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Walsh, Harvey J, Junejo, Rehan T , Lip, Gregory YH and Fisher, James P (2024) The effect of hypertension on cerebrovascular carbon dioxide reactivity in atrial fibrillation patients. Hypertension Research. ISSN 0916-9636

DOI: <https://doi.org/10.1038/s41440-024-01662-2>

Publisher: Springer Science and Business Media LLC

Version: Published Version

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Data Access Statement: Study data are available from the corresponding author upon reasonable request.

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The effect of hypertension on cerebrovascular carbon dioxide reactivity in atrial fibrillation patients

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Received: 25 October 2023 / Revised: 7 March 2024 / Accepted: 17 March 2024
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Abstract

Atrial fibrillation (AF) and hypertension (HTN) are both associated with impaired cerebrovascular carbon dioxide reactivity (CVR_{CO_2}), an indicator of cerebral vasodilatory reserve. We hypothesised that CVR_{CO_2} would be lower in patients with both AF and HTN (AF + HTN) compared to normotensive AF patients, due to an additive effect of AF and HTN on CVR_{CO_2} . Forty AF (68 ± 9 years) and fifty-seven AF + HTN (68 ± 8 years) patients underwent transcranial Doppler ultrasound measurement of middle cerebral artery blood velocity (MCA V_m) during stepped increases and decreases in end-tidal carbon dioxide (P_{ETCO_2}). A cerebrovascular conductance index (CVCi) was calculated as the ratio of MCA V_m and mean arterial pressure (MAP). CVR_{CO_2} was determined from the linear slope for MCA V_m and MCA CVCi vs P_{ETCO_2} . Baseline MAP was higher in AF + HTN than AF (107 ± 9 vs. 98 ± 9 mmHg, respectively; $p < 0.001$), while MCA V_m was not different (AF + HTN: 49.6 [44.1–69.0]; AF: 51.7 [45.2–63.3] cm.s^{-1} ; $p = 0.075$), and CVCi was lower in AF + HTN (0.46 [0.42–0.57] vs. 0.54 [0.44–0.63] $\text{cm.s}^{-1}.\text{mmHg}^{-1}$; $p < 0.001$). MCA V_m CVR_{CO_2} was not different (AF + HTN: 1.70 [1.47–2.19]; AF 1.74 [1.54–2.52] cm/s/mmHg^{-2} ; $p = 0.221$), while CVCi CVR_{CO_2} was 13% lower in AF + HTN (0.013 ± 0.004 vs 0.015 ± 0.005 $\text{cm.s}^{-1}.\text{mmHg}^{-1}$; $p = 0.047$). Our results demonstrate blunted cerebral vasodilatory reserve (determined as MCA CVCi CVR_{CO_2}) in AF + HTN compared to AF alone. This may implicate HTN as a driver of further cerebrovascular dysfunction in AF that may be important for the development of AF-related cerebrovascular events and downstream cognitive decline.

Keywords Atrial fibrillation · Carbon dioxide · Cerebral blood flow · Hypertension

Introduction

Atrial fibrillation (AF) is a supraventricular arrhythmia affecting 0.5–1% of the global population [1], making it the most prevalent sustained cardiac rhythm disorder. Alarmingly, this number is projected to rapidly increase over the next 30 years as populations age and modern healthcare improves survival outcomes for acute cardiac events [1, 2].

Hypertension (HTN) is a powerful risk factor for AF, and has previously been reported in 40–90% of AF cohorts [3]. In addition, HTN is likely responsible for up to 50% of all AF diagnoses [3]. Downstream complications of AF include thromboembolic events such as stroke, of which AF patients are five times more likely to develop [4], and neurodegenerative disorders including cognitive decline and dementia, even in the absence of overt stroke [5]. Similarly, HTN is a known risk factor for stroke, present in ~60% of stroke occurrences [6], as well as cognitive impairment disorders [7]. Possible mechanisms for this phenomena include silent cerebral infarction [8], inflammation [9] and cerebral hypoperfusion [10].

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41440-024-01662-2>.

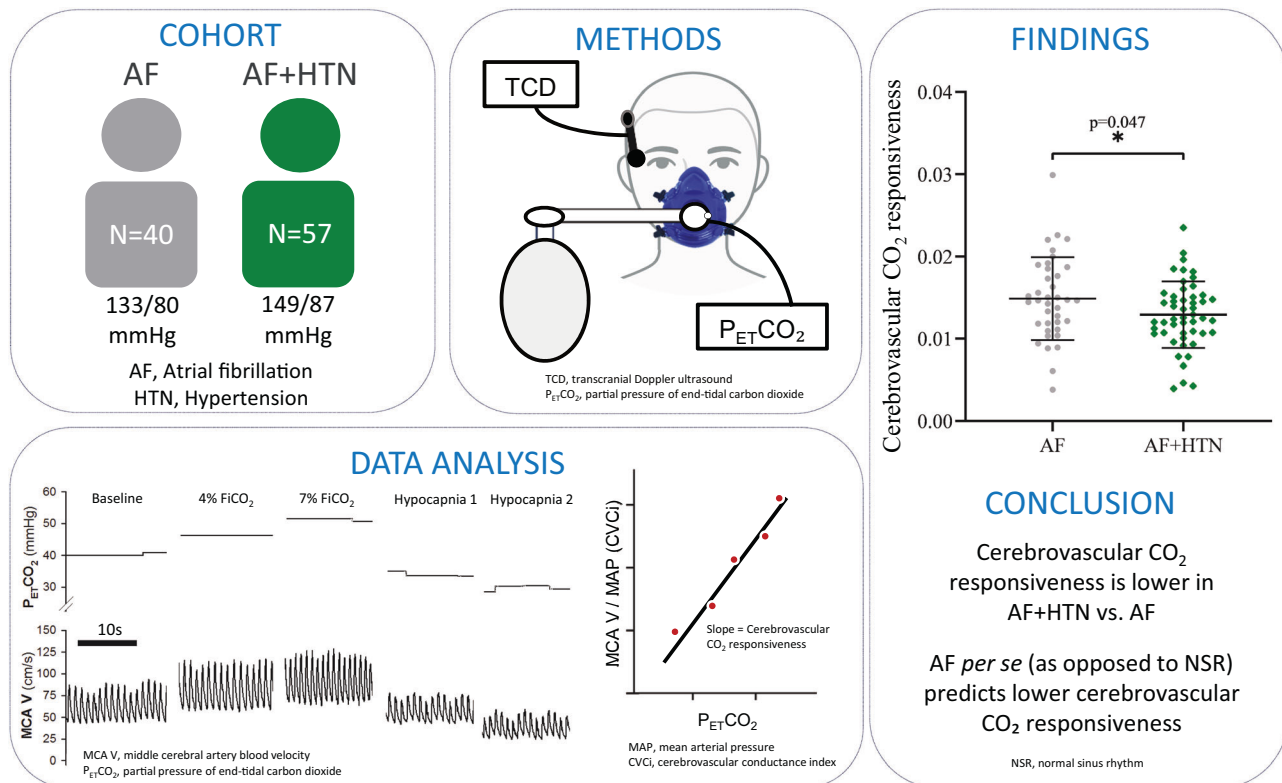
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Graphical Abstract

We demonstrated reduced cerebrovascular CO₂ responsiveness in atrial fibrillation with hypertension (AF+HTN) vs. atrial fibrillation (AF). Furthermore, AF per se (as opposed to normal sinus rhythm) predicts reduced cerebrovascular CO₂ responsiveness. Our findings suggest additional cerebrovascular dysfunction in AF+HTN vs. AF.

Cerebrovascular CO₂ Reactivity in Atrial Fibrillation with/without Hypertension



In AF, emerging evidence suggests that impaired cerebrovascular function may also contribute to this heightened risk of stroke and cognitive decline. It is currently unknown if HTN exacerbates cerebrovascular dysfunction in AF. Peripheral vascular dysfunction is well-documented in AF. Endothelium-dependent brachial artery flow-mediated dilatation is reduced in AF patients and coupled with increased levels of plasma von Willebrand factor, a known biomarker of endothelial dysfunction [11]. Furthermore, increased oxidative stress [12] and the shift to a pro-inflammatory state [13] in AF patients synergistically worsen endothelial function. Moreover, hypertension evokes similar effects on peripheral vascular function. Structural vascular remodelling evoked by increased pressures and pulsatility increases oxidative stress and inflammation [14], causing vessel stiffening and subsequent endothelial dysfunction, as evidenced by reductions in nitric oxide (NO) production in HTN [15]. Interestingly, peripheral vascular function was previously reported to not be different between a group of HTN patients and a group with both AF and HTN (AF + HTN) [16], likely due to the shared vascular pathologies between AF and HTN. Evidence of cerebrovascular dysfunction also exists in AF.

Cerebrovascular CO₂ reactivity (CVR_{CO2}), defined as the change in (Δ) cerebral blood flow (CBF) versus Δ partial pressure of CO₂ (P_aCO₂), is widely recognized as a marker of cerebral vasodilatory reserve, and has been associated with increased risk of mortality when impaired [17]. AF patients exhibit worsened CVR_{CO2} compared to healthy controls, indicative of cerebrovascular dysfunction [18]. Furthermore, neurovascular coupling, whereby cerebral blood flow is increased to support neuronal metabolic needs, is reduced in AF [19]. CVR_{CO2} responses have also been reported to be worsened in hypertension [20] although this is not a universal finding [21]. The combined effects of AF and HTN on CVR_{CO2} are yet to be determined; thus, it is still unknown whether their effects on CVR_{CO2} are additive or occlusive when concurrently present.

The aim of this study was to assess whether AF patients with HTN exhibit worsened cerebral vasodilatory reserve (i.e., poorer CVR_{CO2}) compared to normotensive AF patients. Considering the current evidence indicating the effects of AF and HTN independently on CVR_{CO2}, we hypothesized that AF patients with hypertension would exhibit lowered CVR_{CO2} compared with normotensive AF patients.

Methods

Ethical approval

The National Research Ethics Service Committee West Midlands (15/WM/0447) and North West (17/NW/0714) approved all study procedures, all of which conformed with the Declaration of Helsinki. Prospective participants received an information sheet which they were verbally guided through in detail. After addressing any questions, participants provided written informed consent.

Participant characteristics

Ninety-seven participants were included across two AF groups: AF ($n = 40$) and AF + HTN ($n = 57$). Of these, we included fifteen participants (which met the current inclusion criteria) from a previous study in which we used the same experimental approaches and outcome measures to cross-sectionally analyse cerebral vasodilatory reserve in three groups (AF, HTN and healthy controls) [18]. Patients were recruited from the following sites: Cardiology clinics at City Hospital, Birmingham, UK and Liverpool Heart and Chest Hospital, Liverpool, UK, along with National Institute of Health Research Clinical Research Network General Practitioner clinics in the UK.

All participants had previously been clinically diagnosed with AF and were included regardless of AF temporality (i.e. paroxysmal AF [fibrillation episodes are transient and spontaneously resolve within 48 h] or persistent AF [untreated fibrillation episodes last longer than 7 days before spontaneously resolving]). Study exclusion criteria included major illnesses such as cancer, liver or kidney disease, significant previous cardiovascular disease including myocardial infarction, left ventricular dysfunction, valvular heart disease, uncontrolled thyroid disorders, viral illness, connective tissue, inflammatory or neurological disease, significant cerebrovascular events such as stroke or transient ischaemic attack, alcohol abuse (>28 units per week), intravenous drug use or smoking, premenopausal women, use of oral nitrates or hormone replacement therapy and age <18 years. Tables 1 and 2 list participant characteristics and medication use respectively.

Experimental measures

A thorough participant history was recorded, including medication use, alcohol consumption and smoking habits. Using the recorded participant characteristics, each participant was calculated a CHA₂DS₂-VASc score. Anthropometric measures included height, weight, waist (umbilical level) and hip (femoral trochanter level) circumference. Non-invasive supine brachial BP was measured using an

automated oscillometric device (M2, Omron, Kyoto, Japan). Beat-to-beat BP was continuously recorded by finger photoplethysmography (Finometer MIDI, Finapres Medical Systems, Amsterdam, The Netherlands), and heart rate (HR) by lead II ECG (BioAmp, ADInstruments, Dunedin, New Zealand). An oronasal mask connected to a heated pneumotach (Hans Rudolph, Kansas City, KS, USA) was used to record minute ventilation. A sampling line connected the oronasal mask to a capnograph (RespSense, Nonin Medical, Plymouth, MN, USA) for recording of end-tidal partial pressure of CO₂ (P_{ET}CO₂). Bilateral 2 MHz transcranial Doppler probes (Doppler BosX, DWL, Sipplingen, Germany) were used to insonate the cerebral arteries fixed at their respective temporal windows, providing mean blood flow velocity (V_m) for the left posterior cerebral artery (PCA) and the right middle cerebral artery (MCA). Insonation of the MCA was successful in all participants, but only achieved in forty-seven participants (48%) for the PCA.

Experimental protocol

Pre-study guidelines included no strenuous exercise, food and caffeine intake for 12 h prior to their study, no alcohol the day before and day of their study and to refrain from consuming medication (excluding anticoagulants) on the morning of study. Physiological assessments were undertaken with participants lying supine on a bed, with their head on a pillow. After instrumentation, a 10-minute baseline period was acquired whilst participants breathed room air. During this baseline, the mean of 3 brachial BP recordings was used to correct beat-to-beat BP obtained by finger photoplethysmography. Stepped increases and decreases in P_{ET}CO₂ were then used to assess CVR_{CO2}. Hypercapnic steps involved participants breathing through a Douglas bag circuit containing 4% CO₂, followed by 7% CO₂. Gas mixtures both contained 21% oxygen (N₂ balanced). Each gas mixture was breathed for 4 min. Following hypercapnic steps, participants breathed room air to allow P_{ET}CO₂ to return to baseline. They were then required to alter their respiratory rate and depth to lower their P_{ET}CO₂ to an equal and opposite value to that achieved in the two hypercapnic steps. Each hypocapnic step was 2 minutes in duration. All participants completed the 4% hypercapnic step and its equal opposite hypocapnic step. Two participants did not complete the 7% hypercapnic step and one participant did not complete its equal opposite hypocapnic step. These participants were removed from our CVR_{CO2} analyses.

Data analysis

The ratio of height and weight squared was used to express participants BMI. Waist to hip and waist to height ratios were calculated for each participant. A multi-channel data acquisition system (Powerlab 16/35 and Labchart Pro 8.1.13,

Table 1 Participant characteristics

	AF (<i>n</i> = 40)	AF + HTN (<i>n</i> = 57)	<i>P</i> (<i>d</i> , ϕ)
Age (years)	68 ± 9	68 ± 8	0.950
Women, <i>n</i> (%)	12 (30)	17 (30)	0.985
Weight (Kg)	79 [69–88]	88 [78–100]	0.004 (0.296)
Height (m)	1.73 ± 0.09	1.73 ± 0.10	0.822
BMI (kg.m ⁻²)	26 [24–30]	30 [27–33]	<0.001 (0.355)
Waist (cm)	94 [84–101]	96 [94–105]	0.008 (0.290)
Hip (cm)	102 [99–109]	107 [103–116]	0.003 (0.327)
Waist / Hip	0.90 ± 0.08	0.90 ± 0.11	0.840
Waist / Height	0.54 ± 0.06	0.58 ± 0.06	0.007 (0.652)
Systolic BP (mmHg)	133 ± 16	149 ± 14	<0.001 (1.090)
Diastolic BP (mmHg)	80 ± 9	87 ± 12	0.001 (0.696)
MAP (mmHg)	98 ± 11	107 ± 9	<0.001 (0.908)
HR (b.min ⁻¹)	65 [58–70]	68 [61–81]	0.047 (0.202)
Fibrillating, <i>n</i> (%)	26 (67)	28 (49)	0.089
Persistent AF, <i>n</i> (%)	16 (52)	31 (61)	0.416
Diabetes, <i>n</i> (%)	1 (3)	4 (7)	0.646
CHA ₂ DS ₂ -VASc	1 [1–2]	2 [2–3]	<0.001 (0.372)
MoCA	26 ± 2	26 ± 2	0.889
Previous smoker, <i>n</i> (%)	16 (50)	27 (55)	0.653
Excessive alcohol consumption, <i>n</i> (%)	4 (10)	11 (19)	0.212

Mean ± SD displayed for normally distributed and median [interquartile range] for non-normally distributed continuous variables. Frequency (percentage) displayed for categorical discrete variables. Independent samples *t* test or Mann–Whitney U test used to infer statistical differences for continuous variables and Pearson's or Fisher's Exact Probability test for categorical data. Cohen's *d* (*d*) and Phi (ϕ) reported as effect size for significant continuous and categorical variables, respectively. Patients in AF at the time of data acquisition are identified as 'Fibrillating'. Significance: $P \leq 0.05$

AF atrial fibrillation, AF + HTN atrial fibrillation with hypertension, ϕ , Phi, BMI body mass index, BP blood pressure, HR heart rate, MAP mean arterial pressure, MoCA Montreal Cognitive Assessment

ADInstruments) was used to record and digitize analogue signals at 1 KHz. HR was calculated on a beat-to-beat basis from the ECG. Mean arterial pressure (MAP) and was obtained by integrating the arterial BP waveform over the complete cardiac cycle on a beat-to-beat basis. Similarly, V_m was obtained by integrating the MCA and PCA V_m waveforms over the complete cardiac cycle on a beat-to-beat basis. Cerebrovascular conductance index (CVCi) was calculated as the ratio of MCA V_m or PCA V_m with MAP. CVCi was not calculated if either V_m or MAP values were determined to be statistical outliers. Baseline measures were averaged over the entire 10-minute duration. Hypercapnic and hypocapnic step change measures were obtained from the final minute of the experimental period. The linear slopes of MCA V_m and PCA V_m versus $P_{ET}CO_2$ across the range of hypo- and hypercapnic steps provided CVR_{CO_2} . Outliers were defined as \pm interquartile range (IQR)*2.2 and excluded from analyses.

Statistical analysis

Shapiro-Wilk test was used to assess data normality. Levene's test was used to assess homogeneity of variance

between group data. Independent two-tailed Students *t*-test was implemented to analyse normally distributed continuous data and Mann–Whitney U test for non-normally distributed continuous data. Fisher's Exact Probability Test was used to analyse normally distributed categorical data and Pearson chi-square for non-normally distributed categorical data. Effect size for significant continuous variables reported with Cohen's *d* (*d*) and Phi (ϕ) for significant categorical variables. Two-way analysis of variance (ANOVA) was implemented to compare the effect of patient group and $P_{ET}CO_2$ on MCA V_m , MCA CVCi, PCA V_m , PCA CVCi and MAP. For ANOVA, data normality was assessed by inspection of Q-Q plots for standardized residuals. Mauchly's test of sphericity was used to assess the assumption of sphericity. If the assumption of sphericity was violated, a Greenhouse-Geisser correction was applied. Post-hoc pairwise comparisons were performed upon identification of significant main effects using *t*-test with Bonferroni correction. A forced entry regression model was used to determine the influence of variables of interest on baseline and exponential CVR_{CO_2} parameters (MCA V_m , MCA CVCi, PCA V_m and PCA CVCi). Multicollinearity

Table 2 Cerebrovascular CO₂ parameters

		AF	AF + HTN	<i>P</i> (<i>d</i>)
MCA V_m (cm.s ⁻¹ .mmHg ⁻¹) AF (<i>n</i> = 39), AF-HT (<i>n</i> = 51)	Linear	1.741 [1.543–2.517]	1.701 [1.472–2.186]	0.221
	R ²	0.952 [0.929–0.972]	0.952 [0.917–0.974]	0.533
	Exponent	0.031 [0.029–0.037]	0.032 [0.029–0.035]	0.919
	R ²	0.973 [0.950–0.992]	0.976 [0.949–0.989]	0.347
MCA CVCi (cm.s ⁻¹ .mmHg ⁻¹) AF (<i>n</i> = 38), AF-HT (<i>n</i> = 50)	Linear	0.015 ± 0.005	0.013 ± 0.004	0.047 (0.434)
	R ²	0.957 [0.920–0.984]	0.947 [0.900–0.966]	0.140
	Exponent	0.027 ± 0.007	0.027 ± 0.006	0.851
	R ²	0.957 [0.900–0.985]	0.957 [0.902–0.975]	0.674
PCA V_m (cm.s ⁻¹ .mmHg ⁻¹) AF (<i>n</i> = 19), AF-HT (<i>n</i> = 30)	Linear	1.076 ± 0.246	1.127 ± 0.352	0.587
	R ²	0.948 [0.919–0.979]	0.936 [0.876–0.967]	0.145
	Exponent	0.036 ± 0.011	0.035 ± 0.112	0.648
	R ²	0.968 [0.921–0.987]	0.965 [0.911–0.986]	0.608
PCA CVCi (cm.s ⁻¹ .mmHg ⁻¹) AF (<i>n</i> = 20), AF-HT (<i>n</i> = 29)	Linear	0.008 ± 0.002	0.009 ± 0.003	0.892
	R ²	0.964 [0.899–0.988]	0.935 [0.878–0.978]	0.130
	Exponent	0.031 ± 0.010	0.031 ± 0.013	0.852
	R ²	0.963 [0.885–0.986]	0.949 [0.863–0.967]	0.170

Mean ± SD displayed for normally distributed and median [interquartile range] for non-normally distributed variables. Independent samples t-test or Mann–Whitney U test used to infer statistical differences. Cohen’s *d* reported as effect size for significant variables. Significance: *p* ≤ 0.05

AF atrial fibrillation, AF + HTN, atrial fibrillation with hypertension, CVCi conductance index, MCA middle cerebral artery, PCA posterior cerebral artery, V_m mean velocity

and autocorrelation were tested to reduce the risk of regression model violations. Tolerance, variance inflation factor, and Durbin-Watson statistic were 0.570–0.950, 1.053–1.755 and 1.754–2.520 respectively. Mean ± standard deviation (SD) are presented for normally distributed data, median [interquartile range] for non-normally distributed data and frequency (percentage) for categorical data. Statistical significance was considered as *p* < 0.05. Analysis was performed using SPSS, version 27 (IBM Corp., Armonk, NY, USA).

Results

Participant characteristics

Age and the proportion of males and females was not different in the AF and AF + HTN groups (Table 1). AF + HTN exhibited greater systolic BP (*p* < 0.001), diastolic BP (*p* = 0.001), MAP (*p* < 0.001), HR (*p* = 0.047), weight (*p* = 0.004), BMI (*p* < 0.001), waist (*p* = 0.008) and hip (*p* = 0.003) measurements, waist-to-height ratio (*p* = 0.007), and CHA₂DS₂-VASc scores (*p* < 0.001). The proportion of participants who were fibrillating at the time of the study, had a diagnosis of persistent AF, were diabetic, had previously smoked or previously consumed excessive alcohol (> 14 units a week) were not different between AF and AF + HTN groups (*p* > 0.05). AF + HTN had more frequent

ACE inhibitor (*p* < 0.001), Ca²⁺ channel inhibitor (*p* < 0.001), ARB (*p* < 0.001), statin (*p* = 0.017) and SSR inhibitor (*p* = 0.018) use (Supplementary Table 1).

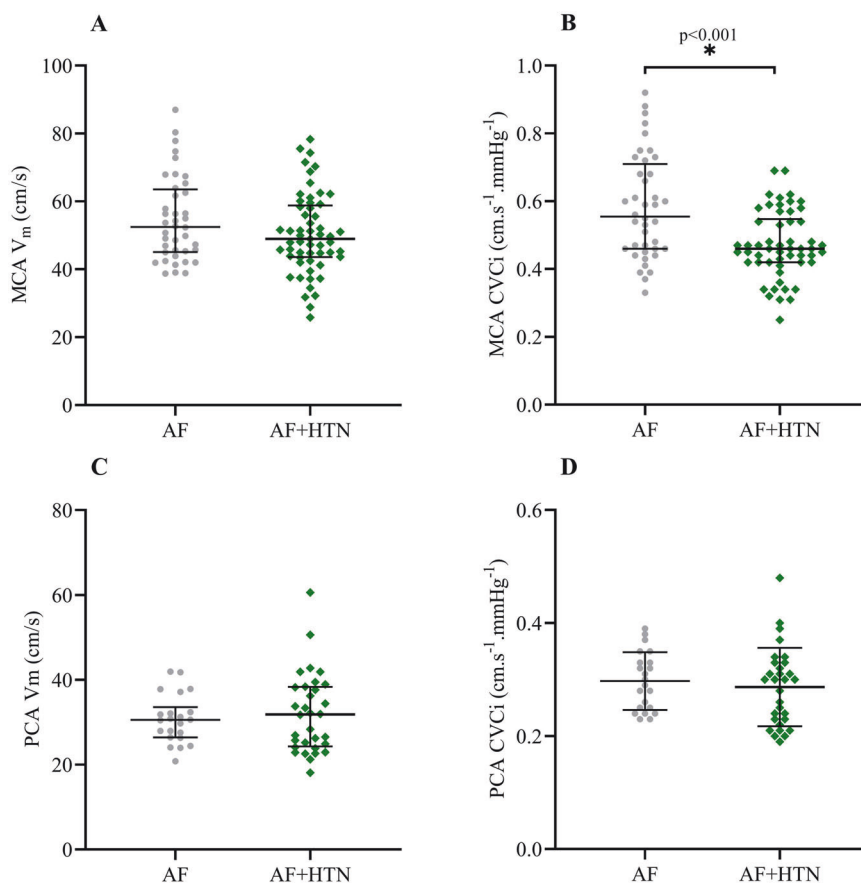
Baseline cerebral hemodynamics

Figure 1 shows baseline cerebrovascular measures. MCA V_m was numerically lower in AF + HTN (49.6 [44.1–60.0] cm.s⁻¹) compared to AF (51.7 [45.2–63.3] cm.s⁻¹), but did not reach statistical significance (*p* = 0.075). MCA CVCi was lower in AF + HTN (0.46 [0.42–0.55] cm.s⁻¹.mmHg⁻¹) compared to AF (0.56 [0.46–0.71] cm.s⁻¹.mmHg⁻¹; *p* < 0.001). No differences were observed between groups for either PCA V_m (AF: 30.5 [26.4–33.6]; AF + HTN: 31.8 [24.3–38.4] cm.s⁻¹; *p* = 0.731) or PCA CVCi (AF: 0.30 ± 0.05; AF + HTN: 0.29 ± 0.07 cm.s⁻¹.mmHg⁻¹; *p* = 0.548). Baseline P_{ET}CO₂ was not different between groups (AF: 39.8 ± 0.7 mmHg; AF + HTN: 40.1 ± 0.7 mmHg; *p* = 0.813).

Cerebrovascular reactivity

MCA V_m, MCA CVCi, PCA V_m, and PCA CVCi increased progressively with each stepped increase in P_{ET}CO₂ (all *p* < 0.001). MAP increased during the 7% hypercapnic step versus all other steps (all *p* < 0.001). MCA CVCi and MAP were lower in AF + HTN than AF (group effect, *p* < 0.001 and *p* = 0.002, respectively), while MCA V_m, PCA V_m and PCA CVCi were not different between AF and AF + HTN

Fig. 1 Baseline MCA V_m (A), MCA CVCi (B), PCA V_m (C), and PCA CVCi (D) in participants with AF or AF + HTN. Individual values plotted with bars displaying median and interquartile range for MCA V_m , MCA CVCi and PCA V_m , and mean and standard deviation for PCA CVCi. AF atrial fibrillation; AF + HTN atrial fibrillation with hypertension; MCA V_m middle cerebral artery mean blood velocity; PCA V_m posterior cerebral artery mean blood velocity; MCA CVCi middle cerebral artery cerebrovascular conductance index; PCA CVCi posterior cerebral artery cerebrovascular conductance index



groups (all $p > 0.05$). No interaction was observed between group and $P_{ET}CO_2$ for any variable examined ($p > 0.05$), although there was a strong tendency ($p = 0.083$) for an interaction between group and $P_{ET}CO_2$ for MCA CVCi (Supplementary Fig. 1).

Indices of CVR_{CO_2} are displayed in Table 2 and Fig. 2. MCA CVCi CVR_{CO_2} was significantly lower in AF + HTN (0.013 ± 0.004 $cm/s/mmHg^{-2}$) compared to AF (0.015 ± 0.005 $cm/s/mmHg^{-2}$; $p = 0.047$). However, MCA V_m CVR_{CO_2} (AF: 1.741 [1.543–2.517]; AF + HTN: 1.701 [1.472–2.186] $cm/s/mmHg^{-2}$; $p = 0.221$), PCA V_m (AF: 1.076 ± 0.246 ; AF + HTN: 1.127 ± 0.352 $cm/s/mmHg^{-2}$; $p = 0.587$) and PCA CVCi (AF: 0.008 ± 0.002 ; AF + HTN: 0.009 ± 0.003 $cm/s/mmHg^{-2}$; $p = 0.892$) were not different between groups.

Forced entry regression

Significant predictors of baseline variables and CVR_{CO_2} as identified from forced entry linear regression are shown in Table 3. Fibrillation (vs normal sinus rhythm [NSR]) at the time of the experimental visit was associated with a lower MCA V_m CVR_{CO_2} . The presence of hypertension was associated with a lower baseline MCA CVCi, and being female was associated with higher baseline MCA V_m and

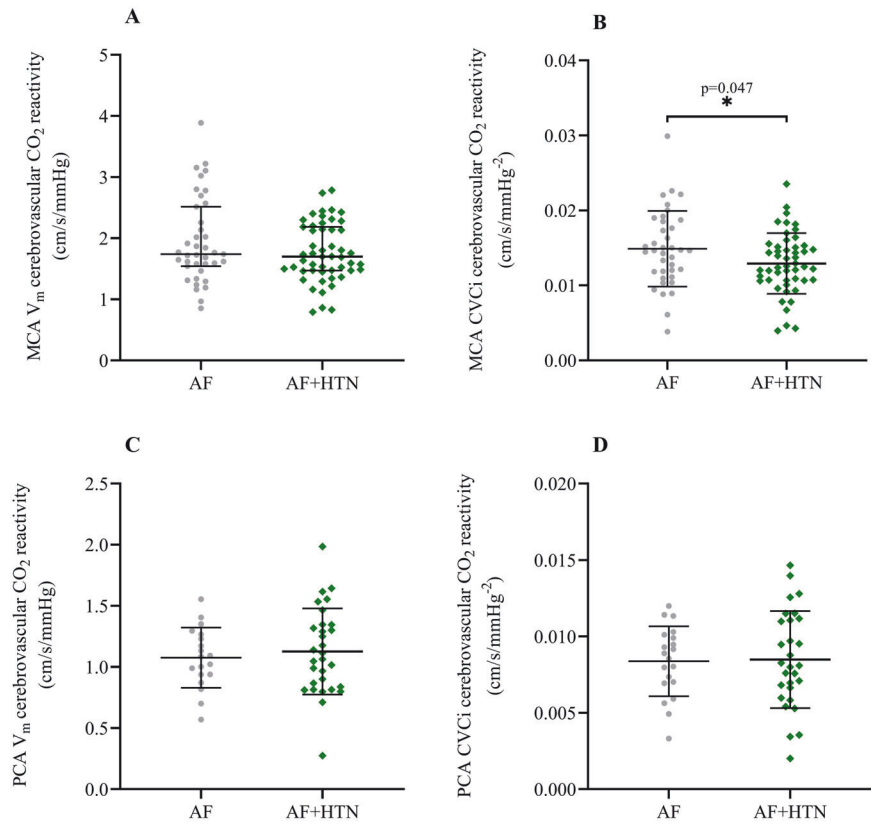
baseline MCA CVCi. None of our entered independent variables were found to be associated with baseline PCA V_m , baseline PCA CVCi, MCA CVCi CVR_{CO_2} , PCA V_m CVR_{CO_2} and PCA CVCi CVR_{CO_2} .

Discussion

This is the first study to investigate whether the presence of HTN as a comorbidity in AF worsens CVR_{CO_2} . The major novel finding of the present study is that CVCi CVR_{CO_2} is lowered in AF + HTN compared to AF, and may implicate an additional level of cerebrovascular dysfunction in AF + HTN. This may be important for the development of cerebrovascular events and downstream cognitive decline commonly associated with AF.

Baseline MCA V_m was not different between AF and AF + HTN groups, indicating that cerebral perfusion at rest is retained in AF + HTN similar to that in AF. It is well accepted that there is a rightward shift in the cerebral autoregulatory curve in HTN, whereby CBF is maintained similarly to that in normotensives with higher MAP [22]. This may explain our conflicting baseline responses in terms of MCA V_m and CVCi. As a consequence of increased baseline MAP in AF + HTN, MCA CVCi is

Fig. 2 MCA V_m (A), MCA CVCi (B), PCA V_m (C) and PCA CVCi (D) CVR_{CO_2} in participants with AF or AF + HTN. CO_2 reactivity is expressed as the change in (Δ) MCA V_m , MCA CVCi, PCA V_m and PCA CVCi versus $\Delta P_{ET}CO_2$ in mmHg. Bars display median and interquartile range for MCA V_m CVR_{CO_2} , and mean and standard deviation for MCA CVCi, PCA V_m and PCA CVCi CVR_{CO_2} . AF atrial fibrillation; AF + HTN atrial fibrillation with hypertension; CVR_{CO_2} cerebrovascular carbon dioxide reactivity; MCA V_m middle cerebral artery mean blood velocity; PCA V_m posterior cerebral artery mean blood velocity; MCA CVCi middle cerebral artery cerebrovascular conductance index; PCA CVCi posterior cerebral artery cerebrovascular conductance index; $P_{ET}CO_2$ partial pressure of end-tidal carbon dioxide



lowered, in order to buffer the transmission of peripheral BP to CBF. This may be explained due to HTN evoked remodelling, hypertrophy and stiffening within the cerebral arteries and arterioles, resulting in increased wall-lumen ratios and decreased vessel diameters [23]. These effects on the vasculature may be explained by a number of interconnected processes. Oxidative stress is heightened in HTN, and promotes proliferation of vascular smooth muscle cells as well as extracellular matrix remodelling [14]. Elevated reactive oxygen species (ROS) can also drive inflammation in HTN, resulting in further vascular hypertrophy. Indeed, elevated markers of inflammation, including C-reactive protein and interleukin-6, are independently associated with HTN [24]. Furthermore, the direct mechanical effects of heightened pressure on vessel walls can promote hypertrophy and remodelling through activation of extracellular matrix protein cascades, whereby noncellular material accumulates within vessel walls [25]. This can also drive ROS production, resulting in a pathological cycle of cerebrovascular remodelling.

Interestingly, in the present study we have shown a reduction in MCA CVCi CVR_{CO_2} in AF + HTN but no difference in MCA V_m CVR_{CO_2} between AF and AF + HTN. This offers distinct insight from our previous work, where we compared CVR_{CO_2} in separate groups with either AF, HTN, or healthy controls (i.e. normotensive and with a normal sinus rhythm), and demonstrated lower MCA V_m

CVR_{CO_2} in AF versus HTN and healthy controls. The current study, in which all patients studied had AF, suggests that in AF + HTN, CO_2 -mediated increases in CBF per unit pressure are blunted. The use of a conductance index allows us to somewhat account for changes in perfusion pressure and provides more insight to vasodilator responsiveness. Lowered CVCi CVR_{CO_2} may be indicative of additional cerebrovascular dysfunction evoked by HTN. The aforementioned HTN induced cerebrovascular remodelling will have functional consequences in terms of vascular responsiveness to CO_2 that may drive differences in CVCi CVR_{CO_2} between our AF + HTN and AF groups. In addition, endothelial damage/dysfunction associated with oxidative stress, inflammation, and reductions in NO bioavailability [26] and known to be present in both HTN and AF may also contribute and summate to worsen CVCi CVR_{CO_2} in AF + HTN. In contrast, brachial artery flow mediated dilatation, a marker of peripheral endothelial function, is not different in HTN versus AF + HTN [16], and might suggest a stronger contribution of HTN than AF to peripheral/cerebrovascular dysfunction [22].

Forced entry regression suggested patients that were fibrillating at the time of study (as opposed to being in NSR) exhibited lower MCA V_m CVR_{CO_2} . MRI and xenon inhalation studies have previously shown improved CBF in AF patients who underwent NSR restoration procedures [27, 28], suggesting a direct effect of fibrillation on cerebral perfusion

Table 3 Forced entry multiple regression with baseline MCA V_m ($\text{cm}\cdot\text{s}^{-1}$), baseline MCA CVCi ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$), baseline PCA V_m ($\text{cm}\cdot\text{s}^{-1}$), baseline PCA CVCi ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$), MCA V_m ($\text{cm}\cdot\text{s}^{-1}$), MCA CVCi ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$), PCA V_m ($\text{cm}\cdot\text{s}^{-1}$) and PCA CVCi ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$) as dependent variables

Dependent variables	β	95% CI for β	p
Baseline MCA V_m ($\text{cm}\cdot\text{s}^{-1}$) R = 0.472; R ² = 0.223; Adjusted R ² = 0.126; p = 0.050			
Sex	0.297	0.915–14.843	0.027
Baseline MCA CVCi ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$) R = 0.590; R ² = 0.348; Adjusted R ² = 0.265; p = 0.002			
Hypertension	-0.373	-0.169–0.036	0.003
Sex	0.302	0.017–0.161	0.016
Baseline PCA V_m ($\text{cm}\cdot\text{s}^{-1}$) R = 0.334; R ² = 0.111; Adjusted R ² = -0.094; p = 0.770			
Baseline PCA CVCi ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$) R = 0.315; R ² = 0.099; Adjusted R ² = -0.117; p = 0.831			
MCA V_m CVR _{CO₂} ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$) R = 0.459; R ² = 0.211; Adjusted R ² = 0.108; p = 0.078			
Fibrillating	-0.466	-0.965–0.138	0.010
MCA CVCi CVR _{CO₂} ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$) R = 0.419; R ² = 0.176; Adjusted R ² = 0.068; p = 0.159			
PCA V_m CVR _{CO₂} ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$) R = 0.405; R ² = 0.164; Adjusted R ² = -0.037; p = 0.568			
PCA CVCi CVR _{CO₂} ($\text{cm}\cdot\text{s}^{-1}\cdot\text{mmHg}^{-1}$) R = 0.297; R ² = 0.088; Adjusted R ² = -0.140; p = 0.880			

Age, sex, cardiac rhythm at the time of data acquisition (AF versus normal sinus rhythm), type of AF (i.e. paroxysmal versus persistent), years since AF diagnosis, and hypertension status (yes/no) variables were entered into the model. The predictor variable ‘Fibrillating’ indicates AF cardiac rhythm (as opposed to normal sinus rhythm) during data acquisition

α alpha, β beta, CI confidence interval, CVCi cerebrovascular conductance index, MAP mean arterial pressure, MCA middle cerebral artery, PCA posterior cerebral artery, V_m mean velocity, AF atrial fibrillation

per se. However, in earlier work [18] we observed that MCA V_m was lower in AF patients that were fibrillating at the time of study compared to those in NSR, but MCA V_m CVR_{CO₂} was not different. Differences in sample size ($n = 97$ in the present study vs. $n = 31$ in Junejo et al. [18]) and the analytical approach employed, may partly explain the discrepant findings, and further work is required to better understand how AF per se affects CVR_{CO₂} and by what mechanisms.

The anterior and posterior cerebral circulations differ in regards to CVR_{CO₂}, with the posterior cerebral circulation exhibiting absolute CVR_{CO₂} values ~ 50% lower than that seen in the anterior cerebral circulations [29, 30], which our results generally agree with. Additionally, differences may exist in endothelial function between the two circulations, as endothelium-derived NO has been shown to play a greater role in vasodilatory responses in the anterior cerebral circulation [31]. Notably, baseline PCA and PCA CVR_{CO₂} measures were not different between AF and AF + HTN. This may indicate preserved endothelial function in the posterior cerebral circulation in AF + HTN vs. AF groups.

Our findings should be interpreted in light of several experimental considerations. While transcranial Doppler ultrasound offers real-time measurements of cerebrovascular function, is non-invasive and easy to implement

during physiological interventions, its inability to directly measure blood flow is a limitation. Vessel diameter cannot be measured with transcranial Doppler, thus changes in cerebral blood velocity may not be directly indicative of CBF changes. However, as transcranial Doppler-derived V_m changes have been significantly correlated with gold standard measures of CBF (i.e., gadolinium tracer MRI and arterial spin labelling MRI [32]) V_m values are generally considered proportional to CBF. P_{ET}CO₂ has a strong positive correlation with P_aCO₂ [33], and acts as a reliable non-invasive surrogate measure, though we acknowledge its possible underestimation of P_aCO₂ at rest [34]. There is debate surrounding the optimal method for assessing cerebrovascular function [35]. The advantages of using fixed concentrations of CO₂ (4 and 7%) as in the present study, is that the experimental set-up is relatively simple, inexpensive, convenient in the clinic, does not require a complex computerised gas delivery system, and requires minimal participant cooperation. This method has also shown good between-day test-retest reliability [18]. Our primary measure of cerebrovascular responsiveness (i.e., CVCi CVR_{CO₂}) was derived from the linear slope of the relationship between P_{ET}CO₂ and MCA CVCi for each patient and was significantly ($p = 0.047$) lower in AF + HTN

versus AF. While a tendency ($p = 0.083$) for an interaction between Group and $P_{ET}CO_2$ was observed for MCA CVCi (Supplementary Fig. 1B) this did not reach significance. This discrepancy is likely caused by differences in the methods of data analysis used. We did not screen for the presence of subclinical brain infarcts, although patient history and clinical records did not suggest any presence of these. In addition, although participants were requested to refrain from consuming medications on the morning prior to their study visit, it is unlikely that this was sufficient to cause full washout prior to data acquisition. Finally, it is a limitation of the current study that a healthy control group (i.e., normotensive and NSR) was not recruited, however we believe that this does not diminish our ability to achieve the primary aim of the study which was to determine whether the presence of HTN in AF worsens cerebrovascular responsiveness.

In conclusion, this is the first study that demonstrates reduced CVR_{CO_2} in AF patients with concurrent HTN as compared to normotensive AF patients. This may be important for clinical management due to the possible heightened risk of cerebrovascular events and downstream cognitive decline.

Data availability

Study data are available from the corresponding author upon reasonable request.

Acknowledgements We wish to thank all the volunteers for their enthusiastic participation in this study.

Author contributions JPF and GYHL conception, RTJ data collection and extraction, HJW data analysis, statistical analysis, figure preparation and draft of manuscript, HJW, RTJ, GYHL and JPF revision, critique and final manuscript approval.

Funding This study was supported by Bristol-Myers Squibb / Pfizer Alliance Project Grant CV185-481, British Heart Foundation Project Grant PG/15/45/31579, Royal Society Te Apārangi Marsden Fund UOA1903, and the National Institute of Health Research Clinical Research Network (NIHR CRN). Open Access funding enabled and organized by CAUL and its Member Institutions.

Compliance with ethical standards

Conflict of interest GYHL is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseeon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and DaiichiSankyo. No fees are directly received personally. JPF has received funding from BMS/Pfizer for an investigator-led and competitively reviewed research project. RTJ was previously employed by University of Birmingham as a research fellow on BMS/Pfizer funded, investigator-led and competitively reviewed research project which he managed. This required regular contact with funders for continued project grant support. No fees/funds were directly received personally.

Ethical approval Ethical approval was received from the National Research Ethics Service Committee West Midlands (15/WM/0447) and North West (17/NW/0714).

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