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Influence of the time on the prevalence of drug-related resuscitated sudden death during these past 20 years

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ABSTRACT

The use of drugs is the subject of numerous recommendations. The purpose of this study was to evaluate the prevalence of drug-related sudden deaths (SD) and the possible changes during these past 20 years.
Methods: 271 patients, 205 men, 66 women aged from 12 to 88 years (mean 59 ± 15) were admitted after SD resuscitation outside the acute phase of myocardial infarction, 146 before 2000 (group I), 125 between 2000 and 2010 (group II). Complete check-up was performed.
Results: Ischemic HD (41%) vs (37%), idiopathic dilated cardiomyopathy (12%) vs (11%), various HD (5%) vs (8%) were as frequent in groups I and II. Valvular HDs were more frequent in group I than II (12%) vs 6% ($p<0.01$). Abnormalities at ECG (preexcitation syndrome, conduction disturbance, atrial fibrillation or ion channel disorders) were less frequent in group I than II (8%) vs (18%) ($p<0.02$). Drug-facilitated or related SD's did not change in groups I and II: 54 patients presented a drug-related ventricular fibrillation or asystole, 16% in group I and 24% (NS) in group II. SD was caused by hypokalemia, QT interval increase or conduction disturbance. HD or abnormal ECG was present in 42 patients. Digoxin, diuretics, calcium inhibitors, betablockers, antiarrhythmic drugs alone or in association were mainly implicated.
Conclusion: Drug-related arrhythmias continue to explain or favour at least 20% of SDs. Despite numerous recommendations on the use of drugs, the prevalence of fatal events that may be attributed to a cardiovascular drug does not decrease between the years before 2000 and after 2000.

1. Introduction

Most sudden cardiac arrests are related to ventricular fibrillation (VF) and ischemic heart disease. Sudden death occurring outside an acute phenomenon frequently leads to indicate the implantation of a cardiac defibrillator [1–3]. However, the causes for sudden death are complex and various and some of them could be provoked by a specific and treatable cause [4–12]. We previously reported the various causes of resuscitated sudden cardiac arrest among 122 patients recruited between 1989 and 1999 [12]. Some sudden deaths (SD) occurred in patients without apparent structural heart disease (HD) and some of them were drug-related.

After this report, recommendations for the indication of treatments were published during these last years [13,14]. Some medical treatments are recommended or should be avoided according to different situations associated with the heart disease or other organic diseases.

The purpose of this study was to evaluate the prevalence of drug-related or facilitated SDs before the year 2000 and after and the possible changes during these past 20 years.

2. Population

A series of 958 consecutive patients were admitted to a general cardiology hospital during a period of 20 years (1989–September 2011) after successful resuscitation from cardiac arrest without no important neurological sequelae after one month of hospitalization.

Patients with an acute myocardial infarction (n = 555) were excluded. Those with a non-cardiac cause of cardiac arrest such as pulmonary embolism or a neurological accident were also excluded (n = 132).

More than 750 patients were not referred either because a variety of advanced diseases were identified or because of important neurological sequelae. More than 4000 calls for possible cardiac arrest were recorded during this period, but the patient was not resuscitated successfully. Suicide attempts by drug ingestion were excluded.

As a result the study population consisted of 271 patients, 205 men, 66 women, aged from 12 to 88 years (mean 59 ± 15) were suffering from cardiac arrest, defined as an unexpected death from a cardiac cause (excluding myocardial infarction) within a short time period (<1 h) after the onset of symptoms, occurring in a person without any prior condition that could account for an arrest [15,16].

One hundred forty six patients were admitted before 2000.

One hundred twenty five patients were admitted between 2000 and 2011.

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The patients were admitted initially to the emergency room and were transferred to our hospital after return of spontaneous circulation and normal consciousness.

3. Methods

Patients underwent a series of investigations in the absence of antiarrhythmic drugs after giving informed consent. Personal and familial clinical history, list of drugs taken at the time of cardiac arrest and clinical examination were initially noted.

The following noninvasive studies were performed:

- 12-lead surface ECG;
- 24-hour Holter monitoring (Elatec, Ela medical);
- 2D transthoracic echocardiography;
- signal-averaged ECG (Fidelity 2000 of Cardionics);
- if possible a bicycle exercise-test;
- in the last 30 patients: cardiac magnetic resonance imaging (MRI);

The following invasive studies were performed:

- right and left ventricular angiography and coronary angiography. The diagnosis of right ventricular dysplasia included abnormalities of systematic right ventriculography;
- ergonovine injection during coronary angiography in patients with normal coronary arteries and history of chest pain;
- complete electrophysiologic study (EPS) according to a previously reported protocol except in 3 patients [17]: The protocol included assessment of sinoatrial conduction function and atrioventricular conduction and programmed atrial stimulation. Programmed right ventricular stimulation using one ventricular extrastimulus (S2) and double ventricular extrastimuli (S2 and S3) were introduced during sinus rhythm and paced cycle lengths (600 and 400 ms), at right ventricular apex and subsequently at right ventricular outflow tract. A third extrastimulus was added if a sustained ventricular tachycardia or fibrillation was not induced. If the study remained negative, the protocol was repeated after 2 to 4 μg/min isoproterenol infusion. Short coupling intervals (<200 ms) were not used in our study. Ajmaline test (1 mg/kg) was performed in patients suspected of infrahisian AV block or in those suspected of Brugada syndrome since 1992 [18].

Abnormal electrophysiological findings were categorized as sinus node dysfunction, conduction disturbances, hypervagotonia, inducible supraventricular tachyarrhythmia, or inducible ventricular tachyarrhythmia according to classical diagnostic criteria [17]. When several anomalies were noted, including the induction of a ventricular tachyarrhythmia, the presumed cause for sudden arrest was categorized in ventricular tachyarrhythmia.

Induced ventricular tachyarrhythmias were categorized monomorphic ventricular tachycardia (VT) when the rate was less than 275 bpm or ventricular flutter when the rate of monomorphic VT was more than 270 bpm or ventricular fibrillation (VF) that was a polymorphic VT requiring cardioversion to stop it.

3.1. Therapy and follow-up

Patients were treated according to the cause that was identified to be responsible for the arrest. For example in patients in whom the arrest was related to rapid atrial fibrillation associated with a Wolff–Parkinson–White syndrome, radiofrequency ablation of the accessory pathway was performed.

In the patients in whom a ventricular arrhythmia was found to be the cause, treatment has changed with time: until 1995/1996 an electrophysiologically guided antiarrhythmic treatment was initiated when the ventricular arrhythmia could be induced during EPS, attempting to render the tachycardia non-inducible. After this period an ICD was implanted, regardless of the results of a controlled EPS under antiarrhythmic treatment.

An ICD was implanted systematically in patients in whom VF was documented as the cause of cardiac arrest in resuscitated patients and in whom all above-mentioned investigations were negative.

Mortality data were obtained by sending each patient a questionnaire on his or her current well-being. If the patient had died, the patient's general practitioner was contacted to provide information regarding the circumstances of death.

3.2. Statistical analysis

Continuous data are expressed as mean ± standard deviation. Frequencies were compared with the Chi-square statistic and continuous variables with the *t*-test, using SPSS®.

4. Results

4.1. General causes for SD

SD was related to a ventricular tachyarrhythmia in 238 patients requiring cardioversion; in the remaining 33 patients, the exact arrhythmia responsible for the arrest was not documented and the patient was resuscitated with external chest compressions and/or defibrillation without documentation of VF.

Eighty nine patients did not have apparent structural heart disease: The echocardiography and the coronary angiography were normal. Among these patients 7 had a coronary spasm with ergonovine test. Thirty four patients had an abnormal ECG at admission: preexcitation syndrome (n = 5), pace-maker (n = 1), bundle branch block (n = 7), atrial fibrillation (n = 7), long QT syndrome (n = 9), early repolarization syndrome (n = 2) or Brugada syndrome (n = 3).

One hundred eighty two patients had a history of heart disease or an abnormal echocardiography. One hundred six patients had a history of coronary heart disease (HD), 26 a valvular heart disease, 32 a dilated cardiomyopathy and 18 had various heart diseases including hypertrophic cardiomyopathy (n = 5) and congenital or acquired heart diseases. One of the patients with valvular heart disease also had a preexcitation syndrome.

Classical substrates favouring SD did not change generally between both periods except for the incidence of valvular heart diseases, more frequent before 2000 than after 1999 and the frequency of abnormalities at ECG (Table 1). Abnormal ECG (preexcitation syndrome, conduction disturbance, atrial fibrillation or ion channel disorders) was noted more frequently in the second period. This increase is probably related to the relatively recent knowledge of ion channel disorders such as the early repolarization syndrome or the Brugada syndrome.

4.2. Role of drugs in SD

A drug used at therapeutic ranges was the unique cause or more frequently the favouring cause of SD in 54 patients (prevalence 20%).

Drug-related SDs did not change during these periods and tend to increase even: 54 patients presented a drug-related ventricular fibrillation (VF) or asystole, 24 patients (16%) seen before 2000 had a drug-related or favoured SD and 30 patients (24%) (p 0.12) seen since 2000 had drug-related SD.

Drug-related SD occurred among 18 patients without known structural HD, 4 seen before 2000 and 14 since 2000. Long QT syndrome was discovered at this occasion in 6 patients: "torsade de pointe" and ventricular fibrillation was induced by class I antiarrhythmic (n = 4) given for atrial premature beats, neuroleptic drug associated with cannabis (n = 1), erythromycin (n = 1). Coronary spasm occurred in one patient treated with beta blockers for palpitations. He was awaiting the implantation of a defibrillator and presented a recurrence of event. The case was recently reported [19]. One patient had an unknown bifascicular block and received class I antiarrhythmic drug for palpitations. Two patients received an antipsychotic treatment with neuroleptic. One patient had diuretics and a severe hypokalemia. The remaining patients were treated with beta blockers and or digitalis (n = 2) or class I antiarrhythmic drug (n = 5) for palpitations.

The drug favoured SD among 36 patients with associated myocardial HD, 20 seen before 2000 and 16 since 2000. Heart diseases were ischemic heart disease in 12 patients, valvular heart disease in 10 patients including 3 with a mitral valve prolapse, dilated cardiomyopathy in 10 patients, hypertrophic cardiomyopathy in 2 patients and congenital heart disease in 2 patients. One patient with valvular HD also had a

Table 1
Main substrates of sudden death HD heart disease DCM: dilated cardiomyopathy.

	Before 2000	2000–2011	
Number	146	125	
Ischemic HD	60 (41%)	46 (37%)	NS
DCM	18 (12%)	14 (11%)	NS
Valvular HD	18 (12%)	8 (6%)	P<0.01
Other HD	8 (5%)	10 (8%)	NS
Electrical abnormality	12 (8%)	22 (18%)	P<0.02
Coronary spasm	3 (2%)	4 (3%)	NS
No HD, normal ECG	27 (18%)	21 (17%)	NS