Temporal Variation of Heart Failure Hospitalization: Does It Exist?

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Congestive heart failure (CHF) is the end stage of many cardiac diseases, and one of the leading causes of mortality and morbidity around the world. Coronary heart disease and hypertension (either singly or together) are the main etiology for CHF. It has been reported that major acute cardiovascular events (myocardial infarction, sudden death, cardiac arrest, ischemic and hemorrhagic stroke, pulmonary embolism, rupture/dissection of aortic aneurysms) do not occur randomly through time, but exhibit a specific temporal periodicity characterized by seasonal (winter), weekly (Monday), and circadian (morning) patterns of onset. Thus, because the major causes of CHF present a temporal pattern, in the past several years some studies have investigated the temporal variation of CHF hospitalization and mortality, with results indicating the possibility of a preference for winter months, Mondays, and nighttime, respectively.

[Rev Cardiovasc Med. *2011;12(4):211-218 doi: 10.3909/ricm0579*]

Key words: Heart failure • Chronobiology • Seasons • Hospitalization • Outcome, clinical

Congestive heart failure (CHF), a syndrome that develops as a consequence of many different processes that impair cardiac function, affects 1% to 2% of the world population, and is a leading cause of death and disability.[1] Approximately 30% to 40% of patients die within 1 year from diagnosis, and 60% to 70% within 5 years, despite treatment.[2] CHF causes approximately 5% of hospital admissions and complicates another 10% to 15%.[3]

The progressive aging of the population and the improvements in therapeutic intervention have led to an increased survival in patients with cardiovascular

disease (CVD), and, as a consequence, to an escalating prevalence of CHF. Consequently, CHF has become the most important public health problem in cardiovascular medicine, with a heavy burden on health care systems. In fact, hospitalization of patients with CHF consumes 74% of the total health care costs for heart failure.[4] Moreover, CHF is the most common principal diagnosis among hospitalized adults aged 65 years and older,[5] and in this elderly population arterial hypertension[6] and diabetes mellitus[7] play a pivotal role in the genesis of CVD.

In the past 2 decades, it has been shown that major acute cardiovascular events, such as acute myocardial infarction (MI),[8,9] sudden cardiac death (SCD),[10] stroke and transient ischemic attack,[11,12] rupture/dissection of aortic aneurysms,[13,14] and pulmonary embolism (PE)[15] do not occur randomly through time, but exhibit a specific temporal periodicity, in particular, a seasonal variation with an autumn/winter peak.

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Moreover, a weekly pattern has been demonstrated as well, with Monday representing a critical day for occurrence of acute MI,[9,16,17] ischemic stroke,[18-20] cardiac arrest,[21] and SCD.[10]

Again, the cardiovascular system seems to present a specific circadian pattern with a morning prevalence for acute MI,[22,23] SCD,[24] cardiac arrest,[25-27] PE,[28] ischemic and hemorrhagic stroke,[11,29-32] and rupture/dissection of aortic aneurysms.[13,33] Such morning occurrence may be explained, at least in part, by synergistic triggering effects played by concomitant increases in blood pressure (BP),[34] heart rate,[35] sympathetic activity,[36] and basal vascular tone,[37] together with an imbalance between coagulation and fibrinolysis, characterized by increased platelet aggregability[38,39] and reduced endogenous fibrinolysis.[40]

Because hypertension and coronary heart disease account for the majority of CHF cases, it is reasonable to suppose that a temporal pattern in the incidence of CHF hospitalizations and mortality may exist. This hypothesis may offer clues to precipitating factors, in particular, the influence of climate and other stresses. In recent years a considerable number of investigators have studied seasonal, weekly, and circadian variation of CHF hospitalization.

Seasonal Variation

A seasonal variation in hospitalization for CHF was first described in 1977 by Parry and colleagues.[41] In their series of 753 patients in Nigeria, affected with cardiac failure mainly in the peripartum period (40.6%) and observed over a 3-year period, the authors noted that patients with CHF presented more frequently during the hot, wet months than during the cooler, dry months.

Several decades later, Boulay and associates,[42] in their retrospective national survey in France, confirmed a marked winter and spring predominance for CHF hospitalization and mortality, ranging from 7% to 10% above the mean from December through April, and 9% to 20% below the mean from July through September, with a peak in January for subjects >75 years old and in April for those aged 15 to 74 years.

These reports encouraged several investigators to evaluate if this temporal pattern was consistent across the world, and similar findings were observed in the Northern Hemisphere. In particular, Allegra and coworkers,[43] analyzing data from an emergency department (ED) in the United States, reported an increase in CHF visits during winter months. Reedman and colleagues[44] reported an increase in ED visits for CHF during the Christmas and New Year's holiday season, which was similar to the findings of what Phillips and colleagues[45] demonstrated with cardiac mortality.

In a study conducted in Spain, a clear seasonal variation in CHF hospitalization was observed, characterized by a peak in January and a trough in August.[46,47] This temporal pattern, both for CHF admissions and mortality, has been successively confirmed in Scotland,[48] Canada,[49] Japan,[50] and Turkey.[51] Similar studies have been performed in the Southern Hemisphere as well, indicating the same winter increase in HF hospitalizations and death, with the highest rate between July and August, and the lowest between December and February, in areas of South America,[52,53] Australia,[54] and Africa.[55,56]

These results were confirmed in a recent study we conducted in Italy. We analyzed all hospital admissions for heart failure at the general hospital of Ferrara, in the Emilia-Romagna region of Italy, between 2002 and 2009, and our results confirmed a peak of admissions in winter and a nadir in summer, with no differences

according to sex, age, outcome, and presence of risk factors.[57]

It is interesting to observe that such patterns occurred apparently independent of absolute variations of temperatures during winter or summer. Thus, it is possible CHF mortality may occur when temperatures fall below a certain "threshold" level. In fact, similar trends were observed both in Canada and in Argentina, where temperatures reached -15°C and -8.5°C in winter, and 25°C and 18°C in summer, respectvely.[49,52]

Several potential mechanisms have been proposed to explain the seasonal variation in hospitalization and mortality in CHF patients. In heart failure, physiological reserve to address an increase in cardiac workload is impaired. Physiological changes that occur with temperature reduction may lead to CHF decompensation and increased hospitalization rates: increased heart rate and total peripheral resistance, with consequent increased afterload; decrease in water loss by transpiration and perspiration leading to change of total extracellular volume; and increased BP levels, arrhythmias, and higher rates of MI and infectious diseases, particularly acute respiratory tract infections.[42,47,58] In fact, it has been reported that the risk of hospitalization is 8% to 10% higher during the influenza season compared with the non-influenza season, and hazard ratios for death associated with the influenza season increased by 5% to 8% when adjusted for other variables.[58] Respiratory disorders (exacerbation of chronic obstructive pulmonary disease and pneumonia) also showed a winter peak in patients hospitalized with a primary discharge diagnosis of CHF.[46] Influenza and respiratory infections may be a precipitating factor for patients susceptible to CHF.[59,60]

It is well known that BP levels are higher during winter months, and low ambient temperatures are associated with a rise in both systolic and diastolic BP.[61] This rise in BP can be due to different factors induced by low temperatures: increased sodium[62] and alcohol intake,[63] reduced physical activity,[64,65] vasoconstriction secondary to both increased sympathetic tone, and increased release of circulating catecholamines.[66,67] These factors induce an increase in cardiac work and afterload, and the end-stage failing heart is unable to cope with this increased demand. Thus, cold weather may cause acute pulmonary edema by overloading the left ventricle, particularly in those predisposed to hypertension.[68-70]

During the winter months, exogenous seasonal effects such as daytime length may affect the endogenous rhythm.[71] Hormonal mechanisms such as aldosterone secretion, catecholamines, renin activity, and thyroid system activity occur to defend seasonal changes in BP and to mediate the changes in hemodynamics.[72]

Weekly Variation

Available evidence suggests a weekly variability in cardiovascular morbidity and mortality, especially among the working population. The first observation on the European Registry of the World Health Organization, in 1976, showed a peak on Mondays and Saturdays,[73] but several further studies reported an increased incidence of MI on Mondays.[9,16,17,74] A similar weekly variation was found for cardiac arrest in a series of more than 6000 out-of-hospital cardiac arrests in Seattle, Washington,[21] and in a cohort of more than 24,000 sudden deaths in Berlin.[10] Among Scottish men and women under age 50 years, mortality from coronary artery disease was approximately 20% higher on Mondays compared with the other days of the week.[75] Increased mortality from CVD has been observed in Lithuania throughout the weekend and on Mondays, perhaps due to alcohol use.[76] Again, a Monday peak has been observed for ischemic stroke in an Italian population.[18]

Little is known about day-of-week CHF hospitalization and clinical outcome. Allegra and colleagues[43] found an increased incidence of ED visits for CHF on Mondays, and a decreased incidence on Saturdays. The same Monday peak was confirmed by Fonarow and associates in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry,[77] in which Monday was the most frequent day of admission for CHF (17.8%) and Saturday was the least frequent day (10.8%).

Our group has recently analyzed 15,954 CHF cases admitted during 8 consecutive years to the general hospital of Ferrara, Italy. We confirmed a Monday prevalence for heart failure hospital admissions (17.1%) independent of sex, age, presence of main risk factors, and patients' clinical outcome (fatal/nonfatal).[78]

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There are several possible explanations for this pattern. Patients may delay medical care over the weekend due to less physician availability, leading to a weekend decline and a Monday peak.[43] Moreover, the

findings of a highest number of events on Monday, and decreasing number from Monday to Sunday, raised the question of a possible relationship with the beginning of the working week. The Monday increase of MI and sudden deaths seems to be more pronounced in younger subjects,[10] and this may depend more on employment status than on age. Employed subjects probably experience a more stressful transition from weekend leisure activities to work on Monday,[16,17] which culminates in an increase of catecholamine levels and elevated BP.[79,80] The start of work activity seems also to induce a series of biochemical changes associated with cardiovascular risk. In fact, data from a Norwegian study suggested that hematological and biochemical factors were less favorable on Mondays compared with other days of the week.[81] These changes favor a thrombogenic condition that could explain, at least in part, the increased risk of cardiovascular events such as MI.[16] Because elevated BP levels and myocardial ischemia are the major cause of CHF, their Monday peak could play a role in the Monday CHF peak.

Many studies have also investigated the relationship between day of hospitalization and clinical outcome, indicating that patients admitted on weekends were 15% more likely to die than patients admitted during weekdays.[82] Barnett and coworkers[83] observed a 9% increase in risk-adjusted death rate among patients admitted to intensive care units on weekend days compared with weekdays. This increase in mortality has been found for various cardiovascular events, such as MI,[84] PE,[85] stroke,[86,87] and rupture/dissection of aortic aneurysms.[88]

The OPTIMIZE-HF registry has demonstrated that, among a large, representative population of patients admitted to the hospital for CHF, no differences in in-hospital or early postdischarge death rates by the day of admission were evident. The risk of postdischarge death/rehospitalization or rehospitalization also did not differ by day of admission. Furthermore, the day of week in which hospital discharge occurred did not appear to influence postdischarge clinical outcomes. Conversely, day of hospital admission for CHF significantly influenced hospital length of stay, and Thursday and Friday were associated with prolonged length of stay.[77]

These findings provide important insights into factors that may or may not influence the quality and efficiency of hospital care and outcomes for HF patients. Hospital staffing is reduced on Saturdays and Sundays in both the number of staff and level of experience.[89,90] Also, fewer supervisors are present in the hospital on weekends.[90] In addition, the level of physician coverage for patients also differs on weekends in most hospital settings, and the weekend physician staff frequently provide coverage for other heath professionals and therefore may be less familiar with the patients under their care.[91,92] The differences in hospital and physician staffing may result in shortfalls in quality of care and outcomes depending on the day of admission. Differences in clinical outcomes by the admission day of week could reflect differences in the characteristics of patients hospitalized. Prior studies have suggested that the rate of admission and the severity of acute coronary syndromes may vary according to the day of week.[93]

There is inconsistent evidence with regard to the relationship among weekend hospitalization, treatment decisions, quality of care, and outcomes.[82,83,92,94] One study of approximately 4 million hospitalizations in Ontario, Canada, from 1988 to 1997,[83] found that, for certain medical conditions, patients admitted on weekends were more likely to die in the hospital than patients admitted during the week. The Myocardial Infarction Data Acquisition System (MIDAS) study reported an increase of in-hospital risk of death that persisted up to 1 year for patients admitted during weekends.[84] A large analysis of hospitals participating in the National Registry of Myocardial Infarction (NRMI) also suggested that off-hours presentation for acute MI was associated with a higher in-hospital death rate.[94] For patients hospitalized with CHF, admission on weekend days compared with weekdays has not been associated with an increase in mortality in prior studies. Among the 141,687 CHF hospitalizations included in the Canadian study, the in-hospital death rate did not differ by weekday compared with weekend days. An unadjusted analysis of administrative records for patients hospitalized in California in 1998 revealed that, for patients with CHF, there was no difference in death rate for weekend admission.[92] The OPTIMIZE-HF registry did not find that risk of death among patients hospitalized

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with CHF varied by admission day of week or by weekday/weekend admission.[77] These findings suggest that, for CHF patients, there may be adequate medical care and staffing without significant weekend treatment differences that would lead to higher rates of death.

Circadian Variation

Previous investigations have identified a circadian distribution in the onset of several cardiovascular diseases, such MI and SCD,[95] PE,[28] rupture/dissection of aortic aneurysms,[32,96] and cerebrovascular accidents.[11] Interestingly, all of these unfavorable events show a biphasic pattern characterized by a main peak in the morning and a smaller one in the evening; a constellation of multiple triggering factors may play a role.[97]

A few studies have investigated the circadian pattern of CHF, and most are related to its life-threatening manifestation, acute pulmonary edema. Anecdotal reports suggested a nighttime preference for acute cardiogenic pulmonary edema. Cugini and colleagues[98] studied patients presenting to an Italian ED with acute pulmonary edema, and found a predominant peak at 10:00 PM, and a secondary peak at 2:00 AM. Another 5-year Italian study, conducted on 1204 cases of acute cardiogenic pulmonary edema, found maximum incidence during nighttime and minimum incidence around noon, without any differences in subgroups by sex, age, history of hypertension, and coronary artery disease.[99] The same higher nighttime incidence was found by another Italian group.[100] Conversely, Barash and coworkers[101] found that the greatest number of visits to an ED for pulmonary edema occurred between 12:00 AM and 4:00 AM. Fava and Azzopardi,[102] on the isle of Malta, found a circadian variation in the onset of acute pulmonary edema only in nondiabetic patients, with a peak incidence in the first and last quarters (midnight to 6 AM and 6 PM to midnight) of the day. Buff and associates[103] and Allegra and colleagues,[43] in two different studies, found a morning peak, with a significant peak onset between 6:00 AM and 11:59 AM and 8:00 AM and 3:00 PM, respectively. Because MI exhibits a well-known morning peak, the authors hypothesized that a time lapse of several hours could be reasonably expected before hemodynamic effects become fully manifest. The circadian variation in onset of acute cardiogenic pulmonary edema has also been studied by our group, which analyzed 1321 consecutive cases arrived to the ED of Ferrara, Italy, during a 7-year period (1992–1998).[104] An evident nighttime preference was shown, both for total cases and considered subgroups (sex, age, hypertension, diabetes, acute MI, CVD, previous MI, CHF, dilatated cardiopathy, chronic atrial fibrillation, vascular disease, chronic obstructive pulmonary disease, chronic cor pulmonale, malignancy, chronic renal failure) with a peak between 1:00 AM and 4:00 AM.

Many factors are involved to explain such nighttime preference for acute pulmonary edema. The interrelationships among several endogenous circadian rhythms, sleep, and diseases play an important role in the distribution of the onset of acute CVD.[97,105] The increase in venous blood return, which is caused by a clinostatic position during sleep, leads to an abnormal rise in intracardiac blood pressure and may play a role.[106] In patients with CHF, aldosterone and cortisol fluctuate as a circadian rhythm, with the lowest value in the evening and a progressive increase until the highest in the morning.[107] Also, catecholamine levels increase in the morning, upon awakening,[108,109] and β-blockers may be effective in preventing episodes of CHF.[110] Again, in patients with CHF, a loss of the circadian rhythm of atrial natriuretic peptide has been reported,[111] and significant modifications of the circadian rhythms in arterial BP and heart rate have been reported,[112] characterized by a lack of nocturnal dip.[107] Moreover, adrenergic tone is reduced during nighttime (with the exception of rapid eye movement [REM] sleep period), and it can lead to an abnormal response to changes in intracardiac blood volume and to a decrease in cardiac inotropism.[107] The REM phase sleep can be considered a time of increased risk: heart rate (which normally decreases by 5%-10% during sleep) and sympathetic nerve activity both increase markedly,[36] thus favoring arrhythmic episodes.[105,112] All these modifications, usually present in a diseased heart with reduced systolic function, may trigger the onset of an acute pulmonary edema.

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Conclusions

Peculiar temporal patterns of hospitalization seem to be present in CHF. The finding of a temporal pattern might have other clinical implications, such as an increased level of

clinical alertness, optimization of the organization of health resources, availability of appropriate measures of prevention, and education of CHF patients (especially the elderly) and general practitioners to be alert in higher-risk periods, to optimize early recognition and intervention. Moreover, pneumococcal and influenza immunization should be strongly encouraged, not just to avoid these infections, but also for their potential role in winter exacerbations of CHF.[113] Finally, an appropriate timing of medications could help to ensure maximum effectiveness during more vulnerable periods.[114] ■

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Main Points

- Congestive heart failure (CHF) is a syndrome developed as a consequence of many different processes; it impairs cardiac function and is a major cause of death and disability.
- Major acute cardiovascular events (acute myocardial infarction, sudden cardiac death, stroke and transient ischemic attack, rupture/dissection of aortic aneurysms, and pulmonary embolism) exhibit a specific temporal periodicity, with peaks during winter months, on Mondays, and during morning hours.
- The finding of a temporal pattern might have other important clinical implications, such as an increased level of clinical alertness, optimization of health resources, availability of appropriated measures of prevention, and education of patients and general practitioners.

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