Circadian rhythm of hospital deaths: comparison between intensive care unit and non-intensive care unit

Antônio Sérgio Cordeiro da Rocha[1], Mônica Peres de Araújo[2], Augusta Campos[3], Rubens Costa Filho[4], Evandro Tinoco Mesquita[5], Marcus Vinicius Santos[6]

[1]PhD in Cardiology; Universidade de São Paulo (USP); Coordinator, Clinical Unit, Hospital Pró-Cardíaco, Rio de Janeiro, RJ, Brazil
[2]MSc in Cardiology, Universidade Federal Fluminense (UFF); Physician, Hospital Pró-Cardíaco, Rio de Janeiro, RJ, Brazil
[3]Board Certified Cardiologist, Sociedade Brasileira de Cardiologia (SBC); Physician, Hospital Pró-Cardíaco, Rio de Janeiro, RJ, Brazil
[4]Coordinator, Intensive Care Unit, Hospital Pró-Cardíaco, Rio de Janeiro, RJ, Brazil
[5]PhD in Cardiology, USP; Medical Director, Hospital Pró-Cardíaco, Rio de Janeiro, RJ, Brazil
[6]General Director, Hospital Pró-Cardíaco, Rio de Janeiro, RJ, Brazil

Summary

Objective: The demonstration that cardiovascular mortality follows a circadian rhythm led us to verify whether patients dying at the intensive unit care (ICU) and at the non-intensive unit care (non-ICU) follow that rhythm. **Methods:** All hospital's deaths occurring between January 1, 2006 and July 31, 2010 were analyzed. The circadian pattern of the time of death was analyzed in twelve 2-hour intervals. The Chi-square test was used to compare proportions, and Student's *t* test or ANOVA single factor to compare continuous variables. A p-value ≤ 0.05 was considered statistically significant. **Results:** During the study period 700 deaths occurred in the hospital, 211 (30.1%) at the ICU and 88 (12.6%) at the non-ICU. There were more deaths in the first hours of the day, between 6 am and 12 am, at the non-ICU in comparison to the ICU (38% vs. 21%; p = 0.004). In the ICU, we observed that 21% of the deaths occurred between 6 am and 12 pm, 30% between 12 pm and 6 pm, 26% between 6 pm and 12 am and 24% between 12 am and 6 am (p = 0.13) , whereas, at the non-ICU, 38% of the deaths occurred between 6 am and 12 pm, 18% between 12 pm and 6 pm, 19% between 6 pm and 12 am and 25% between 12 am and 6 am (p = 0.005). **Conclusion:** At the non-ICU, deaths occur more often in the morning period and follow a circadian rhythm, which does not occur at the ICU.

Keywords: Hospital mortality; circadian rhythm; chronobiological disorders.

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Correspondence to:
Antônio Sérgio Cordeiro da Rocha
Rua General Polidoro, 192
2º andar
Rio de Janeiro - RJ, Brazil
CEP: 22280.000
ascrbr@centroin.com.br

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Introduction

Because of the Earth's rotation, all living species on the planet's surface are exposed to the standard of 24 hours of light and darkness. In response to this regular variation of the light/dark cycle, living beings have developed an endogenous circadian rhythm that repeats itself every 24 hours. With the knowledge obtained over time, we know that this rhythm is important in maintaining the life of living organisms in response to environmental changes. However, changes in human behavior over the centuries, promoted by the modernization of customs and habits, brought a threat of disruption to this rhythm[1-5].

In fact, when observing that cardiovascular mortality follows a rhythm, which accompanies neuroendocrine and metabolic alterations, one understands the importance of this biological process on human nature[6,7]. Within this context, several authors have studied the differences in outcomes of patients admitted during the day compared to those admitted during shifts in intensive care units (ICU), but no studies have been dedicated to compare the time of occurrence of deaths in the ICU and the non-intensive care unit (non-ICU)[8-12].

The objective of this study is to observe the differences in time of deaths in an ICU compared with the non-ICU and whether there is a circadian pattern of these deaths occurring in these two hospital units.

Methods

This is a retrospective case-series study, which included all deaths occurring in a private hospital, with open medical staff, between January 1, 2006 and July 31, 2010. Based on a protocol developed by the Committee for the Investigation of Hospital Deaths, a database was created with the minimum necessary information to outline the clinical profile of patients who died, as well as the time of occurrence of these deaths in the institution.

We collected the data on all deaths that occurred in the intensive care unit (ICU) and the non-intensive care unit (non-ICU). Thus, this analysis excluded deaths that occurred in the coronary unit, post-operative adult and child units and the emergency department of the institution.

The following data were collected: demographic characteristics, diagnosis of underlying diseases, direct cause of death and time of occurrence of deaths.

We considered cardiovascular disease as the presence of any one of the following pathologies: coronary artery disease, cerebrovascular disease, peripheral vascular disease or thoracic or abdominal aortic disease documented by clinical, laboratory or angiographic pictures compatible with the diagnosis. As infectious diseases, we considered the presence of clinical and laboratory pictures consistent with the presence of any infectious agent of any etiology and affecting any organ system. As cancer, we considered the presence of documented malignancy affecting any organ or system. Neoplasias were considered as direct causes of deaths whenever there was cachexia or multiple organ metastases. As for pulmonary embolism (PE), angiographic evidence of thrombus involving the pulmonary artery circulation was considered. As dementia, we considered the association of memory impairment and some type of cognitive impairment. As kidney failure, we considered the presence of serum creatinine > 2 mg/dL or need for dialysis. Acute myocardial infarction (AMI) was considered when it met the ACC/ESC criteria[13]. Cerebrovascular accident (CVA) was considered in the presence of clinical evidence associated with imaging consistent with the diagnosis. We also evaluated the percentage of patients who were receiving comfort measures in the two units.

The circadian pattern of occurrence of deaths was obtained by dividing the 24 hours of the day in 2-hour periods.

The data are shown as absolute numbers or proportions. For comparison of continuous variables Student's *t* test or one-way analysis of variance (ANOVA) was used and the Chi-square test or Fisher's exact test was used to compare categorical variables. The significance level was set at 5% and all calculations were two-tailed.

Results

Between January 1, 2006 and July 31, 2010 there were 700 deaths in the entire institution, corresponding to a hospital mortality rate of 3.6%. Of the 700 deaths, 211 (30.1%) occurred in the ICU and 88 (12.6%) in non-ICU.

There was no difference in age between the patients who died in the ICU (80 ± 12 years) compared to non-ICU (78 ± 14 years) (p = 0.13), as there was no difference in the proportion of women between the ICU and non-ICU (44% vs. 49%, respectively, p = 0.56).

As a direct cause of death (Table 1) neoplasms were more prevalent in the non-ICU than in the ICU (45.5% vs. 7.0%, respectively, p = 0.0001), while sepsis was more prevalent in the ICU, although not statistically significant (65% vs. 23.7%, p = 0.07). All patients that died of sep-

Table 1 – Direct causes of deaths

Causes	ICU (n = 211)	Non-ICU (n = 88)	p
Sepsis (%)	64.9	23.1	0.0001
Neoplasias (%)	6.8	42.3	0.0001
CVA (%)	5.2	5.8	0.74
AMI (%)	2.8	0	0.61
PTE (%)	1.0	0	1.0
Others (%)	20.4	28.8	0.19

ICU, intensive care unit; non-ICU, non-intensive care unit; CVA, cerebrovascular accident; AMI, acute myocardial infarction; PTE, pulmonary thromboembolism.

sis at the non-ICU were receiving comfort measures. The prevalence of AMI as the direct cause of death was similar between the ICU and the non-ICU (2.8% vs. 1%, p = 0.61); the same was observed regarding cerebrovascular accident (5.2% vs. 5.7%, p = 1.0) and thromboembolism (1.0% vs. 1.1%, p = 1.0).

As for the underlying disease (Table 2), cardiovascular diseases were more prevalent in patients who died in the ICU than in non-ICU (46.0% vs. 17.0%, p = 0.0001), while neoplasias were more prevalent in the non-ICU (65.9% vs. 17.0%, p = 0.0001).

Table 2 – Distribution of underlying diseases at the two treatment units

Underlying disease	ICU (n = 211)	Non-ICU (n = 88)	p
CVD (%)	46.0	15.4	0.0001
Neoplasias (%)	16.6	65.4	0.0001
Infectious D. (%)	30.8	11.5	0.004
Others (%)	28.0	40.4	0.09
> 1 underlying cause (%)	62	44	0.02

ICU, intensive care unit; non-ICU, non-intensive care unit; CVD, cardiovascular disease; Infectious D., infectious diseases.

Infectious disease as the underlying cause of death was more prevalent in the ICU than in the non-ICU (30.8% vs. 11.4%, p = 0.001). On the other hand, there was no significant difference in the prevalence of dementia (2.4% and 4.5%, p = 0.45), kidney failure (10.4% vs. 4.5%, p = 0.11) and other diseases together (28% vs. 36.4%, p = 0.16) between the ICU and non-ICU, respectively. More patients in the ICU had more than one underlying cause of death than those admitted at the non-ICU (62% vs. 44%, respectively, p = 0.02).

Of the patients who died at the non-ICU, 68 (77.3%) received comfort measures, compared with 30 (14.2%) at the ICU (p = 0.0001).

When comparing the time of occurrence of deaths in the ICU and the non-ICU, it was observed that significantly more deaths occurred in the early hours of the day, between 6 am and 12 pm, in the first compared to the second (38% vs. 21%, p = 0.004).

When analyzing the period of occurrence of deaths in the ICU, we observed that 21% of the deaths occurred between 6 am and 12 pm, 30% between 12 pm and 6 pm, 26% between 6 pm and 12 am and 24% between 12 am and 6 am (p = 0.13) , whereas, at the non-ICU, 38% of the deaths occurred between 6 am and 12 pm, 18% between 12 pm and 6 pm, 19% between 6 pm and 12 am and 25% between 12 am and 6 am (p = 0.005).

Analyzing the occurrence of deaths every two hours, it can be observed that in the non-ICU there is an increase in the number of deaths from 4 am, peaking at around 8 am and with a small increase between 12 pm and 6 pm, i.e., those deaths follow a periodicity (Figure 1), whereas this pattern is not observed in the ICU (Figure 2).

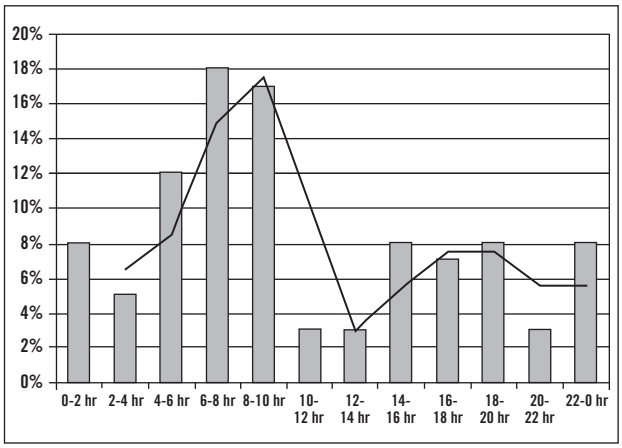

Figure 1– Variation in time of the deaths throughout the 24 hours of the day, every two hours in the non-intensive care unit – non-ICU (p < 0.0001).

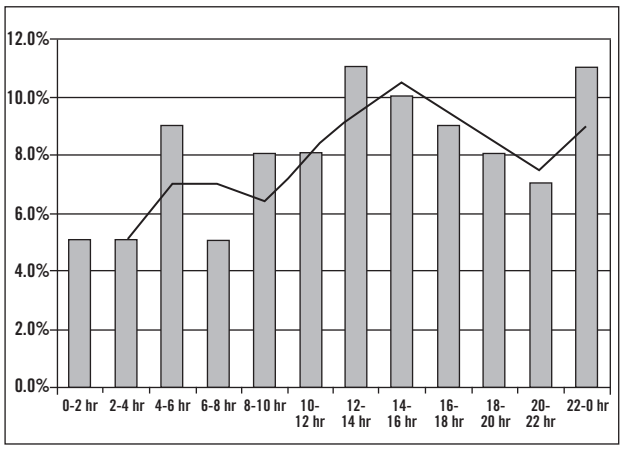

Figure 2 – Variation in time of the deaths throughout the 24 hours of the day, every two hours in the intensive care unit - ICU (p = 0.49).

Discussion

Our study shows that, when analyzing the occurrence of deaths in relation to the circadian pattern, there was no time of day associated with increased mortality in the ICU, i.e., the circadian rhythm in this unit mortality was for some reason disrupted (Figure 2). Also, there was no difference in the occurrence of deaths between the routine hours (6 am to 6 pm) and the shifts in the ICU (6 pm to 6 am), i.e., 51% versus 49% (p = 1.0). On the other hand, we observed a higher mortality rate in the non-ICU in the morning hours, when compared to other periods of the day, which configures the maintenance of the circadian pattern of mortality in this unit (Figure 2). Considering

these results, we speculate that patients admitted to the non-ICU preserve the circadian periodicity, regardless of the underlying disease that affects them.

In the ICU, on the other hand, the role of several factors might change that frequency, either due to the confinement, the uninterrupted use of light throughout the day, use of vasoactive drugs, sedation, intubation, etc. To the best of our knowledge, this observation of the circadian pattern maintenance in the deaths occurring in the non-ICU had not been previously published. However, it coincides with the description by other authors of the occurrence of acute myocardial infarction and sudden death in the general population[6,7].

Additionally, Meynaar et al.[8], when analyzing the influence of admission out of the routine schedule (shifts) on mortality in the ICU showed that admission at these times was not associated with increased mortality. In our study, although we did not analyze the association of the time of admission with mortality, we observed that there was no difference in mortality between the four analyzed periods of the day in the ICU.

As expected, the number of deaths in the ICU was higher than in the non-ICU, which is consistent to what has been observed in other services[14-16]. Our study also shows that 77.3% of patients who died at the non-ICU were receiving comfort measures compared to 14% in the ICU.

These data are consistent with those reported in the literature[15,17]. Analyzing our data within the context of terminal life, it is evident that neoplasias had a significant effect on the difference observed between the two units. Furthermore, all patients that died as a direct consequence of sepsis in the non-ICU were receiving comfort measures. It is important to report that the reason why the proportion of patients receiving comfort measures in the ICU was lower than that in the non-ICU, was that many of the deaths occurring in the ICU were due to multiple organ failure, therefore constituting an end-of-life process and the uselessness of maintaining therapeutic measures that would extend the vital status of patients.

Regarding sex, our study shows that there was prevalence of males in both units, that is, 56% in the ICU and 51% in the non-ICU, although not statistically significant. These data are different from those reported by Toscanini et al.[18] in an analysis of deaths in various hospitals in Italy, which showed a predominance of female deaths in those institution wards. Moritz et al.[15], in a study conducted in our country, observed the equivalence between the sexes in the deaths that occurred in a university hospital in the state of Santa Catarina, notwithstanding the predominance of male deaths in the ICU of that institution.

An unusual aspect of the results of our study was the prevalence of more than one underlying disease and cardiovascular diseases in patients who died in the ICU, when compared with those who died at the non-ICU, especially when there is no difference in age or sex between the patients from the two analyzed units. Assuming that 77% of patients who died at the non-ICU were receiving comfort measures as a result of the terminal stages of their illnesses, we imply that the presence of more than one underlying disease in these patients was as prevalent as that in patients who died in the ICU.

This fact is even more relevant when one considers that cancer and cardiovascular diseases have common risk factors, subjecting, at least theoretically, their carriers to the same possibilities of concomitant diseases[19]. Another possibility is the lack of information about concomitant diseases in the death certificate files that come from the non-ICU. According to Marins et al.[20], in 52.8% of all deaths in the city of Ribeirão Preto, there was no reference to secondary diagnoses in the death investigations.

When analyzing the report by Toscanini et al.[18] regarding deaths that occurred in the wards of several hospitals in Italy, we found that, similarly to our study, there was a prevalence of malignancy as the underlying disease in patients that died in those institutions.

Limitations

Our study has several limitations. As records were not analyzed in their entirety, it is possible that other factors, which were not assessed, might have somehow modified the results. Due to this limitation we were unable to assess the type of medication that patients were using in their respective units at the hour, on the days or in the weeks before the deaths. Additionally, we did not assess the impact of therapeutic measures used, especially in the ICU on the circadian variation of death occurrence. We emphasize that our analysis was restricted to deaths, and thus, the clinical profile does not accurately depict the patients admitted to the studied units.

Conclusion

At the non-ICU, deaths occur more often in the morning period and follow a circadian rhythm, which does not occur at the ICU.

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