Circadian rhythm in cardiac arrest: the Singapore experience

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ABSTRACT

Introduction: There appears to be a circadian rhythm in the timing of cardiovascular and neurovascular events. The majority of studies have been conducted in western populations. This is the first study to look at the peaks and distribution of out-of-hospital cardiac arrest (OHCA) patients in Singapore.

Methods: The Cardiac Arrest and Resuscitation Epidemiology Studies I and II were prospective observation studies on OHCA in Singapore from October 1, 2001 to October 14, 2004. This study analysed data for patients older than 16 years. All data was collected and recorded as per the Utstein style template. Analysis was done for each of the quadrants of the 24-hour clock: 0001–0600, 0601–1200, 1201–1800 and 1801–2400 hours.

Results: Of the 2,428 cases, 2,167 OHCA patients qualified for the final analysis. Their mean ages were in the 60s for all the four quadrants, with a male predominance. The two peaks noted were at 0800 and 1900 hours for cardiac causes of death (n = 1,591), and at 0900 and 2000 hours for non-cardiac causes of death (n = 576). At all times of the day, the majority of OHCA occurred in residences and the bystander cardiopulmonary resuscitation rate ranged from 14.6 to 24.3 percent in the different quadrants of the day.

Conclusion: OHCA has a bimodal distribution in our local cohort of patients. The information obtained will be utilised for fine-tuning emergency medical services strategies, as we strive to improve our current survival rates for OHCA.

Keywords: cardiac arrest, circadian rhythm, out-of-hospital cardiac arrest, ventricular fibrillation, emergency medical services

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INTRODUCTION

Circadian rhythm is the external expression of an internal clock mechanism that measures daily time. The daily light-dark cycle represents the most dominant and potent stimulus in mammals, including man.[1] Circadian rhythms are controlled by a transcriptional feedback system, fluctuating as a function of the light-dark cycle. The molecular control of a circadian clock has been described in detail in the fruit fly.[2] In the mammalian brain, molecular clock mechanisms have been identified in the suprachiasmatic nuclei comprising the master circadian clock mechanism. This master clock sets the phase for intrinsic molecular clocks identified in peripheral tissues such as the heart and the vasculature.[3]

There has been much discussion on the diurnal pattern in several cardiovascular events, such as myocardial infarction, sudden death and acute cerebrovascular disease. Several physiological variables, including blood pressure, suggest that a certain dynamic process may contribute to the circadian distribution and onset of acute events. The pathophysiological mechanisms underlying circadian periodicity are complex and may relate to the interaction between triggering factors (e.g. morning stress, change in posture from supine to upright, change in blood pressure, vascular tone and hormonal concentration of adrenaline, renin and cortisol), protective elements (e.g. being on beta-blockers and aspirin) and environmental factors.[4-7] Most of the studies looking at the circadian or diurnal variation have focused on the Caucasian population. There may be differences in these results compared to Asian results due to genetic, environmental or even lifestyle factors. One study done in Singapore showed an interesting trend in acute myocardial infarction patients presenting to the emergency department, with some differences from the findings in the western cohort of patients.[8]

Singapore is a cosmopolitan city state at the crossroads of Asia, with a land area of 704 square kilometres and a population of 4.5 million. It is densely populated and urban, with a multiracial population. The ethnic distribution comprises 76.2% Chinese, 13.8% Malay, 8.3% Indian, and 1.7% Eurasian and other races.

The emergency medical services (EMS) is run by the Singapore Civil Defence Force (SCDF) under the Ministry of Home Affairs. There are 50 ambulances stationed at 14 fire stations and ten satellite stations. These ambulances all operate with a three-man crew, which includes the driver. They tend to emergencies throughout the country 24 hours per day. It is a single tier system with paramedics providing basic cardiac life support (BCLS), defibrillation with the automated external defibrillator (AED), use of airway

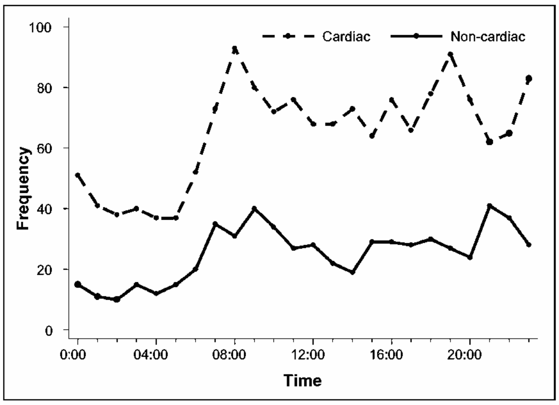

Fig. 1 Graph shows hourly frequencies of OHCA in a 24-hour cycle.

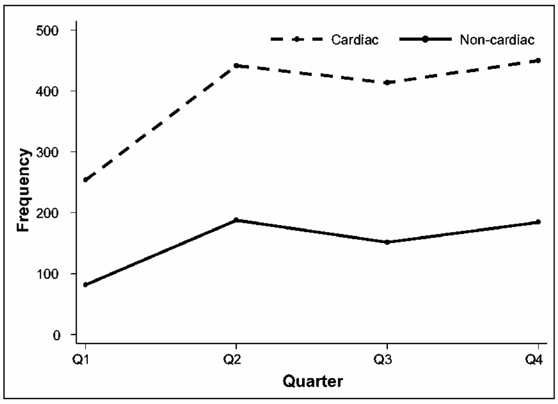

Fig. 2 Quarterly frequencies of OHCA during the 24-hour day cycle.

adjuncts including laryngeal mask airway as well as the delivery of certain approved drugs and medication.[9,10] This study aims to determine if there exists a circadian pattern in the presentation of the local cohort of patients with sudden out-of-hospital cardiac arrests (OHCA). It will also assess if there are significant factors which may impact the circadian variability, and thus help us explore possible strategies that may improve survival outcomes.

METHODS

All the data and patients were obtained from the Cardiac Arrest and Resuscitation Epidemiology (CARE) I and II studies, which comprised all eligible OHCA patients in Singapore.[10] The CARE studies are prospective observational studies of OHCA patients conveyed by ambulance services to all emergency departments in Singapore, during the period October 1, 2001 to October 14, 2004.[11,12]

Patients aged 16 years and older were included. The paediatric group of patients were not included in this study. In Singapore, 16 years of age is usually used as the upper age limit for admission into children's hospital units. Exclusion criteria were those who had traumatic cardiac arrest and those who were "obviously dead" as defined by presence of decomposition, rigor mortis or dependent lividity. Resuscitation was not attempted for the latter group of patients and death was usually pronounced on-scene. All data was collected and recorded as per the Utstein style, and all watches and clocks were synchronised with the central dispatch clock at the beginning of each shift. The 24-hour day was divided into the following four quadrants: 0001–0600, 0601–1200, 1201–1800 and 1801–2400 hours. Death was divided into cardiac (e.g. acute myocardial infarction, acute coronary occlusion) and non-cardiac causes, based on postmortem reports. Analyses were performed using the Statistical Package for Social Sciences version 11.0 for Windows (SPSS Inc, Chicago, IL, USA). The statistical tests utilised included the one-way ANOVA test, Fisher's exact test, and the Krukal Wallis and chi-square tests. Statistical significance was set at $p < 0.05$.

RESULTS

For the study period, there were 2,428 OHCA patients. Of these, the following were excluded:

(1) 175 were trauma arrests;
(2) 69 were of the paediatric age group (< 16 years);
(3) 17 cases had multiple missing data.

Therefore, a total of 2,167 OHCA patients were included in the final analysis.

The mean ages of the OHCA patients were 63.8, 64.1, 62.8 and 64 years, in the four quadrants, respectively. There was also a general male predominance in all the four quadrants. The racial distribution is comparable to the national racial distribution, except for the Indians, who had a proportionately higher representation. In all quadrants, the majority of arrests occurred in the victims' residence ($p < 0.001$). The bystander cardiopulmonary resuscitation (CPR) rate ranged from 14.6% at 0100–0600 hours to 24.3% at 1201–1800 hours ($p = 0.012$) (Table I).

Ventricular fibrillation (VF) was respectively seen in 14.5%, 21.6%, 24.7% and 19.1% of patients, at the four different quadrants. Asystole and pulseless electrical activity accounted for the majority of the presenting rhythm at all quadrants; being 85.1%, 77.8%, 74.7% and 80.1%, respectively ($p = 0.024$) (Table I).

The admission rate post-emergency department resuscitation was 9.8%, 7.8%, 8.9% and 8.8%, respectively ($p = 0.86$, Fisher's exact test), but the survival at 30 days was correspondingly 0.9%, 1.4%, 2.7% and 1.1%, respectively, for the four quadrants ($p = 0.13$, Fisher's exact test)(Table I).

There were generally two peaks (bimodal) noted throughout the 24-hour period: 0800 and 1900 hours, and

Table I. Patient characteristics by quarter of the day, for time of collapse.

Characteristics	00:01–06:00 (n = 336)	06:01–12:00 (n = 630)	12:01–18:00 (n = 566)	18:01–24:00 (n = 635)	p-value
Mean (SD) age (years)	63.8 (15.7)	64.1 (15.8)	62.8 (15.8)	64.0 (15.1)	0.49*
Gender					
Male	223 (66.4)	417 (66.2)	398 (70.3)	434 (68.3)	0.43
Female	113 (33.6)	213 (33.8)	168 (29.7)	201 (31.7)	
Race					
Chinese	215 (64.0)	453 (71.9)	390 (68.9)	453 (71.3)	0.16
Indian	60 (17.9)	91 (14.4)	93 (16.4)	81 (12.8)	
Malay	48 (14.3)	58 (9.2)	60 (10.6)	70 (11.0)	
Others	13 (3.9)	28 (4.4)	23 (4.1)	31 (4.9)	
Diabetes mellitus	96 (29.8)	158 (28.1)	126 (25.3)	172 (30.3)	0.29
Heart disease	129 (40.1)	221 (39.3)	189 (37.9)	227 (40.0)	0.90
Hypertension	118 (36.6)	214 (38.0)	168 (33.7)	234 (41.2)	0.086
Stroke	10 (3.1)	50 (8.9)	40 (8.0)	56 (9.9)	0.003
Cancer	24 (7.5)	46 (8.2)	37 (7.4)	58 (10.2)	0.33
Asthma	20 (10.3)	32 (9.4)	29 (10.2)	37 (10.1)	0.99
Renal disease	15 (7.7)	16 (4.7)	17 (6.0)	25 (6.8)	0.51
Location					
Residence	259 (77.1)	343 (54.5)	286 (50.6)	394 (62.0)	< 0.001
Other	77 (22.9)	286 (45.5)	279 (49.4)	241 (38.0)	
Collapse witnessed					
Bystander	173 (51.5)	341 (54.3)	324 (57.7)	386 (60.9)	0.001
Ambulance	42 (12.5)	48 (7.6)	69 (12.3)	62 (9.8)	
Not witnessed	121 (36.0)	239 (38.1)	169 (30.1)	186 (29.3)	
Rhythm of arrest at presentation					
VF	46 (14.5)	125 (21.6)	127 (24.7)	113 (19.1)	0.024
VT	1 (0.3)	4 (0.7)	3 (0.6)	4 (0.7)	
Asystole	171 (53.9)	313 (54.0)	244 (47.5)	321 (54.3)	
PEA	99 (31.2)	138 (23.8)	140 (27.2)	153 (25.9)	
Bystander CPR					
Present	43 (14.6)	128 (22.1)	120 (24.3)	129 (22.6)	0.012
Absent	251 (85.4)	451 (77.9)	373 (75.7)	441 (77.4)	
Outcome of patient at ED					
Admitted	33 (9.8)	47 (7.5)	49 (8.7)	54 (8.5)	0.86†
Transferred to ICU	0 (0.0)	2 (0.3)	1 (0.2)	2 (0.3)	
Patient died	303 (90.2)	581 (92.2)	516 (91.2)	579 (91.2)	
Patient alive at 30 days	3 (0.9)	9 (1.4)	15 (2.7)	7 (1.1)	0.13†

Data is expressed in no. (%), unless otherwise stated. Percentages may not add to 100 due to rounding.
*One-way ANOVA F-test; †Fisher's exact test; chi-square for all other tests.
Missing values: comorbidities: 215; location: 2; collapse witnessed: 7; presenting rhythm: 165; bystander CPR: 231

0900 and 2000 hours, respectively, for cardiac (n = 1,591, p = 0.0167) and non-cardiac (n = 576, p = 0.021) causes of death (Fig. 1). When translated into the four quadrants of the day, the distribution is as shown in Fig. 2. When looking at the prevalence of coronary artery disease risk factors (CADRF) and other medical history, the range in the four time quadrants were as follows: diabetes mellitus 25.3%–30.3%, hypertension 33.7%–41.2%, and history of ischaemic heart disease 37.9%–40.1%. There were no statistically significant differences noted between the quadrants for the numbers of victims who had history of the above diseases (Table I).

DISCUSSION

The analysis excluded paediatric patients as their cardiac arrests have a different range of aetiologies from that of adults. Trauma arrests were also excluded as these tend to be affected by a multitude of external confounding factors.[13-15] The mean age of the cardiac arrest victims is in their sixties, for both cardiac and non-cardiac causes at all times of the day, with female patients making up about a third of the victims. As for the racial distribution, this is similar to the ethnic distribution in Singapore, except for a higher incidence in Indians. This is likely to be linked to the genetic predisposition of this racial group.[16-19] It was also interesting to note that there was no obvious dominant prevalence of CADRF in any of the four quadrant in the cohort studied, e.g. those with hypertension or known ischaemic heart disease did not show any statistically significant predominance in any specific quadrant. Cardiac arrest rates are not constant throughout the 24-hour period, but this may vary across different populations. Some of the differences noted may be due to the methodology of the studies, the use of definition, the accuracy of reported timings in acute events, the diligence and accuracy with which data collection is carried out as well as certain differences in configuration of death certificate data for the underlying cause of death. In this study, we had two peaks

Table II. Time taken in minutes from call for ambulance to arrival at scene.

Cause of arrest	00:01–06:00	06:01–12:00	12:01–18:00	18:01–24:00	p-value*
Cardiac	8.0 (6.3–10.2)	9.1 (7.0–11.7)	8.8 (6.4–11.0)	9.1 (7.0–11.8)	< 0.001
Non-cardiac	9.0 (7.0–11.4)	9.8 (7.1–11.9)	8.1 (6.7–10.7)	9.3 (7.0–12.6)	0.052
Overall	8.3 (6.6–10.4)	9.3 (7.0–11.9)	8.6 (6.5–10.9)	9.1 (7.0–12.0)	< 0.001

*Kruskal-Wallis test
Data is expressed as median (interquartile range)

Table III. Time taken in minutes from call for ambulance to arrival at patient's side.

Cause of arrest	00:01–06:00	06:01–12:00	12:01–18:00	18:01–24:00	p-value*
Cardiac	10.8 (9.0–13.0)	11.2 (9.0–14.3)	11.0 (8.6–13.3)	11.6 (9.0–14.0)	0.019
Non-cardiac	11.9 (9.8–14.2)	12.0 (9.7–15.0)	10.8 (8.5–14.1)	12.0 (9.3–14.6)	0.13
Overall	11.0 (9.0–13.1)	11.4 (9.0–14.6)	11.0 (8.6–13.3)	11.7 (9.1–14.2)	0.0038

*Kruskal-Wallis test
Data is expressed as median (interquartile range)

at 0800 and 1900 hours for those with cardiovascular-related causes of death. For those with non-cardiac related causes of death, slight peaks were seen at 0900 and 2100 hours. These peaks for cardiac causes were similar to some urban cities, like Seattle and Berlin.[20-22] The p-values were significant for these peaks.

To explain the morning peak, there is a suggestion that there exists a circadian rhythm in the basal vascular tone which could be either partly or entirely due to increased alpha-sympathetic vasoconstrictor activity in the morning. This variation may contribute to increased blood pressure and incidence of cardiovascular events at this time of the day.[23,24] The possible reasons for the peak morning incidence being more sharply defined for the first three hours after awakening could be explained by rising plasma epinephrine and norepinephrine levels, increased platelet aggregability and increased vascular resistance.[25-28] Beta blockers and aspirin have been found to blunt this morning peak in the presentation of ischaemic events and sudden cardiac death.[29,30]

VF with its age-related variability too have been shown to have a predominance in the earlier half of the day (0600 till before 1200 hours).[24,31-33] The slightly lower evening peak, too, has been identified. Some have called this the "happy hour" time, i.e. between 1700 and 2000 hours. Different factors may be at play here, perhaps more environmental factors rather than biological-physiological factors.[34] From a more basic science perspective, the circadian rhythm seems to be controlled by a transcriptional feedback system, which fluctuates as a function of the light-dark cycle. A molecular clock mechanism has been identified in the suprachiasmal nuclei, also known as the master clock in the mammalian brain. It involves phasic changes in gene expression, which has relation to oxygen consumption, carbohydrate oxidation and contractile performance of the heart.[35]

The survival rates were also low, and possible reasons include the very low pre-paramedic arrival or bystander CPR rate and the response times (Tables II and III).[21,22] There was a delay between arrival at scene and getting to the patients' side because in highly urbanised, high-rise Singapore, paramedics upon arrival at the car park of these high-rise buildings, will need to take the elevator, locate the exact unit and access the unit. These results can be correlated to the low bystander CPR rate across all quadrants of the day and especially at night.[36] Thus, it may be good to target CPR/BCLS training for spouses and family members of patients with coronary artery ischaemic heart disease. This relevance is again noted, as the majority of the OHCAs take place in homes and residences. In Singapore, public access defibrillation is still in its infancy stage and is not widely and readily available. Although all SCDF ambulances are equipped with AEDs, this is very dependent on response and arrival times.

Strategies to help improve the survival rates include creation of awareness through the following measures:
(1) Public education, which will encourage people to attend training and preventive measures with the understanding of triggers and risks with their predilection for certain times of the day.
(2) Implementation of public access defibrillation on a large scale, and greater understanding of information on circadian variation which can be incorporated into a software utilised for advising ambulance deployment at different times of the day. It may be worth to consider decentralising ambulances away from the current station concept to a more flexible and movable base. This can be effected after a careful study of the geographical locations and plots of the OHCA cases.
(3) Enhancement and expansion of BCLS and CPR training to more sectors of society, including schools,

offices, companies, institutions of higher learning, the police force, all national service personnel, community leaders and volunteers. This will help create awareness and garner more support for the paramedics at the scene; e.g. the local community can help with directing them to the exact household unit and keeping the elevators immediately available for use when they arrive. This will certainly help ensure all delays at the scene are minimised up to the point when the paramedics reach the patient's or victim's side literally.

Circadian rhythm has a role in explaining OHCA distribution and peaks. There was no statistically significant difference in the incidence or predominance of any risk factors or factors which were seen in all the quadrants. The information obtained will be utilised for fine-tuning EMS strategies in Singapore, as we strive to improve our survival rates from OHCA.

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