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Impaired cerebrovascular reactivity in patients with atrial fibrillation: A novel mechanism for cerebrovascular events

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Abbreviations: AF, atrial fibrillation; CVR_{CO2}, cerebrovascular reactivity to carbon dioxide; $MCAv_{mean}$, middle cerebral artery mean blood flow velocity; $P_{ET}CO_2$, end-tidal carbon dioxide partial pressure.

Atrial fibrillation (AF) is the most common sustained cardiac rhythm abnormality and associated with substantial risk of stroke and thromboembolism, leading to low quality of life and high mortality. Patients with AF are at heightened risk of cognitive decline and dementia, even in the absence of a medical history of past stroke (1). One factor that potentially contributes to these complications is an impairment in cerebrovascular reactivity. The cerebral vasculature is very sensitive to changes in arterial carbon dioxide. Cerebrovascular CO_2 reactivity (CVR_{CO2}) is impaired in several neurodegenerative disorders, and independently predicts the occurrence of ischemic stroke (2) and cardiovascular mortality. We aimed to test the hypothesis that CVR_{CO2} is reduced in AF.

CVR_{CO2} was determined in patients with AF (n=31, 69 [64, 72] years, median [interquartile range]), hypertension (n=31, 68 [65, 72] years) and healthy controls (n=30, 69 [66, 73] years), from the slope of the change in middle cerebral artery mean blood flow velocity ($MCAv_{mean}$; transcranial Doppler ultrasound) versus end-tidal CO_2 partial pressure ($P_{ET}CO_2$) between two 4-min hypercapnic steps of 4% and 7% CO_2 (~21% Oxygen, Nitrogen balanced) delivered via the open circuit steady-state method (3). AF patients had a diagnosis of paroxysmal or persistent AF, whilst hypertensives were also clinically diagnosed (i.e., consistent non-clinical ambulatory blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg). Patients with hypertension served as a ‘disease control’ group to account for the effect of medications and comorbidities. All procedures performed were approved by the National Research Ethics Service Committee West Midlands (13/WM/0210 and 15/WM/0447) and conformed to the Declaration of Helsinki (2008).

CVR_{CO2} was ~31% lower in patients with AF versus healthy controls and patients with hypertension ($P<0.001$) (Figure 1A). Systemic endothelial dysfunction (increased plasma von Willebrand factor, reduced nitrite/nitrate product and impaired brachial artery flow-mediated dilatation) has been reported in AF, possibly due to the irregular heart rhythm

causing alterations in shear stress pattern (5), and may account for the diminished CVR_{CO2} observed. Cerebral perfusion, (i.e., $MCAv_{mean}$) was ~16% lower in patients with AF (51.0 [12.9] $cm \cdot s^{-1}$, mean [standard deviation]) and ~13% lower in patients with hypertension (53.1 [11.1] $cm \cdot s^{-1}$), when compared to healthy controls (60.9 [12.9] $cm \cdot s^{-1}$) (P=0.006). AF patients that were fibrillating when studied (55% of total) had a lower MCA V_{mean} (31.1 [8.7] $cm \cdot s^{-1}$) than those not fibrillating (59.2 [10.5] $cm \cdot s^{-1}$) (P<0.001). Low cerebral perfusion can lead to vasodilatation of cerebral arterioles, thus reducing vasodilatory reserve and interfering with cerebral autoregulation. However, CVR_{CO2} was not different between AF sub-groups (P=0.303) (Figure 1B) suggesting that baseline cerebral perfusion *per se* was not a major determinant of the blunted CVR_{CO2} response, pointing to another shared factor (e.g., endothelial dysfunction).

CVR_{CO2} was not different in hypertensives and normotensives, in agreement with some, but not all previous studies. These inconsistent findings may be attributable to differences in patient characteristics (medications, hypertension etiology and severity) and the methodological approach utilized. A variety of approaches have been developed to determine CVR_{CO2} and the relative merits are debated (4). CVR_{CO2} and $MCAv_{mean}$ showed a good between-day test-retest reliability (intraclass correlation of 0.938 [95% CI 0.759-0.985] P<0.001and 0.981 [0.923-0.995] P<0.001; co-efficient of variation for the method error of 6.06% and 2.95%, respectively), and CVR_{CO2} demonstrated an area under the receiver operating characteristic curve of 0.78 [0.66, 0.89].

In summary, AF patients had a lower cerebral perfusion and impaired CVR_{CO2} when compared to healthy controls. A poor CVR_{CO2}, indicative of a limited cerebral vascular reserve, may serve as an “early warning” of cerebrovascular dysfunction and worsen stroke outcome in AF by further compromising the cerebral circulation, increasing infarction size, and delaying functional recovery after ischemia. AF patients that were fibrillating when

examined had a worse cerebral perfusion than those who were not. Low cerebral perfusion is associated with white matter damage and lower cognitive test scores. Collectively, our observations may have implications for AF-related cognitive decline, cerebrovascular events and mortality, and require further exploration.

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FIGURE

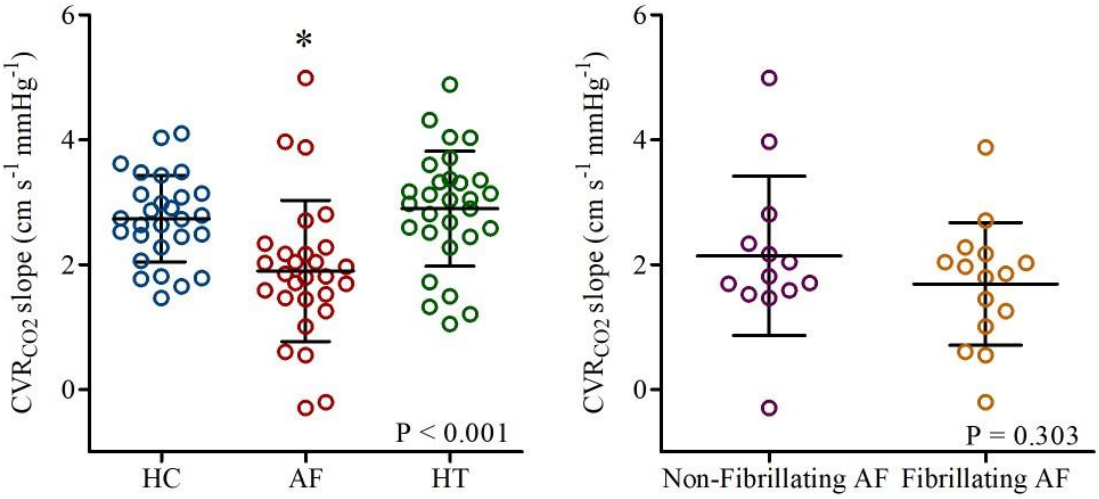

Figure 1. Cerebrovascular carbon dioxide reactivity (CVR_{CO2}) in healthy controls (HC), patients with atrial fibrillation (AF) and hypertension (HT) (left), along with AF-sub-groups (right). Horizontal bars show mean and standard deviation. *P<0.05 vs. HC and HT.