimating carotid-femoral pulse wave velocity (PWV). Other methods aim to quantify the hemodynamic consequences of aortic stiffness through analysis of aortic pulse pressure waveform morphology and determination of central augmentation index (AIx) as a measure of pressure wave reflection [6]. There are also other systems that use heart-ankle PWV or brachial-ankle PWV which incorporates not only the stiffness of aorta (central elastic vessel), but also the stiffness of medium-sized muscular vessels [7]. It is also possible to study local arterial stiffness [8], for example, by studying pressure-diameter relationship throughout the cardiac cycle for arteries such as the common carotid artery (elastic) or radial artery (muscular). Due to the heterogeneity of the arterial wall composition and dimension, various vascular segments behave differently in response to pathological conditions, volume status, blood pressure, heart rate and sympathetic activity. To what extent a single session of HD affects these measurements is not only important scientifically, but also clinically. Indeed, if the timing of measurement, with respect to HD, is important, it could have a significant impact on the predictive value of these mechanical biomarkers. Furthermore, because of the heterogeneity of the arterial tree and the various methods used to estimate vascular stiffness, conclusions drawn from different observations may vary according to site of measurement and methodology. Finally, studies addressing this question are scarce, and usually include a small number of subjects, which could hamper the reliability of their conclusions. Therefore, we propose to conduct a systematic review and a meta-analysis to estimate the impact of a single session of HD on markers of arterial stiffness in an attempt to recommend the best timing of measurement with respect to HD. If possible, we will examine whether all vascular segments and markers of arterial stiffness point towards the same conclusion. Whilst pursuing these goals, this review will highlight the strengths and weaknesses of the reported studies, and determine if there is a need for further well-designed investigations.

Objectives

The major objective of this review is to determine the acute effect of a single HD session on mechanical biomarkers of arterial stiffness including: carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, aortic pulse wave analysis, central pulse wave analysis (augmentation index and central pulse pressure), aortic/carotid/femoral/radial distension metrics, compliance or incremental elastic modulus.

METHODS

Design

We will conduct this systematic review and meta-analysis in accordance with this predefined protocol which is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA-P) checklist [9, 10].

Population and eligibility criteria

In this review, we will include all studies conducted amongst adult patients (≥ 18 years old) with ESRD undergoing chronic HD, either in hospital setting or at home.

Intervention

In this review, a single HD session will be considered as the main intervention.

Outcomes

The primary outcome will be the change in arterial stiffness using PWV-based measurements. Pulse wave velocity is the most widely accepted and used method to measure arterial stiffness by determination of pulse transit time between two points over an arterial segment (m/s). Arterial segments may include central large elastic and peripheral muscular arteries in different proportions such as carotid-femoral PWV, estimated aortic PWV, brachial-ankle PWV, carotid-radial PWV, femoral-distal PWV.

Secondary outcomes will be based on biomarkers of arterial stiffness such central pulse pressure, central augmentation index, arterial distensibility, compliance and incremental elastic modulus of aorta, carotid, femoral and radial arteries. We will report absolute values as well as between-group mean differences in their respective units of measurement per biomarker.

Study design

We will include all observational studies with repeated measures of arterial stiffness or central pressure with a before-and-after design surrounding a HD session. In the case of interventional studies, the values of the reference group (standard care) will be used in the analysis. We will exclude non-human studies, narrative reviews, in-vitro or mathematical modeling reports. Duplicate or sub-study of previously published investigations will be removed.

Search Strategy

Our search strategy includes bibliographic databases (PubMed, Embase, The Cochrane Library and Web of Science), references lists of eligible studies and review articles, trials registers and grey literature from inception to October 16th 2020. MeSH terms will be used to target articles relevant to the research question. Our proposed literature search strategy is outlined in *Appendix 1.* Manual screening of the reference list will be conducted based on pre-defined criteria listed in *Table 1*. No language restrictions or publication period will be imposed on the initial searches; however, our final analysis will be limited to articles originally reported in English, French, Italian and Spanish. Searches will be re-run just before the final analyses and any further identified studies will be retrieved for inclusion. Unpublished studies will not be sought. Duplicate citations will be removed.

Study screening and exclusions

An iterative process of study selection will be conducted using the inclusion and exclusion criteria detailed in *Table 1*. The study selection will be done by 2 pairs of independent reviewers, each pair screening half of the records. In case of a disagreement between individual judgment, a third reviewer will decide. Decisions will be recorded in an Excel spreadsheet. First, citations will be screened by title and abstract. After this first round of selection, materials and methods sections of the selected articles will be screened to confirm the appropriateness of the study design and of the arterial stiffness assessment method relative to the review question. Before data extraction, another round of selection will be performed by both reviewers at the full-text level.

Data extraction

A data extraction form will be prepared a-priori with consensus amongst the investigators. Extracted data will include: a) ***Study characteristics, design and methods***: title, first and last author, journal and year of publication, research team or country where research was based, language of publication, sources of funding, study design, , inclusion and exclusion criteria, point measurements, type of arterial stiffness instrumentation, method used to identify the foot of the pulse wave when applicable, position of subjects during measurements; b) ***Sample characteristics***: age at the time of measurement, sex distribution, HD vintage, comorbidities (diabetes, hypertension, smoking status, prior history of cardiovascular disease), HD session duration, electrolyte concentration of dialysate (calcium, magnesium), dialysis filter, volume overload; c) ***Outcomes***: peri and intra-dialytic changes in arterial stiffness based on the above-mentioned methods (carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, aortic and central pulse wave analysis (augmentation index and central pulse pressure), stiffness index and local vascular distensibility, compliance and incremental elastic modulus, heart rate, and arterial pressure. Study investigators will be contacted by email to gather unreported data or additional details. Extraction of data will be done by two independent reviewers, on separate Excel spreadsheet. Disagreements will be resolved by a third reviewer.

Risk assessment of bias

Internal validity of randomized controlled trials will be assessed using the Cochrane Collaboration Risk of Bias tool. In the case of non-randomized studies, risk of bias will be assessed using the ROBINS-I tool. Two reviewers will independently evaluate the possibility of bias in seven different domains including confounding factors (heart rate, mean arterial pressure, fluid removal by HD), selection of participants (unstable participants), classification of the intervention (hypotensive event-free), deviation from the intended intervention, missing data, measurement of outcomes (seated vs supine) and selection of the reported results. Each domain will be judged as either low, moderate, serious or critical risk of bias or no information available. An overall assessment of study bias summarizing all domains will be tabulated. A third reviewer will settle unresolved disagreements. In addition, information on the source of funding will be collected to assess conflicts of interest.

Data synthesis and analysis plan

All studies fulfilling the eligibility criteria will be included in quantitative and qualitative synthesis. Study characteristics will be presented as means and standard deviation or median and inter-quartile ranges for continuous variables and numbers and percentages for categorical variables. For continuous data, an inverse variance method with random effect models will be used to pool the mean difference or standardized mean difference if studies reported different scales for the assessment of the same outcome. Dichotomous variables will be extracted from individual studies and combined using Mantel-Haenszel method with random effects models to pool relative risks. All analyses will be performed with RevMan 5.3 (Computer program, Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Pooled effect sizes and their 95% confidence limits will be reported. If quantitative synthesis is not appropriate, studies will be described individually according to intervention and outcomes reported in a summary table.

Between-study heterogeneity will be characterized with the Cochrane's I^2 and will be interpreted as low (0-30%), moderate (30-60%), and considerable >60%.

A meta-regression is planned in case of a considerable heterogeneity among studies and if the number of studies is sufficient (> 10 by covariate) [11]. Factors such as age of participants, HD vintage, comorbidities (diabetes, heart failure, etc.), amount of liquid overload, heart rate, and mean arterial pressure will be considered as covariates if adjusted outcomes are not available or stratification has not been performed. These analyses will be performed using R (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) with the Metafor package (Viechtbauer W (2010). "Conducting meta-analyses in R with the metafor package." Journal of Statistical Software, 36(3), 1–48. https://www.jstatsoft.org/v36/i03/).

Sensitivity analysis

Sensitivity analysis according to study design and high risk of study bias will be performed to explore sources of statistical heterogeneity.

Subgroup analysis

Peripheral arterial segments are constituted of a higher proportion of vascular smooth muscle cells, in contrast with the high elastin and collagen content of the aorta. Due to intravascular volume correction and sympathetic activation at the end of a HD session, we hypothesized that PWV of central large arteries and peripheral muscular arteries will not respond to the same extent despite adjustments for arterial pressure and heart rate. Therefore, we plan to perform subgroup analysis to pool data of PWV with respect elastic (aorta), muscular-medium sized arteries (carotid-radial PWV, femoral-pedal PWV), and global PWV, which includes both elastic and muscular vessels (brachial-ankle PWV, carotid-pedal PWV). We will also plan another subgroup analysis by pooling regional PWV or local biomarkers of arterial stiffness depending on whether the information involves elastic versus muscular vessels.

Meta-bias

We will attempt to avoid reporting bias by using a sensitive and reproducible search strategy, including as many keywords and synonyms as possible. We will also assess the risk of publication bias with funnel plots if at least 10 studies comparing the same group of treatment are included as recommended by the Cochrane handbook [12].

Quality of evidence

To assess the certainty of the evidence and strength of recommendations on the effects of a HD session on arterial stiffness, 2 reviewers will evaluate quality of evidence for each outcome measure according to the 5 domains of GRADE recommendations [13].

Amendments

Any protocol amendments will be summarized in the form of a Table, where date of amendment, description of changes and rationale will be provided.

DISCUSSION

Patients with ESRD are at increased risk of aortic stiffness, a known non-traditional marker of cardiovascular morbidity and mortality. In this population, optimization of non-traditional risk factors may not be as effective in improving clinical outcomes compared to general population [14], highlighting the importance of addressing aortic stiffness and limiting its consequences, namely on end-organ damage. However, adequate risk prediction, and eventually intervention, requires that aortic stiffness be measured in a reliable and systematic way, which can be challenging in some clinical settings. Furthermore, there is still limited understanding of how measurements of vascular stiffness differ along the arterial tree [15], especially under conditions of hemodynamics stress, such as with HD.

Vascular stiffness assessment in ESRD patients is usually made in the pre-dialytic period to avoid having patients come in for clinical evaluation on their HD-free days. ESRD patients undergoing HD generally receive this intermittent treatment thrice weekly in clinical setting, few having the autonomy and/or support necessary for at-home HD. As a result, assessing aortic stiffness before or after HD appears as the most convenient timing. However, little is known as to the effect of the treatment itself on the reliability of vascular stiffness assessments, few studies having considered this issue, and generally with a small number of subjects.

Measurements and estimates of aortic stiffness are used as mechanical biomarkers in the clinical evaluation of ESRD patients. Pulse wave velocity based methodologies are most commonly and reliably used to evaluate arterial stiffness, both in central elastic vessels (aorta, carotid artery) and in more peripheral medium-sized muscular arteries (brachial, radial arteries). The pulse transit times obtained with these methods reflect the stiffness of the arterial segment between measurement sites. In addition, hemodynamic consequences of aortic stiffness can be evaluated using analysis of aortic or otherwise central pulse pressure waveform morphology, whilst local arterial mechanics (dispensability, compliance or incremental elastic modulus) can be evaluated in a site-specific manner either at central or peripheral arterial sites [7].

As described earlier, HD is not a physiological treatment. Its known effects on blood pressure, intravascular volume, tissue perfusion and sympathetic nervous activation are likely to alter measures and estimates of arterial stiffness, at the very least in some arterial segments [1, 16, 17]. Inconsistent methodologies and consequent findings not only obscure our understanding of the determinants of vascular stiffness in ESRD, but may also hinder the predictive value of these mechanical biomarkers when assessing cardiovascular risk in this population [18, 19]. This proposed review aims to resolve these issues by evaluating the acute effect of HD on measurements and estimates of vascular stiffness, and by suggesting the most appropriate, yet convenient, timing for vascular stiffness assessment in ESRD.

CONCLUSIONS

End-stage renal disease patients are at high risk of cardiovascular morbidity and mortality, a risk which is mediated in part by increased aortic stiffness, a non-traditional cardiovascular risk factor. Various mechanical biomarkers are used to measure or estimate aortic and arterial stiffness. However, little is known of the robustness of each of these parameters under extreme hemodynamic conditions that occur during a hemodialysis treatment. Our review will provide a better understanding of the impact of hemodialysis on measures of aortic stiffness and provide the necessary evidence to recommend the most adequate timing of vascular assessment in ESRD patients.

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Author statement

All authors contributed towards the submitted final manuscript. CF is a kinesiologist specialised in chronic kidney disease and postdoctoral researcher. MA is a nephrologist, the lead supervisor and corresponding author. PB is co-supervisor. CF, HO and MP drafted the initial manuscript and received guidance on content, methodology and analysis from AS and MA. MP and CAG are first reviewers, CF and HO are second reviewers. All authors have read and agreed the final manuscript.

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Conflicts of interests

Competing interests: None to declare

Technical appendix, statistical code, and dataset available from the Dryad repository

N/A

Table 1. List of inclusion and exclusion criteria for study selection

	Inclusion	**Exclusion**
Population	• End-stage renal disease (Stage 5 CKD) patients undergoing hemodialysis;	• Pediatric population (<18 years old) • Incident hemodialysis patients (<1month) • Critically ill (ex: intensive care unit)
Intervention	• Dialysis centre-base hemodialysis; • Home-based hemodialysis	• Peritoneal dialysis • Non-standard hemodialysis settings (electrolyte concentrations of dialysate, temperature, etc.) • Unrelated interventions such as nutritional, pharmaceutical and physical exercise interventions.
Outcome	• Functional indices of arterial stiffness: carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, cardio-ankle vascular index, pulse wave analysis (augmentation index and central pulse pressure), stiffness index, compliance and distensibility	• Peripheral pressure (brachial, finger, toe, etc.)
Study design	• Repeated measures surrounding a single hemodialysis session. • Randomized controlled and cross-over trials (if standard care group); • Non-randomized prospective studies (before-and-after design). • Articles in English, French, Italian and Spanish languages.	• In-vitro or mathematical modeling reports; • Case reports • Animal studies; • Sub-studies of previously reported trials; • Narrative reviews; • Duplicates.

Appendix 1. Comprehensive Search Strategy for MEDLINE

Mesh terms:

- **Population:**
  a) Chronic Renal or Kidney Failure
  b) End Stage Renal or Kidney Disease

- **Intervention**
  c) Renal Dialysis; renal, extracorporeal
  d) Hemodialysis
  e) Home Hemodialysis
  f) Hemodialysis Solutions, Dialysate

- **Comparator**

No restriction

- **Outcomes**

Metrics of arterial stiffness:

g) Vascular stiffness, arterial stiffness, stiffness, aortic stiffness, carotid stiffness, central artery stiffness, large artery stiffness
h) Stiffness, peripheral, small artery, brachial, femoral
i) Carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity, femoral-distal pulse wave velocity, pulse transit time,
j) Brachial-ankle pulse wave velocity
k) Augmentation index, Pulse wave analysis, central pulse pressure, pressure waveforms
l) Distensibility, elasticity,
m) β-stiffness, CAVI

Database: PubMed from inception t0 2020 October 14.

Search Strategy (Intervention AND Outcomes)

1 Kidney Failure, Chronic/ (94 073)
2 Renal Failure ti.ab.(90 187)
3 Kidney Failure ti.ab. (8 750)

4 (#2 or #3) AND chronic ti ab.(35 520)
5 Renal disease* ti.ab.(66 784)
6 Kidney disease* ti.ab (86 384)
7 (OR #2, #3, #5, #6) AND End-Stage ti.ab. (44 753)
8 ESKD ti.ab (1 262)
9 ESRD ti.ab (16 791)
10 (OR #1, #4, #7, #8, #9) (131 528)
11 Renal Dialysis/ (114 412)
12 Dialysis ti.ab.OR Dialyses ti.ab.(110 444)
13 Renal ti.ab. AND #12 (43 530)
14 Extracorporeal ti.ab. AND #12 (1 657)
15 Hemodialys* ti.ab.OR haemodialys* ti.ab. (78 417)
16 Hemodialysis Solutions/ (1 606)
17 Hemodialysis, Home/ (1 943)
18 Dialysate ti.ab. (10 831)
19 (OR #11, #13, #14, #15, #16, #17, #18) (154 493)
20 Vascular Stiffness/ (6 198)
21 Pulse Wave Analysis/ (4 305)
22 Carotid-Femoral Pulse Wave Velocity/ (27)
23 Elastic Modulus/ (10 317)
24 Vascular Capacitance/ (287)
25 Cardio Ankle Vascular Index/ (18)
26 Carotid Intima-Media Thickness/ (5 028)
27 Vascular ti.ab. AND Stiffness ti.ab. (6 881)
28 Arter* ti.ab. AND Stiffness ti.ab. (13 560)
29 Aort* ti.ab. AND Stiffness ti.ab. (5 547)
30 Pulse wave velocit* ti.ab (9 442)
31 Pulse wave analys* ti.ab (1 199)
32 Pulse wave transit time* ti.ab (98)
33 PWV ti.ab. (4 722)
34 Pulse transit time* ti.ab. (626)
35 Carotid femoral pulse wave velocit* ti.ab. (1 576)
36 Carotid femoral PWV ti.ab. (316)
37 CfPWV ti.ab. (254)
38 Carotid radial pulse wave velocit* ti.ab. (108)
39 Carotid radial PWV ti.ab. (78)
40 Cr PWV ti.ab. (27)
41 Carotid brachial pulse wave velocit* ti.ab. (5)
42 Carotid brachial PWV ti.ab. (5)
43 Cb PWV ti.ab. (1)
44 Brachial ankle pulse wave velocit* ti.ab. (1 439)
45 Brachial ankle PWV ti.ab. (200)
46 ba PWV ti.ab. (118)
47 (aorta ti.ab.OR aortic ti.ab.) AND pulse wave velocit* ti.ab. (3 481)
48 (aorta ti.ab.OR aortic ti.ab.) AND PWV ti.ab. (1 850)
49 Ao PWV ti.ab.(9)
50 Femoral ankle pulse wave velocit* ti.ab. (10)

51 Femoral ankle PWV ti.ab. (22)
52 Augmentation index ti.ab. (2 998)
53 AIx ti.ab. (1493)
54 Central pulse pressure ti.ab. OR central PP ti.ab. (489)
55 aortic pulse pressure ti.ab. OR aortic PP ti.ab. (301)
56 Elastic modulus ti.ab. (9 499)
57 (Young ti.ab. OR young's ti.ab.) AND modulus ti.ab. (8 810)
58 Vascular capacitance ti.ab. (186)
59 Cardio ankle vascular index ti.ab. (584)
60 CAVI ti.ab. (654)
61 distensibility ti.ab. (4 626)
62 arterial elasticity ti.ab.(519)
63 stiffness index ti.ab. OR β stiffness ti.ab. (1 597)
64 (OR #20-#64) (53 637)

64 (#19 AND #64) (1 081)

65 AND humans[filter] (987)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			

Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	18-20
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-10

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9-10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9-10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11

Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

None This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Changes in arterial stiffness indices during a single hemodialysis session in end-stage renal disease population -- A systematic review and meta-analysis protocol

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Secondary Subject Heading:	Cardiovascular medicine
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Changes in arterial stiffness indices during a single hemodialysis session in end-stage renal disease population -- A systematic review and meta-analysis protocol

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ABSTRACT

Introduction: End-stage renal disease patients are at higher risk of cardiovascular morbidity and mortality, a risk mediated in part by increased aortic stiffness. Arterial stiffness is assessed at different anatomical locations (central elastic or peripheral muscular arteries) using a variety of mechanical biomarkers. However, little is known on the robustness of each of these mechanical biomarkers following a hemodynamic stress caused by a single hemodialysis session.

Methods and analysis: A systematic review has been designed and reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols. A targeted search strategy applicable in key databases (PubMed, Embase, the Cochrane Library, Web of Science and grey literature) is constructed to search articles and reviews from inception to October 16th 2020. Only articles of studies conducted with adults under chronic hemodialysis for kidney failure, with repeated measures of arterial stiffness metrics (pulse wave velocity, augmentation index, arterial distensibility or stiffness) following a before-and-after design surrounding a hemodialysis session will be selected. The screening process, data extraction and assessment of risk bias (ROBINS-I tool) will be done by two independent pairs of reviewers. Meta-analysis will enable adjustments for potential confounders and subgroup analyses will be performed to discriminate changes in arterial stiffness metrics from elastic, muscular or global arterial territories.

Prospero registration number: CRD42020213946

Keywords: hemodialysis, end-stage renal disease, arterial stiffness, pulse wave velocity, PWV, pulse wave analysis, augmentation index, central pulse pressure, distensibility, arterial compliance.

ARTICLE SUMMARY

Strengths and limitations

- Selection of before-and-after design studies will enable a better comprehension of the effect of hemodynamic stress that occurs during hemodialysis session on arterial mechanical properties.
- Subgroup analysis according to site of blood vessels (central elastic vs. peripheral muscular) is a relevant approach to explain discrepancies of arterial stiffness changes during hemodialysis, as large elastic and medium-sized muscular arteries may behave differently during excess liquid removal and sympathetic activation.
- Meta-regression will help assessing the extent of the impact of potential clinical and hemodynamic confounders on the different arterial stiffness indices during a hemodialysis session
- Implementing well-validated scales for the assessment of risk of bias and certainty of evidence will minimize misinterpretation.
- Potential diversity and heterogeneity of arterial stiffness markers may limit quantitative analyses.

INTRODUCTION

Hemodialysis (HD) is the most common treatment for patients with end-stage renal disease (ESRD). Its intermittent regimen, usually thrice weekly, leads to inexorable retention of solutes, toxins, and excess volume during the interdialytic period (2-3 days), which are partially corrected during the subsequent HD (i.e. usually 4 hours). Despite its vital role, HD is not a physiological treatment. A high ultrafiltration rate during this short period reduces intravascular blood volume leading to a decrease in blood pressure and coronary flow, hypoperfusion of vital vascular beds, and reflex activation of sympathetic nervous system which causes tachycardia [1]. Moreover, during HD, the dialysis membrane is a site where blood has substantial contact with non-biological material, activating white blood cells and their downstream biological reactions which involve activation of complement alternative pathway [2]. In addition, electrolyte composition of dialysis solution may alter cardiovascular response through the acute changes in serum calcium and magnesium concentrations [3].

Patients with chronic kidney disease are at increased risk of aortic stiffness through various biological processes [4]. Aortic stiffness is a non-traditional mechanical biomarker of cardiovascular morbidity and mortality [5], which increases cardiac workload and pulse pressure transmission along the arterial tree. Classically, aortic stiffness is evaluated non-invasively by measuring or estimating carotid-femoral pulse wave velocity (PWV). Other methods aim to quantify the hemodynamic consequences of aortic stiffness through analysis of aortic pulse pressure waveform morphology and determination of central augmentation index (AIx) as a measure of pressure wave reflection [6]. There are also other systems that use heart-ankle PWV or brachial-ankle PWV which incorporates not only the stiffness of aorta (central elastic vessel), but also the stiffness of medium-sized muscular vessels [7]. It is also possible to study local arterial stiffness [8], for example, by studying pressure-diameter relationship throughout the cardiac cycle for arteries such as the common carotid artery (elastic) or radial artery (muscular). Due to the heterogeneity of the arterial wall composition and dimension, various vascular segments behave differently in response to pathological conditions, volume status, blood pressure, heart rate and sympathetic activity. To what extent a single session of HD affects these measurements is not only important scientifically, but also clinically. Indeed, if the timing of measurement, with respect to HD, is important, it could have a significant impact on the predictive value of these mechanical biomarkers. Furthermore, because of the heterogeneity of the arterial tree and the various methods used to estimate vascular stiffness, conclusions drawn from different observations may vary according to site of measurement and methodology. Finally, studies addressing this question are scarce, and usually include a small number of subjects, which could hamper the reliability of their conclusions. Therefore, we propose to conduct a systematic review and a meta-analysis to estimate the impact of a single session of HD on markers of arterial stiffness in an attempt to recommend the best timing of measurement with respect to HD. If possible, we will examine whether all vascular segments and markers of arterial stiffness point towards the same conclusion. Whilst pursuing these goals, this review will highlight the strengths and weaknesses of the reported studies, and determine if there is a need for further well-designed investigations.

Objectives

The major objective of this review is to determine the acute effect of a single HD session on mechanical biomarkers of arterial stiffness including: carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, aortic pulse wave analysis, central pulse wave analysis (augmentation index and central pulse pressure), aortic/carotid/femoral/radial distension metrics, compliance or incremental elastic modulus.

METHODS

Design

We will conduct this systematic review and meta-analysis in accordance with this predefined protocol which is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA-P) checklist [9, 10].

Population and eligibility criteria

In this review, we will include all studies conducted amongst adult patients (≥ 18 years old) with ESRD undergoing chronic HD, either in hospital setting or at home.

Intervention

In this review, a single HD session will be considered as the main intervention.

Outcomes

The primary outcome will be the change in arterial stiffness using PWV-based measurements. Pulse wave velocity is the most widely accepted and used method to measure arterial stiffness by determination of pulse transit time between two points over an arterial segment (m/s). Arterial segments may include central large elastic and peripheral muscular arteries in different proportions such as carotid-femoral PWV, estimated aortic PWV, brachial-ankle PWV, carotid-radial PWV, femoral-distal PWV.

Secondary outcomes will be based on biomarkers of arterial stiffness such central pulse pressure, central augmentation index, arterial distensibility, compliance and incremental elastic modulus of aorta, carotid, femoral and radial arteries. We will report absolute values as well as between-group mean differences in their respective units of measurement per biomarker.

Study design

We will include all observational studies with repeated measures of arterial stiffness or central pressure with a before-and-after design surrounding a HD session. In the case of interventional studies, the values of the reference group (standard care) will be used in the analysis. We will exclude non-human studies, narrative reviews, in-vitro or mathematical modeling reports. Duplicate or sub-study of previously published investigations will be removed.

Search Strategy

Our search strategy includes bibliographic databases (PubMed, Embase, The Cochrane Library and Web of Science), references lists of eligible studies and review articles, trials registers and grey literature from inception to October 16th 2020. MeSH terms will be used to target articles relevant to the research question. Our proposed literature search strategy is outlined in *Appendix 1.* Manual screening of the reference list will be conducted based on pre-defined criteria listed in *Table 1*. No language restrictions or publication period will be imposed on the initial searches; however, our final analysis will be limited to articles originally reported in English, French, Italian and Spanish. Searches will be re-run just before the final analyses and any further identified studies will be retrieved for inclusion. Unpublished studies will not be sought. Duplicate citations will be removed.

Table 1. List of inclusion and exclusion criteria for study selection

	Inclusion	Exclusion
Population	• End-stage renal disease (Stage 5 CKD) patients undergoing hemodialysis; .	• Pediatric population (<18 years old) • Incident hemodialysis patients (<1month) • Critically ill (ex: intensive care unit)
Intervention	• Dialysis centre-base hemodialysis; • Home-based hemodialysis	• Peritoneal dialysis • Non-standard hemodialysis settings (electrolyte concentrations of dialysate, temperature, etc.) • Unrelated interventions such as nutritional, pharmaceutical and physical exercise interventions.
Outcome	• Functional indices of arterial stiffness: carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, cardio-ankle vascular index, pulse wave analysis (augmentation index and central pulse pressure), stiffness index, compliance and distensibility	• Peripheral pressure (brachial, finger, toe, etc.)
Study design	• Repeated measures surrounding a single hemodialysis session. • Randomized controlled and cross-over trials (if standard care group); • Non-randomized prospective studies (before-and-after design). • Articles in English, French, Italian and Spanish languages.	• In-vitro or mathematical modeling reports; • Case reports • Animal studies; • Sub-studies of previously reported trials; • Narrative reviews; • Duplicates.

Study screening and exclusions

An iterative process of study selection will be conducted using the inclusion and exclusion criteria detailed in *Table 1*. The study selection will be done by 2 pairs of independent reviewers, each pair screening half of the records. In case of a disagreement between individual judgment, a third reviewer will decide. Decisions will be recorded in an Excel spreadsheet. First, citations will be screened by title and abstract. After this first round of selection, materials and methods sections of the selected articles will be screened to confirm the appropriateness of the study design and of the arterial stiffness assessment method relative to the review question. Before data extraction, another round of selection will be performed by both reviewers at the full-text level.

Data extraction

A data extraction form will be prepared a-priori with consensus amongst the investigators. Extracted data will include: a) ***Study characteristics, design and methods***: title, first and last author, journal and year of publication, research team or country where research was based, language of publication, sources of funding, study design, inclusion and exclusion criteria, time point measurements, type of arterial stiffness instrumentation, method used to identify the foot of the pulse wave when applicable, position of subjects during measurements; b) ***Sample characteristics***: age at the time of measurement, sex distribution, HD vintage, comorbidities (diabetes, hypertension, smoking status, prior history of cardiovascular disease), HD session duration, electrolyte concentration of dialysate (calcium, magnesium), dialysis filter, volume overload; c) ***Outcomes***: peri and intra-dialytic changes in arterial stiffness based on the above-mentioned methods (carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, aortic and central pulse wave analysis (augmentation index and central pulse pressure), stiffness index and local vascular distensibility, compliance and incremental elastic modulus, heart rate, and arterial pressure. Study investigators will be contacted by email to gather unreported data or additional details. Extraction of data will be done by two independent reviewers, on separate Excel spreadsheet. Disagreements will be resolved by a third reviewer.

Risk assessment of bias

Internal validity of randomized controlled trials will be assessed using whether the Cochrane Collaboration Risk of Bias tool for randomized controlled trials, the ROBINS-I tool in the case of non-randomized studies, or the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study without control group. Two reviewers will independently evaluate the possibility of bias in seven different domains including confounding factors (heart rate, mean arterial pressure, fluid removal by HD), selection of participants (unstable participants), classification of the intervention (hypotensive event-free), deviation from the intended intervention, missing data, measurement of outcomes (seated vs supine) and selection of the reported results. Each domain will be judged as either low, moderate, serious or critical risk of bias or no information available. An overall assessment of study bias summarizing all domains will be tabulated. A third reviewer will settle unresolved disagreements. In addition, information on the source of funding will be collected to assess conflicts of interest.

Data synthesis and analysis plan

All studies fulfilling the eligibility criteria will be included in quantitative and qualitative synthesis. Study characteristics will be presented as means and standard deviation or median and inter-quartile ranges for continuous variables and numbers and percentages for categorical variables. For continuous data, an inverse variance method with random effect models will be used to pool the mean difference or standardized mean difference if studies reported different scales for the assessment of the same outcome. Dichotomous variables will be extracted from individual studies and combined using Mantel-Haenszel method with random effects models to pool relative risks. All analyses will be performed with RevMan 5.3 (Computer program, Version 5.3 Copenhagen:

The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Pooled effect sizes and their 95% confidence limits will be reported. If quantitative synthesis is not appropriate, studies will be described individually according to intervention and outcomes reported in a summary table.

Between-study heterogeneity will be characterized with the Cochrane's I^2 and will be interpreted as low (0-30%), moderate (30-60%), and considerable >60%.

A meta-regression is planned in case of a considerable heterogeneity among studies and if the number of studies is sufficient (> 10 by covariate) [11]. Factors such as age of participants, HD vintage, comorbidities (diabetes, heart failure, etc.), amount of liquid overload, heart rate, and mean arterial pressure will be considered as covariates if adjusted outcomes are not available or stratification has not been performed. These analyses will be performed using R (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) with the Metafor package (Viechtbauer W (2010). “Conducting meta-analyses in R with the metafor package.” Journal of Statistical Software, 36(3), 1–48. https://www.jstatsoft.org/v36/i03/).

Sensitivity analysis

Sensitivity analysis according to study design and high risk of study bias will be performed to explore sources of statistical heterogeneity.

Subgroup analysis

Peripheral arterial segments are constituted of a higher proportion of vascular smooth muscle cells, in contrast with the high elastin and collagen content of the aorta. Due to intravascular volume correction and sympathetic activation at the end of a HD session, we hypothesized that PWV of central large arteries and peripheral muscular arteries will not respond to the same extent despite adjustments for arterial pressure and heart rate. Therefore, we plan to perform subgroup analysis to pool data of PWV with respect elastic (aorta), muscular-medium sized arteries (carotid-radial PWV, femoral-pedal PWV), and global PWV, which includes both elastic and muscular vessels (brachial-ankle PWV, carotid-pedal PWV). We will also plan another subgroup analysis by pooling regional PWV or local biomarkers of arterial stiffness depending on whether the information involves elastic versus muscular vessels.

Meta-bias

We will attempt to avoid reporting bias by using a sensitive and reproducible search strategy, including as many keywords and synonyms as possible. We will also assess the risk of publication bias with funnel plots if at least 10 studies comparing the same group of treatment are included as recommended by the Cochrane handbook [12].

Quality of evidence

To assess the certainty of the evidence and strength of recommendations on the effects of a HD session on arterial stiffness, 2 reviewers will evaluate quality of evidence for each outcome measure according to the 5 domains of GRADE recommendations [13].

Amendments

Any protocol amendments will be summarized in the form of a Table, where date of amendment, description of changes and rationale will be provided.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

DISCUSSION

Patients with ESRD are at increased risk of aortic stiffness, a known non-traditional marker of cardiovascular morbidity and mortality. In this population, optimization of non-traditional risk factors may not be as effective in improving clinical outcomes compared to general population [14], highlighting the importance of addressing aortic stiffness and limiting its consequences, namely on end-organ damage. However, adequate risk prediction, and eventually intervention, requires that aortic stiffness be measured in a reliable and systematic way, which can be challenging in some clinical settings. Furthermore, there is still limited understanding of how measurements of vascular stiffness differ along the arterial tree [15], especially under conditions of hemodynamics stress, such as with HD.

Vascular stiffness assessment in ESRD patients is usually made in the pre-dialytic period to avoid having patients come in for clinical evaluation on their HD-free days. ESRD patients undergoing HD generally receive this intermittent treatment thrice weekly in clinical setting, few having the autonomy and/or support necessary for at-home HD. As a result, assessing aortic stiffness before or after HD appears as the most convenient timing. However, little is known as to the effect of the treatment itself on the reliability of vascular stiffness assessments, few studies having considered this issue, and generally with a small number of subjects.

Measurements and estimates of aortic stiffness are used as mechanical biomarkers in the clinical evaluation of ESRD patients. Pulse wave velocity based methodologies are most commonly and reliably used to evaluate arterial stiffness, both in central elastic vessels (aorta, carotid artery) and in more peripheral medium-sized muscular arteries (brachial, radial arteries). The pulse transit times obtained with these methods reflect the stiffness of the arterial segment between measurement sites. In addition, hemodynamic consequences of aortic stiffness can be evaluated using analysis of aortic or otherwise central pulse pressure waveform morphology, whilst local arterial mechanics (dispensability, compliance or incremental elastic modulus) can be evaluated in a site-specific manner either at central or peripheral arterial sites [7].

As described earlier, HD is not a physiological treatment. Its known effects on blood pressure, intravascular volume, tissue perfusion and sympathetic nervous activation are likely to alter measures and estimates of arterial stiffness, at the very least in some arterial segments [1, 16, 17]. Inconsistent methodologies and consequent findings not only obscure our understanding of the determinants of vascular stiffness in ESRD, but may also hinder the predictive value of these mechanical biomarkers when assessing cardiovascular risk in this population [18, 19]. This proposed review aims to resolve these issues by evaluating the acute effect of HD on measurements and estimates of vascular stiffness, and by suggesting the most appropriate, yet convenient, timing for vascular stiffness assessment in ESRD.

CONCLUSIONS

End-stage renal disease patients are at high risk of cardiovascular morbidity and mortality, a risk which is mediated in part by increased aortic stiffness, a non-traditional cardiovascular risk factor. Various mechanical biomarkers are used to measure or estimate aortic and arterial stiffness.

However, little is known of the robustness of each of these parameters under extreme hemodynamic conditions that occur during a hemodialysis treatment. Our review will provide a better understanding of the impact of hemodialysis on measures of aortic stiffness and provide the necessary evidence to recommend the most adequate timing of vascular assessment in ESRD patients.

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Author statement

All authors contributed towards the submitted final manuscript. CF is a kinesiologist specialised in chronic kidney disease and postdoctoral researcher. MA is a nephrologist, the lead supervisor and corresponding author. PB is co-supervisor. CF, HO and MP drafted the initial manuscript and received guidance on content, methodology and analysis from AS and MA. MP and CAG are first reviewers, CF and HO are second reviewers. All authors have read and agreed the final manuscript.

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Conflicts of interests

Competing interests: None to declare

Ethics and dissemination: This study does not require ethical approval. Findings will be submitted for publication to relevant peer-reviewed journals and will be presented at profession-specific conferences.

Technical appendix, statistical code, and dataset available from the Dryad repository

N/A

Appendix 1. Comprehensive Search Strategy for MEDLINE

Mesh terms:

- **Population:**
  a) Chronic Renal or Kidney Failure
  b) End Stage Renal or Kidney Disease

- **Intervention**
  c) Renal Dialysis; renal, extracorporeal
  d) Hemodialysis
  e) Home Hemodialysis
  f) Hemodialysis Solutions, Dialysate

- **Comparator**

No restriction

- **Outcomes**

Metrics of arterial stiffness:

g) Vascular stiffness, arterial stiffness, stiffness, aortic stiffness, carotid stiffness, central artery stiffness, large artery stiffness
h) Stiffness, peripheral, small artery, brachial, femoral
i) Carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity, femoral-distal pulse wave velocity, pulse transit time,
j) Brachial-ankle pulse wave velocity
k) Augmentation index, Pulse wave analysis, central pulse pressure, pressure waveforms
l) Distensibility, elasticity,
m) β-stiffness, CAVI

Database: PubMed from inception t0 2020 October 14.

Search Strategy (Intervention AND Outcomes)

1 Kidney Failure, Chronic/ (94 073)
2 Renal Failure ti.ab.(90 187)
3 Kidney Failure ti.ab. (8 750)

4 (#2 or #3) AND chronic ti ab.(35 520)
5 Renal disease* ti.ab.(66 784)
6 Kidney disease* ti.ab (86 384)
7 (OR #2, #3, #5, #6) AND End-Stage ti.ab. (44 753)
8 ESKD ti.ab (1 262)
9 ESRD ti.ab (16 791)
10 (OR #1, #4, #7, #8, #9) (131 528)
11 Renal Dialysis/ (114 412)
12 Dialysis ti.ab.OR Dialyses ti.ab.(110 444)
13 Renal ti.ab. AND #12 (43 530)
14 Extracorporeal ti.ab. AND #12 (1 657)
15 Hemodialys* ti.ab.OR haemodialys* ti.ab. (78 417)
16 Hemodialysis Solutions/ (1 606)
17 Hemodialysis, Home/ (1 943)
18 Dialysate ti.ab. (10 831)
19 (OR #11, #13, #14, #15, #16, #17, #18) (154 493)
20 Vascular Stiffness/ (6 198)
21 Pulse Wave Analysis/ (4 305)
22 Carotid-Femoral Pulse Wave Velocity/ (27)
23 Elastic Modulus/ (10 317)
24 Vascular Capacitance/ (287)
25 Cardio Ankle Vascular Index/ (18)
26 Carotid Intima-Media Thickness/ (5 028)
27 Vascular ti.ab. AND Stiffness ti.ab. (6 881)
28 Arter* ti.ab. AND Stiffness ti.ab. (13 560)
29 Aort* ti.ab. AND Stiffness ti.ab. (5 547)
30 Pulse wave velocit* ti.ab (9 442)
31 Pulse wave analys* ti.ab (1 199)
32 Pulse wave transit time* ti.ab (98)
33 PWV ti.ab. (4 722)
34 Pulse transit time* ti.ab. (626)
35 Carotid femoral pulse wave velocit* ti.ab. (1 576)
36 Carotid femoral PWV ti.ab. (316)
37 CfPWV ti.ab. (254)
38 Carotid radial pulse wave velocit* ti.ab. (108)
39 Carotid radial PWV ti.ab. (78)
40 Cr PWV ti.ab. (27)
41 Carotid brachial pulse wave velocit* ti.ab. (5)
42 Carotid brachial PWV ti.ab. (5)
43 Cb PWV ti.ab. (1)
44 Brachial ankle pulse wave velocit* ti.ab. (1 439)
45 Brachial ankle PWV ti.ab. (200)
46 ba PWV ti.ab. (118)
47 (aorta ti.ab.OR aortic ti.ab.) AND pulse wave velocit* ti.ab. (3 481)
48 (aorta ti.ab.OR aortic ti.ab.) AND PWV ti.ab. (1 850)
49 Ao PWV ti.ab.(9)
50 Femoral ankle pulse wave velocit* ti.ab. (10)

51 Femoral ankle PWV ti.ab. (22)
52 Augmentation index ti.ab. (2 998)
53 AIx ti.ab. (1493)
54 Central pulse pressure ti.ab. OR central PP ti.ab. (489)
55 aortic pulse pressure ti.ab. OR aortic PP ti.ab. (301)
56 Elastic modulus ti.ab. (9 499)
57 (Young ti.ab. OR young's ti.ab.) AND modulus ti.ab. (8 810)
58 Vascular capacitance ti.ab. (186)
59 Cardio ankle vascular index ti.ab. (584)
60 CAVI ti.ab. (654)
61 distensibility ti.ab. (4 626)
62 arterial elasticity ti.ab.(519)
63 stiffness index ti.ab. OR β stiffness ti.ab. (1 597)
64 (OR #20-#64) (53 637)

64 (#19 AND #64) (1 081)

65 AND humans[filter] (987)

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

Registration

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2

Authors

Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18

Amendments

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A

Support

Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A

Introduction

Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	19-21
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-10

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11

Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11-12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

BMJ Open

Changes in arterial stiffness indices during a single hemodialysis session in end-stage renal disease population -- A systematic review and meta-analysis protocol

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Changes in arterial stiffness indices during a single hemodialysis session in end-stage renal disease population -- A systematic review and meta-analysis protocol

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ABSTRACT

Introduction: End-stage renal disease patients are at higher risk of cardiovascular morbidity and mortality, a risk mediated in part by increased aortic stiffness. Arterial stiffness is assessed at different anatomical locations (central elastic or peripheral muscular arteries) using a variety of mechanical biomarkers. However, little is known on the robustness of each of these mechanical biomarkers following a hemodynamic stress caused by a single hemodialysis session.

Methods and analysis: A systematic review has been designed and reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols. A targeted search strategy applicable in key databases (PubMed, Embase, the Cochrane Library, Web of Science and grey literature) is constructed to search articles and reviews from inception to October 16th 2020. Only articles of studies conducted with adults under chronic hemodialysis for kidney failure, with repeated measures of arterial stiffness metrics (pulse wave velocity, augmentation index, arterial distensibility or stiffness) following a before-and-after design surrounding a hemodialysis session will be selected. The screening process, data extraction and assessment of risk bias (ROBINS-I tool) will be done by two independent pairs of reviewers. Meta-analysis will enable adjustments for potential confounders and subgroup analyses will be performed to discriminate changes in arterial stiffness metrics from elastic, muscular or global arterial territories.

Ethics and dissemination: This study does not require ethical approval. Findings will be submitted for publication to relevant peer-reviewed journals and will be presented at profession-specific conferences.

Prospero registration number: CRD42020213946

Keywords: hemodialysis, end-stage renal disease, arterial stiffness, pulse wave velocity, PWV, pulse wave analysis, augmentation index, central pulse pressure, distensibility, arterial compliance.

ARTICLE SUMMARY

Strengths and limitations of this study

- Selection of before-and-after design studies will enable a better comprehension of the effect of hemodynamic stress that occurs during hemodialysis session on arterial mechanical properties.
- Subgroup analysis according to site of blood vessels (central elastic vs. peripheral muscular) is a relevant approach to explain discrepancies of arterial stiffness changes during hemodialysis, as large elastic and medium-sized muscular arteries may behave differently during excess liquid removal and sympathetic activation.
- Meta-regression will help assessing the extent of the impact of potential clinical and hemodynamic confounders on the different arterial stiffness indices during a hemodialysis session
- Implementing well-validated scales for the assessment of risk of bias and certainty of evidence will minimize misinterpretation.
- Potential diversity and heterogeneity of arterial stiffness markers may limit quantitative analyses.

INTRODUCTION

Hemodialysis (HD) is the most common treatment for patients with end-stage renal disease (ESRD). Its intermittent regimen, usually thrice weekly, leads to inexorable retention of solutes, toxins, and excess volume during the interdialytic period (2-3 days), which are partially corrected during the subsequent HD (i.e. usually 4 hours). Despite its vital role, HD is not a physiological treatment. A high ultrafiltration rate during this short period reduces intravascular blood volume leading to a decrease in blood pressure and coronary flow, hypoperfusion of vital vascular beds, and reflex activation of sympathetic nervous system which causes tachycardia [1]. Moreover, during HD, the dialysis membrane is a site where blood has substantial contact with non-biological material, activating white blood cells and their downstream biological reactions which involve activation of complement alternative pathway [2-3]. In addition, electrolyte composition of dialysis solution may alter cardiovascular response through the acute changes in serum calcium and magnesium concentrations [4-5].

Patients with chronic kidney disease are at increased risk of aortic stiffness through various biological processes [6]. Aortic stiffness is a non-traditional mechanical biomarker of cardiovascular morbidity and mortality [7-9], which increases cardiac workload and pulse pressure transmission along the arterial tree. Classically, aortic stiffness is evaluated non-invasively by measuring or estimating carotid-femoral pulse wave velocity (PWV). Other methods aim to quantify the hemodynamic consequences of aortic stiffness through analysis of aortic pulse pressure waveform morphology and determination of central augmentation index (AIx) as a measure of pressure wave reflection [10-11]. There are also other systems that use heart-ankle PWV or brachial-ankle PWV which incorporates not only the stiffness of aorta (central elastic vessel), but also the stiffness of medium-sized muscular vessels [12-13]. It is also possible to study local arterial stiffness [14], for example, by studying pressure-diameter relationship throughout the cardiac cycle for arteries such as the common carotid artery (elastic) or radial artery (muscular). Due to the heterogeneity of the arterial wall composition and dimension, various vascular segments behave differently in response to pathological conditions, volume status, blood pressure, heart rate, and sympathetic nervous activity. To what extent a single session of HD affects these measurements is not only important scientifically, but also clinically. Inconsistent methodologies and consequent findings not only obscure our understanding of the determinants of vascular stiffness in ESRD, but may also hinder the predictive value of these mechanical biomarkers when assessing cardiovascular risk in this population [15, 16]. Finally, studies addressing this question are scarce, and usually include a small number of subjects, which could hamper the reliability of their conclusions. Therefore, we propose to conduct a systematic review and a meta-analysis to estimate the impact of a single session of HD on markers of arterial stiffness in an attempt to recommend the best timing of measurement with respect to HD. If possible, we will examine whether all vascular segments and markers of arterial stiffness point towards the same conclusion. Whilst pursuing these goals, this review will highlight the strengths and weaknesses of the reported studies, and determine if there is a need for further well-designed investigations.

Objectives

The major objective of this review is to determine the acute effect of a single HD session on mechanical biomarkers of arterial stiffness including: carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, aortic pulse wave analysis, central pulse wave analysis (augmentation index and central pulse pressure), aortic/carotid/femoral/radial distension metrics, compliance or incremental elastic modulus.

METHODS

Design

We will conduct this systematic review and meta-analysis in accordance with this predefined protocol which is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA-P) checklist [17, 18].

Population and eligibility criteria

In this review, we will include all studies conducted amongst adult patients (≥ 18 years old) with ESRD undergoing chronic HD, either in hospital setting or at home.

Intervention

In this review, a single HD session will be considered as the main intervention.

Outcomes

The primary outcome will be the change in arterial stiffness using PWV-based measurements. Pulse wave velocity is the most widely accepted and used method to measure arterial stiffness by determination of pulse transit time between two points over an arterial segment (m/s). Arterial segments may include central large elastic and peripheral muscular arteries in different proportions such as carotid-femoral PWV, estimated aortic PWV, brachial-ankle PWV, carotid-radial PWV, femoral-distal PWV.

Secondary outcomes will be based on biomarkers of arterial stiffness such central pulse pressure, central augmentation index, arterial distensibility, compliance and incremental elastic modulus of aorta, carotid, femoral and radial arteries. We will report absolute values as well as between-group mean differences in their respective units of measurement per biomarker.

Study design

We will include all observational studies with repeated measures of arterial stiffness or central pressure with a before-and-after design surrounding a HD session. In the case of interventional studies, the values of the reference group (standard care) will be used in the analysis. We will exclude non-human studies, narrative reviews, in-vitro or mathematical modeling reports. Duplicate or sub-study of previously published investigations will be removed.

Search Strategy

Our search strategy includes bibliographic databases (PubMed, Embase, The Cochrane Library and Web of Science), references lists of eligible studies and review articles, trials registers and grey literature from inception to October 16th 2020. MeSH terms will be used to target articles relevant to the research question. Our proposed literature search strategy is outlined in *Appendix 1*. Manual screening of the reference list will be conducted based on pre-defined criteria listed in *Table 1*. No language restrictions or publication period will be imposed on the initial searches; however, our final analysis will be limited to articles originally reported in English, French, Italian and Spanish. Searches will be re-run just before the final analyses and any further identified studies will be retrieved for inclusion. Unpublished studies will not be sought. Duplicate citations will be removed.

Table 1. List of inclusion and exclusion criteria for study selection

	Inclusion	Exclusion
Population	• End-stage renal disease (Stage 5 CKD) patients undergoing hemodialysis;	• Pediatric population (<18 years old) • Incident hemodialysis patients (<1month) • Critically ill (ex: intensive care unit)
Intervention	• Dialysis centre-base hemodialysis; • Home-based hemodialysis	• Peritoneal dialysis • Non-standard hemodialysis settings (electrolyte concentrations of dialysate, temperature, etc.) • Unrelated interventions such as nutritional, pharmaceutical and physical exercise interventions.
Outcome	• Functional indices of arterial stiffness: carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, cardio-ankle vascular index, pulse wave analysis (augmentation index and central pulse pressure), stiffness index, compliance and distensibility	• Peripheral pressure (brachial, finger, toe, etc.)
Study design	• Repeated measures surrounding a single hemodialysis session. • Randomized controlled and cross-over trials (if standard care group); • Non-randomized prospective studies (before-and-after design). • Articles in English, French, Italian and Spanish languages.	• In-vitro or mathematical modeling reports; • Case reports • Animal studies; • Sub-studies of previously reported trials; • Narrative reviews; • Duplicates.

Study screening and exclusions

An iterative process of study selection will be conducted using the inclusion and exclusion criteria detailed in *Table 1*. The study selection will be done by 2 pairs of independent reviewers, each pair screening half of the records. In case of a disagreement between individual judgment, a third reviewer will decide. Decisions will be recorded in an Excel spreadsheet. First, citations will be screened by title and abstract. After this first round of selection, materials and methods sections of the selected articles will be screened to confirm the appropriateness of the study design and of the arterial stiffness assessment method relative to the review question. Before data extraction, another round of selection will be performed by both reviewers at the full-text level.

Data extraction

A data extraction form will be prepared a-priori with consensus amongst the investigators. Extracted data will include: a) ***Study characteristics, design and methods***: title, first and last author, journal and year of publication, research team or country where research was based, language of publication, sources of funding, study design, inclusion and exclusion criteria, time point measurements, type of arterial stiffness instrumentation, method used to identify the foot of the pulse wave when applicable, position of subjects during measurements; b) ***Sample characteristics***: age at the time of measurement, sex distribution, HD vintage, comorbidities (diabetes, hypertension, smoking status, prior history of cardiovascular disease), HD session duration, electrolyte concentration of dialysate (calcium, magnesium), dialysis filter, volume overload; c) ***Outcomes***: peri and intra-dialytic changes in arterial stiffness based on the above-mentioned methods (carotid-femoral PWV, carotid-radial PWV, brachial-ankle PWV, femoral-tibial PWV, aortic and central pulse wave analysis (augmentation index and central pulse pressure), stiffness index and local vascular distensibility, compliance and incremental elastic modulus, heart rate, and arterial pressure. Study investigators will be contacted by email to gather unreported data or additional details. Extraction of data will be done by two independent reviewers, on separate Excel spreadsheet. Disagreements will be resolved by a third reviewer.

Risk assessment of bias

Internal validity of randomized controlled trials will be assessed using whether the Cochrane Collaboration Risk of Bias tool for randomized controlled trials, the ROBINS-I tool in the case of non-randomized studies, or the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study without control group. Two reviewers will independently evaluate the possibility of bias in seven different domains including confounding factors (heart rate, mean arterial pressure, fluid removal by HD), selection of participants (unstable participants), classification of the intervention (hypotensive event-free), deviation from the intended intervention, missing data, measurement of outcomes (seated vs supine) and selection of the reported results. Each domain will be judged as either low, moderate, serious or critical risk of bias or no information available. An overall assessment of study bias summarizing all domains will be tabulated. A third reviewer will settle unresolved disagreements. In addition, information on the source of funding will be collected to assess conflicts of interest.

Data synthesis and analysis plan

All studies fulfilling the eligibility criteria will be included in quantitative and qualitative synthesis. Study characteristics will be presented as means and standard deviation or median and inter-quartile ranges for continuous variables and numbers and percentages for categorical variables. For continuous data, an inverse variance method with random effect models will be used to pool the mean difference or standardized mean difference if studies reported different scales for the assessment of the same outcome. Dichotomous variables will be extracted from individual studies and combined using Mantel-Haenszel method with random effects models to pool relative risks. All analyses will be performed with RevMan 5.3 (Computer program, Version 5.3 Copenhagen:

The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Pooled effect sizes and their 95% confidence limits will be reported. If quantitative synthesis is not appropriate, studies will be described individually according to intervention and outcomes reported in a summary table.

Between-study heterogeneity will be characterized with the Cochrane's I^2 and will be interpreted as low (0-30%), moderate (30-60%), and considerable >60%.

A meta-regression is planned in case of a considerable heterogeneity among studies and if the number of studies is sufficient (> 10 by covariate) [18]. Factors such as age of participants, HD vintage, comorbidities (diabetes, heart failure, etc.), amount of liquid overload, heart rate, and mean arterial pressure will be considered as covariates if adjusted outcomes are not available or stratification has not been performed. These analyses will be performed using R (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) with the Metafor package (Viechtbauer W (2010). "Conducting meta-analyses in R with the metafor package." Journal of Statistical Software, 36(3), 1–48. https://www.jstatsoft.org/v36/i03/).

Sensitivity analysis

Sensitivity analysis according to study design and high risk of study bias will be performed to explore sources of statistical heterogeneity.

Subgroup analysis

Peripheral arterial segments are constituted of a higher proportion of vascular smooth muscle cells, in contrast with the high elastin and collagen content of the aorta. Due to intravascular volume correction and sympathetic activation at the end of a HD session, we hypothesized that PWV of central large arteries and peripheral muscular arteries will not respond to the same extent despite adjustments for arterial pressure and heart rate. Therefore, we plan to perform subgroup analysis to pool data of PWV with respect elastic (aorta), muscular-medium sized arteries (carotid-radial PWV, femoral-pedal PWV), and global PWV, which includes both elastic and muscular vessels (brachial-ankle PWV, carotid-pedal PWV). We will also plan another subgroup analysis by pooling regional PWV or local biomarkers of arterial stiffness depending on whether the information involves elastic versus muscular vessels.

Meta-bias

We will attempt to avoid reporting bias by using a sensitive and reproducible search strategy, including as many keywords and synonyms as possible. We will also assess the risk of publication bias with funnel plots if at least 10 studies comparing the same group of treatment are included as recommended by the Cochrane handbook [19].

Quality of evidence

To assess the certainty of the evidence and strength of recommendations on the effects of a HD session on arterial stiffness, 2 reviewers will evaluate quality of evidence for each outcome measure according to the 5 domains of GRADE recommendations [20].

Amendments

Any protocol amendments will be summarized in the form of a Table, where date of amendment, description of changes and rationale will be provided.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics and dissemination: This study does not require ethical approval. Findings will be submitted for publication to relevant peer-reviewed journals and will be presented at profession-specific conferences.

CONCLUSIONS

End-stage renal disease patients are at high risk of cardiovascular morbidity and mortality, a risk which is mediated in part by increased aortic stiffness, a non-traditional cardiovascular risk factor. Various mechanical biomarkers are used to measure or estimate aortic and arterial stiffness. However, little is known of the robustness of each of these parameters under extreme hemodynamic conditions that occur during a hemodialysis treatment. Our review will provide a better understanding of the impact of hemodialysis on measures of aortic stiffness and provide the necessary evidence to recommend the most adequate timing of vascular assessment in ESRD patients.

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Author statement

All authors contributed towards the submitted final manuscript. CF is a kinesiologist specialised in chronic kidney disease and postdoctoral researcher. MA is a nephrologist, the lead supervisor and corresponding author. PB is co-supervisor. CF, HO and MP drafted the initial manuscript and received guidance on content, methodology and analysis from AS and MA. MP and CAG are first reviewers, CF and HO are second reviewers. All authors have read and agreed the final manuscript.

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Conflicts of interests

Competing interests: None to declare

Technical appendix, statistical code, and dataset available from the Dryad repository

N/A

Word Count: 2877 words

Appendix 1. Comprehensive Search Strategy for MEDLINE

Mesh terms:

- **Population:**
  - a) Chronic Renal or Kidney Failure
  - b) End Stage Renal or Kidney Disease

- **Intervention**
  - c) Renal Dialysis; renal, extracorporeal
  - d) Hemodialysis
  - e) Home Hemodialysis
  - f) Hemodialysis Solutions, Dialysate

- **Comparator**

No restriction

- **Outcomes**

Metrics of arterial stiffness:

- g) Vascular stiffness, arterial stiffness, stiffness, aortic stiffness, carotid stiffness, central artery stiffness, large artery stiffness
- h) Stiffness, peripheral, small artery, brachial, femoral
- i) Carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity, femoral-distal pulse wave velocity, pulse transit time,
- j) Brachial-ankle pulse wave velocity
- k) Augmentation index, Pulse wave analysis, central pulse pressure, pressure waveforms
- l) Distensibility, elasticity,
- m) β-stiffness, CAVI

Database: PubMed from inception t0 2020 October 14.

Search Strategy (Intervention AND Outcomes)

1 Kidney Failure, Chronic/ (94 073)
2 Renal Failure ti.ab.(90 187)
3 Kidney Failure ti.ab. (8 750)

4 (#2 or #3) AND chronic ti ab.(35 520)
5 Renal disease* ti.ab.(66 784)
6 Kidney disease* ti.ab (86 384)
7 (OR #2, #3, #5, #6) AND End-Stage ti.ab. (44 753)
8 ESKD ti.ab (1 262)
9 ESRD ti.ab (16 791)
10 (OR #1, #4, #7, #8, #9) (131 528)
11 Renal Dialysis/ (114 412)
12 Dialysis ti.ab.OR Dialyses ti.ab.(110 444)
13 Renal ti.ab. AND #12 (43 530)
14 Extracorporeal ti.ab. AND #12 (1 657)
15 Hemodialys* ti.ab.OR haemodialys* ti.ab. (78 417)
16 Hemodialysis Solutions/ (1 606)
17 Hemodialysis, Home/ (1 943)
18 Dialysate ti.ab. (10 831)
19 (OR #11, #13, #14, #15, #16, #17, #18) (154 493)
20 Vascular Stiffness/ (6 198)
21 Pulse Wave Analysis/ (4 305)
22 Carotid-Femoral Pulse Wave Velocity/ (27)
23 Elastic Modulus/ (10 317)
24 Vascular Capacitance/ (287)
25 Cardio Ankle Vascular Index/ (18)
26 Carotid Intima-Media Thickness/ (5 028)
27 Vascular ti.ab. AND Stiffness ti.ab. (6 881)
28 Arter* ti.ab. AND Stiffness ti.ab. (13 560)
29 Aort* ti.ab. AND Stiffness ti.ab. (5 547)
30 Pulse wave velocit* ti.ab (9 442)
31 Pulse wave analys* ti.ab (1 199)
32 Pulse wave transit time* ti.ab (98)
33 PWV ti.ab. (4 722)
34 Pulse transit time* ti.ab. (626)
35 Carotid femoral pulse wave velocit* ti.ab. (1 576)
36 Carotid femoral PWV ti.ab. (316)
37 CfPWV ti.ab. (254)
38 Carotid radial pulse wave velocit* ti.ab. (108)
39 Carotid radial PWV ti.ab. (78)
40 Cr PWV ti.ab. (27)
41 Carotid brachial pulse wave velocit* ti.ab. (5)
42 Carotid brachial PWV ti.ab. (5)
43 Cb PWV ti.ab. (1)
44 Brachial ankle pulse wave velocit* ti.ab. (1 439)
45 Brachial ankle PWV ti.ab. (200)
46 ba PWV ti.ab. (118)
47 (aorta ti.ab.OR aortic ti.ab.) AND pulse wave velocit* ti.ab. (3 481)
48 (aorta ti.ab.OR aortic ti.ab.) AND PWV ti.ab. (1 850)
49 Ao PWV ti.ab.(9)
50 Femoral ankle pulse wave velocit* ti.ab. (10)

51 Femoral ankle PWV ti.ab. (22)
52 Augmentation index ti.ab. (2 998)
53 AIx ti.ab. (1493)
54 Central pulse pressure ti.ab. OR central PP ti.ab. (489)
55 aortic pulse pressure ti.ab. OR aortic PP ti.ab. (301)
56 Elastic modulus ti.ab. (9 499)
57 (Young ti.ab. OR young's ti.ab.) AND modulus ti.ab. (8 810)
58 Vascular capacitance ti.ab. (186)
59 Cardio ankle vascular index ti.ab. (584)
60 CAVI ti.ab. (654)
61 distensibility ti.ab. (4 626)
62 arterial elasticity ti.ab.(519)
63 stiffness index ti.ab. OR β stiffness ti.ab. (1 597)
64 (OR #20-#64) (53 637)

64 (#19 AND #64) (1 081)

65 AND humans[filter] (987)

Reporting checklist for protocol of a systematic review.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			

Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6,8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	18-20
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-12

Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12