JACC: CARDIOVASCULAR INTERVENTIONS VOL. 4, NO. 2, 2011

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2010.09.025

Circadian Variation in Coronary Stent Thrombosis

Karim D. Mahmoud, BSc,*† Ryan J. Lennon, MS,‡ Henry H. Ting, MD, MBA,*§ Charanjit S. Rihal, MD, MBA,* David R. Holmes, Jr, MD*

Rochester, Minnesota; and Groningen, the Netherlands

Objectives We sought to determine the circadian, weekly, and seasonal variation of coronary stent thrombosis.

Background Other adverse cardiovascular events such as acute myocardial infarction are known to have higher incidences during the early morning hours, Mondays, and winter months.

Methods The Mayo Clinic Percutaneous Coronary Intervention Registry was searched for patients admitted to our center who underwent repeat percutaneous coronary intervention in a previously stented coronary artery segment. Stent thrombosis was confirmed by angiographic review, and date and time of symptom onset were obtained from medical records.

Results We identified 124 patients with definite stent thrombosis and known date and time of symptom onset. In these patients, onset of stent thrombosis was significantly associated with time of day ($p = 0.006$), with a peak incidence around 7:00 AM. When patients were subdivided into early stent thrombosis (0 to 30 days; $n = 49$), late stent thrombosis (31 to 360 days; $n = 30$), and very late stent thrombosis (>360 days; $n = 45$), only early stent thrombosis remained significantly associated with time of day ($p = 0.030$). No association with the day of the week was found ($p = 0.509$); however, onset of stent thrombosis did follow a significant seasonal pattern, with higher occurrences in the summer ($p = 0.036$).

Conclusions Coronary stent thrombosis occurs more often in the early morning hours. Early stent thrombosis follows a circadian rhythm with a peak at 7:00 AM. This pattern was not significant in late and very late stent thrombosis. Occurrences throughout the week were equally distributed, but stent thrombosis was more likely to occur in the summer months. (J Am Coll Cardiol Intv 2011;4: 183–90) © 2011 by the American College of Cardiology Foundation

From the *Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; †Groningen International Program of Science in Medicine GIPS-M, University of Groningen, Groningen, the Netherlands; ‡Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; and the §Knowledge and Encounter Research Unit, Mayo Clinic, Rochester, Minnesota. Mr. Mahmoud has the following grant sponsors: Netherlands Heart Foundation, Groningen University Fund, Marco Polo Fund, and the Jan Kornelis de Kock Foundation. All other authors have reported that they have no relationships to disclose.

Manuscript received June 22, 2010; revised manuscript received July 30, 2010, accepted September 3, 2010.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 2, 2011
FEBRUARY 2011:183–90

Twenty-four-hour (circadian) patterns are present in numerous physiological processes. Circadian variation with a morning peak has been found in heart rate, blood pressure, (1,2) and levels of multiple hormones such as renin, aldosterone, and cortisol (3,4). It is becoming increasingly clear that adverse events follow circadian patterns as well. Circadian variation with a peak in the morning has been observed in stroke (5), unstable angina pectoris (6), acute myocardial infarction (AMI) (7,8), and sudden cardiac death (7,9). In addition, weekly patterns with a peak on Monday and seasonal patterns with a peak in the winter have been reported in AMI (10–12) and sudden cardiac death (13,14). Most of these temporal patterns seem to be attributable to triggering factors, such as hemodynamic and hemostatic changes, physical exertion, and mental stress (15–18).

In theory, it is likely that coronary stent thrombosis also follows a circadian pattern, due to an increased tendency toward thrombosis in the morning hours (18–20). However, this hypothesis has only been confirmed by 1 report with a sample size of 21 patients (21). Furthermore, the role of triggering factors in stent thrombosis onset has been suggested in a case report (22). More insight in patterns of onset of stent thrombosis and potential triggers might help to prevent stent thrombosis by optimizing medical treatment during high-risk intervals throughout the day, week, and year.

Abbreviations and Acronyms

AMI = acute myocardial infarction
IQR = interquartile range
MET = metabolic equivalent
PCI = percutaneous coronary intervention

To address the hypothesis that stent thrombosis follows a circadian pattern, we performed an analysis of the Mayo Clinic Percutaneous Coronary Intervention Registry. Second, we assessed weekly and seasonal patterns and characterized potential triggering events preceding stent thrombosis onset.

Methods

Study design. After obtaining institutional review board approval, a retrospective analysis was performed, with the Mayo Clinic Percutaneous Coronary Intervention Registry. This database includes baseline, procedural, angiographic, and outcome data on all patients undergoing percutaneous coronary intervention (PCI) at the Mayo Clinic, Rochester, Minnesota. For this registry, data are prospectively collected by experienced interventional cardiology data technicians. The database supervisor performs routine audits of 10% of the records for quality control purposes. We identified patients admitted to our center who had undergone a repeated PCI procedure in a coronary artery segment where a stent had been previously placed and who had experienced sudden onset or worsening of anginal symptoms within 1 week of this repeated PCI procedure. The later criterion was determined by medical record review. We excluded patients with unknown symptom onset date and time and patients who had previously declined to have their medical records reviewed for research, as is required by Minnesota state law. We did not study patients with sudden death, because angiographic evidence of stent thrombosis could not be obtained in these patients. Subsequently, angiograms of eligible study subjects were reviewed for angiographic evidence of stent thrombosis by experienced interventional cardiology trainees blinded to the primary outcome of this study. Thus, the subjects we identified by means of this method have definite stent thrombosis according to the Academic Research Consortium definition: "an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion" (23). In addition, medical records were reviewed for level of physical activity before symptom onset, and other events that had potentially triggered stent thrombosis were identified.

Definitions. In accordance with the Academic Research Consortium definition, stent thrombosis was subdivided into early stent thrombosis (0 to 30 days), late stent thrombosis (31 to 360 days), and very late stent thrombosis (>360 days) (23). Multivessel disease was defined as the number of vessels wherein the first had at least 70% stenosis and subsequent vessels had at least 50% stenosis. For the index procedure (initial stent placement), lesion dissection was defined as the presence of an intimal tear during the procedure, regardless of its persistence after completion of the procedure; and stent size was defined as the smallest diameter of any stent placed in the coronary artery segment where stent thrombosis would later occur. Finally, arterial calcification and lesion calcification were defined as any visible calcium during coronary angiography. The level of physical activity before stent thrombosis symptom onset was graded with metabolic equivalents (METs). One MET was defined as the energy spent/minute by a subject sitting quietly and is equivalent to 3.5 ml of oxygen uptake/kilogram of body weight/minute by a 70-kg adult (15). This method has previously been used in studies assessing physical activity as a potential trigger of myocardial infarction (15,17). We defined the categories: sleeping (1 MET), lying or sitting (1 to 2 METs), light to moderate exertion (3 to 5 METs), and heavy exertion (≥6 METs). Furthermore, we reviewed medical records for other potential triggers of stent thrombosis. This included documented medication noncompliance and patients who were initially admitted to our center for other medical conditions but developed stent thrombosis during their hospital stay. Patients who were admitted for stent thrombosis but were found to have other important medical conditions at admission (e.g., infection) were also considered to have a potential triggering factor for stent thrombosis.

Statistical analysis. Continuous variables are summarized as mean ± SD, unless otherwise specified. Discrete variables are presented as fractions and percentages. Group differ-