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RESEARCH LETTER

Inflammation and Incident Conduction Disease

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Cardiac conduction disease is an important predictor of heart failure and death,[1] but no strategies to prevent it currently exist. Autopsy studies have revealed conduction system fibrosis among deceased individuals manifesting the disease, but the initial cause remains unknown.[2] Inflammation is a common harbinger of fibrosis,[3] but whether systemically identifiable inflammation in the general population might predict cardiac conduction disease has not been explored. The existence of such a relationship might provide a novel target for prevention strategies.

We investigated longitudinal data from the CHS (Cardiovascular Health Study) to determine whether elevated levels of a common inflammatory marker, hs-CRP (high-sensitivity C-reactive protein), would predict incident conduction disease.

The authors will make the methods for statistical analysis available to any researcher on request. The data belong to the CHS, and the authors therefore do not have the authority to share the study data with investigators outside the University of California, San Francisco. CHS is a prospective, population-based cohort study established in 1989, which enrolled individuals aged ≥65 years sampled from Medicare eligibility lists. hs-CRP was measured using an ultrasensitive ELISA, developed at the CHS Central Laboratory, from serum obtained at baseline. All participants provided informed consent, and a certificate of approval from the University of California, San Francisco, Institutional Review Board was obtained to conduct the current study.[4]

For the current analyses, participants with prevalent conduction disease, atrial fibrillation, or ventricular preexcitation detected on baseline ECGs, a history of myocardial infarction or congestive heart failure, or missing values of hs-CRP at baseline were excluded. Incident conduction disease was identified from annual study ECGs and defined as first-degree atrioventricular block, left anterior or posterior fascicular block, right bundle-branch block, left bundle-branch block, nonspecific intraventricular conduction delay, Mobitz type II block, and third-degree atrioventricular block determined by a core ECG-reading facility.

We used Cox proportional hazard regression models before and after adjusting for covariates associated with the outcome using a P value of <0.10 in unadjusted analyses. Participants were censored at the time of their first detected conduction disease or last study ECG, whichever came first. A sensitivity analysis, including new ventricular pacing detected on study ECGs in the outcome, was assessed. The "percentage treatment effect" method was subsequently used to assess the degree of mediation by time-dependent myocardial infarction after adjustment for potential confounders.[5] A 2-tailed P<0.05 was considered statistically significant. Statistical analyses were performed using STATA 17 (StataCorp, College Station, TX).

Key Words: atrioventricular block ■ bundle-branch block ■ conduction disease ■ CRP ■ inflammation

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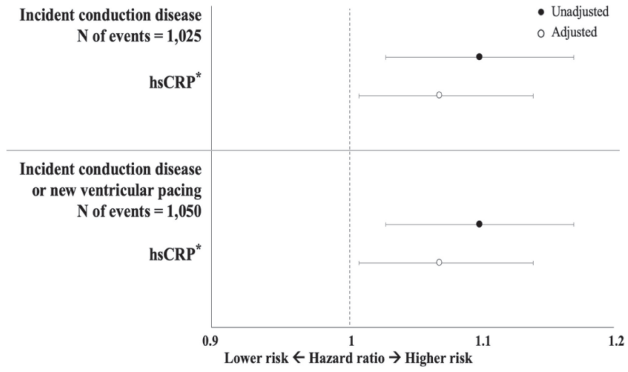

B

Predictor	Adjusted for	HR	95% CI	P value
hsCRP*	--	1.10	1.03-1.17	0.004
	Age	1.10	1.04-1.18	0.003
	Above + Sex	1.10	1.04-1.17	0.002
	Above + Diabetes	1.09	1.02-1.15	0.008
	Above + BMI	1.07	1.04-1.14	0.038
	Above + Physical activity	1.07	1.00-1.14	0.044
	Above + Hypertension	1.07	1.00-1.14	0.049

Figure. The relationship between inflammation and incident conduction disease.
A, Adjusted models included age, sex, body mass index (BMI), diabetes, hypertension, and physical activity. Circles represent hazard ratio (HR), and error bars denote 95% CI. **B**, Table displays the crude HR for incident conduction disease with increasing hs-CRP (high-sensitivity C-reactive protein), cumulatively adjusted for the covariates going down the column. The order of the covariates was chosen by statistical significance (with the least statistically significant at the bottom) using backwards selection. *Interpreted as the hazard increase per every 10-mg/L increase.

A total of 4314 participants (mean age, 72±5 years; 63% women) were included. The median hs-CRP at baseline was 2.4 (interquartile range, 0.012–87.8) mg/L. Compared with the remainder of the cohort, those with baseline hs-CRP levels above the median were more likely to be women and Black race, had a larger body mass index, were more likely to have diabetes, hypertension, and coronary heart disease, engaged in less physical activity, and were more likely to smoke.

During a median follow-up time of 7 (interquartile range, 1–9) years, 1025 exhibited incident conduction disease (422 with first-degree atrioventricular block, 128 with left anterior fascicular block, 17 with left posterior fascicular block, 165 with right bundle-branch block, 75 with left bundle-branch block, 186 with intraventricular conduction delay, and 32 with >1 type of conduction disease).

Higher levels of baseline hs-CRP were associated with heightened risk of incident conduction disease in both unadjusted and adjusted models, which remained significant in sensitivity analyses when including new ventricular pacing in the outcome (Figure). When restricting the outcome to each type of conduction disease, higher levels of hs-CRP were associated with a higher risk of left posterior fascicular block, right bundle-branch block, and left bundle-branch block in unadjusted analyses, which only remained significant for left bundle-branch block after multivariable adjustment (hazard ratio per 10-mg/L increase, 1.21 [95% CI, 1.04–1.40]; *P*=0.014).

Time-dependent myocardial infarction (n=238) did not appear to mediate the relationship between hs-CRP and incident conduction disease (percentage treatment effect, 1% [–7% to 9%]; *P*=0.82). Analyses using log-transformed hs-CRP and repeated analyses excluding hs-CRP >10 mg/L failed to reveal significant associations, suggesting nonlinear relationships driven predominately by those with the highest levels of hs-CRP.

It is important to acknowledge several limitations of this study. Given the observational study design, the findings are prone to residual or unmeasured confounding, preventing clear causal interferences. The primary exposure, hs-CRP, was based only on a baseline ascertainment, and we did not use serial measurements to assess relationships with changes in hs-CRP over time.

In conclusion, these observations suggest that higher levels of baseline inflammation evaluated using hs-CRP may predict incident conduction disease, potentially identifying a modifiable target that may be influenced to prevent this common and clinically important condition. These findings suggest that inflammation in general may predict incident conduction disease; if causal effects are operative, future studies would need to elucidate the specific inflammatory pathways responsible.

ARTICLE INFORMATION

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Disclosures

Dr Kizer reports stock ownership in Abbott, Bristol Myers Squibb, Johnson & Johnson, Medtronic, Merck, and Pfizer. The remaining authors have no disclosures to report.

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