temperature was infused at 20 ml/min through the RayFlow catheter to measure hyperemic absolute flow (4,5). Under this steady state hyperemia, the balloon catheter was slowly inflated to obtain a graded, controlled stenosis. **Figure 1A** shows the simultaneously recorded aortic and distal coronary pressures and thermodilution-derived proximal LAD flow (Q_S) during steady state maximal hyperemia. **Figure 1B** shows the corresponding hyperemic pressure-flow relationship. Aortic and distal coronary pressures were corrected for a coronary wedge pressure of 20 mm Hg (P_w, measured but not displayed). This relationship is linear, and its intercept is close to zero ($y = 0.87x + 0.04$; $R = 0.99$ [95% confidence interval: 0.98 to 0.99]; $p < 0.001$).

These results confirm earlier animal data and demonstrate the linearity of the hyperemic pressure/flow relationship during hyperemia in humans, thus confirming the theoretical background of FFR measurements.

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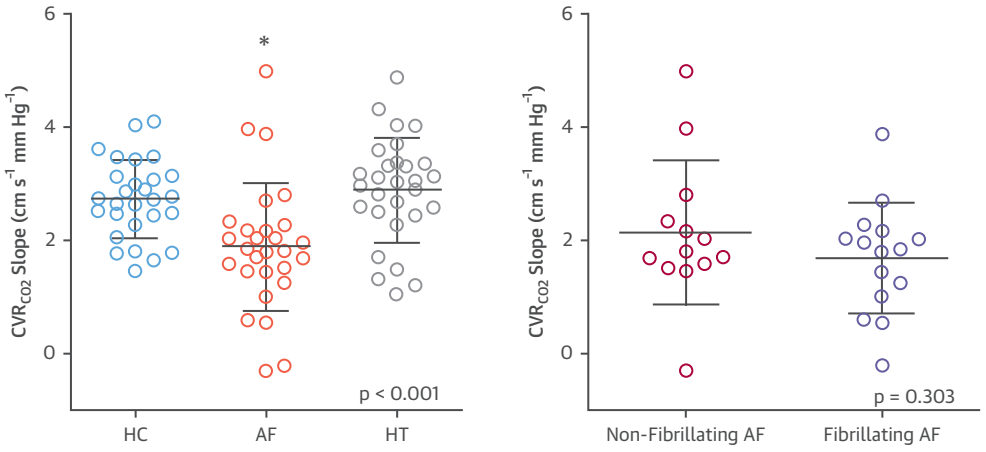
Impaired Cerebrovascular Reactivity in Patients With Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac rhythm abnormality and is 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 (CO_2). 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 ($n = 31$; median age 69 years [interquartile range (IQR): 64 to 72 years]), patients with hypertension ($n = 31$; median age 68 years [IQR: 65 to 72 years]), and healthy control subjects ($n = 30$; median age 69 years [IQR: 66 to 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 2 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, while hypertensive patients were also clinically diagnosed (i.e., consistent nonclinical ambulatory blood pressure of systolic >140 mm Hg and/or diastolic >90 mm Hg). 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 control subjects and patients with hypertension ($p < 0.001$) (**Figure 1A**). Systemic endothelial dysfunction (increased plasma von Willebrand factor,

FIGURE 1 CVR_{CO2} in HC, in Patients With AF and HT, and in AF Subgroups



Cerebrovascular carbon dioxide reactivity (CVR_{CO2}) in healthy controls (HC) and in patients with atrial fibrillation (AF) and hypertension (HT) **(left),** along with AF subgroups **(right). Horizontal bars** show mean and SD. *p < 0.05 versus HC and HT.

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 (4), and may account for the diminished CVR_{CO2} observed. Cerebral perfusion, (i.e., $MCAv_{mean}$) was ~16% lower in patients with AF (mean 51.0 ± 12.9 $cm \cdot s^{-1}$) and ~13% lower in patients with hypertension (53.1 ± 11.1 $cm \cdot s^{-1}$) when compared with healthy control subjects (60.9 ± 12.9 $cm \cdot s^{-1}$) ($p = 0.006$). AF patients who were fibrillating when studied (55% of total) had a lower $MCAv_{mean}$ (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 subgroups ($p = 0.303$) (**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 hypertensive and normotensive patients, 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 (5). CVR_{CO2} and $MCAv_{mean}$ showed a good between-day test-retest reliability (intraclass correlation of 0.938; 95% confidence interval [CI]: 0.759 to 0.985; $p < 0.001$; and 0.981; 95% CI: 0.923 to 0.995; $p < 0.001$; coefficient 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 (95% CI: 0.66 to 0.89).

In summary, AF patients had a lower cerebral perfusion and impaired CVR_{CO2} when compared with healthy control subjects. 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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Racial Differences in SCD Risk

No Easy Explanations

I read with interest the recent paper by Deo et al. (1), which investigated differences in sudden cardiac death (SCD) risk between blacks and whites. The authors demonstrate that in a large cohort, after hierarchical adjustment for a number of risk factors, blacks have a 2-fold higher risk of SCD than whites.

I was dismayed, however, to read their conclusion that "racial differences in the underlying pathophysiology of SCD" may explain this difference in risk, which persists even "after controlling for sociodemographic and cardiovascular risk factors." The implication is that blacks may possess an "underlying susceptibility to fatal arrhythmias" (1).

Our understanding of human genetics does not support this notion. Race is a complex, socially-constructed phenomenon encompassing an individual's experience across the life course. It is not based in any essential quality specific to 1 group (2). Even in those cases where black ancestry-related gene variants have been associated with disease (e.g., *APOL1*, where certain variants are overrepresented among persons of African descent), their absolute contribution to excess mortality is small (3).

The authors do acknowledge the possibility of residual confounding, especially relating to covariates of education and income. Education and income variables, as they are often interpreted in published health disparities data, are at best weak proxies for what they purport to measure—in the case of blacks in the United States, the sequelae of historically rooted structural racism (4).

The authors rightly call for additional research into racial differences in SCD risk. But it is inaccurate to conjecture that these differences are due to some underlying racial predisposition. To do so is to elide the larger-scale, societal causes of black-white health disparities in the United States while reifying the pernicious idea that people can be placed into biologically distinct categories.

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