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The Prevalence and Outcomes of Influenza Virus Infection in Heart Failure Patients in Brazil: Influenza Infection in Heart Failure

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Abstract

Background: Respiratory tract infections were associated with acute exacerbations of heart failure (HF). However, the role of the influenza virus, a major agent of such infections, in this population remained unclear. Method: During the influenza virus seasons of 2013 and 2014 we prospectively assessed influenza respiratory illnesses in a cohort of adults primarily hospitalized for management of acute decompensated HF and a cohort of HF outpatients. Qualitative RT-PCR for influenza A (A/H1, A/H12009pdm, A/H3) and B virus testing was performed on nasopharyngeal swab samples. Result: A total of 121 patients were included, 58.3% males (n = 70), mean age 57.7 years old (±14.0), mean left ejection fraction 35.3 (±9.8). Of these, 50.4% were inpatients (n = 61). The prevalence of symptoms of respiratory infections was 28.0% (n = 34) and 4.9% (n = 6) of all samples were positive for influenza virus. Only influenza A was detected and all cases were among inpatients. Influenza-positive patients had a greater need for antimicrobials (83.3%, n = 5; 16.3%, n = 9; p = 0.001) and for mechanical ventilation (50.0%, n = 3; 3.6%, n = 2; p < 0.001) than Influenza-negative patients. The prevalence of influenza virus was not related to mortality (OR 4.58; p = 0.16). Conclusion: Although not common, the influenza virus infection resulted in worst outcomes, with a greater need for antimicrobials and mechanical ventilation. Immunization and antiviral treatment in high risk patients may positively impact their outcomes.

Keywords

Influenza Virus, Heart Failure, Epidemiology

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1. Introduction

The influenza virus is one of the most frequent agents causing respiratory infections [1]. Each year, between 5 and 20% of the world population is infected [2], with up to 200,000 hospitalizations and 36,000 deaths in the US alone [3]. While most people experience an acute, febrile, self-limited illness with mild respiratory symptoms, some groups are considered at risk of hospitalization and death, such as children, the elderly and the chronically ill [4].

Several studies suggest that viral respiratory infections lead to an exacerbation of chronic pulmonary diseases, resulting in an excess of hospitalizations and deaths [5] [6], but little is known about the impact of these infections on patients with heart failure (HF). Hospitalizations for HF increase significantly in winter, even in tropical countries like Brazil [7]-[9]. Godoy *et al*. [7] showed a consistent increase in the number of HF hospitalizations during the winter months over a period of 20 years. Sandoval *et al*., while retrospectively assessing the impact of two influenza virus seasons on the population from the Studies of Left Ventricular Dysfunction (SOLVD), found a significantly higher risk of hospitalization for HF, but no increase in mortality rates [10].

In addition, many patients with HF may be hospitalized for other causes related to influenza virus, such as bacterial pneumonia, where the viral etiology is not investigated or identified [4]. In the Organized Program to Initiate a Lifesaving Treatment in Hospitalized Patients with Heart Failure Registry (OPTIMIZE-HF) [11], respiratory infections are the precipitating factors in 15.3% of the patients hospitalized for HF. These patients also stay longer in hospital and their risk of death during hospitalization is 60.0% higher.

HF is the main cause of hospitalization among North American adults older than 65; there are over 3.6 million hospitalizations per year with high hospital mortality rates and significantly elevated costs [7] [12]-[14]. It is very important to understand which factors contribute to the exacerbation of HF, especially preventable ones, since this may favorably influence the management of HF. Despite the fact that influenza virus is a public health issue and is the only respiratory virus for which effective prophylaxis and treatment are available, no study has directly assessed the impact of influenza infection on the HF population to date.

2. Materials and Methods

This was a single center, prospective cohort study. Study approval was obtained from the Institutional Review Board. During the influenza virus seasons of 2013 and 2014 two different cohorts of HF patients were analyzed and compared for the prevalence of influenza virus infection: (1) inpatients sequentially hospitalized primarily for management of acute decompensated HF, and (2) outpatients from the institution's HF clinic. They were matched for sex, age and left ventricle ejection fraction. Patients aged less than 18 years old and those with congenital heart disease were excluded. The diagnosis of acute decompensated HF was made according to ACC/AHA guidelines [13]. Symptoms of respiratory tract infection within 5 days of admission (fever, sneezing, running nose, myalgia, chills, sore throat, and cough) were searched for in all patients, but they were not a mandatory requirement for inclusion. Outpatients were followed up after 30 days of study inclusion in the HF clinic or by telephone when necessary. The study investigators were not involved in the patients' clinical management.

Nasopharyngeal swab samples were collected within 24 hrs of hospital admission. A qualitative RT-PCR for influenza virus A (A/H1, A/H12009pdm, A/H3) and B was performed according to the Centers for Disease Control and Prevention protocol [14]. Blood tests were also performed for NT pro-BNP (N-terminal pro b-type natriuretic peptide), C-reactive protein, hemoglobin count, white blood count, serum creatinine, serum sodium, and left ventricular ejection fraction obtained by transthoracic echocardiography. Clinical outcomes were investigated, including in-hospital mortality rate for any reason; need for antimicrobial therapy for any reason within 72 hrs of hospitalization; intravenous inotropic drug infusion (dobutamine, milrinone, other); mechanical ventilation; and incidence of cardiorenal syndrome, defined as an increase of 0.5 mg/dL in serum creatinine levels during hospitalization. Any outpatient hospital admission within 30 days of study inclusion was also investigated.

Categorical variables are presented in percentages. Continuous variables are expressed as means ± standard deviation (SD). Categorical variables were compared using the Fisher's exact test, and continuous variables using Student's *t* test or the Mann Whitney *U* test. Stepwise forward logistic regression was used for multivariate analysis. $P < 0.05$ was considered statistically significant.

3. Results

In total, 121 patients were included, 58.3% males ($n = 70$), mean age 57.7 years old (±14.0), mean left ejection

fraction 35.3 (±9.8). Of these, 50.4% were decompensated HF patients (n = 61). There was a 16.0% mortality rate (n = 8) among the decompensated HF patients and 1.6% in outpatients HF group (n = 1). In comparison with inpatients, more of the outpatients were immunized against influenza virus (p = 0.028), and were following the ACC/AHA HF guidelines' recommended therapy (**Table 1**).

The overall prevalence of influenza virus was 4.9% (n = 6), and all infections were among decompensated patients (9.8%; n = 6). Nevertheless the number of patients with symptoms of respiratory tract infection was similar between groups (inpatients 31.1%, n = 19; outpatients 25.0%, n = 15; p = 0.481, respectively) (**Table 1**). Only influenza A was observed and all positive patients were symptomatic for respiratory tract infection.

The clinical characteristics of inpatients who were RT-PCR-positive or -negative for influenza virus were similar (**Table 2**), however positive patients had a greater need for antimicrobials (83.3%, n = 5; 16.3%, n = 9; p = 0.001, respectively) and mechanical ventilation (50.0%, n = 3; 3.6%, n = 2; p < 0.001) (**Table 2**). The odds ratio was 4.58 for mortality from influenza virus (p = 0.16), and 12.6 for the use of mechanical ventilation (p = 0.05) (**Table 3**).

4. Discussion

The influenza virus season in Brazil usually starts in April and ends in September and is often accompanied by other respiratory viruses, particularly the respiratory syncytial virus (RSV) [15]. However, the influenza virus is the only respiratory virus for which effective prophylaxis and treatment are available. One third of patients in our sample have symptoms of respiratory tract infection, but influenza virus activity is only documented among inpatients during the two consecutive seasons. In comparison with outpatients, fewer inpatients mention regular use of ACE inhibitors and beta blockers or immunization against influenza virus. Sandoval *et al*. [10] found that influenza infection was responsible for 11.0% of all HF hospitalizations in the retrospective SOLVD study.

Table 1. Clinical characteristics of study population.

Characteristics	Inpatients (n = 61)	Outpatients (n = 60)	p
Male (%)	32 (52.5)	38 (63.3)	0.318
Age (SD)	57.3 (±14.2)	56.9 (±13.8)	0.855
Left ventricular ejection fraction (SD)	36.6% (±11.5)	34.9% (±8.7)	0.393
Atrial fibrillation (%)	24 (39.3)	19 (31.6)	0.309
Hemoglobin (g/dL)	12.6 (±2.1)	13.4 (±2.3)	0.402
Creatinine (mg/dL)	1.6 (±1.1)	1.4 (±0.8)	0.031
Sodium (mEq/L)	136 (±4.1)	138 (±3.1)	0.608
White blood count (/mm^3)	8,889 (±4,620)	8,577 (±3,085)	0.006
C-reactive protein (mg/L)	36.5 (±55.4)	6.5 (±9.9)	0.0001
NT pr-BNP (pg/mL)	10,278 (±8,957)	1,080 (±320)	0.0001
Respiratory tract infections	19 (31.1)	15 (25.0)	0.418
RT-PCR Influenza virus (%)	6 (9.8)	0	0.008
Immunization against influenza virus (%)	21 (34.4)	33 (55.0)	0.028
Beta blockers (%)[1]	47 (77.0)	58 (96.6)	0.002
ACE inhibitors/ARB (%)[1]	51 (81.3)	57 (95.0)	0.068
Aldosterone receptor antagonist (%)[1]	33 (54.1)	42 (70.0)	0.090
Hospital admissions (%)	-	5 (8.3)	-
Deaths (%)	8 (13.1)	1 (1.6)	0.016

SD: standard deviation; [1]prior to hospital admission.

Table 2. Clinical characteristics and outcomes in RT-PCR influenza virus positive patients.

Variables	Influenza virus positive (n = 6)	Influenza virus negative (n = 55)	p
Male (%)	3 (50.0)	29 (52.7)	1.0
Age (SD)	61.6 (±10.8)	56.9 (±14.6)	0.662
Left ventricular ejection fraction (SD)	43.8% (±12.3)	36.1% (±11.1)	0.118
Atrial fibrillation (%)	3 (50.0)	21 (38.2)	0.670
Antimicrobial use (%)	5 (83.3)	9 (16.3)	0.001
Inotropic drugs (%)	2 (33.3)	10 (22.2)	0.616
Mechanical ventilation (%)	3 (50.0)	2 (3.6)	< 0.001
Cardiorenal syndrome (%)	5 (83.3)	21 (42.9)	0.09
Deaths (%)	2 (33.3)	6 (10.9)	0.173

SD: standard deviation.

Table 3. Multivariate analysis for mortality in the study cohort.

	OR	CI (95.0%)	p
Age	1.005	0.86 - 70.32	0.88
Gender FEMALE	1.716	1.47 - 31.26	0.60
Antimicrobial use	2.784	1.47 - 31.26	0.41
Atrial fibrillation	2.041	1.05 - 35.58	0.50
Cardiorenal syndrome	1.082	0.52 - 80.11	0.94
Influenza virus	4.58	1.05 - 20.45	0.16
Inotropic drugs	1.924	2.95 - 32.70	0.65
Left ventricular ejection fraction	53.593	1.05 - 75.83	0.42
Mechanical ventilation	12.606	1.36 - 20.25	0.05
Respiratory tract infections	0.424	0.25 - 12.36	0.63

OR: Odds Ratio.

The patients at highest risk in this study are those with symptomatic HF (NYHA > 2) and those who are not on ACE inhibitors. We thus hypothesize that the better the HF care, the lower the risk of influenza infection.

In our study, which to our knowledge is the first to prospectively investigate influenza virus in HF patients, the overall prevalence of infection is lower than expected [15] [16]. Previous surveys in the general Brazilian population demonstrated a prevalence of influenza virus of about 20.0%. However the detection of virus activity in Brazil had declined since the 2009 pandemic, reflecting the lower circulation of the virus over the years and the increased prevalence of vaccination among the Brazilian population [15]-[17].

More than 70.0% of the general Brazilian population has been vaccinated over the years thanking to a successful government campaign [15]. Although patients with chronic disease may be vaccinated, the main target populations are children, pregnant women and the elderly, which may have contributed to the low rate of immunization in our population. Although different guidelines for HF management recommend immunization against influenza virus [1] [4] [14] [18], no vaccination studies have included HF patients. In coronary artery disease patients [19], one vaccination study shows a 75.0% reduction in the risk of cardiovascular death, and further 50.0% reduction in reinfarction or re-hospitalization for myocardial ischemia.

While dyspnea and respiratory failure are common findings during HF exacerbations, our data suggest more severe disease in infected patients, with a 7-fold increased risk of mechanical ventilation. In fact, the main clini-

cal syndrome of influenza virus leading to ICU hospitalization is viral pneumonitis. During the 2009-2010 pandemic, this syndrome accounted for approximately half the ICU admissions and a higher rate of use of mechanical ventilation [20]-[23]. A highly amplified inflammatory response and direct alveolar damage have been shown to play a contributory role in the higher rate of respiratory distress and hypoxemia [24] [25].

The appropriate use of diagnostic tests, along with early administration of antiviral drugs, may improve the clinical outcomes of influenza virus infections, reducing the incidence of secondary bacterial infections and the use of antimicrobials [4]. In our study, the use of antimicrobials (appropriate or not) is 4 times more common among patients with influenza virus. In adults and adolescents with a proven influenza illness, oseltamivir treatment reduces overall antibiotic use for any reason by 26.7% and the incidence of influenza-related lower respiratory tract complication resulting in antibiotic therapy by 55.0% compares with placebo [26].

Our study has several limitations. The observational design of the study precludes determination of causality of HF hospitalization. Also, our relatively small sample size limits the statistical power to detect clinically meaningful associations or confounding factors. Due to the lack of statistical power for these subjects, these results should be interpreted with caution.

Under such conditions, we conclude that influenza virus infection was not a prevalent co-morbidity among HF patients during 2013-2014 virus seasons; however the presence of influenza virus infection may interfere unfavorably in the outcome of patients with HF exacerbations, especially by causing respiratory failure with need for mechanical ventilation. Therefore, influenza virus infection surveillance should be intensified among HF patients during the influenza season. Patients at high risk for hospitalization should be immunized, and antiviral treatment may positively impact the clinical outcome.

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Disclosures

None.

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