Circadian Variation In Acute Coronary Syndromes

Corresponding Author:
Dr. Muralikrishna Gopal,
MD, Division of Pulmonary-Critical Care, Montefiore Medical Center - United States of America

Submitting Author:
Dr. Muralikrishna Gopal,
MD, Division of Pulmonary-Critical Care, Montefiore Medical Center - United States of America

Article ID: WMC00533
Article Type: Research articles
Submitted on: 06-Sep-2010, 09:54:43 PM GMT    Published on: 06-Sep-2010, 10:21:44 PM GMT
Article URL: http://www.webmedcentral.com/article_view/533
Subject Categories: CARDIOLOGY
Keywords: Acute Coronary Syndromes, Circadian, Variation, Hypertension

How to cite the article: Gopal M, Boopathy N, Venkatesan R, Jagannathan V. Circadian Variation In Acute Coronary Syndromes. WebmedCentral CARDIOLOGY 2010;1(9):WMC00533

Source(s) of Funding:
None

Competing Interests:
None
Circadian Variation In Acute Coronary Syndromes

Author(s): Gopal M, Boopathy N, Venkatesan R, Jagannathan V

Abstract

Background: Studies have shown that a circadian rhythm may exist in the onset of acute coronary syndromes. More studies are needed in the Indian population to confirm the existence of this circadian variation and add to the existing literature in the Indian population. Methods: Two hundred twenty consecutive patients with acute coronary syndromes, admitted to the coronary care unit were included in the study. The time of onset of symptoms was noted into six categories of four hours each. Results: The statistical analysis of the data obtained showed that acute coronary syndromes was commonest from 4am to 8 am (35%, P value Conclusions The circadian variation in the time of onset of acute coronary syndromes in an Indian population is similar to data published in the western literature, with a peak in the early morning. This variation appears to be exaggerated in the treatment naïve-hypertensive population. Further research is needed to assess the cellular and neuro-hormonal mechanisms of this circadian variation and may have implications in therapeutics.

Introduction

Circadian rhythms are biological rhythms that occur endogenously in most biological organisms. The effect that these biological oscillations have on the pathophysiology of various diseases is currently the focus of numerous research studies. The increased risk of occurrence of acute coronary syndromes in the early morning has been demonstrated in a few studies1,2,3,11,12,17,25,26. A meta-analysis showed a 40% increase in risk of myocardial infarction between 6 am and noon1 and another showed an increased occurrence of ischemic stroke in the morning18. The pathogenetic mechanism of this circadian variation is a subject of ongoing research. It is also now known that the pathogenetic mechanisms of cardiovascular disease in the Indian population may be different from the western population. In the scientific literature, only one prior study7 has published attempting to determine if this circadian variation in acute coronary syndromes exists in the Indian population, in addition to one other study, that shows a circadian variation in the onset of ischemic stroke in a geriatric population in India18. The sub-group analysis of one study involving over one thousand patients done in the United Kingdom did not show a circadian variation in the south Asian population13. Current research has also focused on the variation in the circadian rhythm in acute coronary syndromes in patients with co-morbidities, especially diabetes13,15, which has shown no circadian variation in diabetic patients. So far, studies have not focused on the circadian variation of acute coronary syndromes in hypertensives. In normal subjects, blood pressure appears to fall nocturnally, whereas, it has been shown that a sub-group of patients with hypertension do not exhibit this nocturnal fall in blood pressure16, so called non-dippers, and this may contribute to an increased occurrence of acute coronary syndromes, especially in the early morning in this population. We wanted to further delineate this relationship by performing a sub-group analysis of hypertensive as compared to non-hypertensive patients.

Methods

Patients presenting to the Coronary Care Unit (CCU) with a diagnosis of acute coronary syndrome-unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) were included in the study. Exclusion criteria included the absence of chest pain, treatment with fibrinolysis/ PCI prior to admission to coronary care unit, current use of anti-hypertensive medications, current use of aspirin, inability to provide history at time of admission, presence of malignant hypertension and secondary causes of hypertension. Patients with a history of hypertension and on anti-hypertensive medications were excluded due to prior studies showing significant effects of these medications, especially beta blockers13 and angiotensin converting enzyme inhibitors on the circadian rhythm of the autonomic nervous system10 and acute coronary syndromes13. Ours is a single centre study which enrolled two hundred twenty consecutive patients selected from a group of 316 patients. 96 patients were excluded based on the exclusion criteria. The study was conducted at the Coronary Care Unit (CCU) of the Department of Cardiology, Government General Hospital, Chennai. The time of onset of...
symptoms were then divided into six periods of four hours each: 12-4am, 4-8am, 8-12 am and so on. These patients were then treated in the CCU according to the existing management protocols. Also, after the acute phase management, the patients were then enquired as to whether they had been diagnosed with hypertension in the past, and if so, a detailed medication history was obtained. The results are summarized in table 1. The statistical analysis performed from the data of the above table with the help of chi-square plots, Mann Whitney tests, continuity correction gave the results as follows.

Results

Among the 220 patients enrolled in the study, 76% were male. 26% of the patients self-reported a prior history of diabetes. 81 patients self-reported a prior diagnosis of hypertension and not being on anti-hypertensive medications (36%). 46% of patients self-reported a history of smoking.

The time of onset for each patient in the study, and sub-tabulation of the time of onset in two groups of hypertensives and non-hypertensives was noted and the results are summarized in table 1. Table 1 shows that 79 patients had a time of onset between 4 am and 8 am. This amount to 35% of the study population compared to significantly lower percentages at other times of the day. This difference was statistically significant, P value < 0.005. A sub-group analysis was conducted based on the presence of pre-existing hypertension that was treatment-naive. The circadian variation in the time of onset of acute coronary syndromes in the non-hypertensive subgroup showed a marked bimodal rhythm. i.e., patients in the non-hypertensive population showed an early morning peak in the onset of acute coronary syndromes accompanied by a late evening rise (4 am to 8 am -32.3%, 4 pm-8 pm -22.3%). This result was statistically significant since P value was

Discussion

The results of the study are consistent with prior studies in the literature both in the western and Indian literature with a peak occurrence of acute coronary syndromes between 4 am and 8 am. Several mechanisms have been proposed for the pathogenesis of this relationship. Platelet aggregation in response to epinephrine, adenosine diphosphate, and thrombin is heightened during the early morning hours, particularly after arising from sleep. Anti-thrombin levels decline and fibrinogen levels increase during this time period as well. Plasminogen activator inhibitor activity shows a marked increase in the early morning hours. One study also showed a relative resistance to thrombolysis in the early morning hours and another showed poorer outcomes with PCI done in the early morning and this was attributed to “time of PCI” rather than “time to PCI”, when comparing off-duty and off-hour PCI to regular times. The results appear to indicate that the circadian variation in the time of onset of acute coronary syndromes is different in hypertensives when compared to non-hypertensives. Thus hypertensives exhibit a circadian rhythm that is exaggerated in the early morning and blunted in the late evening. The circadian variation of acute coronary syndromes in hypertensive patients maybe clinically significant because understanding of the basis of the circadian variation is essential for instituting pharmacological therapy aimed at modifying the circadian rhythm of various physiological variables. Numerous 24 hour blood pressure recordings have shown that the blood pressure fluctuates widely from time to time but exhibits a significant nocturnal fall of 30-50 mm Hg and an early morning rise. Of greater significance are studies showing the lack of a nocturnal decrease in blood pressure in a sub-population of hypertensives which may contribute to an increased occurrence of acute coronary syndromes in this population. It has been shown in clinical studies that the circadian rhythm of acute coronary syndromes correlates very well with the changes in blood pressure. Since it is clear that early morning peak of acute coronary syndromes is due to the elevation of blood pressure, pharmacologic therapy aimed at blunting the early morning rise with the aid of nocturnal dosing of anti-hypertensive therapy could reduce the occurrence of acute coronary syndrome in this population. This is currently the subject of research, which has been labeled chronotherapeutics. One study showed the lack of a circadian variation of acute coronary syndromes in patients taking beta-blockers.

Our study has several limitations. Our study population of 220 is smaller than the prior study in an Indian population, which included 605 patients, but larger than one other study in a geriatric population in India, which included cardiovascular and cerebrovascular disease, and included 158 patients. Our sample size was also severely limited by the exclusion of patients on aspirin and anti-hypertensives, which form a significant proportion of patients presenting with acute coronary syndromes, because of prior studies suggesting a blunting of the circadian rhythm in...
patients on these medications. Due to the lack of established medical records for most patients admitted to the coronary care unit, we had to rely on a self-reported history of diabetes and hypertension. It is possible that a small population of the "non-hypertensive" population could have had previously undiagnosed hypertension. Because of the use of onset of chest pain, although used by prior studies as well, patients with silent myocardial ischemia are likely to be missed in the study population.

**Conclusion(s)**

There are two major conclusions we can infer from the study. Firstly, a circadian rhythm exists in the time of onset of acute coronary syndromes in the Indian population as well. Understanding of the mechanism of this circadian rhythm may lead to therapeutic strategies that can reduce the incidence of acute coronary syndromes by blunting this peak. The exaggeration of the early morning peak seen in hypertensive patients could be related to non-dipping, as suggested by one prior study. If this is confirmed by continuous blood pressure recordings in larger studies, this could identify a sub-group of patients with hypertension who maybe at higher risk of acute coronary syndromes than those who experience a nocturnal fall in their blood pressure. As a corollary, institution of pharmacologic therapy aimed at decreasing blood pressure during this period of the day may reduce the peak in the time of onset of acute coronary syndromes in this population. Further prospective, controlled trials are needed to confirm the translation of this pathophysiologic benefit to clinical practice.

**References**


23) Zwolle Myocardial Infarction Study GroupHenriques JPS, Haasdijk AP, Zijlstra F. Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus off-hours. J Am Coll Cardiol.


Illustrations

Illustration 1

Table 1: Cross tabulation of hypertension vs. time of onset of symptoms

<table>
<thead>
<tr>
<th>TIME OF ONSET OF SYMPTOMS</th>
<th>12am-4am</th>
<th>4am-8am</th>
<th>8am-12pm</th>
<th>12pm-4pm</th>
<th>4pm-8pm</th>
<th>8pm-12am</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensives</td>
<td>10</td>
<td>34</td>
<td>11</td>
<td>7</td>
<td>10</td>
<td>9</td>
<td>81</td>
</tr>
<tr>
<td>Non-hypertensives</td>
<td>16</td>
<td>45</td>
<td>18</td>
<td>14</td>
<td>31</td>
<td>15</td>
<td>139</td>
</tr>
<tr>
<td>All patients</td>
<td>26</td>
<td>79</td>
<td>29</td>
<td>21</td>
<td>41</td>
<td>24</td>
<td>220</td>
</tr>
</tbody>
</table>
Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.