

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

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27 Short Title: Daytime variation of PMI in non-cardiac surgery

28 Word count: 2998 words

29 Study type : Research – Cohort study (prospective)

30 Keywords: Acute myocardial infarction, Troponin, perioperative care
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39 **ABSTRACT (250 words)**

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

43 **Methods:** In a prospective diagnostic study we evaluated the presence of daytime
44 variation in PMI in patients at increased cardiovascular risk undergoing non-cardiac
45 surgery, as well as its possible impact on the incidence of acute MI (AMI), and death
46 during one-year follow-up in a propensity-score matched cohort. PMI was defined as
47 an absolute increase in high-sensitivity cardiac troponin T (hs-cTnT) concentration of
48 ≥ 14 ng/L from preoperative to postoperative measurements.

49 **Results:** Of 1641 patients, propensity score matching defined 630 with similar baseline
50 characteristics, half undergoing non-cardiac surgery in the morning (starting from 8
51 a.m. to 11 a.m.) and half in the afternoon (starting from 2 p.m. to 5 p.m.). There was
52 no difference in PMI incidence between both groups (morning: 50, 15.8% (95%-CI
53 12.3-20.3), afternoon: 52, 16.4% (95%-CI 12.7-20.9), $p=0.94$), nor if analyzing hs-cTnT
54 release as a quantitative variable (median morning group: 3ng/L (95%CI 1-7ng/L);
55 median afternoon group: 2ng/L (95%CI 0-7ng/L; $p=0.16$). During one-year follow-up,
56 the incidence of AMI was 1.2% (95%CI, 0.4-3.2%) among morning surgeries versus
57 4.1% (95%CI, 2.3-6.9%) among the afternoon surgeries (corrected HR for afternoon
58 surgery 3.44, bootstrapped 95%CI 1.33-10.49, $p\text{-log-rank}=0.03$), whereas no
59 difference in mortality emerged ($p=0.70$).

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

63 ***Clinical Trial Registration***— URL: <https://www.clinicaltrials.gov>. Unique identifier:

64 **NCT02573532**.

65

66 **Key questions**

- 67 • What is already known about this subject?

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

- 71 • What does this study add?

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

- 76 • How might this impact on clinical practice?

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

79

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81

82 **INTRODUCTION**

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

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

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

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

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

110

111

112 **METHODS**

113

114 **Patients**

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

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

126

127 **Procedures: Detection of PMI and follow-up**

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

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

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

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

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

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

154

155 **Objectives**

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

159 The secondary objective of this study was to assess whether the incidence AMI, all-
160 cause death or cardiovascular death during one-year follow-up differs depending on
161 the timing of the surgery (morning vs afternoon) in a propensity-matched cohort.

162 Additionally, differences in other well-validated quantitative surrogate markers of other

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

165

166 **Daytime variation**

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

172

173 **Statistical Analysis**

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

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

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

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

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

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

206 **RESULTS:**

207

208 **Patients characteristics:**

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

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

218

219 **Propensity-score matched cohorts**

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

226 One-year follow-up was available in 100% of patients for death and in 99.4% of patients
 227 (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

228 Data are presented as number (%) and compared using Mann-Whitney-U test for continuous variables
229 and either Pearson Chi-square test or Fisher-exact test for categorical variables, as appropriate.
230 AMI=Acute myocardial infarction, AT= Angiotensin, CAD= Coronary Artery Disease, COPD=Chronic
231 Obstructive Pulmonary Disease, ESC = European Society of Cardiology, hs-cTnT= high sensitivity
232 cardiac troponin T, IDDM = insulin-dependent diabetes mellitus, NIDDM = non insulin-dependent
233 diabetes mellitus, Sd = standard deviation, TIA = Transient Ischemic Attack.
234

235

236 **PMI incidence: morning versus afternoon surgery**

237 In the bootstrapped matched cohort, 52 (16.4%, 95%-CI 12.7-20.9) patients operated
238 in the morning and 50 (15.8%, 95%-CI 12.3-20.3; p=0.94) patients operated in the
239 afternoon experienced a PMI in the 3 days following surgery (Figure 1A). Logistic
240 regression corrected for residual imbalance in baseline comorbidities between the
241 morning and afternoon cohort (vascular surgery, effective surgery duration, PAD and
242 COPD) did not show any significant impact of the timing of surgery on the incidence of
243 PMI (bootstrapped OR = 0.95 for a surgery in the afternoon, bootstrapped 95% CI =
244 0.62-1.45, p=0.74).

245

246 **Perioperative cardiomyocyte injury as a continuous variable**

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

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

256

257 **Renal function and systemic inflammation in the cohort of matched patients**

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

262

263 **Survival analysis in the cohort of matched patients**

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

273

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

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

277

278 **Sensitivity analyses in the whole cohort**

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

282 **DISCUSSION**

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

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

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

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

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

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

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

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

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

376

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

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

394
395 In conclusion, our propensity-score matched study did not identify any daytime
396 variation in PMI in patients undergoing non-cardiac surgery. However, we observed a
397 higher incidence of AMI during one-year follow-up in patients undergoing surgery in
398 the afternoon, which requires further study.

399

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408 **Funding :**

409 This study was funded by the University Basel, the University Hospital Basel, the
410 Swiss Heart Foundation, Abbott, Astra Zeneca, the PhD Educational Platform for
411 Health Sciences, the Forschungsfond Kantonsspital Aarau, and the Cardiovascular
412 Research Foundation Basel. The funders had no role in the design, data collection,
413 statistical analysis, writing of this manuscript, or decision to publish.

414 **Conflict of Interests Statement:**

415 Dr Puelacher reports grants from PhD Educational Platform for Health Sciences and
416 the University Hospital Basel during the conduct of the study. Dr. Lurati Buse reports
417 grants from University of Basel during the conduct of the study. Dr. Twerenbold
418 reports research support from the Swiss National Science Foundation (Grant No
419 P300PB 167803), the Swiss Heart Foundation, the Cardiovascular Research
420 Foundation Basel, the University of Basel and the University Hospital Basel and
421 speaker honoraria/consulting honoraria from Roche, Abbott, Siemens, Singulex and
422 ThermoScientific BRAHMS. Dr. Mueller reports grants from the Swiss Heart
423 Foundation and grants and non financial support from several diagnostic companies
424 during the conduct of the study, as well as grants, personal fees, and non financial
425 support from several diagnostic companies outside the submitted work. All other
426 authors report no conflicts of interest.

427 **Contributorship Statement:**

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

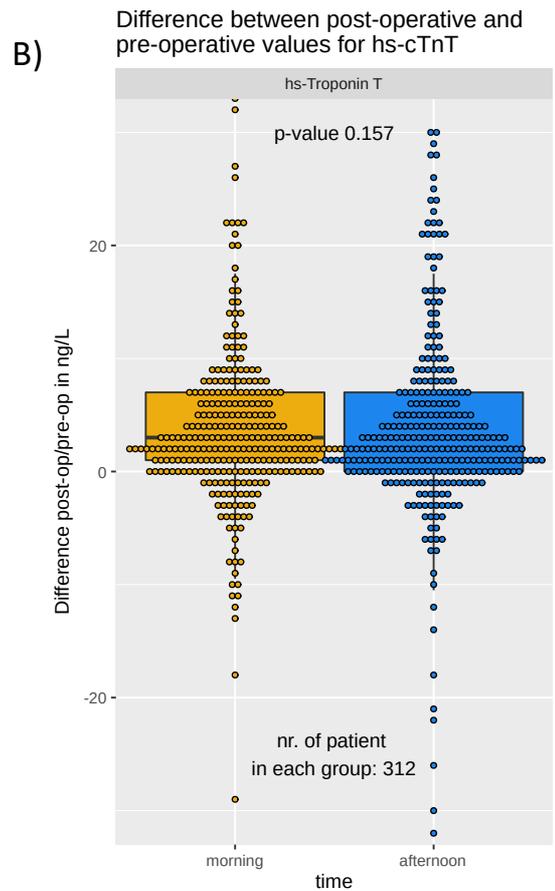
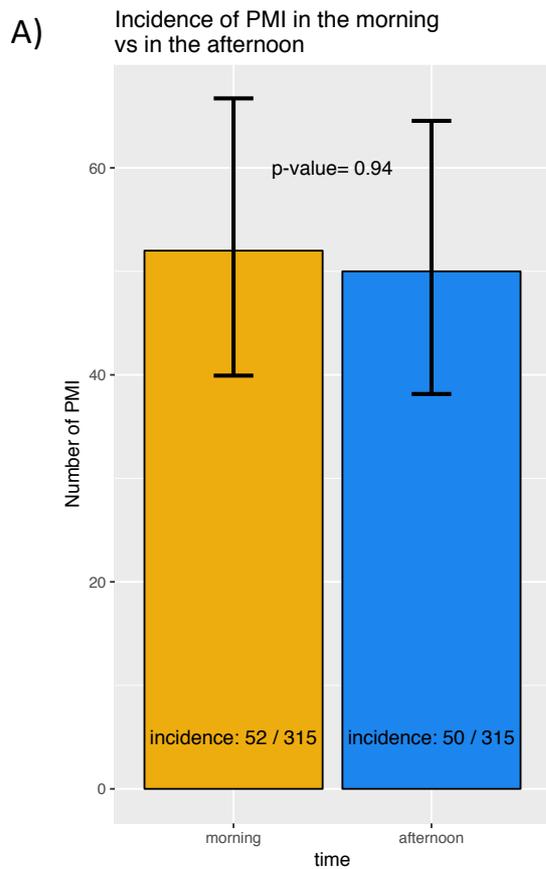
431 and interpretation of data; JdF, CP, CM - drafting of the manuscript and final
432 approval; KR, AB – Coordination of laboratory measurements.

433

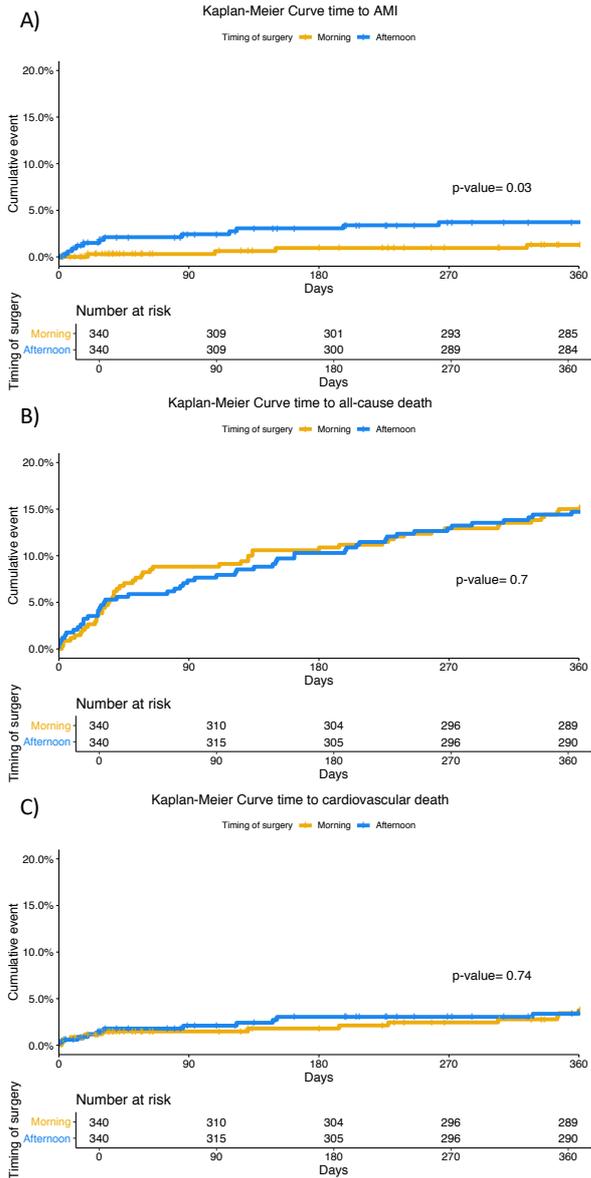
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440 **Figure legends :**
441



442 **Figure 1A:** Incidence in perioperative myocardial injury (PMI) stratified according to
443 the daytime of surgery
444 **Figure 1B:** Preoperative increase in high-sensitivity cardiac troponin T
445 Stratified according to the daytime of surgery. P-value is given by a Kruskal-Wallis
446 test.
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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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