ORIGINAL INVESTIGATION

Use of Sympathomimetic Drugs Leads to Increased Risk of Hospitalization for Arrhythmias in Patients With Congestive Heart Failure

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Background: Sympathomimetic agents have a direct positive chronotropic effect on heart rate and may cause hypokalemia, even when administered by inhalation. In selected patients (eg, patients with congestive heart failure [CHF]) this can lead to arrhythmias. Despite the potential adverse effects of these agents, they are used frequently in patients with CHF, due to a high incidence of respiratory comorbidity. This study investigates the effects of sympathomimetics on the incidence of hospitalizations for arrhythmias in patients with CHF.

Methods: In a cohort of 1208 patients with a validated hospital discharge diagnosis of CHF, we identified 149 cases with a readmission for arrhythmias, and compared these in a nested matched case-control design with 149 controls from the remainder of the cohort with no hospital readmission for any cardiac cause. Conditional logistic regression was used to calculate the risk for hospitalization for arrhythmias associated with exposure to sympathomimetic agents, expressed as odds ratios.

Results: Of 149 case patients, a total of 33 (22.1%) were treated with any sympathomimetic agent, and 6 patients (4.0%) were treated with systemic sympathomimetics. The use of any sympathomimetic drug was associated with an increased risk of admission for arrhythmia (odds ratio, 4.0; 95% confidence interval, 1.0-15.1). For systemic sympathomimetic drugs, the corresponding odds ratio was 15.7 (95% confidence interval, 1.1-228.0).

Conclusions: The results of this study strongly suggest an increased risk of hospitalization for arrhythmias in patients with CHF treated with sympathomimetic drugs. Sympathomimetics should be given under close surveillance to patients with CHF.

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ARRHYTHMIAS can be induced or aggravated by a variety of drugs, which include cardiotonic drugs (digoxin, sympathomimetics, and antiarrhythmics), and by drugs that lower plasma potassium levels, such as diuretics and corticosteroids. A special group comprises drugs that lengthen QT interval and can lead to induction of torsade de pointes (eg, antihistamines, antidepressants, macrolide antibiotics, cisapride, and antipsychotics).[1]

Sympathomimetic drugs have a direct positive chronotropic effect that can promote arrhythmia. Moreover, sympathomimetics can induce hypokalemia and further worsen arrhythmias.[2,3] Studies on chronotropic and hypokalemic effects of sympathomimetics have shown small but significant effects, which can even be induced by inhalation of sympathomimetics.[4,5] At the introduction of selective β_2-sympathomimetics, a limited number of small-scale studies suggested that these drugs could be safely used in patients with chronic obstructive pulmonary disease (COPD).[6] By now, however, evidence accumulates that arrhythmias due to systemic use of sympathomimetics do occur occasionally.[7,8] Even the occurrence of arrhythmias after inhalation of sympathomimetics has incidentely been reported.[9]

Elderly patients and patients with congestive heart failure (CHF), renal or hepatic dysfunction, electrolyte disturbance (hypokalemia, hypomagnesemia), or a history of arrhythmias are probably more prone to the proarrhythmic effect of sympathomimetics.[10] Moreover, patients with CHF often use diuretics. The hypokalemic response to diuretics could be additive to that of sympathomimetics.[11,12]

Cardiac arrest and arrhythmia are the major causes of death in patients with CHF.[13] Despite the potential negative effects of sympathomimetics in patients with CHF, they often receive

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PATIENTS AND METHODS

SETTING

Data were used from the PHARMO record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of 6 medium-sized cities in the Netherlands.[14]

Medication histories and hospital data were collected from 1986 to 1992. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification. Hospital discharge records were coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*.[15] Clinical modification codes were used.

PATIENTS

A total of 1208 patients with a validated hospital discharge diagnosis for CHF were included in the study.[16] These patients were followed up for a total of 5038 person-years (mean follow-up, 4.2 years per patient). In this cohort we identified a total of 454 readmissions for cardiac causes, including myocardial infarction, angina pectoris, arrhythmias, and CHF. We found 149 patients with a rehospitalization for arrhythmias (cases). For each case, a control was sampled randomly from the remainder of the cohort who were not readmitted for any cardiac cause and matched according to follow-up time. An index date was assigned to each control matching the hospitalization date of the case.

EXPOSURE DEFINITION

A patient was defined as exposed when there was at least 1 prescription filled for a given drug in the 3 months before hospital admission for the cases or the corresponding index date for the controls.

DATA ANALYSIS

We performed a nested case-control analysis comparing exposure in cases vs controls. Odds ratios (ORs) were calculated for exposure to sympathomimetic agents, at the time of the hospitalization due to arrhythmias (cases) or matched index date (controls). Conditional logistic regression techniques were applied to adjust for potential confounders. All statistical analyses were performed with Egret software (Egret for Windows, version 2.0, Cytel Software Corporation, Cambridge, Mass).

POTENTIAL CONFOUNDERS

This study was done in a group of patients with a high frequency of comorbidity. Arrhythmia is a common complication in patients with CHF. Left ventricular hypertrophy and local ischemia of heart tissue may contribute to arrhythmogenic effects.

Arrhythmias frequently occur in patients with COPD. An important risk factor is the occurrence of hypoxemia in patients with COPD. An increased risk for hospital admissions for arrhythmias could therefore be related to the underlying disease instead of the use of sympathomimetics. On the other hand, sympathomimetics can also aggravate the effects of hypoxemia.[17]

In addition, a broad range of drugs could affect the occurrence of arrhythmias by direct effect on heart rate (eg, angiotensin-converting enzyme inhibitors, β-blockers, calcium antagonists, digoxin, antiarrhythmics, and ibopamin), blood potassium levels (eg, angiotensin-converting enzyme inhibitors, corticosteroids, diuretics, and laxatives), or QT interval (eg, antihistaminic drugs, antidepressants, antipsychotics, macrolides, and cisapride).

We corrected for these potential confounders by including the presence of hospital admissions for arrhythmias, myocardial infarction, angina pectoris, asthma, and COPD in the year preceding the hospitalization for CHF and the use of aforementioned drugs in the 3 months prior to the hospital admission in the multiple regression model.

such drugs, due to a high incidence of respiratory comorbidity (in particular COPD). This study investigates the effects of sympathomimetics on the incidence of hospitalizations due to arrhythmias in patients with CHF.

RESULTS

Table 1 details the general characteristics of the study population. The majority of arrhythmias were classified as atrial fibrillation (n=98, 60%). The other frequently seen arrhythmias were ventricular tachycardia (n=15, 9%) and fibrillation (n=16, 10%). The characteristics of users of sympathomimetics differed in some aspects from patients not using these drugs (eg, sex, use of corticosteroids, and prior hospital admissions for COPD). The following inhalation sympaticomimetics were used: albuterol, 94% of all prescriptions; and terbutaline sulfate, 6% of all prescriptions. Systemic sympaticomimetics used were albuterol in 74% and terbutaline in 26%. There was only 1 nasal sympaticomimetic used, which was xylometazoline hydrochloride.

Of the 149 cases and controls 33 (22%) and 17 (11%) were treated with any sympathomimetic agent, yielding a crude OR of 2.2 (95% confidence interval [CI], 1.2-4.3). We adjusted for a number of possible confounders, notably, sex, age, prior hospitalizations for arrhythmia, asthma, COPD, myocardial infarction, and angina pectoris. In addition, we adjusted for the use of a broad range of drugs that may have direct proarrhythmic effects, give rise to hyperkalemia or hypokalemia, or are markers for a history of rhythm disturbances, such as digoxin, calcium channel inhibitors, β-blockers, oral anticoagulants, antiarrhythmics, angiotensin-converting enzyme inhibitors, corticosteroids, laxatives, diuretics, nitrates, neuroleptics, H_1-antihistamines, antidepressants, and ibopamin. Adjusted ORs were 4.0 (95% CI, 1.0-15.1) for the use of any sympathomimetic drug and 15.7 (95% CI, 1.1-228.0) for the use of systemic sympathomimetic drugs

(**Table 2**). Separate ORs for inhalation and nasal sympathomimetics and theophylline were not significantly associated with hospitalization for arrhythmia.

COMMENT

Our results strongly suggest an increased risk (OR, 4.0; 95% CI, 1.0-15.1) for hospitalization for arrhythmias in patients with CHF using sympathomimetic drugs. This risk was much higher (OR, 15.7; 95% CI, 1.1-228) in patients using systemic sympathomimetics than in patients using inhalation sympathomimetics (OR, 2.4; 95% CI, 0.5-13.1). Possibly due to the relatively small number of patients, the risk found for the inhalation group was not statistically significant, but data suggest that use of sympathomimetics by inhalation also leads to an increase in the risk of arrhythmia.

Surprisingly, we did not find an increased risk for arrhythmias in patients taking theophylline. This is difficult to explain, since the hypokalemic and heart rate effects of theophylline are well known. Perhaps, physicians are familiar with these effects and only prescribe theophylline for low-risk patients. Moreover, theophylline is usually prescribed as a maintenance dose. Sympathomimetics are probably more often used "on demand." Patients with acute dyspnea due to CHF could overuse these bronchodilators, while they are already more susceptible to develop arrhythmias.

In this study there were no patients using long-acting sympathomimetics. Studies suggest that these drugs have systemic effects comparable to those of short-acting sympathomimetics.[18] More research on their effects in patients with CHF is warranted.

We did not have direct data on the severity of CHF. However, we tried to compensate for this by correcting for a variety of comedications and previous hospitalizations that we see as "proxies" for the severity of CHF. After adjustment for possible confounders such as sex, age, prior hospitalizations for arrhythmia, asthma, COPD, myocardial infarction, angina pectoris, and the use of a broad range of comedications, the OR remained statistically significant. These findings remain suggestive of a causal relation between use of sympathomimetics and arrhythmias. We were not able to control for caffeine use, which could also be a confounder.

This study was conducted in a selected group of seriously ill patients. Use of β_2-sympathomimetics is generally safe in patients with asthma or COPD.[19] However, patients with severe cardiac comorbidity are probably more prone to their systemic effects.

Sudden death—often due to arrhythmias—is the major cause for mortality in patients with CHF.

This study was not designed to reveal the incidence of sudden death outside the hospital. The effects of sympathomimetics could therefore even be more deleterious. In this light, it seems important to avoid every possible factor that could lead to arrhythmias in these patients. Due to the high rate of comorbidity, the complete avoidance of sympathomimetics is often not possible. However, the necessity of the use of sympa-

Table 1. Characteristics of Patients With Congestive Heart Failure According to the Use of Sympathomimetic Agents*

Characteristic	No Sympathomimetics (n = 248)	Use of Sympathomimetics (n = 50)
Age, y		
≤64	32 (12.9)	5 (10)
65-74	89 (35.9)	14 (28)
≥75	127 (51.2)	31 (62)
Male	109 (44.0)	37 (74)
Hospital admissions in preceding year		
General	85 (34.3)	16 (32)
With arrhythmia	22 (8.9)	4 (8)
With COPD, asthma, or emphysema	3 (1.2)	8 (16)
With myocardial infarction	12 (4.8)	3 (6)
With angina pectoris	7 (2.8)	1 (2)
Type of arrhythmia during follow-up†		
Paroxysmal supraventricular tachycardia	2 (0.8)	1 (2)
Paroxysmal ventricular tachycardia	15 (6.0)	0
Paroxysmal tachycardia	1 (0.4)	0
Atrial fibrillation	73 (29.4)	25 (50)
Atrial flutter	6 (2.4)	1 (2)
Ventricular fibrillation	14 (5.6)	2 (4)
Cardiac arrest	7 (2.8)	0
Premature heartbeats	2 (0.8)	3 (6)
Sino-atrial knot dysfunction	1 (0.4)	1 (2)
Cardiac dysrhythmia	6 (2.4)	2 (4)
Cardiac dysrhythmia, NOS	2 (0.8)	0
Comedication use		
Systemic corticosteroids	7 (2.8)	6 (12)
Inhalation corticosteroids	5 (2.0)	18 (36)
Digoxin	109 (44.0)	33 (66)
Oral anticoagulants	127 (51.2)	17 (34)
Verapamil or diltiazem	44 (17.7)	13 (26)
Dihydropyridines	29 (11.7)	6 (12)
ACE inhibitors	119 (48.0)	21 (42)
β-Blockers	30 (12.1)	5 (10)
Ibopamine	8 (3.2)	1 (2)
Laxatives	22 (8.9)	9 (18)
Antiarrhythmics	26 (10.5)	6 (12)
Thiazide diuretics	2 (0.8)	1 (2)
Thiazide diuretics + potassium-sparing diuretics	32 (12.9)	5 (10)
Loop diuretics	171 (69.0)	35 (70)
Potassium-sparing diuretics	53 (21.4)	11 (22)
Nitrates	118 (47.6)	18 (36)
Any proarrhythmic drug‡	14 (5.6)	3 (6)
Antidiabetic drugs	51 (20.6)	5 (10)

*Values are number (percentage) of patients. The observation period for the no sympathomimetics group was 414 days and for the sympathomimetics group was 535 days. COPD indicates chronic obstructive pulmonary disease; NOS, not otherwise specified; and ACE, angiotensin-converting enzyme.

†The total number of arrhythmias exceeds 149, because of multiple types of arrythmia during 1 hospital admission.

‡Antipsychotic, antidepressant, antihistaminic, macrolide, or cisapride.

Table 2. Association Between Use of Sympathomimetic Agents and Risk of Hospitalization for Arrhythmia

	No. (%)		Odds Ratio (95% Confidence Interval)*	
	Cases (n = 149)	Controls (n = 149)	Crude	Adjusted†
Current use of any sympathomimetics	33 (22.1)	17 (11.4)	**2.2 (1.2-4.3)**	**4.0 (1.0-15.1)**
Systemic sympathomimetics	6 (4.0)	1 (0.7)	6.0 (0.7-49.8)	**15.7 (1.1-228)**
Inhalation sympathomimetics	21 (14.1)	12 (8.1)	1.8 (0.9-3.8)	2.4 (0.5-13.1)
Nasal sympathomimetics	2 (1.3)	1 (0.7)	2.0 (0.2-22.1)	3.5 (0.2-70.5)
Theophylline	14 (9.4)	12 (8.1)	1.2 (0.5-2.6)	1.4 (0.3-5.7)

**Significant effects are in boldface.*

†Adjusted for age, sex, prior hospital admissions (for arrhythmia, chronic obstructive pulmonary disease, asthma, emphysema, myocardial infarction, or angina pectoris) in the preceding year, and concomitant use of corticosteroids, digoxin, oral anticoagulants, calcium antagonists, angiotensin-converting enzyme-inhibitors, β-blockers, ibopamine, laxatives, antiarrhythmics, (potassium-sparing) diuretics, nitrates, any proarrhythmic drugs (antipsychotic, antidepressant, antihistaminic, macrolide, or cisapride), and antidiabetics.

thomimetics should be evaluated critically. The beneficial effects of bronchodilators in patients with heart failure and shortness of breath should be clearly documented by pulmonary function test before these drugs are prescribed. Oral sympathomimetics should be avoided in all patients. When patients have problems with inhalation, extra attention should be given to inhalation instruction. Potassium levels should be measured regularly and the clinician should be alert for the occurrence of arrhythmias.

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