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ORIGINAL ARTICLE

Plasma Serotonin in Heart Failure: Possible Marker and Potential Treatment Target

Q1 **Ahmed M. Selim, MD *, Nitasha Sarswat, MD, Iosif Kelesidis, MD, MSc, Muhammad Iqbal, MBBS, Ramesh Chandra, MD, Ronald Zolty, MD, PhD**

Division of Cardiology, Albert Einstein College of Medicine/Weiler Division, Bronx, NY, USA

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Background The relationship between heart failure (HF) and the serotonergic system has been established in animal studies. However, data on human plasma serotonin level in HF and its significance over the course of the disease is lacking.

Methods Serotonin levels were measured in 173 patients (108 males, 65 females), 116 were stable HF and 40 were acute decompensated HF patients. The normal control group included 17 healthy volunteers with no known medical or psychiatric conditions. Patients receiving medications affecting serotonin receptors and those with pulmonary hypertension were excluded. All patients, except for those in the decompensated group, were on stable doses of HF medications.

Results Plasma serotonin levels were significantly elevated in decompensated HF patients compared with stable patients (P=0.002). Higher plasma serotonin levels were associated with worse HF symptoms (NYHA class) and the presence of systolic dysfunction, and was borderline associated with low peak oxygen consumption during cardiopulmonary exercise testing (P=0.055). These results were independent of age, gender, race, hypertension, diabetes, renal failure, weight, coronary artery disease (CAD), atrial fibrillation and medication use.

Conclusions Serotonin is a marker for decompensation in patients with chronic heart failure. Higher serotonin levels were associated with worse HF symptoms and systolic dysfunction.

Keywords Serotonin • Heart Failure • Decompensated HF • Marker

Background

Serotonin (5-HT) is a biogenic monoamine found in platelets, enterochromaffin cells and the central nervous system. Its action contributes to multiple body functions, including the control of appetite, sleep, memory, learning, temperature regulation, behaviour and endocrine regulation. Serotonin receptors are found throughout the body and are classified into seven families (5-HT_{1-7}) that have different biological effects [1,2].

Serotonin receptors in the heart were first described more than a decade ago. At that time, 5-HT_{2B} receptor was demonstrated to regulate the differentiation and proliferation of the developing heart [3]. Further exploration of the effects of serotonin receptors on cardiac muscle has led to a better understanding of their role in the pathogenesis of several cardiac conditions. All 5-HT receptor families with the exception of 5-HT_6 were found to play a role in the cardiovascular system in response to serotonin stimulation.

*Corresponding author at: University of Minnesota, G217 Mayo Memorial Building, 420 Delaware Street S.E., MMC 95 Minneapolis, MN, 55455,
Emails: ahmed_selim@live.com, aaselim@umn.edu

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The effects of stimulating these receptors include tachycardia, bradycardia, vasoconstriction, vasodilation, inotropism and the development of cardiac hypertrophy and fibrosis [4,5]. However, most of the knowledge on the effects of serotonin on the cardiovascular system is based on animal studies.

This study investigated whether plasma serotonin levels were different in patients with heart failure (HF). It aims at exploring a possible relationship between serotonin plasma concentrations and concurrent symptomatic status, degree of acuity and systolic function.

Methods

This study was approved by the institutional review board (IRB) of Montefiore Medical Center (MMC). This prospective observation study was designed to explore the relationship between plasma serotonin levels in different forms of HF, systolic vs. diastolic and stable vs. decompensated conditions. The study also investigated serotonin correlations with the severity of heart failure symptoms in these patients.

Subject Enrolment

Normal healthy volunteers with no known medical or psychiatric conditions were enrolled as normal controls through advertisements. A screening process was performed that included a complete medical history, vital sign measurement and physical exam followed by a screening transthoracic echocardiogram to rule out any myocardial dysfunction or pulmonary hypertension. Special attention was given to exclude subjects with active depression or on any medication affecting serotonin receptors. Patients with known HF who followed up in the HF clinic of MMC were identified and screened. Enrolled patients were 18 years or older with symptomatic HF (NYHA 2 and higher) of any aetiology. They had an echocardiogram with left ventricular ejection fraction (EF) reported within one year prior to participating in the study and at least one of the following objective measures within the last year: (1) left ventricular ejection fraction (LVEF) <40% via echocardiogram; (2) chest X-ray with evidence of heart failure (pulmonary congestion, cardiomegaly); (3) Pro-BNP >900; or (4) documented evidence of congestion (including jugular venous distention > 10 cm or rales post cough). The compensated HF patients had to be on stable doses of HF medications (ACE inhibitors, β blockers and spironolactone) for at least three months. They were further classified into systolic and diastolic HF, with systolic HF patients identified as those with EF<40% on the most recent echocardiogram, and diastolic HF patients were those with echocardiographic or right heart catheterisation findings consistent with diastolic dysfunction. Patients using any antidepressants including, but not limited to, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) as well as mood stabilising medications (i.e., lithium) were excluded from the study. Other patients excluded from the study were those diagnosed with a serotonin-related syndrome (i.e., carcinoid syndrome), those with documented bipolar disorder, and those with evidence of substance abuse or dependency during the previous 12 months and those with a significantly reduced life expectancy due to another co-morbidity. Q2

Screening of the Decompensated (Acute) Heart Failure Patients

Patients admitted to MMC (both the medical floors or in ICU) with a diagnosis of acute decompensated heart failure were screened. The same inclusion/exclusion criteria that were used to screen patients in the compensated HF group were applied here, with the exception of the criteria related to the stability of HF symptoms and medications prior to enrolment. For a patient to be included in the decompensated heart failure group, he/she had to have worsening dyspnoea associated with at least two objective findings at the time of enrolment (i.e., JVD, rales, congestion on chest X-ray, elevated pro-BNP>900 or respiratory rate >20).

Quality of life assessment

All compensated heart failure patients were requested to answer the Minnesota Living with Heart Failure (MLWHF) Questionnaire. The form consists of 21 items focussed on patient perceptions concerning the effects of congestive heart failure on their physical, psychological, and socioeconomic lives [6]. Individuals rank the degree of impairment attributable to each item using the same response format ranging from none (0) to very high (5). The degree of impairment is quantified by the sum of the ranks.

Cardiopulmonary Stress Testing

Maximum oxygen consumption during exercise, known as peak VO_2, was used as a surrogate marker for the maximal cardiac output that a subject could achieve. The peak VO_2 was shown to be a good predictor for outcomes in HF patients; peak VO_2 was also used to evaluate patients prior to cardiac transplant. A peak VO_2 of less than 14 ml/kg/min was taken as a predictor of worse outcomes [7]. A subgroup of 57 compensated HF patients (40 systolic and 17 diastolic HF patients) had cardiopulmonary exercise testing with VO_2 reported at the time of enrolment.

Serotonin Level Measurements

After obtaining formal written informed consent from the patients, they were counselled to avoid serotonin-rich foods, alcohol and coffee for 48 hours prior to phlebotomy. Blood collection took place in the HF clinic for stable HF patients, and within 24 hours of hospital admission for the decompensated HF patients. Using a 20-gauge angiocatheter, blood

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