Daytime variation of perioperative myocardial injury in non-cardiac surgery and effect on outcome

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ABSTRACT (250 words)

Objective: Recently, daytime variation in perioperative myocardial injury (PMI) has been observed in patients undergoing cardiac surgery. We aim at investigating whether daytime variation also occurs in patients undergoing non-cardiac surgery.

Methods: In a prospective diagnostic study we evaluated the presence of daytime variation in PMI in patients at increased cardiovascular risk undergoing non-cardiac surgery, as well as its possible impact on the incidence of acute MI (AMI), and death during one-year follow-up in a propensity-score matched cohort. PMI was defined as an absolute increase in high-sensitivity cardiac troponin T (hs-cTnT) concentration of ≥14 ng/L from preoperative to postoperative measurements.

Results: Of 1641 patients, propensity score matching defined 630 with similar baseline characteristics, half undergoing non-cardiac surgery in the morning (starting from 8 a.m. to 11 a.m.) and half in the afternoon (starting from 2 p.m. to 5 p.m.). There was no difference in PMI incidence between both groups (morning: 50, 15.8% (95%-CI 12.3-20.3), afternoon: 52, 16.4% (95%-CI 12.7-20.9), p=0.94), nor if analyzing hs-cTnT release as a quantitative variable (median morning group: 3ng/L (95%CI 1-7ng/L); median afternoon group: 2ng/L (95%CI 0-7ng/L; p=0.16). During one-year follow-up, the incidence of AMI was 1.2% (95%CI, 0.4-3.2%) among morning surgeries versus 4.1% (95%CI, 2.3-6.9%) among the afternoon surgeries (corrected HR for afternoon surgery 3.44, bootstrapped 95%CI 1.33-10.49, p-log-rank=0.03), whereas no difference in mortality emerged (p=0.70).

Conclusions: Although there is no daytime variation in PMI in patients undergoing non-cardiac surgery, the incidence of AMI during follow-up is increased in afternoon-surgeries and requires further study.

Clinical Trial Registration— URL: https://www.clinicaltrials.gov. Unique identifier: NCT02573532.

Key questions

- What is already known about this subject?

  Acute spontaneous myocardial infarction seems to happen more commonly during the morning hours. Patients undergoing cardiac surgery in the morning seem to present with a higher risk for peri-operative myocardial damage.

- What does this study add?

  Peri-operative myocardial damage following non-cardiac surgery does not seem to be associated with a daytime variation. Patients operated in the afternoon suffered an acute myocardial infarction during one-year follow-up more often than patients operated in the morning.

- How might this impact on clinical practice?

  Understanding surgery-associated biorhythms could allow scheduling the operation during a time interval associated with a lower risk.

INTRODUCTION

Perioperative myocardial injury (PMI) has been identified as an important, yet commonly unrecognized complication after non-cardiac surgery, substantially increasing short- and long-term mortality.[1,2] Considering that >300 million surgeries are performed annually and that demographic change is resulting in an increasing number of surgical patients with elevated cardiovascular risk, a better understanding of the pathophysiology underlying PMI may have the potential to provide major medical benefits.[1–3]

Daytime variations have been observed for various cardiovascular events with most of the events peaking during the morning hours.[4,5] For spontaneous cardiovascular events, the knowledge of the existence of a daytime variation has not yet been able to be translated into direct benefit to patient care. In contrast, knowledge of the possible existence of a daytime variation of iatrogenic cardiovascular complications such as PMI could rather effectively be translated into direct benefit to patient care by scheduling the operation during a time interval associated with a lower risk.

Following this concept, a recent pilot study exclusively enrolling patients undergoing on-pump cardiac aortic valve replacement suggested the presence of a daytime variation for PMI occurring during cardiac surgery with a lower event rate triggered by operations that are performed in the afternoon.[6] Such a daytime-dependent cardioprotective strategy based solely on the time of surgery could represent an inexpensive and easily implementable way to improve short and long-term outcome in patients at increased cardiovascular risk undergoing surgery.[7] It is currently unknown whether a similar daytime variation in PMI also occurs in patients undergoing non-cardiac surgery.

Therefore, in order to address this major gap in knowledge, the aims of the present work were to assess the impact of the timing of surgery first on the incidence of PMI

and, second, on the incidence of AMI, death and cardiovascular death during one-year follow-up in a propensity-score matched cohort.

METHODS

Patients

Between October 2014 and November 2015, we included consecutive patients undergoing non-cardiac surgery at the University Hospital Basel, Switzerland, who were eligible for the institutional routine PMI screening program and provided written general consent to registration in a dedicated prospective database. The study was approved by the local ethics committee (NCT02573532).

Patients were screened if they had a planned hospital stay exceeding 24 hours after surgery and were considered at increased mortality risk, defined as ≥65 years of age, or ≥45 years with history of coronary artery disease (CAD), peripheral artery disease (PAD), or stroke. Patients could be included multiple times into the original PMI cohort but only once in all current analyses (n=1641) as only their first surgery was considered.

Procedures: Detection of PMI and follow-up

Plasma concentrations of high-sensitivity cardiac troponin T (hs-cTnT), a quantitative marker of cardiomyocyte injury[8,9], were measured within 30 days before surgery and on postoperative days 1 and 2, and later if clinically indicated. Overall, 83% of the patients received their pre-operative hs-cTnT measurement within 1 day and 94% within 3 days before surgery. PMI was defined as an absolute increase of hs-cTnT concentrations of 14ng/L or more above baseline concentrations. PMI was centrally adjudicated by 2 independent experts based on all clinical information obtained during index hospitalization. In addition, perioperative cardiomyocyte injury was evaluated using the absolute increase of hs-cTnT concentrations triggered by the operation as a continuous variable[8–10].

Hs-cTnT was measured by using an Elecsys System using the Modular Analytics E170 or the Cobas e602 (Roche Diagnostics) assay with a limit of detection of 5 ng/L, a 10% coefficient of variation at 13 ng/L, and the 99th percentile of a healthy reference population at 14 ng/L.[11]

PMI screening was implemented for patients undergoing visceral, orthopedic, trauma, vascular, urologic, spinal, and thoracic surgical procedures. Serial hs-cTnT measurements were ordered by the treating anesthesiologist.

In case of an absolute increase in hs-cTnT of ≥14 ng/L, a cardiology consultation request was triggered electronically.

During follow-up, patients were contacted after 1 year by mail or telephone, and local death registries checked. In case of suspicion of AMI or death, study personnel requested reports from the general practitioners, treating facilities, or death registries. Patients lost to follow-up were censored at the last contact with the study team, a hospital, or their general practitioner.

AMI during the follow-up was defined according to the Third Universal Definition of MI[12] from the 4th day after surgery and beyond.

Objectives

The primary objective of this study was to assess, whether the incidence of PMI or cardiomyocyte injury quantified as a continuous variable differs depending on the timing of the surgery (morning vs afternoon) in a propensity-matched cohort.

The secondary objective of this study was to assess whether the incidence AMI, all-cause death or cardiovascular death during one-year follow-up differs depending on the timing of the surgery (morning vs afternoon) in a propensity-matched cohort. Additionally, differences in other well-validated quantitative surrogate markers of other

critical organ function (kidney: estimated glomerular filtration rate (eGFR)) and the systemic inflammation (C-reactive Protein (CRP)) were investigated.

Daytime variation

Prior to analysis, we defined morning surgeries as the procedures for which the first incision took place between 8 a.m. and 11 a.m. and afternoon surgeries as the ones for which the first incision took place between 2 p.m. and 5 p.m. These time cut-offs allow for a clear separation of the morning and afternoon, reflect the standard on-duty hours of the study center and are in agreement with the previous study.[6]

Statistical Analysis

Propensity score matching was used to select comparable groups of patients undergoing surgery in the morning and in the afternoon. Details on the matching are available in the supplemental methods.

After estimation of the propensity score, patients in the afternoon group were matched in a 1:1 ratio to those in the morning group. The “nearest neighbour” matching algorithm with a caliper size of 20% of the standard deviation of the estimated propensity score (absolute caliper of 3.1%) was used to construct a matched-paired sample. This caliper size is the one recommended in the literature for propensity score matching in observational studies.[6,13,14]

The primary analysis used a Wilcoxon rank sum test on the difference of the pre-operative and post-operative hs-cTnT values between the morning and afternoon matched cohort. A similar analysis was conducted for the other surrogate markers. Several potential predictors for logged maximal post-operative hs-cTnT were tested in our matched cohort, first in an univariable fashion, and then inserted in a multivariable model. The effect of the timing of surgery on the incidence of PMI and on the difference of the pre-operative and post-operative hs-cTnT values was evaluated using logistic

regression on the matched cohort. In this same matched cohort, the association of the timing of surgery with MACE was evaluated using Kaplan-Meier curves and Cox's proportional hazard regression. To assess reliability of the matching process, we did multiple resampling 10,000 times for the primary and all secondary outcomes involving the matched cohort. We present all the results as median values of the bootstrapped statistics.

Propensity-score matching allows taking into account a relatively large number of confounder variables while still providing accurate statistics. However, as it involves focusing on similar patients and therefore excluding the ones who could not find any match, we performed a sensitivity analysis on the whole cohort of eligible patients using co-variate adjusted analysis and correcting for one covariate per 10 events.

Mann-Whitney-U test was applied for comparison of continuous variables and Pearson Chi-square test or Fisher's exact test for comparison of categorical variables. All hypothesis testing was two-tailed, p-values <0.05 were considered statistically significant. Statistical analyses were performed using the R statistical package (Vienna, Austria).

RESULTS:

Patients characteristics:

Between October 2014 and November 2015, 2350 patients undergoing non-cardiac surgery were screened for PMI, of which 1641 patients were operated in the predefined time frames: 1238 patients in the morning and 403 patients in the afternoon (Supplemental figure 1, Table 1A).

Surgeries in the afternoon were less often urologic or spinal, but more often traumatic or visceral and lasted longer. Patients undergoing surgery during the afternoon more often already underwent a surgery during their hospitalization, had more comorbidities such as diabetes mellitus, renal insufficiency and hypertension, and a higher pre-operative hs-cTnT concentration.

Propensity-score matched cohorts

Among the 403 patients undergoing surgery in the afternoon, 315 patients were successfully matched to a control patient undergoing a surgery in the morning. Accordingly, 630 patients with similar pre-operative characteristics (Table 1B) were available for the primary analysis. The time of the surgery did not influence on the number of post-operative cardiology consultations, the cardiac imaging performed or the medications newly prescribed at discharge (Supplemental table 1).

One-year follow-up was available in 100% of patients for death and in 99.4% of patients (1632/1641) for AMI (Supplemental table 1).

Table 1 : Baseline characteristics	A) Before the match			B) After the match		
	Morning N=1238	Afternoon N=403	p	Morning N=315	Afternoon N=315	p
Age (mean (sd))	73.69 (7.70)	73.18 (8.58)	0.261	73.99 (9.18)	73.44 (8.49)	0.434
Women sex	527 (42.6)	186 (46.2)	0.229	156 (49.5)	145 (46.0)	0.425
Type of surgery						
Urology	246 (19.9)	39 (9.7)	<0.001	26 (8.3)	36 (11.4)	0.229
Orthopedics	141 (11.4)	52 (12.9)	0.465	39 (12.4)	41 (13.0)	0.905
Spinal	231 (18.7)	39 (9.7)	<0.001	39 (12.4)	33 (10.5)	0.531
Thoracic	105 (8.5)	46 (11.4)	0.095	37 (11.7)	37 (11.7)	1.000
Traumatology	169 (13.7)	91 (22.6)	<0.001	83 (26.3)	70 (22.2)	0.265

Table 1 : Baseline characteristics	A) Before the match			B) After the match		
	Morning N=1238	Afternoon N=403	p	Morning N=315	Afternoon N=315	p
Visceral	151 (12.2)	69 (17.1)	0.015	55 (17.5)	51 (16.2)	0.749
Vascular	147 (11.9)	48 (11.9)	1.000	24 (7.6)	35 (11.1)	0.171
ESC Surgical risk[15] (% in categories)						
<1%	372 (30.0)	116 (28.8)	0.675	91 (28.9)	98 (31.1)	0.602
1-5%	739 (59.7)	237 (58.8)	0.798	195 (61.9)	184 (58.4)	0.416
>5%	127 (10.3)	50 (12.4)	0.265	29 (9.2)	33 (10.5)	0.688
Type of anesthesia						
General anesthesia	372 (30.0)	116 (28.8)	0.675	279 (88.6)	272 (86.3)	0.470
Local anesthesia	739 (59.7)	237 (58.8)	0.798	35 (11.1)	41 (13.0)	0.541
Planned surgery duration (median [IQR])	135.0 [105.0, 195.0]	135.0 [105.0, 165.0]	<0.001	135.0 [105.0, 165.0]	135.0 [105.0, 165.0]	0.216
Effective surgery duration (median [IQR])	125.0 [80.0, 183.0]	115.0 [70.0, 170.0]	0.001	116.0 [77.0, 160.0]	120.0 [70.0, 170.0]	0.698
Surgery for a tumor	252 (20.4)	61 (15.1)	0.025	59 (18.7)	53 (16.8)	0.602
Palliative surgery	19 (1.5)	5 (1.2)	0.851	5 (1.6)	3 (1.0)	0.722
Previous surgery in the same hospitalization	62 (5.0)	45 (11.2)	<0.001	31 (9.8)	33 (10.5)	0.895
Urgency of the surgery						
Elective	969 (78.3)	211 (52.4)	<0.001	177 (56.2)	178 (56.5)	0.976
Emergent (<1day)	74 (6.0)	87 (21.6)		50 (15.9)	48 (15.2)	
Urgent (<7days)	195 (15.8)	105 (26.1)		88 (27.9)	89 (28.3)	
Chronic pre-operative medication						
Alpha Blockers	119 (9.6)	34 (8.4)	0.544	21 (6.7)	27 (8.6)	0.453
Calcium antagonists	253 (20.4)	77 (19.1)	0.612	59 (18.7)	62 (19.7)	0.840
Anti-diabetics	216 (17.4)	81 (20.1)	0.260	61 (19.4)	65 (20.6)	0.765
AT-II blockers	621 (50.2)	194 (48.1)	0.517	156 (49.5)	151 (47.9)	0.750
Aspirin	403 (32.6)	138 (34.2)	0.571	101 (32.1)	106 (33.7)	0.734
Beta-blockers	484 (39.1)	159 (39.5)	0.945	128 (40.6)	127 (40.3)	1.000
Nitrate	31 (2.5)	14 (3.5)	0.390	10 (3.2)	13 (4.1)	0.671
Statine	515 (41.6)	150 (37.2)	0.134	117 (37.1)	116 (36.8)	1.000
Past history						
CAD	327 (26.4)	111 (27.5)	0.704	78 (24.8)	86 (27.3)	0.525
Status post AMI	165 (13.3)	55 (13.6)	0.941	41 (13.0)	40 (12.7)	1.000
CHF	125 (10.1)	51 (12.7)	0.177	34 (10.8)	42 (13.3)	0.392
PAD	202 (16.3)	72 (17.9)	0.517	39 (12.4)	52 (16.5)	0.174
Stroke/TIA	109 (8.8)	37 (9.2)	0.897	28 (8.9)	32 (10.2)	0.684
Diabetes						
None	969 (78.3)	303 (75.2)	0.223	245 (77.8)	238 (75.6)	0.572
NIDDM	170 (13.7)	54 (13.4)	0.932	37 (11.7)	44 (14.0)	0.475
IDDM	99 (8.0)	46 (11.4)	0.046	33 (10.5)	33 (10.5)	1.000
Hypertonia	822 (66.4)	237 (58.8)	0.007	199 (63.2)	189 (60.0)	0.461
COPD	167 (13.5)	58 (14.4)	0.708	28 (8.9)	44 (14.0)	0.060
Renal insufficiency	251 (20.3)	108 (26.8)	0.007	75 (23.8)	79 (25.1)	0.781
Smoking			0.061			0.224
Never smoked	317 (47)	141 (55)		73 (45)	103 (54)	
Ex-smoker	225 (33)	67 (26)		54 (34)	51 (27)	
Active smoker	132 (20)	48 (19)		34 (21)	35 (19)	
Medications at discharge						
Alpha Blockers	104 (8.4)	35 (8.7)	0.940	25 (7.9)	29 (9.2)	0.669
Calcium antagonists	286 (23.1)	84 (20.8)	0.382	65 (20.6)	69 (21.9)	0.770
Anti-diabetics	230 (18.6)	80 (19.9)	0.622	62 (19.7)	65 (20.6)	0.843

Table 1 : Baseline characteristics	A) Before the match			B) After the match		
	Morning N=1238	Afternoon N=403	p	Morning N=315	Afternoon N=315	p
AT-II blockers	647 (52.3)	192 (47.6)	0.120	157 (49.8)	151 (47.9)	0.690
Aspirin	482 (38.9)	162 (40.2)	0.694	110 (34.9)	127 (40.3)	0.188
Beta-blockers	492 (39.7)	164 (40.7)	0.779	129 (41.0)	136 (43.2)	0.628
Nitrate	35 (2.8)	12 (3.0)	1.000	14 (4.4)	11 (3.5)	0.683
Statine	520 (42.0)	158 (39.2)	0.351	117 (37.1)	124 (39.4)	0.623
Preoperative hs-cTnT level (median [IQR])	12.0 [7.0, 22.0]	14.0 [8.0, 30.0]	0.005	15.0 [8.0, 26.0]	14.0 [8.0, 27.0]	0.903

Data are presented as number (%) and compared using Mann-Whitney-U test for continuous variables and either Pearson Chi-square test or Fisher-exact test for categorical variables, as appropriate. AMI=Acute myocardial infarction, AT= Angiotensin, CAD= Coronary Artery Disease, COPD=Chronic Obstructive Pulmonary Disease, ESC = European Society of Cardiology, hs-cTnT= high sensitivity cardiac troponin T, IDDM = insulin-dependent diabetes mellitus, NIDDM = non insulin-dependent diabetes mellitus, Sd = standard deviation, TIA = Transient Ischemic Attack.

PMI incidence: morning versus afternoon surgery

In the bootstrapped matched cohort, 52 (16.4%, 95%-CI 12.7-20.9) patients operated in the morning and 50 (15.8%, 95%-CI 12.3-20.3; p=0.94) patients operated in the afternoon experienced a PMI in the 3 days following surgery (Figure 1A). Logistic regression corrected for residual imbalance in baseline comorbidities between the morning and afternoon cohort (vascular surgery, effective surgery duration, PAD and COPD) did not show any significant impact of the timing of surgery on the incidence of PMI (bootstrapped OR = 0.95 for a surgery in the afternoon, bootstrapped 95% CI = 0.62-1.45, p=0.74).

Perioperative cardiomyocyte injury as a continuous variable

The difference between pre- and post-operative hs-cTnT levels as defined as a bootstrapped collective of matched patients undergoing surgery in the morning versus in the afternoon are presented in Figure 1B. There was no difference in the median release of hs-cTnT in the morning or afternoon group (bootstrapped median of pre-operative/post-operative difference for the morning group= 3ng/L (95% CI 1-7), bootstrapped median of pre-operative/post-operative difference for the afternoon

group= 2ng/L (95% CI 0-7), bootstrapped p-value =0.16). While several comorbidities and surgery variables were significantly predicting maximal post-operative hs-cTnT, a surgery in the afternoon (versus in the morning) was not (Supplemental table 2).

Renal function and systemic inflammation in the cohort of matched patients

The perioperative decrease in renal function and perioperative increase in systemic inflammation did not differ between patients undergoing a surgery in the morning and patients undergoing surgery in the afternoon ($p_{comparison\ eGFR}$=0.27 and $p_{comparison\ CRP}$=0.43; Supp. Figure 2)

Survival analysis in the cohort of matched patients

During follow-up, 104 patients died (53 in the morning group, 51 in the afternoon group) and 22 death were recorded as cardiovascular (11 in the morning group and 11 in the afternoon group). 18 patients suffered an AMI (4 in the morning group, 14 in the afternoon group). Bootstrapped estimates corrected for residual imbalance in baseline comorbidities between the morning and afternoon cohort for the three outcomes are presented in table 2. A surgery in the afternoon was associated with a significantly higher risk for AMI during follow-up (bootstrapped HR = 3.44, 95%-CI = 1.33-10.49, p-value = 0.03, Figure 2A). No difference in risk was observed for death or cardiovascular death between the morning and afternoon group (Figure 2B and 2C).

Table 2 : Bootstrapped outcome estimates	Hazard ratio	95%-CI	p-value	Overall event number	Morning event number	Afternoon event number	Number of patients available for the match
All-cause death	0.94	0.64-1.38	0.70	104	53	51	690
Cardiovascular death	1.00	0.44-2.32	0.73	22	11	11	690
AMI	3.44	1.13-10.49	0.03	18	4	14	680

AMI = acute myocardial infarction, CI = confidence interval. All estimated have been corrected for residual imbalance in baseline comorbidities between the morning and afternoon cohort (vascular surgery, effective surgery duration, PAD and COPD).

Sensitivity analyses in the whole cohort

Results of the sensitivity analysis using covariate adjusted analysis as an alternative approach to address differences in baseline characteristics were similar to the results of the matched cohort (Supplementary material).

DISCUSSION

This prospective study evaluated the presence of day-time variation in the incidence of PMI, AMI, death and cardiovascular death following non-cardiac surgery during one-year follow-up in a propensity-score matched cohort. Despite the observational character of the present study, the robust methods used for analysis including bootstrapped estimates obtained after propensity score matching allowed us to minimize the effects of confounders. We report 3 major findings. **First**, the incidence of PMI was comparable among patients undergoing surgery in the morning versus in the afternoon. **Second**, similarly, even when assessing perioperative cardiomyocyte injury as a continuous variable using the hs-cTnT assay, no difference was observed between morning versus afternoon surgery. **Third**, patients undergoing a surgery in the afternoon had more than 3-times the rate of AMI during one-year follow-up as compared to patients undergoing surgery in the morning. No difference in all-cause mortality was observed.

These findings extend and corroborate previous work assessing biorhythms in cardiovascular function, the tolerance of the cardiovascular system to external stressors, and cardiovascular disorders.[16,17] A recent pilot study observed a lower ischemia/reperfusion tolerance and higher incidence of PMI among patients undergoing on-pump aortic valve replacement in the morning as compared to patients undergoing the same operation in the afternoon.[6] This daytime variation in ischemia/reperfusion tolerance achieved enormous attention, as it was associated with a difference in major cardiovascular events during follow-up. Major uncertainties remain regarding the exact pathophysiology underlying this observation, as well as its possible generalizability to other medical interventions. The findings of this study evaluating non-cardiac surgery, in conjunction with prior work assessing other medical

interventions including elective coronary angioplasty and coronary artery bypass grafting revealed either no day-time variation or one that suggested even an inverse susceptibility with more pronounced cardiomyocyte injury as quantified by hs-cTn release during the interventions taking place in the afternoon.[18,19]

These discrepancies may be explained by differences in procedure-specific details including the patient population undergoing these procedures, the exact nature of the procedure, the duration of the surgery or anesthesia, the type of sedative medication used, predominant mechanisms underlying PMI, or aspects of peri-interventional medical care. To the best of our knowledge, the current study is the very first one looking at a possible biorhythm in cardiac susceptibility during various types of non-cardiac procedures. For instance, while our cohort underwent different type of non-cardiac surgeries with variable durations and anesthesia types, and while we enrolled patients at higher cardiovascular risk, the cardiovascular stress introduced by non-cardiac surgeries can be considered smaller than the one produced by on-pump aortic valve replacement. In addition, the predominant pathophysiological mechanism underlying PMI seem to be different between on-pump cardiac surgery versus non-cardiac surgery. For example, during on-pump cardiac surgery, cardiac arrest induced by cardioplegic solution results in a duration of up to one hour of non-beating heart cells with no relevant oxygen supply. All other mechanisms possibly underlying PMI in patients undergoing non-cardiac surgery in addition also seem to apply to patients undergoing on-pump cardiac surgery. These include increased plaque instability or exacerbated myocardial oxygen supply-demand imbalance due to increase in physiological/emotional stress, catecholamine surge, intra-operative tachycardia, bleeding or hypertension. While previous studies suggested the role of certain clock genes in the day-time specific cardiac ischemia-reperfusion tolerance,[6] little is known

on the damage threshold at which the increased susceptibility leads to prognostically relevant cardiac damage. This threshold might not be reached in most of non-cardiac surgeries. Similarly, our data showed no difference in dysfunction induced by non-cardiac surgery in other critical organ systems such as renal function and systemic inflammation when a non-cardiac surgery took place in the morning or in the afternoon. Again, this emphasizes the lack of a systematic day-time dependent perturbation of system-specific circadian clocks following non-cardiac surgery.

The absence of day-time variation in PMI does not necessarily equal the absence of day-time variation in MACE during follow-up. Based on the observed link between daytime variation for PMI and MACE in patients undergoing aortic valve replacement, we had hypothesized that the same link might exist in patients undergoing non-cardiac surgery. However, also other perioperative stressors, including inflammation, thrombogenesis and plaque rupture, might be associated with MACE during follow-up. Despite our morning and afternoon cohort presenting with a similar post-operative cardiac management, other non-measured post-operative factors, for instance staffing, including nurse-per-patient ratio on the intensive care units (ICU), intermediate care and ward, could have impacted on the increased AMI rate in patients undergoing non-cardiac surgery in the afternoon. Accordingly, further studies are necessary to elucidate possible mechanisms underlying this increased AMI rate. So-called “human-factors” more than a real circadian rhythm may have contributed to the higher rate of AMI observed during follow-up in patients operated in the afternoon. First, increased fatigue of the operator might be present during afternoon surgeries, leading to poorer long-term results regarding the site of surgery itself, or possibly also to increased harm at other organ sites. Second, logistic variations on intensive care units (ICUs) (such as the presence of fewer and less experienced staff members in the evening or nightly

hours) could lead to a poorer care for patients undergoing a procedure during the afternoon.[20] Moreover, sleep-wake and fasting-feeding cycles have been recognized as the two major behavioral cycles the heart needs to anticipate[7]. Accordingly, the effect of anesthesia nearer to bed-time[21,22] as well as the negative role of a longer fasting for patients operated in the later hours[19,23] have also been suggested as possible factors influencing patients' heart recovery. Also cell-intrinsic clocks sensible to proinflammatory stimuli, such as a surgical procedure, have been characterized in macrophages and other inflammatory cell lines involved in atherosclerotic plaque stability,[24] possibly impacting on the risk of AMI in the follow-up depending on the time of the intervention.

The findings of this study extend and corroborate multiple prior studies that although commonly combined as MACE in a single end point for statistical reasons (increased power), death and AMI have largely different predictors and triggers.[25,26] E.g. the extent of cardiomyocyte injury present at the time of non-cardiac surgery as quantified by hs-cTnT concentrations is a rather precise predictor of 30-day mortality, but not the incidence of AMI following surgery.[26]

Our finding of no day-time variation on postoperative all-cause mortality at one year is supported by another study showing no day-time variation on postoperative all-cause mortality at 30 days.[27]

Some limitations merit consideration when interpreting our findings. First, in contrast to the small randomized control trial conducted in patients undergoing aortic valve replacement,[6] this analysis was based on a propensity score matched cohort. Despite proving the lack of difference in baseline characteristics of our patients following matching, we cannot exclude that unmeasured confounders might have interacted with the observed outcomes. A similar consideration has to be made for our

survival analysis. However, in the absence of a randomized controlled study in patients undergoing non-cardiac surgery available, the methodology used in this analysis seems the best alternative approach. Still, further studies are warranted to address the remaining uncertainties. Second, our observations are based on patients undergoing different types of surgeries implying different peri- and post-operative risk. We voluntarily avoid focusing on a single type of surgery and corrected for the various risks to estimate the reaction of the human body to an overall surgical stress more than to the stress of few organs undergoing an acute trauma. While allowing us for a general conclusion regarding non-cardiac surgery, the heterogeneity brought by the different surgery types could have weakened or even obscured a potential signal solely associated with specific procedures.

In conclusion, our propensity-score matched study did not identify any daytime variation in PMI in patients undergoing non-cardiac surgery. However, we observed a higher incidence of AMI during one-year follow-up in patients undergoing surgery in the afternoon, which requires further study.

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All the authors are justifiably credited with authorship, according to the authorship criteria. In detail: JdF, CP, GLB, DB, AL, CK, AHL, LG, DMG, MJ, CM — conception, design; DG, RH, LS, JE, ST - acquisition of data; JdF, CP, JW, RT, IS, PB - analysis

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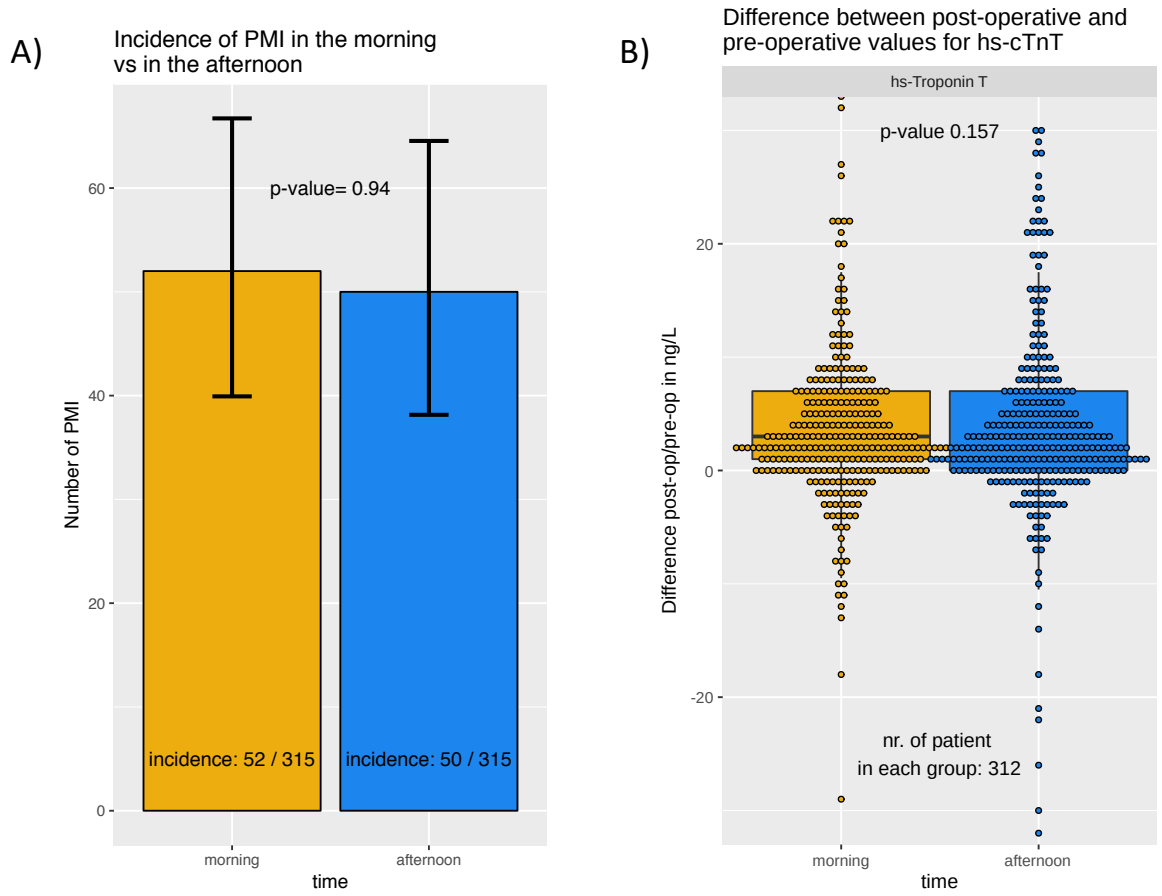

Figure 1A: Incidence in perioperative myocardial injury (PMI) stratified according to the daytime of surgery

Figure 1B: Preoperative increase in high-sensitivity cardiac troponin T Stratified according to the daytime of surgery. P-value is given by a Kruskall-Wallis test.

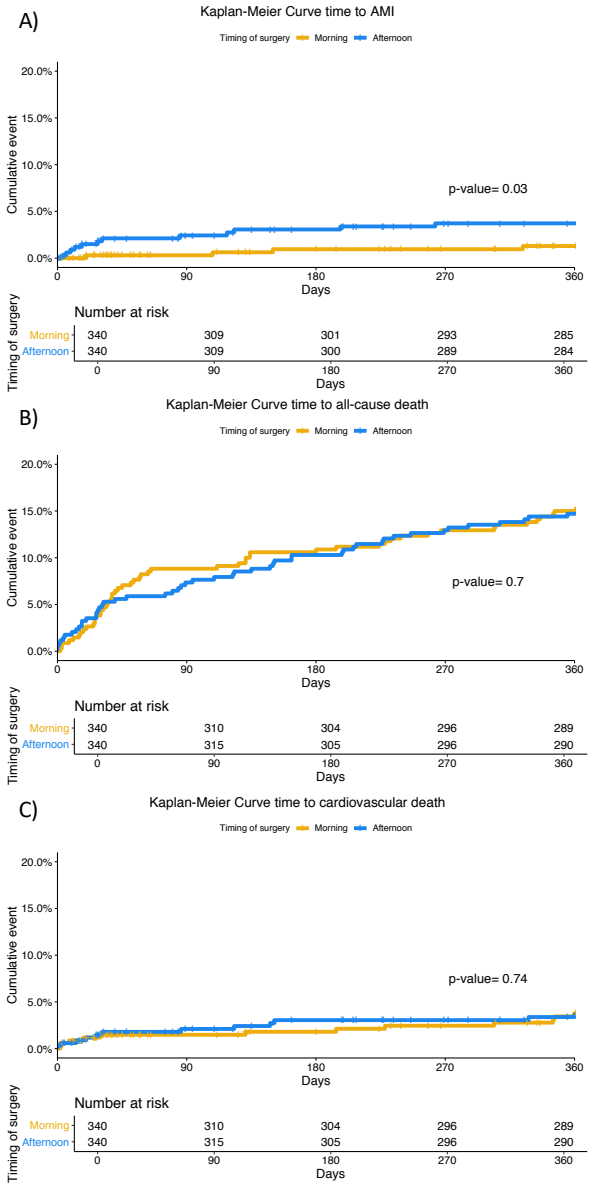

Figure 2: Kaplan Meier curve for the time to A) first AMI (acute myocardial infarction), B) to all-cause death and C) to cardiovascular death in a matched cohort of patients undergoing surgery in the morning or in the afternoon. P-value is the median p-value bootstrapping a cox proportional hazard model correcting for residual imbalance in baseline comorbidities between the morning and afternoon cohort (vascular surgery, effective surgery duration, PAD and COPD).

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