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Circadian Dependence of Infarct Size and Left-Ventricular Function Following ST-Elevation Myocardial Infarction

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Abstract

Rationale—In rodents, infarct size following ischemia/reperfusion (I/R) exhibits a circadian dependence on the time of coronary occlusion. It is not known if a similar circadian dependence of infarct size occurs in humans.

Objective—To determine if humans exhibit a circadian dependence of infarct size in the setting of ST-elevation myocardial infarction (STEMI).

Methods and Results—A retrospective analysis of 1031 patients with STEMI referred for primary PCI with known ischemic times between 1 and 6 hours identified 165 patients with occluded arteries on presentation without evidence of pre-infarction angina or collateral blood flow. Both ischemic duration and angiographic area-at-risk were not dependent on time of infarct onset. We observed that the extent of infarct size measured by CK release was significantly associated with time of day onset of infarction ($p<0.0001$). The greatest myocardial injury occurred at a 1 AM onset of ischemia and 5AM onset of reperfusion with the peak CK measured at the peak of the curve being 82% higher than that recorded at the trough. Similarly, left-ventricular ejection fraction (LVEF) measured within 2 days of infarction was also dependent on time of onset of STEMI with the absolute LVEF at peak more than 7% higher than at trough (43% vs. 51%), ($p< 0.03$). These findings were supported by a subgroup of patients (n=45) who underwent cardiac MRI measurements of infarct size and area-at-risk measurements.

Conclusions—The results of this study demonstrate for the first time in humans that myocardial infarct size and left-ventricular function following STEMI have a circadian dependence on the time of day onset of ischemia.

Keywords

circadian; infarct size; ischemia/reperfusion; STEMI

INTRODUCTION

Circadian rhythms exert a profound influence on cardiovascular physiology (1). Heart rate, blood pressure, and many circulating hormones such as aldosterone and cortisol (2) follow a circadian pattern. In a similar manner, adverse cardiovascular events also demonstrate a time of day dependence with episodes of myocardial infarction (3), sudden cardiac death (4) and stent thrombosis (5) all peaking in the early morning hours. This time of day dependence has

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Disclosures: none

mainly been attributed to non-cardiac factors such as changes in sympathetic tone (6) and circadian variation in coagulation factors (7).

Evidence has recently emerged that circadian clocks intrinsic to cardiac cells may contribute to time of day dependence of cardiovascular physiology. Multiple clock proteins appear to be regulated in a time-dependent manner in cardiomyocytes that may have profound effects on myocardial metabolism, function and response to injury (8). In animal models, the disruption of these circadian clocks has been implicated in the pathogenesis of various cardiovascular diseases (9). Recently, Durgan et al. (10) demonstrated that ischemia/reperfusion (I/R) tolerance is dependent on the time-of-day of coronary occlusion. Using a mouse I/R model, they demonstrated a 3.5-fold variation in infarct size that was dependent on the time of day onset of coronary occlusion. They observed that the largest injury occurred at the sleep to wake transition, which translated into reduced LV function when examined by echocardiography one month later. Furthermore, they demonstrated that the time of day variation in infarct size was abolished in a transgenic mouse with an ablated cardiomyocyte circadian clock.

We investigated if the phenomenon described by Durgan et al. (10) occurs in humans by analyzing if the time of day onset at which the heart is subjected to ischemia influences subsequent infarct size and left ventricular function in a cohort of patients with ST-segment elevation myocardial infarction (STEMI).

METHODS

Study Design

A retrospective analysis was performed on all patients who were admitted to The Minneapolis Heart Institute at Abbott Northwestern Hospital from January 2006 through September 2010 as part of the *Level 1 Acute MI* program. This is a regionalized transfer network for primary percutaneous coronary intervention (PCI) involving 31 community hospitals and emergency departments throughout Minnesota and Western Wisconsin (11). All STEMI patients who present to the referring hospitals are transferred to our institution for primary PCI regardless of time of presentation and no significant difference in pharmacologic therapy or transfer times occur in those patients transferred at night versus daytime (12) (See Supplemental Table I). All patients had well-defined ischemic times and the data was supported by a subgroup with cardiac MRI (cMRI) measurements of infarct size and area-at-risk (AAR). All medical records were reviewed by 2 of the authors blinded to time of presentation to ensure accuracy of the data.

A total of 1031 patients presented with STEMI and ischemic times between 1 and 6 hours. The ischemic time was defined as the time difference between the onset of chest pain to restoration of flow following the first balloon inflation during primary PCI. All patients were pre-medicated with aspirin (325 mg), clopidogrel (600 mg), heparin (60 Units/kg) or bivalrudin (0.75 mg/kg bolus followed by 1.75 mg/kg-hr) and underwent routine PCI of the culprit vessel with the majority of patients receiving drug-eluting stents.

A total of 866 patients were excluded from further analysis based on at least one of the following exclusion criteria (Figure 1): TIMI flow > 0 prior to coronary intervention or collateral filling of the infarct vessel (n=568), presence of pre-infarction angina (n=94), prior CABG or myocardial infarction in the same vascular distribution (n=72), cardiac arrest requiring more than 1 shock or CPR (n=70), peak of cardiac enzymes not recorded (n=44), postconditioning (13) performed during coronary intervention (n=10), vessel could not be opened (n=6), or acute stent thrombosis within 72hrs (n=2). A total of 165 patients (78%

male, 59.5±12.7 yrs) with well-defined times of ischemia onset and duration (183 ± 66 mins) were included in the final analysis (Table 1).

Measurement of Infarct Size and Area-at-Risk by Cardiac MRI

A subgroup of 45 patients underwent cardiac MRI (cMRI) measurements of infarct size and AAR within 3 days following STEMI. Infarct size was determined by delayed enhancement with gadolinium. Endocardial and epicardial borders were manually segmented from base to apex and infarct size was determined using the CIMRA software system (CSON Medical, www.csonmedical.com). AAR was estimated as the total amount of subendocardial surface area containing delayed enhancement as a percentage of the total subendocardial surface area (14). Both infarct size and AAR were expressed as percentage of total LV mass.

The peak creatine kinase (CK) level was used as a surrogate of infarct size as previously described (15–17). The validity of this assumption was also confirmed in the subgroup of patients in our cohort that underwent cardiac MRI, demonstrating a highly significant relationship between peak CK and delayed enhancement with gadolinium. Measurements of CK were performed on presentation and every 6 to 8 hrs for 24 to 48 hours following reperfusion with the highest value designated as the peak CK. Measurement of left-ventricular ejection fraction (LVEF) was obtained by echocardiography in 146 of the 165 patients within 48 hours following reperfusion.

Measurement of the Angiographic Area-at Risk

The angiographic AAR was calculated for each patient using the modified Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) score (18). This method is based on previous pathological studies estimating the percentage of myocardium perfused by each coronary artery. For each patient, an area-at-risk score, expressed as percentage of myocardium, was calculated based on the location of the culprit lesion in the infarct artery (proximal, mid, distal) in relation to major side branches and dominance of the vessel. This method has been previously validated by MRI measurements of AAR (14).

Statistical Analysis

The peak CK and left-ventricular ejection fraction (LVEF) for each patient was plotted against the time onset of ischemia expressed over a 24-hour interval. To determine if ischemic injury in the human heart is dependent on time of onset of infarction (circadian), a periodic sinusoidal regression analysis (19) was performed for both infarct size and LVEF using the online non-linear regression web page (http://statpages.org/nonlin.html) using the following equation:

$$f(t)=a+b*\sin(2\pi*(t-c)/24) \quad (1)$$

with “a” indicating the MESOR (Midline Estimating Statistic Of Rhythm), a measure of the rhythm-adjusted mean value, “b” the amplitude and “c” the origin of the curve. A 24-hour period for circadian rhythm was assumed. Circadian rhythm was deemed to be present if the amplitude of the fitted curve was significantly different from 0 (Wald test).

RESULTS

Peak CK as a Correlation to Infarct Size as Measured by cMRI

Multiple studies have previously demonstrated that peak CK is highly correlated with myocardial infarct size assessed by cMRI (15,16) or SPECT (17). As demonstrated in Figure

2, there was excellent correlation between peak CK and infarct size by cMRI that supports our use of peak CK as a surrogate of infarct size for the entire cohort ($r= 0.76$, $p < 0.0001$).

Determination of the Circadian Dependence of Myocardial Infarct Size Following STEMI

A significant association between time of onset of STEMI and myocardial infarct size as assessed by peak CK was demonstrated following nonlinear regression to a sinusoidal curve (Figure 3). Maximal injury was observed at the time of day onset of chest pain at 1AM. Amplitude of the sinusoidal curve was significantly different from 0 ($p < 0.0001$) with the peak CK of the fitted curve about 82% higher compared to trough suggesting a strong circadian influence. Similar results were obtained when peak troponin was used as a marker for myocardial damage (data not shown). A nearly identical relationship was observed when time of reperfusion was measured instead of onset of ischemia with the curve being shifted to the right by 4 hours (5 AM). Because infarct size is significantly affected by the AAR, we plotted the AAR over the 24-hour cycle and found no variation (Figure 4).

Although intra-hospital transfer times do not vary by time of day in our regionalized system (12), symptom-onset to emergency department presentation times may be delayed at night, potentially leading to longer ischemic times and myocardial injury (20). However, as depicted in Figure 5, ischemic times were relatively evenly distributed throughout the 24-hour day with no circadian relationship ($p = 0.35$) thereby excluding bias of myocardial injury by different ischemic times.

Correlation of Angiographic Area-at-Risk to Measurements Obtained by cMRI

In the subgroup of patients that had paired cMRI measurements we confirmed that the angiographic method of the modified APPROACH score (18) was highly correlated with the AAR obtained by cMRI (Figure 6) ($r=0.65$, $p <0.001$). We then plotted the Peak CK normalized by the angiographic AAR (Figure 7a) or AAR measured by cMRI (Figure 7b) against the time of onset of ischemia to demonstrate maintenance of a circadian relationship.

Assessment of Circadian Dependence of Left-Ventricular Function Following STEMI

LVEF was plotted against time of onset of infarction as a nonlinear (periodic) regression to a sinusoidal curve (Figure 9) in 146 of the 165 patients who had left-ventricular function measurements performed within 48 hours following STEMI. Amplitude (LVEF) of the resulting curve was significantly different from 0 ($p < 0.03$), demonstrating circadian influence with phase of the peak LVEF correlated with the trough of the peak CK curve (Figure 3). The absolute LVEF at peak was more than 7% higher than at trough (43% vs. 51%).

DISCUSSION

This study details one of the first descriptions in humans of a clear circadian distribution of myocardial infarct size in the setting of STEMI that is dependent on the time of coronary occlusion. The results are bolstered by a similar, but time-shifted circadian pattern of the degree of LV dysfunction that results following myocardial infarction. These findings build upon previous descriptions of circadian cardiovascular influences in humans such as onset of myocardial infarction (3) or sudden cardiac death (4). However, whereas many previous descriptions are likely related to non-cardiac circadian processes such as sympathetic tone (6) and coagulation factors (7), recent animal studies (9,10) demonstrate circadian influences on transcriptional events in cardiomyocytes that may lead to varying degrees of myocardial protection throughout a 24-hour cycle. These pre-clinical observations and our findings may be relevant to clinical trials examining interventions to reduce infarct size since they demonstrate that the time of coronary occlusion will influence the subsequent degree of

infacrtion. In agreement with the findings of Muller et al. (1), we did observe that the majority of STEMIs (31%) occurred between 6AM and noon in our Level 1 patient population of more than 3000 subjects.

Many factors may ultimately affect final infarct size following prolonged ischemia. These include the occurrence of pre-infarction angina (21) or presence of collateral blood flow to the dependent myocardial region (22) among others, that may reduce infarct size for a given duration of ischemia and obscure potential circadian effects of myocardial protection based on the time of onset of ischemia. We carefully reviewed each chart and angiogram so that patients with these infarct-sparing mechanisms were excluded. Additionally, all patients had occluded arteries on presentation during their primary PCI so that the ischemic duration could be reasonably assessed.

We observed that the peak myocardial injury occurred at 1 AM when measured by time of symptom onset, and at 5 AM when measured by time of reperfusion. These findings are similar to those of De Luca et al. (23) who measured infarct size by enzyme analysis in 1548 consecutive patients with STEMI referred for primary PCI. By dividing the time of reperfusion into six, 4-hour increments, they observed that the largest infarctions occurred between 4 AM and 8 AM, a time period that was associated with the highest platelet aggregation. Our data also correlates well with the data of Durgan et al. (10) who observed that peak myocardial injury occurred near the sleep to wake transition in the nocturnal rodent following a 45-min coronary occlusion. Our analysis of LV function also reveals that the greatest decrease in LV function occurred in those patients whose infarction began around 1 AM, consistent with previous human data showing a peak incidence of CHF in those patients whose infarct began at nighttime (24).

Studies from human cardiac tissue taken at the time of transplant surgery reveal significant circadian transcriptional variation in the principal cardiomyocyte clock genes, with *PER1* and *PER2* peaking in the morning and *BMAL1* peaking in the evening (8). These variations in clock gene expression are 12 hours out of phase with the nocturnal rodent and are consistent with the time difference in their respective sleep to wake cycles. The results of Durgan et al (10) demonstrated significant diurnal variations in the phosphorylation status of proteins well known to modulate I/R injury including Akt and glycogen synthase kinase-3b (GSK-3b), which influences the opening of the mitochondrial permeability transition pore, the end-effecter of reperfusion injury (25). In their study, the nadir of the phosphorylation status of Akt and GSK-3b occurred at the time-point of greatest myocardial injury and overall phosphorylation status of both proteins were linearly-related to infarct size. In a secondary study, these findings were supported by observations in a circadian clock mutant mouse that is resistant to infarction due to chronic elevations in the phosphorylation status of these two proteins.

In a recent publication, Suarez-Barrientos et al. (26) measured myocardial injury by peak CK or troponin-I in patients admitted to their institution with their first STEMI treated with primary PCI or fibrinolytic therapy. When they divided the presentation of symptom-onset into four, 6-hour blocks, they observed that the largest infarctions occurred when their onset of symptoms began between 6AM and noon with a secondary peak between noon and 6PM. This is several hours later than our observations of peak myocardial injury. However, it is likely that significant differences in methodologies are relevant since no apparent effort was made to exclude patients with modifiers of infarct size such as collateral blood flow or pre-infarction angina, and no measurements of AAR were performed to allow determination if a circadian tolerance to ischemia exists in the human heart.

Study Limitations

Our use of peak CK as a surrogate of infarct size to demonstrate a circadian injury response in the human heart in the setting STEMI warrants comment. The use of peak CK has been validated by multiple groups as an excellent estimate of infarct size (27) using different imaging modalities such as cMRI (15,16) and SPECT (17). Haase et al. (15) prospectively measured infarct size with delayed contrast-enhanced cMRI in 45 patients who underwent primary PCI for STEMI and observed a strong correlation between the absolute size of infarct (grams) and peak CK ($r= 0.72$, $p < 0.001$). Similar findings were also reported by Pride et al. (16) in 78 patients with STEMI utilizing cMRI measurements of infarct size ($r= 0.93$, $p < 0.001$). In the EVOLVE trial, Chia et al. (17) found that peak CK was highly correlated ($r=0.73$) with infarct size as determined by SPECT 5 days following primary PCI in 378 patients. Importantly, the subgroup of patients in our cohort with cMRI measurements of infarct size demonstrated excellent correlation with peak CK and had the same circadian relationship as obtained in the overall study cohort.

We have stipulated the onset of ischemia to be the onset of chest pain but recognize that in some patients this may not be the same timepoint, particularly if the patient was asleep when the infarction began. We cannot rule out that this may have produced a small effect on our data since the duration of ischemia would be longer and time-of-onset of ischemia would be shifted to an earlier timepoint. However, we did have access to all emergency room records where the patients initially presented and all subjects were interviewed the following day as part of our *Level 1* follow-up data collection program. Additionally, we have assumed that the occluded artery on presentation to the catheterization laboratory was closed throughout the entire duration of ischemia. Because the anticoagulation strategy was not controlled for in this cohort of patients, we cannot rule out that it may have had some small effect on the results of this investigation.

To rule out a possible selection bias of patients as a cause for our findings, we compared the baseline demographic data of patients in the Circadian cohort versus all patients in the *Level 1* STEMI program admitted during the same time period (Supplemental Table 1). This analysis showed no important differences between groups except for age (59.5 vs 62.8 yrs), slightly greater Killips class 2–4 (10.4 vs 13.8%) and higher mortality in the overall STEMI population due to our prospective exclusion of cardiac arrest, previous bypass surgery and myocardial infarction in the circadian group. Additionally, no important differences were observed between those patients admitted through our emergency department versus those transferred from outside hospitals (Supplemental Table II).

Conclusions

Our findings demonstrate that humans display a circadian response to myocardial injury and LV function in the setting of STEMI. Maximal injury occurs when infarction begins in early morning hours and reperfusion occurs approximately 4 hours later approaching the sleep to wake transition. These findings imply that there is a time-dependent mechanism of myocardial protection in the human heart that may have implications in clinical trials evaluating therapies to reduce infarct size in the setting of I/R injury. Because this report is from a single center, these results should be confirmed in a larger, prospectively designed, multi-center trial with exclusive use of cMRI to measure infarct size and AAR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Non-standard Abbreviations and Acronyms

AAR	Area-at-Risk
Akt	Protein kinase B
CHF	Congestive heart failure
CK	Creatine kinase
cMRI	cardiac magnetic resonance imaging
GSK-3b	glycogen synthase kinase-3b
I/R	ischemia/reperfusion
LVEF	Left-ventricular ejection fraction
MESOR	Midline Estimating Statistic Of Rhythm
PCI	Percutaneous coronary intervention
SPECT	Single photon emission computer tomography
STEMI	ST-elevation myocardial infarction

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Novelty and Significance

What is Known?

- Circadian rhythms exert a profound influence on cardiovascular physiology including heart rate, blood pressure, and circulating hormones.
- Cardiovascular events such as myocardial infarction, sudden cardiac death and stent thrombosis also demonstrate a circadian dependence.
- In rodents, infarct size following ischemia/reperfusion is dependent on the time of coronary occlusion, with the largest injury occurring at the sleep to wake transition; however, it is not known if this occurs in humans.

What New Information Does This Article Contribute?

- Humans display a circadian rhythm with respect to myocardial infarct size and LV function in the setting of ST-elevation myocardial infarction (STEMI).
- Maximal injury occurs when infarction begins in early morning hours (1 AM) and reperfusion occurs approximately 4 hours later, approaching the sleep to wake transition.

Recent studies demonstrate that myocardial infarct size following ischemia/reperfusion in rodents follows a circadian distribution, with the largest infarct size occurring at the sleep to wake transition. To determine if this occurs in humans, we performed a retrospective of analysis of all patients presenting to our institution with their first STEMI for primary percutaneous coronary intervention (PCI) who had well defined ischemic times between 1 and 6 hours. All patients had an occluded artery on presentation, with no evidence of pre-infarction angina or collateral blood flow. Infarct size was measured using peak CK, which was highly correlated with delayed enhancement in a subgroup of patients with cardiac MRI. Angiographic area-at-risk did not vary over the 24-hour period. We observed that infarct size was significantly associated with time of day onset of infarction. The greatest myocardial injury occurred at a 1 AM onset of ischemia and 5AM onset of reperfusion, with the peak CK measured at the peak of the circadian curve being 82% higher than that recorded at the trough. Similarly, the absolute LVEF at peak (measured 12 hours later) was more than 7% higher than at trough (43% vs. 51%). The results of this study demonstrate for the first time in humans that myocardial infarct size and LV function following STEMI have a circadian dependence on the time of day onset of ischemia. These findings may have implications for clinical trials evaluating therapies to reduce infarct size following ischemia/reperfusion.

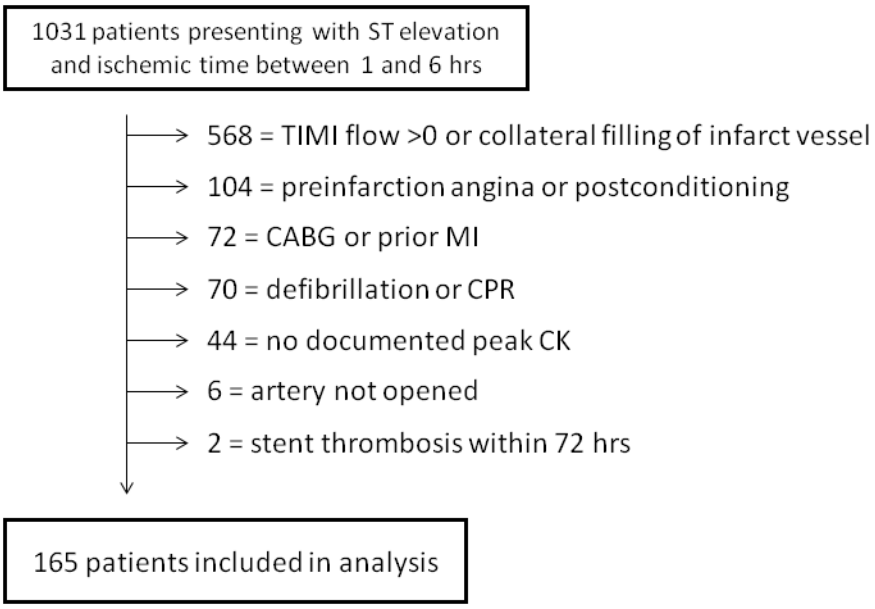

Figure 1.
Study Design: Of 1031 patients presenting with ST elevation and an ischemic Time ≤ 6hrs, 866 patients were excluded for a variety of reasons. Patients could have more than 1 reason for exclusion but only 1 per patient is noted in the diagram.

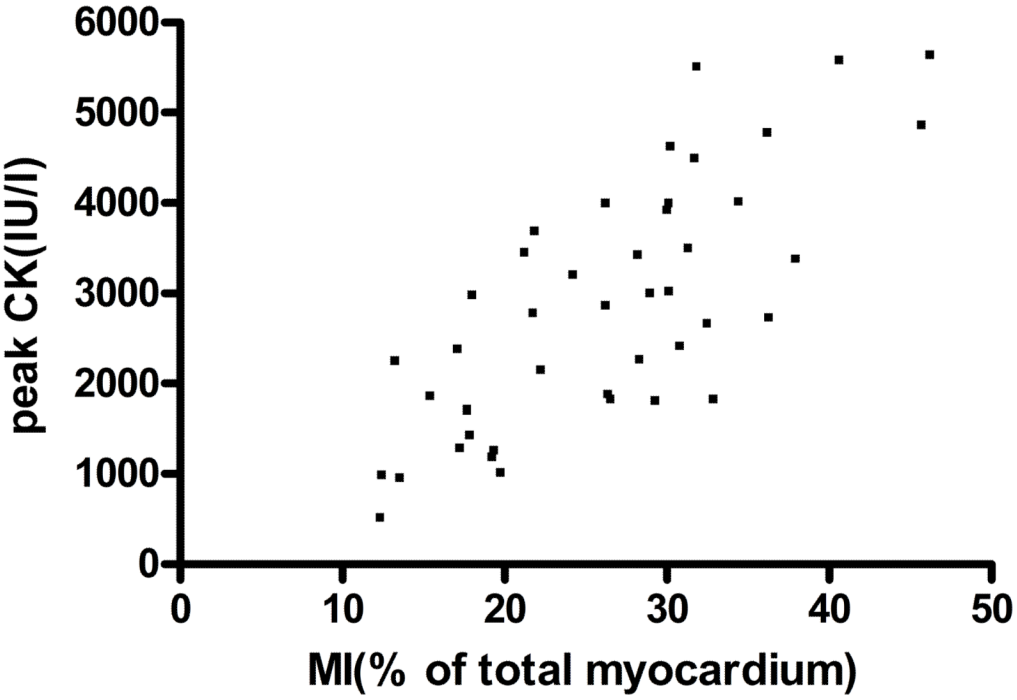

Figure 2.
Correlation of peak CK with infarct size as measured by cardiac MRI: Infarct size was measured by cMRI (n=45), expressed as % of total myocardium and plotted against Peak CK. Correlation is highly significant ($r=0.76$, $p<0.0001$)

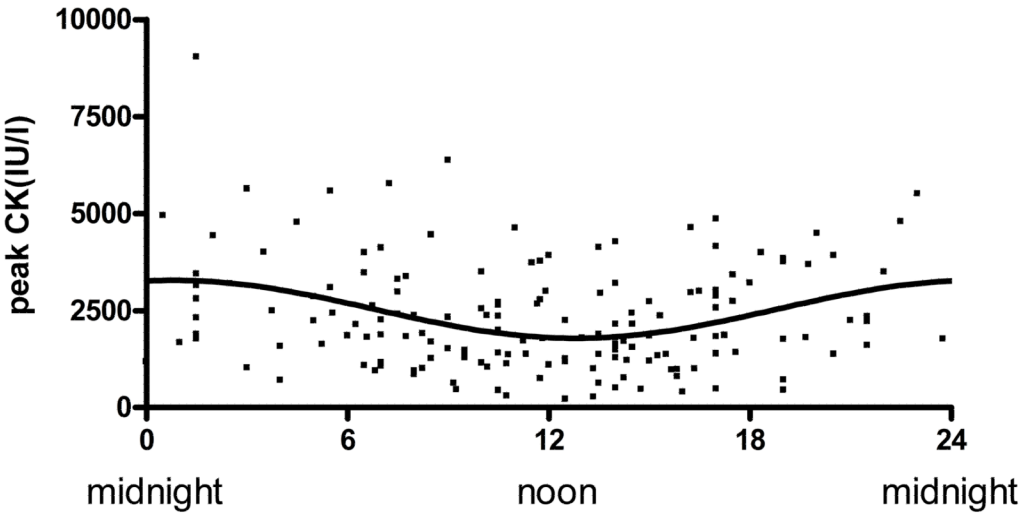

Figure 3.

Time of day dependence of myocardial infarct size with coronary occlusion: Peak CK was plotted against time onset of ischemia. Line represents the fitted sinusoidal curve: CK= 2543+739 × sin (2π x (onset hour-18.72)/24). Amplitude of the fitted curve is significantly different from 0 ($p<0.0001$) indicating Circadian influence on myocardial infarct size.

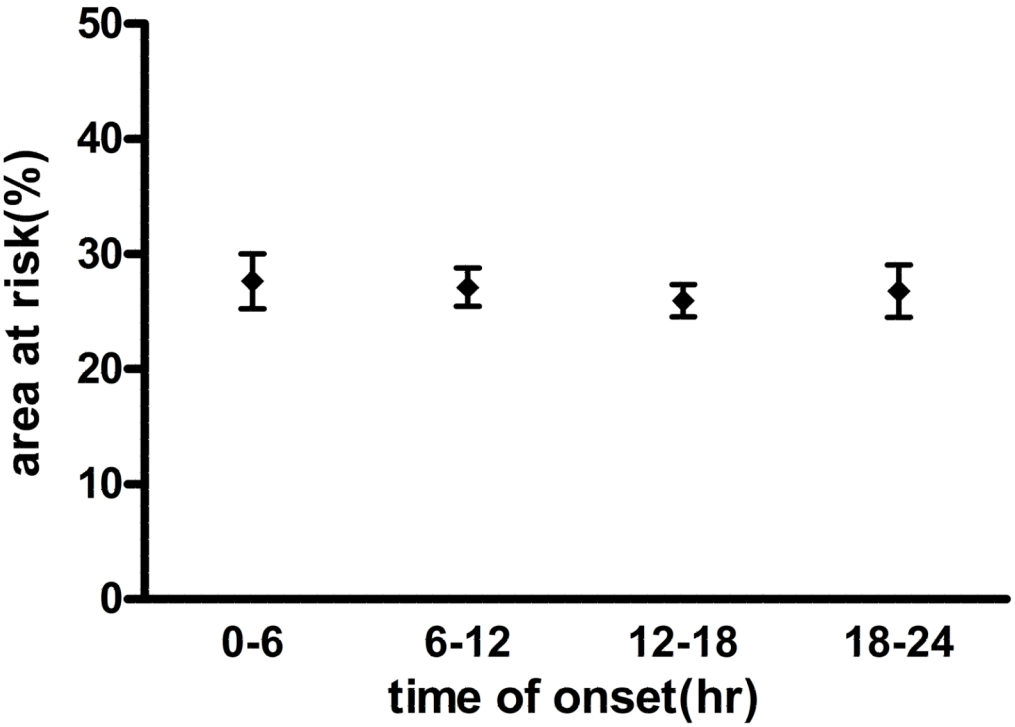

Figure 4.
Angiographic Area-at-Risk versus time of onset of ischemia over 24-hour cycle: No significant change in AAR is observed over time as expressed as four, 6-hour intervals

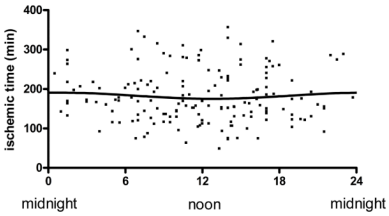

Figure 5.

Ischemic time (IT) versus time of day onset of myocardial infarction: IT was plotted against time of onset of ischemia. Line represents the fitted sinusoidal curve: IT= 183.36+7.61 × sin (2π x (onset hour-18.47)/24). Amplitude of the fitted curve is not significantly different from 0 (p=0.35) thereby demonstrating no Circadian influence on ischemic time.

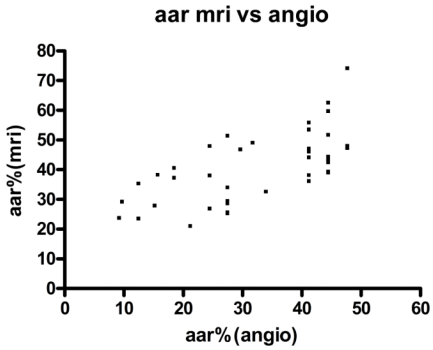

Figure 6.
Correlation of area-at-risk assessment (AAR) by MRI with AAR assessment by angiography: AAR measured by MRI and angiography are plotted against each other. Correlation is highly significant ($r=0.65$, $p<0.0001$).

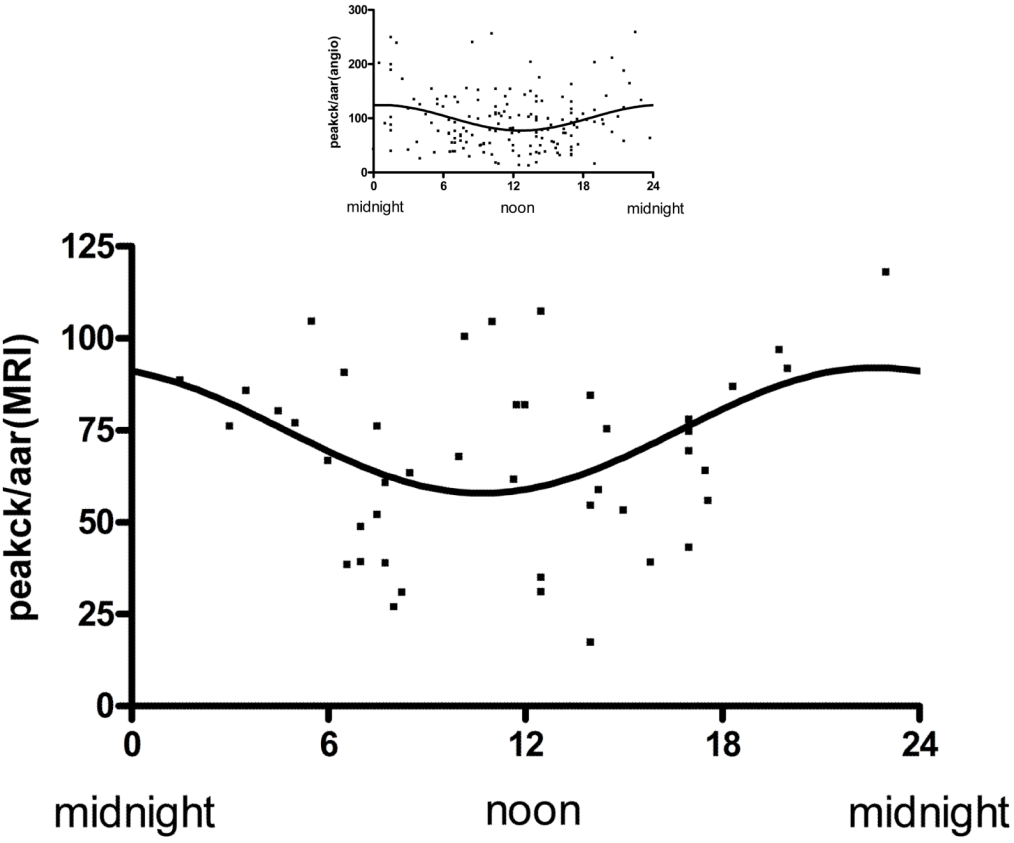

Figure 7.

Circadian variation of myocardial infarct size when corrected for area at risk: Peak CK was divided by area at risk measured by angiography (a) and MRI (b). Lines represent the fitted sinusoidal curves. CK/AAR(angio)=99.95+22.16 × sin (2π x (onset hour-18.22)/24) (a) and CK/AAR(MRI)=73.2+16.64 × sin (2π x (onset hour-17.28)/24) (b). Amplitude of the fitted curves are significantly different from 0 ($p<0.001$(a) and $p<0.02$(b) confirming Circadian influence on myocardial infarct size when corrected for area at risk.

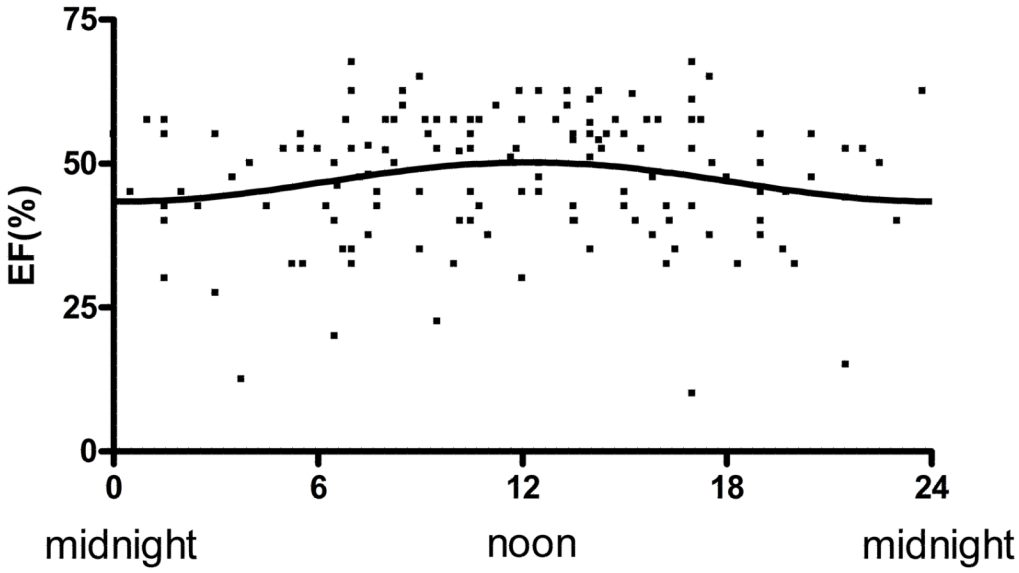

Figure 8.

Left-ventricular ejection fraction versus time of day onset of STEMI. Ejection Fraction (EF) was plotted against time onset of ischemia. Line represents the fitted sinusoidal curve: EF=46.83+3.41 × sin (2π x (onset hour-6.20)/24). Amplitude of the fitted curve is significantly different from 0 ($p<0.03$) indicating circadian influence on ejection fraction following STEMI.

TABLE 1

Baseline Demographics

Baseline Demographics (N=165)	
Age (years)	59.5 ± 12.7
% Male	79
Ischemic Time (mins)	183 ± 66
HTN (%)	48
Dyslipidemia (%)	48
Diabetes (%)	12
Infarct Artery (n) LAD	65
CX	29
RCA	71