

## Do the Natriuretic Peptides Cause Atrial Fibrillation or is it Not So Black and White?

Arthur Mark Richards, BA, MB ChB, MD, PhD, DSc

In community-based populations, whites incur higher incident atrial fibrillation (AF) compared with blacks and other ethnicities.<sup>1</sup> Plasma concentrations of NT-proBNP (N-terminal probrain natriuretic peptide), a marker of cardiovascular risk, are higher in whites than blacks.<sup>2</sup> Both phenomena occur in spite of a greater burden of risk factors in blacks compared with whites. In this issue of the *Journal of the American Heart Association (JAHA)*, Whitman et al have confirmed both paradoxical interracial differences in 4731 (770 black) participants in the CHS (Cardiovascular Health Study), corroborated in 12 418 (3091 black) participants from the ARIC (Atherosclerotic Risk in the Community) study.<sup>3</sup> In both cohorts, plasma NT-proBNP was  $\approx 40\%$  higher in whites than in blacks. Among CHS participants, whites had a greater risk of incident AF than blacks (hazard ratio 1.60, 95% CI 1.31–1.93,  $P < 0.001$ ). Whites in the ARIC study also had a greater risk of incident AF than blacks (1.93, 95% CI 1.57–2.27,  $P < 0.001$ ). These data confirm these 2 inter-ethnic differences as previously documented separately.<sup>1,2</sup> Each doubling of NT-proBNP was associated with an  $\approx 50\%$  increase in incident AF.<sup>3</sup>

The investigators report “NT-proBNP levels explained a significant proportion of the racial difference in AF risk (CHS: 36.2%, 95% CI 23.2–69.2%; ARIC: 24.6%, 95% CI 14.8–39.6%).” This conclusion was derived from Cox multivariable analyses for predictors of incident AF. Analyses were adjusted for age, sex, body mass index, diabetes mellitus, hypertension, coronary artery disease, left ventricular hypertrophy, chronic kidney disease (in CHS), creatinine (in ARIC),

smoking status, alcohol consumption, level of education, and income. To assess the degree to which NT-proBNP “explains” the interracial difference in incident AF, the authors calculated the percentage change in the point estimate for race after addition of NT-proBNP to the multivariate Cox model.<sup>3</sup>

In interpreting their results, the authors suggest that NT-proBNP may play a causative role in AF: “. . . understanding the effects of NT-proBNP in the atria may elucidate why higher NT-proBNP levels are associated with AF and may provide a potential therapeutic target for AF prevention” and later “. . . the higher baseline level of natriuretic peptides in whites may have a direct atrial effect that increases AF susceptibility.” In the Discussion they state their finding: “. . . raises the question as to whether natriuretic peptides may have a direct causal relationship with AF.” Despite this strong thematic thrust by the investigators, among the limitations they list for their analysis they correctly state a crucial caveat: “Finally, as this is an observational study, the relationships described should be interpreted as associations and no conclusions regarding causality can be made.” Hence, although the authors invoke the concepts of “explanation” and “mediation,” they have simply reported the interplay of 2 variables, race and NT-proBNP, in a multivariate model aimed at identifying independent predictors of incident AF. This is, at most, hypothesis-generating and far from compelling evidence of an explanatory mechanism operating directly between NT-proBNP and AF. The remainder of this editorial will address the plausibility of NT-proBNP as a putative causative factor for AF and consider alternative hypotheses for the observed differences between blacks and whites in both plasma NT-proBNP and incident AF.

Multivariable analyses can only address the data incorporated in the model and the current report does not allow interracial comparisons of potentially relevant variables, many of which the CHS and ARIC investigators have reported upon previously. These include selected genotyping, details of cardiac structure and function, renin–angiotensin–aldosterone status, obstructive sleep apnea, sedentary lifestyle, or frequency of premature atrial contractions.<sup>4–6</sup> These variables present alternative plausible hypotheses to explain the 2 interracial differences under consideration without the

From the Christchurch Heart Institute, Christchurch, New Zealand; Cardiovascular Research Institute, National University of Singapore, Singapore.

**Correspondence to:** A. Mark Richards, Department of Medicine, Christchurch Heart Institute, University of Otago, Christchurch, PO Box 4345, Christchurch Hospital, Riccarton Ave, Christchurch 8014, New Zealand. Cardiovascular Research Institute, National University of Singapore, 1E Kent Ridge Rd, NUHS Tower Block, Level 9, Department of Cardiology, Singapore 119228. E-mails: mdcarthu@nus.edu.sg, mark.richards@cdhb.health.nz  
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need to invoke a culprit role for NT-proBNP in the genesis of AF.

NT-proBNP is unlikely to mediate any cardiovascular effect. It is the inert amino terminal byproduct of cleavage of proBNP into NT-proBNP and BNP. Bioactivity resides in the 32 amino acid BNP. The 76 amino acid NT-proBNP does not activate any of natriuretic peptide receptors, NPR-A, NPR-B, or NPR-C and does not trigger production of cyclic guanosine monophosphate (cGMP), the second messenger for the cardiac natriuretic peptides (NPs).<sup>7</sup> Nor has NT-proBNP any known bioactivity independent of the natriuretic peptide receptor pathways. The claims from Whitman et al that NT-proBNP has diuretic effects, “. . .NT-proBNP levels are higher in whites. . . and have diuretic effects . . .;” “. . .serum levels of NT-proBNP . . . are known to have diuretic effects. . .,” and “. . .NT-proBNP . . . via the diuretic action of this protein, may also render whites. . .” are incorrect. If NT-proBNP is providing any signal of a causative pathway to AF it is doing so indirectly, acting as a surrogate for the true effector(s) involved. Plasma NT-proBNP is correlated with plasma ANP, BNP, and CNP, which are biologically active. Whitman et al have not reported on the bioactive forms of NPs. Could these active NPs contribute to the genesis of AF?

The authors point out that NPs are associated with atrial dysfunction, atrial fibrosis, and incident AF, while AF itself is associated with higher NPs, which decrease in the event of successful cardioversion.<sup>8–10</sup> They then contend “because higher levels of baseline natriuretic peptide predict incident AF, the relationship likely goes ‘both ways.’” This is not a powerful argument. Plasma cardiac NP concentrations rise early in response to any form of acute and chronic cardiac injury or overload and the vast majority of AF is the consequence of cardiac disease, which may be of ischemic, hypertensive, cardiomyopathic, valvular, inflammatory, or toxic cause. Therefore, it is likely that plasma NPs reflect the background cardiac abnormality, which is the true substrate for AF. The rise in NPs precedes but does not cause AF. Many substrates (Table) will increase circulating NPs and concurrently increase risk of incident AF without any compelling evidence that the elevated NPs cause the AF. In this regard, reporting of cardiac imaging to provide insights into cardiac structure and function preceding onset of AF would have been invaluable.

The profile of NP bioactivity casts further doubt on any putative causative role in AF. The bioactive members of this family have antihypertrophic and antifibrotic effects. In addition, the NPs suppress sympathetic traffic and renin–angiotensin–aldosterone activity. Deletion of *NPPA*, *NPPB*, and *NPR-A* genes causes hypertension, cardiac hypertrophy, cardiac fibrosis, and vulnerability to heart failure.<sup>7</sup> The actions of NPs are cardioprotective and would mitigate against atrial remodeling and onset of AF. Furthermore, no trial-based

**Table.** Causes of Concurrent Elevations in NT-proBNP and Increased Risk of Incident AF

Left ventricular hypertrophy/dilatation
Right ventricular hypertrophy/dilatation
Left and/or right atrial dilatation
Mitral, tricuspid, aortic, pulmonary valve disease
Cardiomyopathy of hypertensive, ischemic, inflammatory, or familial cause
Endocarditis
Myocarditis
Alcohol and other toxins
Athlete's heart
Thyroid disease
Congenital heart disease
Hypoxic conditions

AF indicates atrial fibrillation; NT-proBNP, N-terminal pro-brain natriuretic peptide.

evidence supports the idea of raised atrial natriuretic peptide (ANP) or BNP as a trigger for AF in the heart failure population. In clinical trials of nesiritide (recombinant human BNP), no reports of excess incident AF have emerged. The use of recombinant human ANP in myocardial infarction in Japan has not triggered such reports either. Short-term elevation of plasma NPs, by infusions of exogenous peptide, do not appear to cause AF. The salutary long-term clinical benefit in heart failure from combined angiotensin receptor blocker and neprilysin inhibition therapy with sacubitril-valsartan is thought to be mediated by enhanced NPs. Trials such as PARADIGM (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity) have not reported an increased incidence of AF in those patients randomized to angiotensin receptor blocker and neprilysin inhibition therapy.

It is true that intracardiac electrophysiological studies of intravenous infusions of ANP demonstrated shortened atrial conduction time and effective refractory period.<sup>11</sup> In dogs, ANP dose-dependently shortened the atrial monophasic action potential and effective refractory period through an autonomically mediated mechanism. In isolated atrial cells ANP, in concentrations up to a thousand times the circulating levels observed in humans, increased the rate of activation of the hyperpolarization-activated current, and reduced both L-type calcium current and calcium-independent outward potassium current. However, on the background of clinical data from NP infusion and angiotensin receptor blocker and neprilysin inhibition trials together with an absence of compelling supportive epidemiology, this body of largely nonphysiological preclinical data do not support modest increases in circulating wild-type ANP and BNP as causative for AF.

Reports on the phenotype associated with gain-of-function variants in NP genes are not accompanied by any reports of increased incident AF with some clear exceptions. Patients with a rare form of familial AF harbor a mutation of *NPPA* generating high circulating levels of a mutant ANP peptide with an extended carboxyl tail.<sup>12</sup> In isolated heart experiments, this mutant peptide caused clear reductions in monophasic action potential and effective refractory period, whereas wild-type ANP did not. In this rare case, it appears that high levels of an *abnormal* ANP peptide can cause AF. Two other single nucleotide polymorphisms (SNPs) leading to generation of mutant ANP peptide variants also appear to trigger AF.

However, more common genotypes that result in modest lifetime elevations in plasma wild-type ANP and/or BNP lower blood pressure and reduce the risk of stroke without increased risk of AF.<sup>13,14</sup> Minor alleles of SNPs in the *NPPA* gene, associated with both increased atrial NP and BNP levels, are associated with less hypertension. There are several common SNPs in the *NPPB* gene encoding for BNP. Among these, rs198389 is a functional variant in the gene's promoter region resulting in gain of function and elevated plasma NT-proBNP and BNP. The ARIC investigators have reported the rs198389, GG genotype to be associated with reduced systolic and diastolic blood pressure, a 20% lower prevalence of hypertension, and lower cardiovascular mortality (hazard ratio 0.75; 95% CI 0.61–0.92).<sup>14</sup> Notably, this SNP was similarly distributed with similar associations in whites and blacks. This report demonstrates that a single NP-related SNP could strongly associate with NT-proBNP levels in the general population. If other SNPs, with a similar magnitude of effect upon plasma NPs, were to be unequally distributed between blacks and whites, it is plausible they could contribute to interracial differences in plasma NT-proBNP. Notably, a loss-of-function genetic variant of corin, an enzyme essential to cleavage of precursor NPs to their bioactive forms, is much more frequent in blacks than whites with an associated increased risk of hypertension.<sup>15</sup> The need to fill in the unknowns in genetic control of race-specific levels of plasma NPs provides a rich vein for further investigation.

The current article offers no information on the many non-NP-related genetic mutations predisposing to AF including variants of genes encoding ion channels, connexin, ryanodine receptor 2, T-box transcription factor, nucleoporins, and zinc-finger transcription factor. The first known mutation responsible for AF was located in the *KCNQ1* in 1997. Since then further mutations have been identified in at least 25 genes: *KCNQ1*, *SCN5A*, *KCNH2*, *KCNE2*, *KCNE3*, *KCNE5*, *KCNJ2*, *KCNA5*, *ABCC9*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN4B*, *RYR2*, *NKX2.5*, *NPPA*, *TBX5*, *NUP155*, *GJA1*, *GJA5*, *JPH2*, *PITX2c*, *GATA4*, *GATA5*, and *GATA6*. Little is known about the relative distribution of these mutant alleles in whites compared with

blacks, and this is a further area that warrants full exploration.<sup>5</sup>

The absence of data from Whitman et al on details of cardiac structure and function means we have no information on the presence or absence of abnormalities preceding the onset of AF and cannot compare the relative prevalence in whites compared with blacks of wall motion abnormalities and valvular dysfunction, left atrial size, or left ventricular mass or normal cardiac dimensions in blacks compared with whites. All of these elements are potentially pertinent to intergroup differences in plasma NT-proBNP and may contribute to incident AF independent of NT-proBNP. Cardiac release of NP is primarily determined by wall stress. The law of La Place indicates wall stress is proportional to intracardiac pressure and the chamber radius and inversely related to wall thickness. Therefore, all other things being equal, a minor but consistent interracial difference in atrial or ventricular dimensions will translate into a consistent interracial difference in circulating NPs. In future this will hopefully be addressed by the ARIC and CHS investigators who have echocardiographic data on many of their participants, have previously reported on echocardiographic findings in blacks with respect to incident AF, and should be well placed to establish and compare normal echocardiographic dimensions in blacks and whites.<sup>4</sup> A meta-analysis of echocardiographic findings from over 22 000 healthy people found that the upper reference values for left ventricular end-diastolic and end-systolic diameters were higher in Europeans than in East Asians, South Asians, and Africans.<sup>16</sup> The CARDIA (Coronary Artery Risk Development in Young Adults) investigators reported that adjusted left atrial dimensions were larger in whites than blacks, although they had earlier reported larger left ventricles in blacks compared with whites.<sup>17</sup> Whether or not normal ventricular and/or atrial dimensions differ between blacks and whites remains uncertain. In the present state of knowledge, we cannot rule out larger cardiac dimensions in whites as 1 possible explanation for their higher levels of plasma NT-proBNP.

Finally, we should not consider 1 established interracial difference in circulating vasoactive peptides without considering another well-established neurohormonal distinction between blacks and whites that is likely to interact with the NPs. For decades it has been repeatedly reported that blacks have generally lower activation of the renin–angiotensin–aldosterone system than whites.<sup>18</sup> Angiotensin 2 and aldosterone both exert pro-fibrotic effects on the heart, which will foster incident AF. Introduction of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists all reduce incident AF in heart disease.<sup>19</sup> In addition, crosstalk exists between the renin–angiotensin–aldosterone system and the NPs with angiotensin 2 known to promote NP expression.<sup>20</sup> It is

reasonable to suggest that a less activated renin–angiotensin–aldosterone system exposes the atria to a less adverse neurohumoral milieu (thus lowering the risk of AF) and at the same time reduces the overall drive for cardiac production of NPs. This alternative hypothesis reconciles lower NT-proBNP with concurrent lower incidence of AF in blacks without invoking any causative role for NT-proBNP.

## Conclusion

Whitman et al have provided a stimulus for careful thought on why both incident AF and plasma concentrations of NPs differ between blacks and whites in an apparently paradoxical manner. However, their contribution does not provide strong evidence that NPs cause AF. Appropriately comprehensive observational analyses that make full use of available data and that consider the full spectrum of previous findings should precede targeted interventional studies conducted in preclinical models and eventually in the clinic. We have the tools and cohorts to solve this conundrum, which will not be unraveled by isolated statistical analyses that do not include key variables. To obtain more definitive knowledge and generate well-founded hypotheses, multivariable analyses aimed at these questions must be expanded to include details of cardiac structure and function and genotyping relevant to AF, NPs, and the renin–angiotensin–aldosterone system as well as incorporating information on renin–angiotensin–aldosterone system status, age, sex, sedentary lifestyle, smoking, obesity, diabetes mellitus, obstructive sleep apnea, hypertension, heart failure, myocardial infarction, and burden of premature atrial contractions. Well-resourced cohorts such as CHS and ARIC must rise to the challenge to properly integrate existing data and extend data sets to fill in the obvious gaps in information.

## Disclosures

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