Is there any effect of chronobiological changes on coronary angioplasty?

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Aims We hypothesized that If there is a chronobiologic variation in the development of acute ischaemic events which is mainly attributed to the tendency for thrombus formation in the morning hours, same time dependent variations must also be seen in the development of ischaemic events after percutaneous transluminal coronary angioplasty (PTCA) and PTCA with stent implantation.

Methods Enrolled in this study were 349 consecutive patients with single vessel disease and undergoing elective single vessel angioplasty. Patients had been observed for the development of immediate postprocedural ischaemic events. Working hours of our laboratory were divided into 2-hourly intervals in order to define the ending time of procedure. Analysis of acute complications was carried out according to the ending time of procedure.

Results There was no difference with regard to clinical presentation, but patients who had complications had higher blood cholesterol level ($P < 0.05$). Patients with stent implantation had more adverse events than the PTCA group, but this difference did not reach the statistical significance ($P = 0.07$). The time interval between 10:30 a.m.–12:30 p.m. was found to be an independent risk factor for the negative outcomes ($P = 0.043$, Relative Risk 4838).

Conclusion The results of our study have demonstrated that postprocedural complications after angioplasty is related to the procedure time These patients may be observed more closely for the development of immediate postprocedural ischaemic events. *J Cardiovasc Risk* 8:15–19 © 2001 Lippincott Williams & Wilkins.

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Introduction

The chronobiologic changes have been shown in human physiology. Previous studies have demonstrated that most of the ischaemic events, such as angina pectoris, myocardial infarction, sudden cardiac death and stroke, are under the influence of circadian rhythms and have a tendency to occur in the morning hours [1–6]. These ischaemic events are found to be related to the increased plasminogen activator inhibitor activity [7], tissue plasminogen activator antigens [8], platelet aggregation [9], plasma epinephrine and norepinephrine levels [10,11] in the morning hours. Furthermore Kurnik has described a circadian variation in the efficacy of intravenous tissue-type plasminogen activator in patients with acute myocardial infarction, with decreased efficiency in the morning hours [12].

Percutaneous transluminal coronary angioplasty (PTCA) is used widely in the treatment of atherosclerotic coronary artery stenosis. However, immediate postprocedural ischaemic events remain a major drawback [13–16]. There is considerable evidence that platelet aggregation and platelet thromboxane A2 interactions play a major role in the occurrence of acute ischaemic events in patients undergoing PTCA [17,18].

Accordingly, we hypothesized that if there is a chronobiologic variation in the development of acute ischaemic events which is mainly attributed to the tendency for thrombus formation in the morning hours, same time dependent variations must also be seen in the development of ischaemic events after PTCA and PTCA with stent implantation. In order to test this hypothesis, we have evaluated the development of complications after coronary angioplasty according to time of procedure.

Materials and methods

Between December 1997 and July 1998, 349 consecutive patients with single vessel disease and undergoing elective single vessel angioplasty were enrolled in this study. Coronary angioplasties were performed with conventional balloon angioplasty technique via femoral route in all patients. During the procedure, patients

Table 1 **Clinical and demographic characteristics of the patients**

Characteristics	
Demography	
Age, year	57 ± 9.8
Male Sex, *n* (%)	283 (81)
Current smokers, *n* (%)	144 (41.3)
Clinical	
Hypertension, *n* (%)	183 (52.4)
Diabetes mellitus, *n* (%)	116 (33.2)
Hypercholesterolaemia, *n* (%)	129 (37)

received an initial bolus injection of heparin (15 000 Units). A successful outcome from PTCA was defined as a $>20\%$ decrease in diameter stenosis and a residual diameter stenosis $<50\%$ of the vessel lumen after PTCA. Indications for stent implantation include elective, suboptimal result or severe dissection after PTCA procedure and restenotic lesions.

Stent implantation was performed with high-pressure (12–15 atm) balloon inflation. Patient who underwent PTCA received aspirin and antianginal medication (such as nitrates and beta-blockers) before and after the procedure; all patients with stent implantation received aspirin, ticlopidine and low molecular weight heparin before and after the procedure for reducing immediate postprocedural ischaemic complications. Patients who were accepted as at a high risk of early thrombosis (e.g. visualization of thrombus or poor distal blood flow in stented vessel) had received continuous heparin infusion for 24 h with the control of activated clotting time measurements at 6-hourly intervals. But, because we did not have glycoprotein IIb–IIIa receptor antagonists in our country during the time period of this study, we did not use these agents on our patients.

Complications after angioplasty was defined as acute myocardial infarction, repeat PTCA (indication of repeat PTCA was acute occlusion which were represented by chest pain, ECG changes), need for emergency coronary artery bypass grafting or death. Patients had been observed for the development of acute complications for 12 h after the procedure. Patients were analysed according to demographic characteristics, clinical presentation, PTCA and PTCA plus stent implantation and according to the ending time of the procedure. Working hours of our laboratory were divided into 2-hourly intervals in order to define the ending time of procedure.

The independent Student t test was used for comparisons of age and comparisons of stent diameters and lengths. The χ^2 test was used to assess the differences in the distribution of patients and the adverse events according to time intervals. We used the logistic regression model to determine the relations between the time of day and the development of acute ischaemic events after PTCA. Statistical significance is accepted as $P < 0.05$.

Results

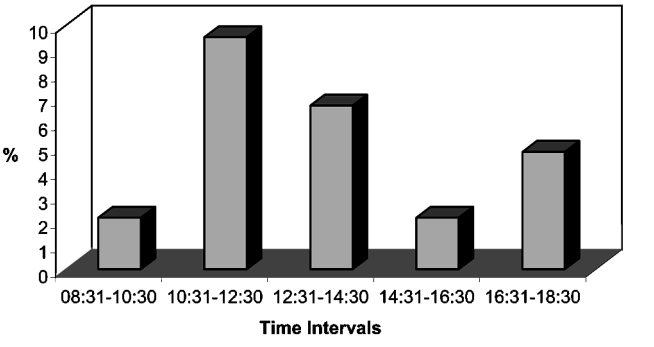
The study population included 349 patients, 66 women and 283 men, with a mean age of 57 ± 9.8 years (range, 25 to 81 years). Clinical and demographic variables were summarized in Table 1. Of the patients 37% had hypercholesterolaemia, 52.4% had hypertension, 33.2% had diabetes mellitus, and 41.3% are current smokers.

Among 349 patients, 160 patients (45.8%) had stent implantation. Patients who have stent implantation were younger than the PTCA group ($P < 0.001$). There were no differences in distribution of number of PTCA or stent implantation between the time intervals ($P > 0.05$). Four patients had two-stent implantation and one patient had three-stent implantation because of the consecutive lesions. Indications for stent deployment included dissection in 79 patients (49.4%), suboptimal result (42%) and stent implantation were performed electively in 13 patients (8.0%).

According to time intervals, the distribution of the adverse events after angioplasty was shown in Figure 1. Within the entire cohort multivariate logistic regression analysis was performed to evaluate the relation of the time intervals for the development of immediate postprocedural ischaemic events. The time interval between 10.30 and 12.30 was found to be associated with an increased risk of negative outcomes ($P = 0.043$, relative risk 4838, Table 2).

Within the entire cohort, 20 patients (5.7%) had imme-

Fig. 1



The distribution of the adverse events according to time intervals.

Table 2 **Multivariate relations of the time intervals for the development of immediate postprocedural ischaemic events in all patients**

Complication	Multivariate relations			
	Coefficient (B)	Standard error	*P*	Exp. B
Time intervals*				
10:31 A.M –12:30 P.M.	1.575	0.778	0.043	4.830
12:31 P.M–14: 30 P.M.	1.197	0.885	0.176	3.309
14:31 P.M–16:30 P.M.	0.037	1.240	0.976	1.038
16:31 P.M–18:30 P.M.	0.907	1.254	0.470	2.477

* 08:31a.m.–10:30 a.m. time interval was taken as reference category.
Exp. B,

diate postprocedural ischaemic events. Patients with stent implantation had more adverse events than the PTCA group (7 in PTCA group, 13 in stent group), but this difference did not reach statistical significance ($P = 0.07$). Six patients (three in the PTCA group and three in the stent group) had acute myocardial infarction, four patients died (one in the PTCA group and three in the stent group) and 10 patients had repeat PTCA (three in the PTCA group and seven in the stent group).

To evaluate the influence of clinical presentation on the development of complications, clinical and angiographic data of the patients were compared according to five time periods (Table 3). There was no difference regarding baseline characteristics except for hypercholesterolaemia between the five time periods. The incidence of the hypercholesterolaemia was higher in the time period 10:31–12:30 ($P < 0.05$, Table 3).

The comparison of stent diameter and length is shown in Table 4. There were no differences between patients treated during the 10:31–12:30 time period and those treated at other time intervals concerning adverse events ($P > 0.05$). No significant difference was found regarding stent diameter and length during the 10:31–12:30 time period. However, with the exception of 10:31–12:30 time period, the length of stents, implanted in the patients with an adverse event, was found to be significantly longer than in those without adverse events ($P < 0.05$).

Discussion

The main finding of our study is that the time interval between 10:31–12:30 is an independent risk factor for the development of immediate postprocedural ischaemic events after coronary angioplasty. For most catheter laboratories there is a tendency to take patients with high risk to catheterization laboratory in the morn-

Table 3 **Clinical and angiographic characteristics of the patients according to time intervals**

Characteristics	08:30–10:30	10:31–12:30	12:31–14:30	14:31–16:30	16:31–18:30
n	94	126	60	48	21
Age, year	56 ± 10	57 ± 10	56 ± 9	58 ± 8	57 ± 23
Male sex, n (%)	79 (84)	102 (81)	49 (82)	37 (77)	16 (77)
Current smokers, *n* (%)	41 (43.6)	51 (40.5)	24 (40)	20 (42)	8 (38)
Hypertension, *n* (%)	48 (51)	71 (56.3)	31 (52)	23 (48)	10 (47.6)
Diabetes, *n* (%)	31 (33)	39 (31)	21 (35)	17 (35.4)	8 (38.1)
Hypercholesterolaemia, *n* (%)	38 (40.4)	36 (28.6) §	26 (43.3)	22 (46)	11 (52.4)
Angina (CCS), *n* (%)*					
I	29 (30.9)	55 (43.6)	19 (31.6)	15 (31.2)	6 (28.6)
II	28 (29.8)	20 (15.9)	19 (31.6)	14 (29.2)	7 (33.3)
III	32 (34)	46 (36.5)	21 (35)	15 (31.3)	7 (33.3)
IV	5 (5.3)	5 (4)	1 (1.8)	4 (8.3)	1 (4.8)
Lesion (AHA/ACC), *n* (%)†					
Type A	27 (28.7)	32 (25.4)	16 (26.7)	14 (29.2)	6 (28.6)
Type B1	34 (36.2)	45 (35.7)	22 (36.7)	17 (35.4)	7 (33.3)
Type B2	29 (30.9)	41 (32.5)	17 (28.3)	14 (29.2)	6 (28.6)
Type C	4 (4.2)	8 (6.4)	5 (8.3)	3 (6.2)	2 (9.5)
Duration of procedure ‡	31 ± 8.6	30.5 ± 9.9	27.5 ± 9.4	28.3 ± 10.1	26.5 ± 8.8
Vessel treated, *n* (%)					
Left anterior descending	48 (51)	63 (50)	29 (48.4)	23 (47.9)	9 (42.8)
Circumflex	22 (23.4)	29 (23)	14 (23.3)	11 (22.9)	5 (23.8)
Right coronary artery	23 (24.5)	29 (23)	15 (25)	13 (27.1)	6 (28.6)
Graft	0 (0)	3 (2.4)	2 (3.3)	1 (2.1)	0 (0)
Ramus medianus	1 (1.1)	2 (1.6)	0 (0)	0 (0)	1 (4.8)

*According to the classification system of the Canadian Cardiovascular Society: †, AHA/ACC classification of lesions according to lesion morphology, ‡, minute ± standard deviation, §, $P < 0.05$; when compared with other time intervals.

Table 4 **The comparison of stent diameter and length**

	10:30–12:30 time period		Other time periods	
	Patients with adverse events	Patients without adverse events	Patients with adverse events	Patients without adverse events
n	8	53	5	94
Stent diameter (±SD)	3.0 ± 0.0	2.9 ± 0.3	2.8 ± 0.3	2.9 ± 0.3
Stent length (±SD)	18.6 ± 4.5	16.9 ± 3.6	20.0 ± 3.7*	16.7 ± 2.9*

SD, standard deviation.
* $P < 0.05$.

ing hours. This may explain the high complication rate seen in the morning hours. However, analysis of our data showed that there was no difference in the clinical presentation with respect to procedure time. Furthermore, there was no difference in the treated coronary vessel, frequency of angioplasty performed and size of the stents, which may be related to development of complications after angioplasty.

The higher incidence of adverse events in the stented group (it is not statistically significant) may be related to not using glycoprotein IIb–IIIa receptor antagonists.

The experience of the operators is important for good angioplasty results, but this was ignored since team working in the coronary angiography laboratory was the same.

The increasing risk in the 10:31–12:30 time interval may be associated with circadian triggering factors. The role of platelets in adverse event after angioplasty is known. Vascular damage caused by angioplasty is quite similar to spontaneous plaque rupture seen in acute ischaemic events. Exposure of subendothelial collagen to blood leads to platelet adhesion. After the adhesion, activated platelet release TxA2 and serotonin and cause platelet aggregation [17,18].

Platelet aggregation has circadian rhythm and increases in the morning hours [9]. Like platelets, fibrinolytic activity has circadian variation and decreases in the morning hours. They lead to activation of the coagulation system and increase the risk of thrombus formation in coronary vasculature [19]. Thrombi formed in the morning hours are rich in platelet content [12] so they are resistant to fibrinolysis [19]. Because of the impaired release of endothelium derived relaxing factor [20], the sheering effect of the double product on vasculature is more pronounced in patients with coronary artery disease [21]. Thus, we may speculate that immediate postprocedural ischaemic events may increase because of the tendency to thrombus formation and activation of coagulation system in the morning hours.

As the study population composed of the patients performed angioplasty between 08:30–18:30, which are the working hours of the catheterization laboratory, we could not include circadian rhythm of immediate postprocedural ischaemic events. However, the distribution of the adverse events after angioplasty is similar to the circadian pattern of acute ischaemic events which, it has been clearly demonstrated, has a tendency to occur in the morning hours.

The results of our study have demonstrated that procedure time is an independent risk factor for the development of complications after angioplasty. These patients may be observed closely for the development of immediate postprocedural ischaemic events. We believe that further prospective randomized studies could provide an opportunity to examine the relation of circadian rhythm to the acute complications of percutaneous interventions.

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