

Central-to-brachial blood pressure amplification in type 2 diabetes:  
a systematic review and meta-analysis

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## Abstract

1  
2 Due to systolic blood pressure (SBP) amplification, brachial SBP may not accurately  
3 reflect central SBP, the pressure the organs are exposed to. Patients with type 2 diabetes  
4 (T2D) have vascular irregularities that may affect blood pressure (BP) amplification  
5 and central BP indices (i.e. augmentation index [AIx] and augmentation pressure [AP]).  
6 By systematic review and meta-analysis, this study aimed firstly to determine the  
7 magnitude of central-to-brachial SBP and pulse pressure (PP) amplification in T2D  
8 compared to healthy controls and secondly, the difference in AIx and AP between the  
9 groups. Online databases were searched for published studies reporting invasive or non-  
10 invasive central and brachial SBP in T2D and healthy controls up to the 20<sup>th</sup> of February  
11 2018. Random effects meta-analyses and meta-regression were used to analyse the  
12 studies.

13 18 studies (all non-invasive; 17 radial tonometry, 1 carotid tonometry, 2 brachial  
14 oscillometry) with a total of 2,758 patients with T2D and 10,561 healthy controls were  
15 identified. There was no significant difference in SBP amplification between groups  
16 (T2D=9.9±4.7, healthy controls=9.6±4.5 mmHg, p=0.84; pooled difference=0.64  
17 mmHg, 95%CI -0.27 1.54, p=0.17) or PP amplification ratio (p=0.16). However,  
18 among these studies, central BP indices (AIx corrected for heart rate and AP) were  
19 significantly higher in T2D (p<0.05 for both). Despite a similar magnitude of central-  
20 to-brachial SBP amplification, patients with T2D have increased central systolic  
21 loading (AIx and AP) that cannot be discerned from brachial BP alone.

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## Introduction

27 High blood pressure (BP) is associated with adverse cardiovascular (CV)  
28 outcomes (1, 2). In clinical practice, BP is typically measured at the brachial artery by  
29 cuff (3); however, due to potential amplification in systolic BP (SBP), brachial SBP  
30 may not equal the pressure in the aorta (central SBP); the pressure to which the heart,  
31 brain and kidneys are exposed (4-6). Several methods are available to estimate central  
32 BP using non-invasive techniques (7). Indeed, recent meta-analysis of data from such  
33 techniques showed that central SBP had a significantly stronger relationship to target  
34 organ damage and increased CV disease risk, compared with brachial SBP (8).  
35 However, central SBP is influenced by a number of physiological factors. Specifically,  
36 among patients with type 2 diabetes mellitus (T2D), vascular irregularities (e.g.  
37 endothelial dysfunction (9), central (10-12) and peripheral (13) arterial stiffening) and  
38 increased CV disease risk factors (hyperlipidaemia (14) and smoking (15)) may have  
39 a greater influence on central rather than brachial SBP, culminating in higher central  
40 systolic stress. Thus, even taking into account that cuff brachial BP methods have  
41 variable accuracy (6), there may be particular inadequacy in capturing risk related to  
42 central BP in higher risk patients (16, 17), such as those with T2D. We have previously  
43 observed similar central-to-brachial SBP amplification in patients with T2D compared  
44 to healthy controls (18), but this has never been examined by systematic review and  
45 meta-analysis.

46 In patients with T2D, vascular dysfunction may alter the timing and direction  
47 of arterial pressure wave travel in the aorta (19, 20) and other large arteries. Waveform  
48 indices: augmentation pressure (AP); the difference between the second and first central  
49 systolic peaks, and augmentation index (AIx); AP expressed as a percentage of pulse  
50 pressure, are markers of this central systolic load that may be elevated in patients with

51 T2D (12, 21). Despite numerous studies examining AIx and AP in patients with T2D,  
52 it remains unclear as to whether these indices are systematically different compared to  
53 healthy individuals. The primary aim of this study was to determine the magnitude of  
54 central-to-brachial SBP and PP amplification in patients with T2D compared to  
55 apparently healthy controls and secondly, within the same dataset, to determine the  
56 difference in AIx and AP between the groups.

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## Materials and Methods

59 **Literature search and methods.** The search methods used in this study followed the  
60 Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) (22)  
61 and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) (23)  
62 reporting guidelines. Two reviewers (RC and MS) independently conducted a literature  
63 search of six electronic databases (MEDLINE, CINAHL, Cochrane, EMBASE, Scopus  
64 and Web of Science) independently for studies reporting both central and brachial SBP  
65 in patients with T2D from inception up to the 20<sup>th</sup> of February 2018. The screening of  
66 titles, abstracts and full-texts were done independently by the two reviewers and then  
67 the results compared. The literature search was based on the MEDLINE search strategy  
68 (Appendix) and searches of other databases were adapted to meet the specific  
69 requirements of the database. Additionally, the reference lists of relevant original and  
70 review articles were also searched.

71 **Criteria for study inclusion.** Studies were included in the systematic review if they  
72 met the following criteria: 1) a full length publication in a peer-reviewed journal; 2) a  
73 human study involving adults >18 years of age; 3) reported central and brachial SBP  
74 and diastolic BP using invasive or non-invasive techniques; 4) central and brachial SBP  
75 were measured either simultaneously or consecutively and; 5) data were reported

76 separately for individuals with T2D and a control (apparently healthy) group. Since the  
77 criteria for study inclusion could be derived from different types of study designs (e.g.  
78 observational case-control, longitudinal or controlled trials), there was no restriction on  
79 this criteria. Studies for the meta-analyses of AIx and AP were only included if they  
80 met the inclusion criteria for the primary aim as above. The Newcastle-Ottawa Scale  
81 (24) was used to assess the quality of included studies. The Scale awards a maximum  
82 of nine stars across three categories; selection of study participants (4 stars),  
83 comparability between groups of participants (2 stars) and exposure (3 stars). A greater  
84 number of stars indicates a higher quality study.

85 **Outcome measures.** The primary outcome measure was the difference in central-to-  
86 brachial SBP amplification. Secondary outcomes were central-to-brachial PP  
87 amplification, AIx, (including AIx corrected for a heart rate of 75 beats per minute  
88 [bpm]) and AP. SBP amplification was determined as brachial SBP – central SBP, and  
89 was calculated from the average brachial SBP and central SBP if not reported within  
90 individual papers. PP amplification ratio was determined by brachial PP divided by  
91 central PP. If PP (brachial or central) was not reported, it was calculated as SBP –  
92 diastolic BP (for brachial (21, 25-28) and central (21, 29) BP). Where AIx was not  
93 reported but central PP and AP were available or calculated, AIx was calculated via  
94 equation 1 below, with standard deviations calculated by the Delta method (30). In  
95 some cases, AP could not be calculated due to insufficient availability of data within  
96 the individual studies.

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98 Equation 1:

99 
$$AIx = (\text{Augmentation pressure}/\text{central PP}) \times 100$$

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101 **Data extraction.** Two reviewers (RC and PO) extracted data from each eligible study  
102 independently. For the systematic review the following data were extracted from each  
103 individual paper; the characteristics of the study population (including the age, sex,  
104 body mass index [BMI], insulin levels, glycated hemoglobin [HbA1c], medications,  
105 disease status and duration of diabetes), central and brachial SBP and diastolic BP,  
106 central PP, brachial PP, AIx, AP, heart rate, statistical methods and method of  
107 determining central and brachial SBP and diastolic BP (table 1). The study by Maple  
108 Brown et al. (26) was performed in two distinct populations (indigenous Australians  
109 and Australians with European ancestry) in which data were presented for both a group  
110 with T2D and non-diabetic subgroup. Therefore, these populations were treated as  
111 separate studies.

112 **Statistical analysis.** Random effects analyses were performed comparing the  
113 difference in central-to-brachial SBP amplification and PP amplification ratio, AIx and  
114 AP between patients with T2D and apparently healthy controls. Five separate meta-  
115 analyses were performed and studies could be included in more than one meta-analysis  
116 if the appropriate data was reported or able to be calculated. Heterogeneity between  
117 studies was reported using the  $I^2$  statistic and factors associated with heterogeneity were  
118 examined by performing meta-regression analyses to examine the effect of age, sex,  
119 BMI, heart rate, insulin levels, HbA1c, antihypertensive medication use and diabetes  
120 duration (in the diabetic group) on the difference in central-to-brachial SBP  
121 amplification between individuals with and without T2D.

122 Sensitivity analyses were performed to assess whether three studies (29, 31, 32)  
123 that used methods other than radial tonometry calibrated with SBP and diastolic BP to  
124 determine central SBP caused any difference in effect size. Sensitivity analyses were  
125 also performed to assess whether five studies (26, 29, 33-35) in which the age the

126 difference between T2D and controls was  $\geq 10$  years influenced the effect size. Three  
127 studies (21, 31, 36) reported variance as either interquartile range or 95% confidence  
128 intervals and were therefore, converted to standard deviations for analysis. In these  
129 studies, the mean or median was within the confidence intervals or interquartile range  
130 and, therefore, the data was assumed to be normally distributed. Two studies containing  
131 data from similar cohorts were included in separate analyses, one in the analysis of  
132 central-to-brachial SBP and PP amplification (33) and one in the analysis of AIx and  
133 AP (37). All data from each individual study was reported as unadjusted. Publication  
134 bias was assessed visually via funnel plots and with Eggers test for bias.

135

## Results

136 **Literature search and systematic review.** A summary of the literature search  
137 procedure and results is shown in Figure 1. The original search of six online databases  
138 revealed 20,015 original articles of which 19,906 were excluded (due to being  
139 duplications or based on review of title or abstract or both), leaving 109 potentially  
140 relevant articles that required full text reviews. 90 of these were excluded (due to  
141 required data being unavailable, unable to extract T2D data, failing to include a control  
142 group or were conference abstracts/reports), leaving 19 articles for the final systematic  
143 review (table 1) and 18 for the primary meta-analysis (one study was excluded from the  
144 meta-analysis due to duplicate data).

145 **Summary of studies included in meta-analysis.** The 18 studies eligible for meta-  
146 analysis included a total of 2,758 patients with T2D and 10,561 healthy controls.  
147 Patients with T2D were older ( $57 \pm 5$  vs  $51 \pm 5$  years,  $p=0.001$ ), of greater BMI ( $29.9 \pm 1.5$   
148 vs  $26.2 \pm 1.6$  kg/m<sup>2</sup>,  $p < 0.001$ ) and were more likely to be male (55 vs 48%,  $p=0.16$ ;  
149 table 1) compared to apparently healthy controls. The majority of the studies estimated  
150 central SBP using radial applanation tonometry and application of a generalized transfer

151 function, with only three (29, 31, 32) using alternate methods (carotid applanation  
152 tonometry, Mobil-o-graph and Arteriograph). Central and brachial SBP were elevated  
153 in patients with T2D compared to healthy controls (125±9 vs 115±11 mmHg, p=0.007  
154 and 134±9 vs 125±9 mmHg, p=0.003 respectively).

155 **Central-to-brachial SBP amplification.** The pooled central-to-brachial SBP  
156 amplification data from all studies showed that there was minimal difference between  
157 patients with T2D and healthy controls (0.64 mmHg, 95%CI -0.27, 1.54, p=0.17; figure  
158 2). The difference in age between individuals with and without T2D, did not explain  
159 the variance in the pooled central-to-brachial SBP amplification data ( $R^2 = 0\%$ ) nor did  
160 the difference in sex ( $R^2 = 0\%$ ), BMI ( $R^2 = 0\%$ ), heart rate ( $R^2 = 0\%$ ), or  
161 antihypertensive medication use ( $R^2 = 0\%$ ). However, the difference in HbA1c  
162 explained 50.9% (p=0.03) of the heterogeneity in the difference in central-to-brachial  
163 SBP amplification between those with (data available in n=872) and without T2D  
164 (n=732). Further, although non-significant, the duration of diabetes explained 16.3%  
165 (p=0.15) of the variance in central-to-brachial SBP amplification between the groups.

166 Removal of the five studies in which the age difference between patients with  
167 T2D and controls was  $\geq 10$  years, made little difference to the overall pooled result  
168 (1.06 mmHg, 95% CI -0.07, 2.18, p=0.067). Central SBP was estimated from the  
169 carotid artery rather than the aorta in the study by Chirinos et al. (31); however, removal  
170 of this study from the analysis made little difference to the overall pooled result (0.6  
171 mmHg, 95%CI -0.3, 1.5, p=0.18). Furthermore, the removal of the three studies (29,  
172 31, 32) that used alternate methods to determine central SBP other than radial  
173 tonometry, did not affect the overall pooled result (0.6 mmHg, 95%CI -0.5, 1.6,  
174 p=0.28). Stratification of the pooled difference between controls and T2D in central-to-  
175 brachial SBP amplification by quality, showed that in studies of low quality (scoring



176 <5 Newcastle-Ottawa Scale) there was little to no difference between groups (-0.06  
177 mmHg, 95%CI: -1.42 , 1.30) while there was a difference between groups in higher  
178 quality studies (1.08 mmHg, 95%CI: 0.00, 2.17). However, the difference between low  
179 and high quality studies was not statistically significant (p=0.20).

180 **Central-to-brachial PP amplification.** There was no difference between patients with  
181 T2D and healthy controls in central-to-brachial PP amplification (-0.031, 95%CI -  
182 0.074, 0.012, p=0.16; figure 3A). Nor was there a difference in PP amplification when  
183 the five studies with large age differences between groups were removed (-0.02, 95%CI  
184 -0.06, 0.02, p=0.34). The mean PP amplification was  $1.3 \pm 0.1$  mmHg in patients with  
185 T2D, and was  $1.3 \pm 0.1$  mmHg in healthy controls.

186 **Augmentation index and augmentation pressure.** AIx was calculated using equation  
187 1 in two studies (11, 21). However, insufficient data was provided to calculate AIx in  
188 six studies (18, 27, 29, 31, 36, 38) and AP in ten studies (11, 18, 27, 29, 31, 32, 35, 36,  
189 38, 39), and therefore, these studies were excluded from this analysis. Data for AIx  
190 corrected for heart rate was only available in seven studies (27, 29, 36, 37, 39-41). All  
191 but one (32) study used radial applanation tonometry to measure AIx. Of those that did,  
192 the pooled data showed that AIx was elevated in patients with T2D compared to healthy  
193 controls (2.39%, 95% CI 0.18, 4.60, p=0.03; figure 3B), as was heart rate corrected AIx  
194 (4.34%, 95% CI 2.70, 5.97, p<0.001; figure 3C). When the study that used an alternate  
195 method to measure AIx (suprasystolic waveform analysis) was included in the analysis,  
196 the difference in AIx between those with and without T2D was borderline significant  
197 (1.98%, 95% CI -0.18, 4.15, p=0.07). However, removal of the five studies in which  
198 the age difference between patients with T2D and controls was  $\geq 10$  years, rendered the  
199 difference in AIx between groups non-significant (1.53%, 95% CI -0.50, 3.55, p=0.14),  
200 but not for heart rate corrected AIx (4.97%, 95% CI 2.93, 7.02, p<0.0001).

201 AP was significantly greater in patients with T2D compared to apparently  
202 healthy controls (2.93 mmHg, 95% CI 0.93, 4.93, p=0.004; figure 3D) and remained  
203 significant after removal of the studies where the age difference between groups was  $\geq$   
204 10 years (1.87 mmHg, 95% CI 0.39, 3.35, p=0.01).

205 **Publication bias.** Funnel plots (figure 4) and Egger's test indicated that there was  
206 relatively little influence of any publication bias.

207

## 208 Discussion

209 The main findings of this study were; 1) no significant difference in central-to-  
210 brachial SBP amplification or PP amplification ratio between patients with and without  
211 T2D; 2) markers of central systolic load (AIx and AP) were significantly increased in  
212 patients with T2D compared to apparently healthy controls and; 3) both brachial and  
213 central SBP were significantly elevated in patients with T2D compared to controls.  
214 Taken together, these findings suggest that despite no difference in SBP amplification  
215 or PP amplification ratio compared to healthy controls, patients with T2D have  
216 increased central systolic load, which cannot be identified based on a traditional  
217 brachial cuff BP measures alone.

218 Central BP and markers of central systolic load have been shown to be elevated  
219 in populations at increased CV disease risk compared to controls, despite having similar  
220 brachial BP (11, 14, 41-44). In a large cohort of individuals from the Anglo-Cardiff  
221 Collaborative Trial, McEniery et al. (34) reported that diabetes was more strongly  
222 associated with higher central PP relative to brachial PP than other CV risk factors  
223 including hypertension, hypercholesterolemia and smoking. The discrepancy between  
224 central and brachial SBP is purported to be influenced by numerous demographic or  
225 physiological factors including age, sex, body mass index and heart rate (45-47).

226 Different classes of antihypertensive medications can also elicit substantial variability  
227 in SBP amplification (48, 49). Yet in our analysis, none of these potentially influential  
228 factors significantly explained the variance in SBP amplification among the study  
229 populations.

230         The difference in mean HbA1c between individuals with and without T2D  
231 explained a large part of the heterogeneity observed in the central-to-brachial SBP  
232 amplification. However, this finding should be interpreted with caution due to the small  
233 amount of data available on HbA1c. Nonetheless, given that hyperglycaemia (known  
234 to be related to increased arterial stiffness) was well controlled in some patients with  
235 T2D (26, 29, 31) compared to others (25, 26, 28), we speculate there may have been  
236 differing degrees of arterial stiffening that could have influenced central-to-brachial  
237 SBP amplification between the studies included in the meta-analysis. Further, in  
238 patients with T2D, long term exposure to CV risk factors (hyperglycaemia (50),  
239 advanced glycation end products (51)), and the duration of diabetes (52) itself,  
240 contributes to aortic stiffness (42) via adverse changes in the elastin/collagen  
241 composition of the arterial wall (53). Hashimoto and Ito (54) hypothesized that this  
242 increase in aortic stiffness may disrupt blood flow patterns in the proximal aorta (55),  
243 exaggerate diastolic flow reversal (54) and elevate central AIx, AP and SBP. Smaller  
244 aortic root diameter, may be an additional factor further augmenting central systolic  
245 load among patients with T2D (56). Our findings support these data relating to raised  
246 AIx, AP and central SBP among patients with T2D, but the concomitant increase in  
247 brachial SBP meant there was no difference in the level of central-to-brachial SBP and  
248 PP amplification compared to healthy controls. Similarly, some of our previous work  
249 (18), implies that an individual's level of central-to-brachial SBP amplification may be  
250 relatively fixed irrespective of BP level.

251 Most of the studies included in the meta-analysis estimated central SBP from  
252 radial pressure waveforms acquired by tonometry (calibrated with brachial SBP and  
253 diastolic BP) and a generalized transfer function. This approach assumes there is no  
254 SBP amplification from the brachial to radial arteries. However, significant SBP  
255 amplification in this arterial segment has been demonstrated among healthy individuals  
256 (57) as well as patients with T2D, albeit to a lesser degree in the latter ( $14 \pm 7$  vs  $9 \pm 8$   
257 mmHg,  $p=0.042$ ) (58). Failure to account for this additional SBP amplification may  
258 introduce error into estimation of central SBP (and thus, the level of SBP amplification),  
259 the magnitude of which could differ between healthy individuals and those with T2D.  
260 Another source of error among the studies examined was the use of cuff BP to calibrate  
261 waveforms, as this method has variable accuracy for determining either brachial or  
262 aortic (intra-arterial) BP (6). Lastly, diabetic-specific transfer functions to estimate  
263 central SBP may produce more accurate estimations of central SBP (59). Importantly,  
264 none of these limitations will affect AIx as a pressure independent variable.  
265 Nonetheless, more accurate non-invasive measurement of both brachial and central BP  
266 is needed to understand the true level of central-to-brachial SBP amplification in  
267 patients with T2D and healthy controls (60).

268 **Limitations.** Although reviews and reference lists of included studies were searched  
269 for additional studies, we did not search for ongoing studies or grey literature, nor were  
270 study authors contacted and thus some data may have been missed. That said, the  
271 majority of the 37 studies with missing data focused on markers other than central SBP  
272 (i.e. augmentation index) as the main outcome variable and, therefore, this limitation  
273 may not have substantially influenced the findings.

274 **Summary and conclusions.** This is the first systematic review and meta-analysis to  
275 compare central-to-brachial SBP and PP amplification ratio, AIx and AP between

276 patients with T2D and apparently healthy controls. According to conventional methods  
277 to assess these parameters, our data showed that there was no difference in central-to-  
278 brachial SBP or PP amplification between the groups, despite elevated markers of  
279 central systolic load in patients with T2D. Our findings suggest that in patients with  
280 T2D, risk related to BP may not be adequately captured via a measurement of either  
281 brachial or central SBP alone and that pressure-independent parameters such as AIx  
282 may be a useful addition.

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285 **Conflicts of interest:** None.

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### Figure legends.

482 **Figure 1.** Summary of literature search and selection procedure for articles included in  
483 the systematic review and meta-analysis. BP, blood pressure; T2D, type 2 diabetes  
484 mellitus.

485 **Figure 2.** Pooled estimates and 95% confidence intervals for amplification in central to  
486 brachial systolic blood pressure (SBP) in patients with type 2 diabetes mellitus (T2D)  
487 compared to healthy individuals.  $I^2=87.3%$   $p=0.17$ . The forest plot indicates that  
488 central-to-brachial SBP amplification was slightly, although not significantly, higher in  
489 patients with T2D.

490 **Figure 3.** Pooled estimates and 95% confidence intervals for; (A) Amplification in  
491 central to brachial pulse pressure,  $I^2=96.4%$   $p=0.15$ ; (B) augmentation index,  $I^2=90.8%$   
492  $p=0.03$ ; (C) augmentation index adjusted for a heart rate of 75 beats per minute (bpm),  
493  $I^2=61.0%$   $p<0.001$ ; (D) augmentation pressure,  $I^2=91.7%$   $p=0.004$

494 **Figure 4.** Funnel plots representing the publication bias for individual studies for each  
495 meta-analysis. (A) Central to brachial systolic blood pressure amplification; (B) central  
496 to brachial pulse pressure amplification; (C) augmentation index; (D) augmentation  
497 index corrected of heart rate of 75 beats per minute; (E) augmentation pressure. The  
498 results depict the relative absence of any publication bias.