

EDITORIAL COMMENT

Clinical Evidence of the Role of Histamine in Heart Failure*



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The existence of histamine receptors and histamine in the heart has been known since at least the 1940s (1) and cloning of human histamine receptors began around the 1990s (2). Nevertheless, developments relating to histamine have not been highlighted. Also, its role in cardiovascular physiology, such as in the renin-angiotensin or the sympathetic nervous system where it is central to understanding the pathophysiology of chronic heart failure (CHF), is not well understood. The investigation by Leary et al. (3) in this issue of the *Journal* attempts to shed light on histamine in relation to cardiovascular disease (CVD).

SEE PAGE 1544

In the cardiovascular system, histamine is released from mast cells, which are often located in coronary vessels and the myocardium; both mast cells and histamine have been implicated in CVD (4). Histamine is one of the neurohormonal factors that activate various cellular functions by stimulating histamine receptors (5), and histamine H₂ receptors exist in the heart as well as gastric cells. Because histamine H₂ receptors are coupled to G proteins, as well as the beta receptors (6), histamine provokes positive inotropic effects (1,7), and the

blockage of histamine H₂ receptors decreases cardiac output (7).

Increases in mast cells have been observed in the hearts of patients with cardiac hypertrophy, dilated and ischemic cardiomyopathy (8), and myocardial infarction (9). Furthermore, histamine is present in high concentrations in cardiac tissues in most animal species, including humans (6), and its release from cardiac stores and the subsequent actions on the heart may be important in the pathophysiology of CVD.

TRANSLATING BASIC RESEARCH TO CLINICAL MEDICINE

The study from Leary et al. (3) intriguingly reports that histamine H₂ receptor antagonists (H₂RAs) prevent the onset of CHF in a cohort from the MESA study (Multi-Ethnic Study of Atherosclerosis). This is definitively demonstrated by a prospective, observational, and longitudinal study, which is very difficult to perform but provides better evidence than cross-sectional or retrospective analyses like those used in our previous study (10). The authors prospectively followed the residents of 6 U.S. communities for 10 years and observed the onset of CVD in normal subjects who did or did not use blockers of histamine H₂ receptors. In our previous paper (10), we reported that blockers of histamine H₂ receptors are effective for CHF patients in a retrospective cohort study and a prospective randomized study.

These 2 studies (i.e., the present study and ours) appear to be similar, but that is not the case because prevention is the action undertaken before the onset of events and treatment is undertaken after event onset. This is the novel point in the present study: onset of CHF is classified as to ischemic and non-ischemic causes; the former includes coronary artery disease, and the latter includes hypertensive heart disease and diabetic cardiomyopathy. H₂RA users

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in the present study tended to be older, heavier, and had a high prevalence of hypertension and high N-terminal pro-B-type natriuretic peptide levels compared with nonusers. This strongly suggests that the present result is not attributable to the effects of H2RA on the risk factors of CHF, but rather to direct effects on CHF.

Furthermore, the authors revealed H2RA effects on left ventricular (LV) morphology: smaller decreases in stroke volume and LV end-diastolic volume (LVEDV) as well as smaller increases in mass/volume ratio in H2RA users than nonusers. This is contradictory to the effects of H2RA on the LV morphology in the setting of CHF, because we showed that H2RA decreased LVEDV, but did not affect LV fractional shortening. Large LVEDV is a very important marker of CHF progression, which is not the case for the H2RA-induced attenuation of CHF onset. This is another novel point. Taken together, the 2 studies potentially propose histamine as the provoking factor, as well as a worsening factor, for CHF.

Acquired from CHF patients, data from our previous study (10) as well as the MESA Right Ventricle study (11) helped inform the present study in which Leary et al. (3) suggest that histamine may play an important role in the prevention of CVD as well as in its treatment. However, there is theoretically a large gap between the prevention and treatment of CHF. To overcome this chasm, they supported their theory via basic research that has implicated the important role of histamine in preventing atherosclerosis (12), ischemia and reperfusion injury (13,14), and cardiac hypertrophy and CHF (15).

How did we find the importance of histamine in the pathophysiology of CHF? Of course, we did not know its importance to begin with, nor was our investigation the result of basic research articles relating to histamine in the cardiovascular field. Rather, we performed data mining of the clinical database of CHF patients to determine unexpected reasons behind CHF and found that histamine is 1 important candidate (16). Therefore, the seeds for furthering

knowledge in clinical medicine should be obtained from clinical databases and tested for validity and feasibility with basic science research and then the plausible hypothesis studied by clinical investigation, a process we named the “back-and-forth loop” between clinical medicine and basic research (17).

STRENGTHS AND LIMITATIONS

There are many strengths of the present study (3), the first being that whereas a prevention study is difficult to conduct because the researchers must enroll many subjects to obtain clinical outcomes, a treatment trial is rather easy because cardiovascular events occur more frequently than in a prevention study. Secondly, as a multicenter trial, this study was more comprehensive than a single-center trial. Lastly, the authors employed multiple ethnic groups, which increased the feasibility of the present results.

It was limited by being an observational study. The prospective and randomized clinical trial seems to be the most valuable; however, in such studies, the effects of drugs are tested in a limited cohort controlled by inclusion or exclusion criteria. The observational study, such as the present investigation, might be superior in this respect, although an observational study should consider bias and confounding factors.

What's next? Logically, these findings should stimulate development of H2RA agents for the prevention or treatment of CHF, but the response I have received from several pharmaceutical companies on this front has been rather negative. Certainly, there are many reasons, including financial ones, companies do not want to move forward. Nevertheless, we should do so to further our knowledge as well as provide more benefits to patients with CHF.

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