

## The clock that times us – impact of circadian rhythms on drug medication in cardiovascular diseases

### Introduction: The biological clock

Rhythmicity is the most ubiquitous feature of nature. Rhythms are found from unicellular to complex multicellular organisms both in plants, animals and humans. Living organisms are continuously influenced by external stimuli, many of which have rhythmic patterns. Environmental rhythms in daily and seasonal patterns of light, food availability and temperature, etc. are predictable and animals – including humans – have the ability to anticipate these environmental events with periodically and predictably changing internal conditions. These rhythmic patterns of anticipation have clear advantages and survival value (Strubbe and Woods, 2004). The frequencies of rhythms in nature cover nearly every division of time. There are rhythms which oscillate once per second (e.g. in the electroencephalogram), once per several seconds (respiratory rhythm, heart rate), up to rhythms which oscillate once per year (circannual rhythm).

The most evident environmental change which results from the regular spin of the earth around its central axis and resulting in the alternation between day and night seems to have induced the predominant oscillation, the circadian rhythm (the about-24-hour rhythm; circa = about, dies = day, as proposed by (Halberg, 1959, 1969). There is sound evidence that living systems including humans are not only organized in space but are also highly organized in time. One of the first observations on a rhythmic pattern in man was presented by the famous physiologist Sanctorius Sanctorius in 1664 when he described in a self-experiment daily variations in body weight due to transpiration, his famous experimental setting being shown in Fig. 1 (Sanctorius, 1664).

Circadian rhythms have been documented throughout the plant and animal kingdom at every level of eukariotic organization. Circadian rhythms by definition are endogenous in nature, driven by oscillators or clocks (Aschoff, 1954, 1963a,b, 1965), and persist under free-running conditions. In various species (e.g. *Drosophila melanogaster*, *Neurospora*, *Mesocricetus auratus*, *Macacus rhesus*, human and mouse) the genes controlling circadian rhythms have been identified (genes: *per*, *frq*, *clock*, *tau*, *Rev-erb $\alpha$* ) (Takahashi, 1992; Hall, 1998; Hastings, 1998; Reppert, 2000; Albrecht, 2002; Sitzmann et al., 2008). In 1971 Konopka and Benzer (Konopka and Benzer, 1971) were able to identify on the X chromosome of *Drosophila* a region which controlled the period in the eclosion

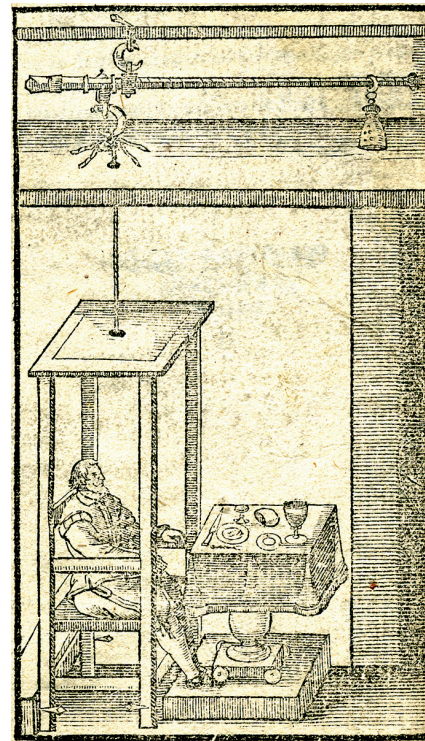


Fig. 1. Day-night variations in body weight due to transpiration. Shown is the experimental setting of Sanctorius. This figure is taken from the original book (Sanctorius, 1664; private library).

rhythm of three mutants (*per* clock gene). In 1984 Bargiello et al. demonstrated that a fragment of the *per* gene injected into embryos of an arrhythmic mutant of *Drosophila* could restore rhythmicity in eclosion (Bargiello et al., 1984). This data provided the first evidence that the biological clock is genetically determined and can even be transplanted from one animal into another thereby inducing the rhythmicity of the donor into the recipient.

Circadian clocks are believed to have evolved in parallel with the geological history of the earth, and have undergone selection pressures imposed by cyclic factors in the environment (Kyriacou et al., 2008). These clocks regulate a wide variety of behavioral and metabolic processes in many life forms (Edmunds, 1997; Hastings, 1997; Tsinkalovsky et al., 2007; Almon et al., 2008). They enhance the fitness of organisms by improving their ability to efficiently anticipate periodic events in their external environments, especially periodic changes in light, temperature and humidity.

The mammalian circadian clocks, located in the neurons of suprachiasmatic nuclei (SCN) in the brain and in cells of peripheral tissues, are driven by a self-sustained molecular oscillator, which generates rhythmic gene expression with a periodicity of about 24h (Reppert and Weaver, 2002; Hastings and Herzog, 2004). This molecular oscillator is composed of interacting positive and negative transcription/translation feedback loops (Rensing, 1997; Hastings, 2003; Hardin, 2004) in which the heterodimeric transcription activator CLOCK/BMAL1 promotes the transcription of E-box containing Cryptochrome (Cry1 and Cry2) and Period (Per1 and Per2) genes, as well as clock-controlled output genes. After being synthesized in the cytoplasm, CRY and PER proteins feed back in the nucleus to inhibit the transactivation mediated by positive regulators (Harms et al., 2004). The mPER2 protein acts at the interphase between positive and negative feedback loops by indirectly promoting the circadian transcription of the Bmal1 gene and by interacting with mCRY proteins (see: Hardin, 2004; Lowrey and Takahashi, 2004).

It is interesting to note that clock genes have now been found in single cells of human skin and mucosa (Bjarnason et al., 2001), furthermore, it has been shown that about 8–10% of all genes are regulated in a circadian fashion (Storch et al., 2002).

In general, the human endogenous clock does not run at a frequency of exactly 24 hours but somewhat slower. The rhythm in human body temperature which is timed by the biological clock has a period of about 24.5-hours under free-running conditions i.e. without environmental time-cues or Zeitgebers (e. g. light, temperature) (Fig. 2).

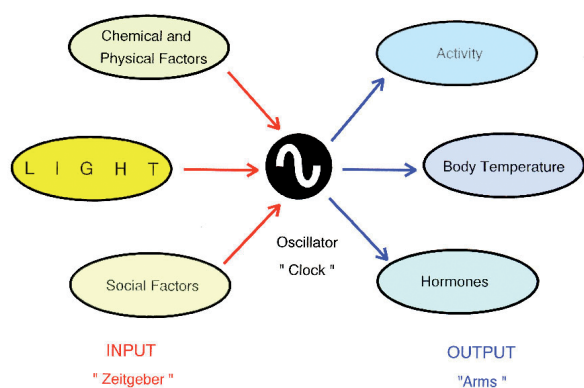


Fig. 2. Input and output factors of the circadian clock.

The term “Zeitgeber” introduced by Aschoff (1954, 1965) is now part of the international scientific language. Mammals such as rodents or humans can entrain their activity to regular light cycles not shorter than 22 or longer than 26 hours (Aschoff and Pöhl, 1978). Zeitgebers entrain the circadian rhythm to a precise 24-hour period. Zeitgebers

are, therefore, necessary to entrain a living subject to a “normal” period of 24 hours!

In experimental animals and in humans, however, most rhythmic fluctuations still cannot be studied under free-running conditions, leaving the answer open to what degree they are really “circadian”. Purely exogenous rhythms are better termed as “24-hour” or “daily” rhythms. Thus, an overt 24-hour rhythm in a given parameter can be endogenous or predominately exogenous in nature. Within the published clinical literature, however, the term “circadian” is not always used in the above mentioned correct sense (as used by chronobiologists), the broader term will be used here, too. Though seasonal rhythms in cardiovascular functions were also described, the present review will focus on circadian rhythms, since much more data were accumulated over a 24-hour scale and the underlying mechanisms studied.

As one example of a seasonal rhythm the yearly pattern in the occurrence of death in one family is presented in which data from 678 deaths out of 1606 family members between the years 1450 to 2008 were available for analysis. In accordance with earlier observations (Smolensky et al., 1972) Fig. 3 shows that death in one family mainly occurs during winter time.



Fig. 3. Month of death of family members, 678 data from 1605 subjects obtained between the years 1405 to 2008, 348 males (blue line) and 330 females. Ordinate: number of deaths/month, abscissa: month of the year, (unpublished data from the author’s family, analysis was done with MacFamilyTree®).

## Rhythms in the cardiovascular system

Heart rate was amongst the earliest physiological functions reported not to be constant throughout the 24 hours of a day. As early as the beginning of the 17<sup>th</sup> century daily variations in pulse rate, as well as a rapid increase on awakening, were described. In the 18<sup>th</sup> and 19<sup>th</sup> centuries

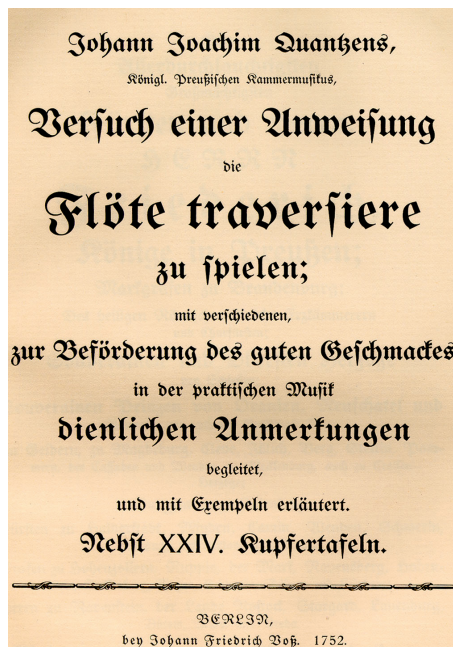
general observations as well as detailed data on daily variations in pulse rate and pulse quality were reported (Lemmer, 1989c, 1991, 2001, 2004a,b, 2005). The pulse of a healthy subject as determined in the late afternoon was even proposed as an easily available “metronome” to be used by musicians (Quantz, 1752). The metronome itself was not invented until 1816 by Mälzel (Lemmer, 2002).

*“What I found to be an appropriate timegiver for the tempo ... is the pulse at the hand of a healthy man.”*

*“One should take the pulse of a merry and good tempered man ... as it is after lunch until evening and the tempo will be fine.”*

From: Johann Joachim Quantz “Versuch einer Anweisung die Flöte traversière zu spielen” (Quantz, 1752) translated by BL, originals see Fig. 4).

Though day-night variations in heart rate and/or blood pressure have already been described since the 17<sup>th</sup> century (see: Lemmer and Portaluppi, 1997; Lemmer, 2001,



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nach zu fassen. Man wird sagen, daß der Puls [267] des Morgens vor der Mahlzeit langsamer, als Nachmittags nach der Mahlzeit, und des Nachts noch geschwinder als Nachmittags schlage: auch daß er bey einem zur Traurigkeit geneigten Menschen langsamer, als bey einem heftigen und lustigen, gehe. Es kann seyn daß dieses seine Richtigkeit hat. Dem ungeachtet aber könnte man auch dießfalls etwas gewisses bestimmen. Man nehme den Pulsschlag, wie er nach der Mittagsmahlzeit bis Abends, und zwar wie er bey einem lustigen und aufgeräumten, doch dabey etwas hitzigen und flüchtigen Menschen, oder, wenn es so zu reden erlaubt ist, bey einem Menschen von cholertisch-fanguinischem Temperamente geht, zum Grunde: so wird man den rechten getroffen haben. Ein niedergeschlagener, oder trauriger, oder kaltfinniger und

Fig. 4. J.J. Quantz' book on “How to play the flute“, and page 206 in which details on heart rate are given (Quantz, 1752; private library)

2004a,b), the recent development of easy-to-use devices to continuously monitor blood pressure and heart rate in man (ABPM = **ambulatory blood pressure monitoring**) demonstrated that blood pressure in normotensive and in hypertensive patients are clearly dependent on the time of day (Smolensky et al., 1976; Millar-Craig et al., 1978; Middeke et al., 1989; Middeke and Schrader, 1994; Parati et al., 1995; Lemmer, 1996b,c,d, 2007b). In Fig. 5 representative 24-hour profiles are shown for young male and female healthy subjects (Hartig and Lemmer, 2003).

Moreover, different forms of hypertension may exhibit different circadian patterns: In normotension as well as in primary hypertension there is in general a nightly drop in

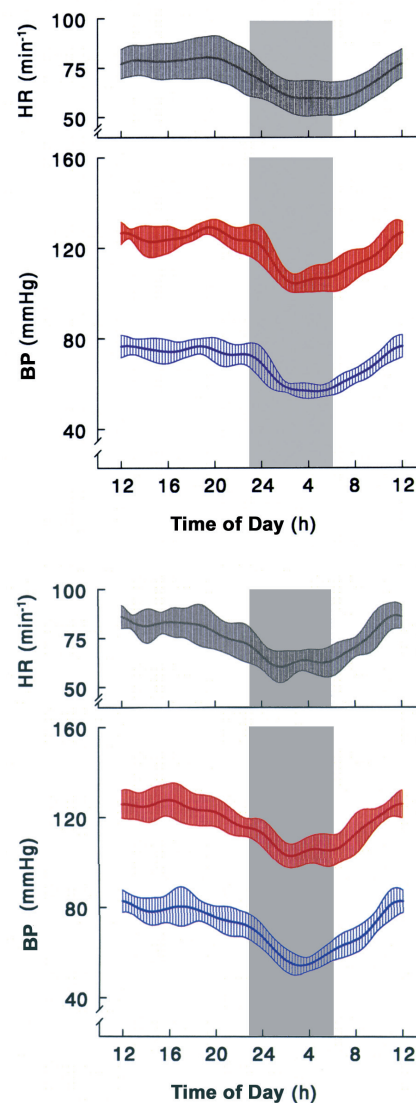


Fig. 5. 24-Hour profiles in blood pressure and heart rate in healthy young (21–23 years) subjects, data were fitted with Chronos-Fit (Zuther and Lemmer, 2004). Shown are group mean values and 95% confidence limits from males (top figure) and females (bottom figure), (data from: Hartig and Lemmer, 2003).

blood pressure (dippers), whereas in secondary hypertension due to e.g. renal disease, pregnancy, diabetes mellitus, Cushing's disease, the rhythm in blood pressure is abolished in about 70% of cases (non-dippers) (Fig. 6)

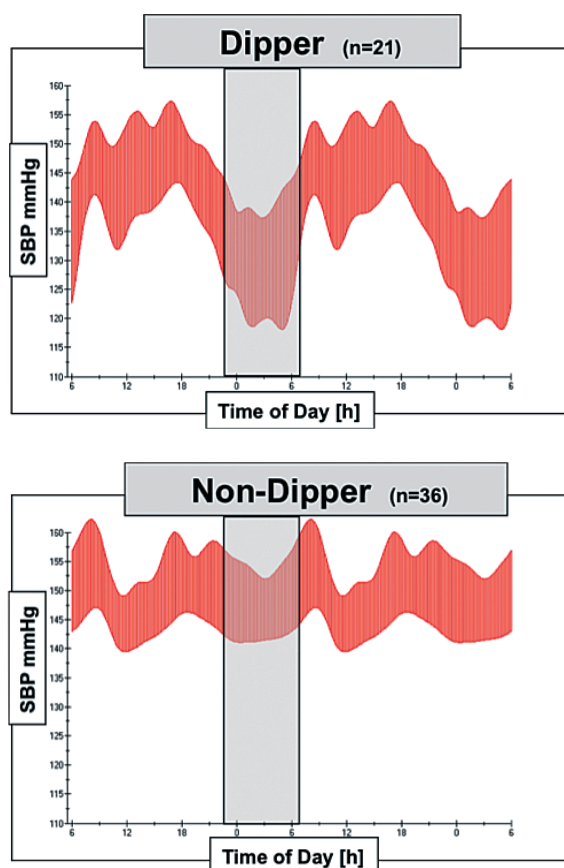


Fig. 6. 24-Hour systolic blood pressure profiles by ABPM in dippers and non-dippers (data from Nold et al., 1998; Lemmer et al., 2002).

or even reversed with highest values at night (risers) (O'Brien et al., 1988; Portaluppi et al., 1991; Middeke and Schrader, 1994; Lemmer and Portaluppi, 1997; Lemmer 2001, 2004a,b; Hermida et al., 2002; Kario and Shimada, 2004; Hamada et al., 2008). This is of particular interest since the loss in nocturnal blood pressure fall correlates with increased end organ damage in cardiac, cerebral, vascular and renal tissues (Fig. 7) (Brunner et al., 1985; Lemmer and Portaluppi, 1997; Kario et al., 2003a; Verdecchia et al., 2003; Cuspidi et al., 2004; Kario, 2004).

It is interesting to note that in young women taking contraceptives the nightly fall in blood pressure was less than in young women without oral contraceptives. Contraceptives also alter various other circadian rhythms such as in cortisol, melatonin, etc. (Heintz et al., 1996b; Reinberg et al., 1996). However, there are no data as to whether taking contraceptives increases the risk of cardiovascular diseases.

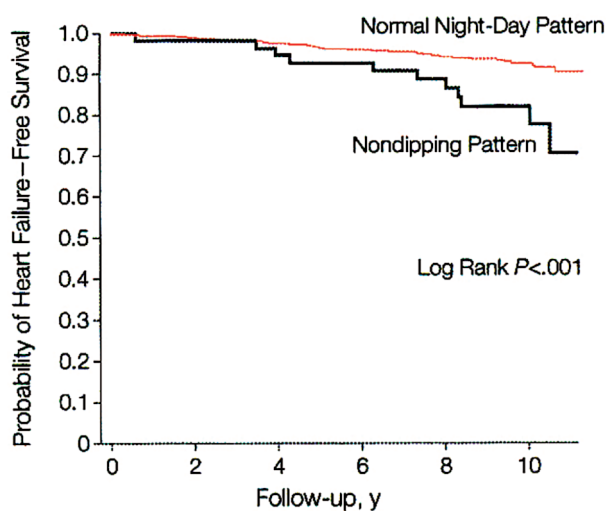


Fig. 7. Kaplan-Meier plots for heart failure-free survival in dippers and non-dippers (data from Ingelsson et al., 2006).

Whilst the rhythms in heart rate and blood pressure are the best-known periodic functions in the cardiovascular system, other parameters have been shown to exhibit circadian variations as well, e.g. stroke volume, cardiac output, blood flow, peripheral resistance, parameters of ECG recordings, in the plasma concentrations of pressor hormones such as norepinephrine, renin, angiotensin, aldosterone, atrial natriuretic hormone and plasma cAMP concentration, in blood viscosity, aggregability and fibrinolytic activity, etc. (Reinberg and Smolensky, 1983; Lemmer, 1989a, 2004a,b; Lemmer and Portaluppi, 1997).

## Chronoepidemiology

Pathophysiological events within the cardiovascular system are random (Reinberg and Smolensky, 1983; Lemmer and Witte, 1996, 2000; Willich and Muller, 1996; Lemmer and Portaluppi, 1997; Manfredini et al., 1997, 2003, 2005; Lemmer, 2004a). Thus, the onset of non-fatal or fatal myocardial infarction predominantly occurs around 06.00h – 12.00h. A similar circadian time pattern has been shown for sudden cardiac death, stroke, ventricular arrhythmias and arterial embolism, symptoms in coronary heart diseased patients such as myocardial ischemia, angina attacks or silent ischemia are also significantly more frequent during the daytime hours than at night, whereas the onset of angina attacks in variant angina peaks around 04.00h (Fig. 8) (Marshall, 1977; Araki et al., 1983; Canada et al., 1983; Waters et al., 1984; von Arnim et al., 1985; Hausmann et al., 1987; Mittler et al., 1987; Lucente et al., 1988; Lanza et al., 1990; Andrews et al., 1993; Willich et al., 1993; Aronow et al., 1994; Manfredini et al., 1994, 2004, 2005; Cannon et al., 1997; Haley et al., 2004). In a large survey of 7,731 patients who were prospectively

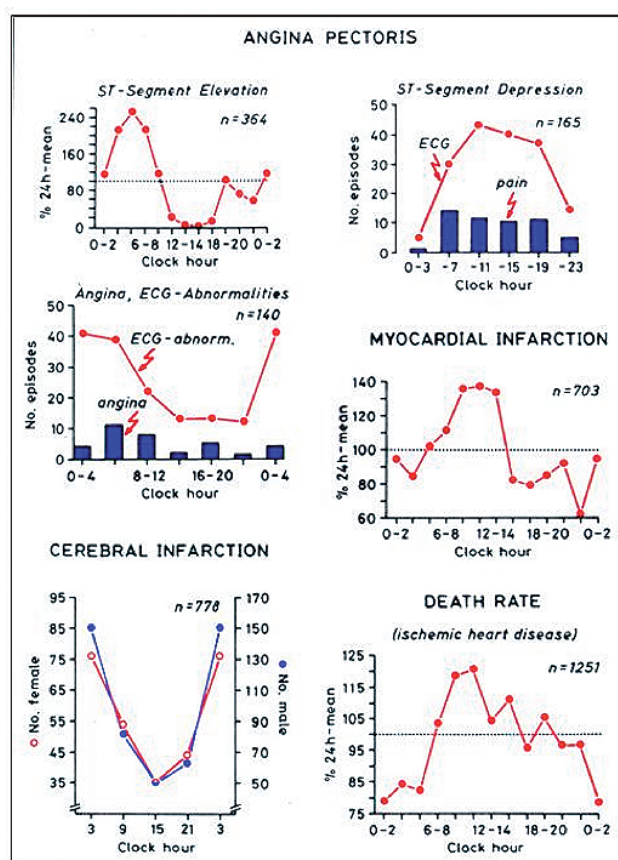


Fig. 8. Chronoepidemiology of cardiovascular disorders, representative examples are shown. (data from: Marshall, 1977; Araki et al., 1983; Waters et al., 1984; v. Arnim et al., 1985; Hausmann et al., 1987; Mittler et al., 1987).

identified in the Thrombolysis in Myocardial Ischemia (TIMI) III Registry (Cannon et al., 1997) gave further evidence for a circadian variation in the onset of pain with a peak between 6.00h and 12.00h. This circadian pattern was observed both in patients with unstable angina and in those with evolving non-Q-wave acute myocardial infarction (Cannon et al., 1997).

It is likely that the well-known circadian rhythms in fibrinolysis, hemostasis and thrombosis contribute to the circadian rhythms in cardiovascular events mentioned above (Andreotti and Kluft, 1991; Andreotti et al., 1996; Kapiotis et al., 1997; Walters et al., 2003; Westgate et al., 2008). Fibrinolytic activity is reduced in the early morning and could favour thrombus formation. Also, the endothelium shows circadian time-dependent variations. Endothelial cells form the interface between the circulating blood and the artery wall and circulating blood exerts shear forces on the endothelium. The endothelium releases several vasoactive compounds (e.g. nitric oxide [NO], thrombin, ADP, prostacyclin). NO has been shown to be involved in the circadian rhythm of the physiologi-

cal blood pressure regulation and NO deficiency in patients with hypertension or atherosclerosis contributes to the disturbed blood pressure regulation in these patients (Panza, 1997; Bode-Boger et al., 2000; Elherik et al., 2000) and may contribute to the increased cardiovascular risk. Variations in endothelial function together with NO-synthase stimulation and circulating estrogen concentrations are observed during the menstrual cycle (Chambliss and Shaul, 2002; Mendelsohn and Karas, 2005). Interestingly, in healthy, young pre-menopausal women higher 24-hour mean values in the circadian excretion rates of NO are found than in aged-matched healthy men (Hartig and Lemmer, 2003). This is consistent with a higher risk of coronary disease for men than for pre-menopausal women (Mendelsohn and Kara, 2005). Following the menopause gender differences in coronary risk are thought to diminish, though sound evidence is still lacking.

In the early morning not only do cardiovascular events predominate but there is also a rapid rise in blood pressure (see Fig. 5) (Kuwajima et al., 1995; Lemmer, 1996d; Middeke and Lemmer, 1996; Shimada et al., 2001; Kaplan, 2003; Kario et al., 2003b; Kario, 2008), an increase in plasma catecholamines and a rapid increase in sympathetic tone (Tuck et al., 1985; Kennedy et al., 1994; Middeke and Lemmer, 1996) and in the concentrations of pressor hormones (Mullen et al., 1981; Tuck et al., 1985; Heintz et al., 1996a; Elherik et al., 2000; Hartig and Lemmer, 2003; Hurwitz et al., 2004) and the highest values in peripheral resistance (Panza et al., 1991; Casiglia et al., 1992; Casiglia et al., 1996; Lemmer, 2006b). Thus, it appears that the early morning hours are the **hours of highest cardiovascular risk**.

### Chronopharmacology of hypertension

Having in mind the organization in time of living systems including man it is easy to conceive that not only must the *right* amount of the *right* substance be at the *right* place, but also that all this be *right* in time. This is the more important when an organism or individual itself has to act or react in favorable biotic or environmental conditions which by themselves are highly periodic. Thus, it is easy to understand that exogenous compounds including drugs may differently challenge the individual depending on the *time* of exposure.

This part of the review will focus on data pertinent to the field of pharmacological intervention into blood pressure regulation (Raftery et al., 1981b; Lemmer, 1989b, 1996a,d, 2001, 2004a, 2005, 2006b, 2007a; Lemmer and Portaluppi, 1997; Deutsche Hochdruckliga, 2003; Hermida et al., 2007a). Drug treatment of hypertension includes various types of drugs such as diuretics,  $\beta$ - and  $\alpha$ -adrenoceptor blocking drugs, calcium channel blockers,

angiotensin converting enzyme inhibitors,  $AT_1$ -receptor blockers and others which differ in their sites of action as well as in half-life, galenic formulations and, thus, in dosing interval. Despite the great number of studies published in evaluating antihypertensive drug efficacy the time of day of drug application was only rarely a specific point of investigation. Therefore, in this review emphasis will be put on cross-over studies (morning vs evening) with antihypertensive drugs to highlight this point more clearly.

In order to adequately compare the results obtained with drugs lowering high blood pressure it is important to note that ABPM (ambulatory blood pressure measurement) is now regarded as the gold standard, i.e. the method of choice, to evaluate blood pressure profiles (White, 1996, 2008; Schrader et al., 2000; Chobanian et al., 2003; Deutsche Hochdruckliga, 2003; Mancia and Parati, 2006; Middeke, 2006).

### Beta-adrenoceptor antagonists

Beta-adrenoceptor antagonists can be divided into four main groups: non-selective (e.g. propranolol, oxprenolol),  $\beta_1$ -selective (e.g. bisoprolol, metoprolol, atenolol), compounds with intrinsic sympathomimetic/agonist activity (ISA, e.g. pindolol, carteolol) and  $\beta$ -adrenoceptor antagonists with additional activities, e.g.  $\alpha$ -adrenoceptor blockade (carvedilol) or nitric oxide (NO) release (nebivolol).

Unfortunately, in hypertensive patients no cross-over (morning versus evening) study with  $\beta$ -adrenoceptor antagonists has been published. From studies performed without time specified drug dosing it is difficult to draw definite conclusions on the influence of the circadian time of drug dosing on antihypertensive drug efficacy. A résumé of 20 “conventionally” performed studies showed that  $\beta$ -adrenoceptor antagonists – either  $\beta_1$ -selective, non-selective, or with ISA – either do not affect or reduce or even abolish the rhythmic pattern in blood pressure. In general, however, there is a tendency for  $\beta$ -adrenoceptor antagonists to reduce daytime blood pressure levels and not to greatly affect night-time values, being less/not effective in reducing the early morning rise in blood pressure (Stanton and O’Brien, 1994). Consistently, decreases in heart rate (HR) by  $\beta$ -adrenoceptor antagonists are more pronounced during the daytime. In healthy subjects a cross-over study with propranolol similarly showed a more pronounced decrease in HR and blood pressure during the day than at night (Langner and Lemmer, 1988) (Fig. 9). Interestingly, the agent with partial agonist activity, pindolol, even increased HR at night (Quyyumi et al., 1984).

In addition, the pharmacokinetics of  $\beta$ -adrenoceptor blocking drugs can also be circadian-phase dependent

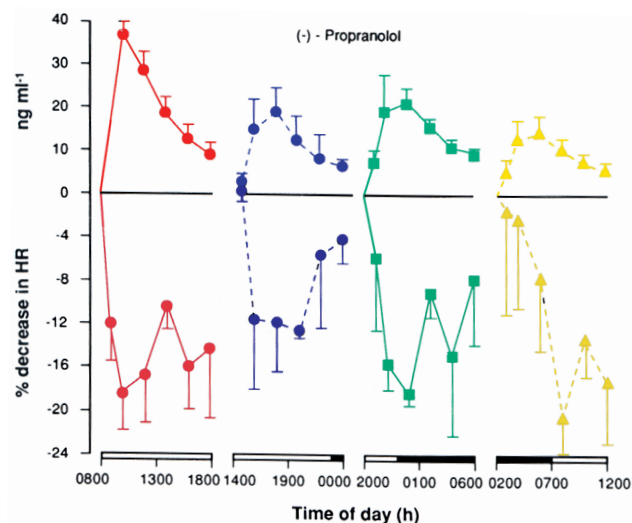


Fig. 9. Chronopharmacology of propranolol in healthy subjects. Propranolol was dosed at four different times of day, shown are the daily variation in the kinetics and in the heart rate lowering effect (data from Langner and Lemmer, 1988).

as demonstrated for the lipophilic drugs oxprenolol and propranolol (Langner and Lemmer, 1988; Koopmans et al., 1993), but not for the hydrophilic compound atenolol (Shiga et al., 1993) (Table 1). Several studies have shown that cardiovascular active compounds such as propranolol, oral nitrates and the calcium channel blocker nifedipine showed higher peak drug concentrations [ $C_{max}$ ] and/or a shorter time-to-peak concentration [ $t_{max}$ ] after morning than evening oral drug dosing, at least when immediate release formulations were used (Table 1). Concerning the underlying mechanisms responsible for this chronokinetic behaviour of these lipophilic compounds, a faster gastric emptying time in the morning (Goo et al., 1987) and, more important, a higher hepatic blood flow – being representative for the gastro-intestinal perfusion – in the morning than in the evening (Lemmer and Nold, 1991) are assumed to be involved (Fig. 10). Both mechanisms could nicely explain higher  $C_{max}$ - and shorter  $t_{max}$ -values after oral ingestion of non-retarded drugs in the morning (Bruguerolle and Lemmer, 1993; Lemmer and Bruguerolle, 1994).

In conclusion, available clinical data indicate that  $\beta$ -adrenoceptor mediated regulation of blood pressure dominates during daytime and is of minor importance during the night and the early morning. This correlates well with the circadian rhythm in sympathetic tone as indicated by the rhythm in plasma norepinephrine and cAMP which are both higher during the day than at night.

Table 1. Pharmacokinetic parameters of cardiovascular active drugs determined in cross-over studies. At least two dosing times (around 6.00-8.00h and 18.00-20.00h) were studied, in some studies up to 6 circadian times were included. Only the parameters Cmax = peak drug concentration, and tmax = time-to-Cmax, are given. sd = single dose, w = weeks, I.R. = immediate-release preparation, S.R. = sustained-release preparation. \*p morning versus evening at least <0.05; <sup>a</sup> bioavailability significantly reduced; <sup>b</sup> significant difference in half-life, <sup>c</sup>(±)-propranolol was given, kinetic data for (-)-propranolol.

Drug	Dose [mg] & Duration	Cmax [ng/ml]		tmax [h]		References
		Morning	Evening	Morning	Evening	
Digoxin	0.5, single dose	3.6*	1.8	1.2	3.2	Bruguerolle et al., 1988
Enalapril	10					
Enalaprilat	single dose	33.8	41.9	4.4	4.5	Witte et al., 1993
Enalaprilat	3 weeks	46.7	53.5	3.5*	5.6	
IS-5-MN I.R.	60, single dose	1605.0	1588.0	0.9*	2.1	Scheidel & Lemmer, 1991 Lemmer et al., 1989
IS-5-MN S.R.	60, single dose	509.0	530.0	5.2	4.9	Lemmer et al., 1991a
Molsidomine	8, single dose	27.0	23.5	1.7	1.7	Nold & Lemmer, 1998b
Nifedipine I.R. <sup>a</sup>	10, single dose	82.0*	45.7	0.4*	0.6	Lemmer et al., 1991a
Nifedipine S.R.	2 x 20, 1 week	48.5	50.1	2.3	2.8	Lemmer et al., 1991a,b
Atenolol	50, single dose	440.0	391.8	3.2	4.0	Shiga et al., 1993
Oxprenolol <sup>b</sup>	80, single dose	507.0	375.0	1.0	1.1	Koopmans et al., 1993
Propranolol (±) <sup>c</sup> (-)- Propranolol	80, single dose	38.6*	26.2	2.5	3.0	Langner & Lemmer, 1988
Propranolol (±)	80, single dose	68.0	60.0	2.3	2.7	Semenowicz-Siuda et al., 1984
Verapamil S.R.	360, 2 weeks	389.0	386.0	7.2*	10.6	Jespersen et al., 1989
Verapamil	80, single dose	59.4*	25.6	1.3	2.0	Hla et al., 1992

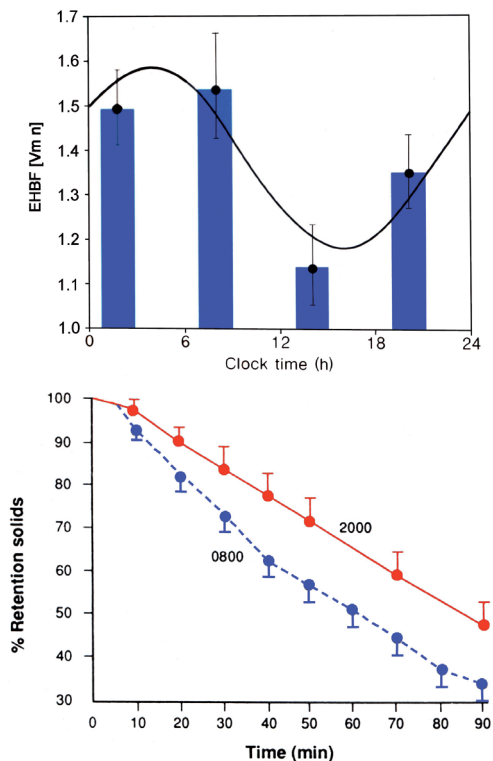


Fig. 10. Daily variation in gastro-intestinal perfusion (Lemmer and Nold, 1991) and in gastric emptying time (Goo et al., 1987) in healthy subjects.

## Calcium channel blockers

Calcium channel blockers are also not a homogenous group of drugs. Vasodilatation by calcium channel blockers occurs at lower concentrations than the cardiodepressant effects. However, the difference between vasodilating and cardiodepressant effects is greater with the 1,4-dihydropyridines (e.g. nifedipine, nitrendipine, isradipine, amlodipine) than with the verapamil- and diltiazem-like compounds. Moreover, these drugs differ in their kinetics with amlodipine having a long half-life *per se*.

The effects of calcium channel blockers were analysed mainly by visual inspection of blood pressure profiles (Lemmer and Portaluppi, 1997; Lemmer, 2001, 2005, 2006b; Hermida et al., 2007c). In primary hypertensives, t.i.d. (three times a day) dosing of non-retarded verapamil did not greatly change the blood pressure profile, being however, less effective at night (Gould and Mann, 1982). A single morning dose of a sustained-release verapamil showed a good 24-hour blood pressure control (Caruana et al., 1987), whereas a sustained-release formulation of diltiazem was less effective at night (Lemmer et al., 1994). Dihydropyridine derivatives, differing in pharmacokinetics, seem to reduce blood pressure to a varying degree during day and night; drug formulation and dosing interval may play an additional role.

Table 2. Effects of calcium channel blockers on the 24-hour pattern in blood pressure in dippers, non-dippers, and normotension, only data obtained in cross-over studies are considered. Drug dose, duration of blood pressure profile, treatment, circadian time of drug application, number of patients, the diagnose as well as the effect on the BP profile are given (rating see Table 1).

Drug	Patients (n)	Dose (mg)	Duration (weeks)	Dosing time	Lowering of Blood Pressure			References
					Day	Night	24h-Profile	
<b>Primary Hypertension (Dipper)</b>								
Amlodipine	20	5	4	morning evening	↓↓↓ ↓↓↓	↓↓↓ ↓↓↓	preserved preserved	Mengden et al., 1992
Amlodipine	12	5	3	08.00h 20.00h	↓ ↓	↓ ↓	preserved preserved	Nold et al., 1998a
Isradipine	18	5	4	07.00h 19.00h	↓↓↓ ↓↓↓	↓↓↓ ↓↓↓	preserved preserved	Fogari et al., 1993
Lacidipine	33	4	6	morning evening	↓↓↓ ↓	↓ ↓-↓↓↓	preserved preserved?	van Montfrans et al., 1998
Nifedipine GITS	10	30	1–2	10.00h 22.00h	↓↓↓ ↓↓↓	↓↓↓ ↓↓↓	preserved preserved	Greminger et al., 1994
Nisoldipine ER	39	20	4	07.00 – 09.00h 21.00 – 23.00h	↓↓↓ ↓↓↓	↓(↓) ↓↓↓	preserved preserved	White et al., 1999
Nitrendipine	41	20	4	06.00h 18.00h	↓ ↓	↓ ↓	preserved preserved	Meilhac et al., 1992
Nitrendipine	6	10	0.5	06.00h 18.00h	↓↓↓ ↓	↓↓↓ ↓↓↓	preserved changed	Umeda et al., 1994
<b>Secondary Hypertension (Non-Dipper)</b>								
Amlodipine	39	5	3	08.00h 20.00h	↓ ↓	↓↓↓ ↓↓↓	normalised normalised	Lemmer et al., 2002
Isradipine	16	5	3	08.00h 20.00h	↓↓↓ ↓	↓↓↓ ↓↓↓	disturbed normalised	Portaluppi et al., 1995
Nisoldipine ER	36	20	4	07.00 – 09.00h 21.00 – 23.00h	↓↓↓ ↓↓↓	↓↓↓ ↓↓↓	normalised normalised	White et al., 1999
<b>Normotension</b>								
Nifedipine I.R	10	12	Single dose	08.00h 19.00h	↓ ↓	↓↓↓ ↓	preserved preserved	Lemmer et al., 1991a

Up to now, 12 studies using a cross-over design (morning vs. evening) have been published (Table 2, for reviews see: Lemmer, 2001, 2004b, 2005, 2006b; Hermida et al., 2007b). In primary (essential) hypertensives with a dipper profile amlodipine, isradipine, nifedipine GITS and nisoldipine did not affect the 24-h blood pressure profile differently after once morning or once evening dosing (Mengden et al., 1992; Fogari et al., 1993; Greminger et al., 1994; Nold et al., 1998; White et al., 1999), whereas with nitrendipine and lacidipine the profile remained unaffected or slightly changed after evening dosing (Meilhac et al., 1992; Umeda et al., 1994; van Montfrans et al., 1998). Most interestingly, the greatly disturbed blood pressure profile in secondary hypertensives (non-dippers) due to renal failure was normalised after evening but not after morning dosing of isradipine (Portaluppi et al., 1995; White et al., 1999; Lemmer et al., 2003) (Fig. 11). Similarly, amlodipine and nisoldipine ER transformed

non-dippers into dippers, both after evening and morning dosing (White et al., 1999; Lemmer et al., 2002, 2003; Lemmer, 2006b), which might be due to the longer “apparent” half-life of these drugs. In normotensives an acute dose of nifedipine i.r. did not significantly modify the circadian blood pressure profile either (Lemmer et al., 1991a,c). These findings demonstrate that time of drug dosing (mainly evening dosing) of a dihydropyridine calcium channel blocker can be advantageous in not only reducing the elevated blood pressure but also normalising the disturbed blood pressure profile.

A time-of-day effect has also been described for the kinetics of various calcium channel blockers (Table 1): The bioavailability of an immediate-release formulation of nifedipine was found to be reduced by about 40% after evening compared to morning dosing with C<sub>max</sub> being higher and t<sub>max</sub> being shorter after morning dosing (Lemmer et al., 1991a). No such circadian time-dependent



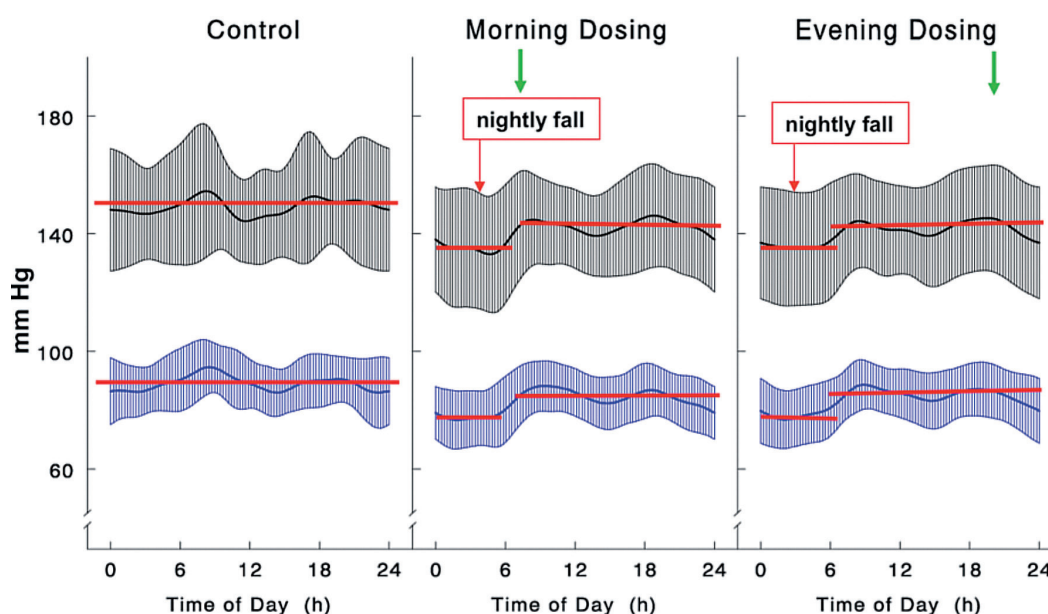


Fig. 11. Effect of the calcium channel blocker amlodipine after evening or morning dosing on the blood pressure profile of hypertensive non-dippers (data from Lemmer et al., 2002).

kinetics were observed with a sustained-release formulation of nifedipine (Lemmer et al., 1991a,b). Also regular as well as sustained-release verapamil displayed higher  $C_{max}$ - and/or shorter  $t_{max}$ -values after morning dosing (Jespersen et al., 1989; Hla et al., 1992). Similar chronokinetics have been reported after oral dosing of other cardiovascular active drugs such as enalapril, propranolol and others (Semenowicz-Siuda et al., 1984; Bruguerolle et al., 1988; Langner and Lemmer, 1988; Koopmans et al., 1991; Witte et al., 1993). Conversely, intravenously infused nifedipine did not display daily variations in its pharmacokinetics (Lemmer et al., 1991a) indicating that gastrointestinal mechanisms must be involved in the drug's chronokinetics.

### Angiotensin converting enzyme (ACE) inhibitors and $AT_1$ -receptor-blockers

Seven cross-over studies (morning vs. evening dosing) with oral dosing of ACE inhibitors in essential hypertensive patients have been published (Table 3). They demonstrate that, in contrast to morning dosing, evening dosing of benazepril, enalapril and perindopril resulted in a more pronounced nightly drop (super/extreme dipping) and the 24-h blood pressure profile was distorted by evening enalapril (Palatini et al., 1993; Witte et al., 1993; Morgan et al., 1997) (Fig. 12). Evening dosing of quinapril and ramipril (Palatini et al., 1992; Myburgh et al., 1995) also resulted in a slightly more pronounced effect than morning dosing, however, the 24-hour pattern was preserved (Table 3), and

no difference was reported with trandolapril (Koroda et al., 2004). Ramipril was only slightly effective during day and nighttime hours (Myburgh et al., 1995). In the light of a reduced cardiac reserve of patients with hypertension at risk a too pronounced nightly drop in blood pressure (i.e. super-dipping) after evening dosing might be a potential risk factor for the occurrence of ischemic events such as cerebral infarction (Kario and Shimada, 2004).

There are only two studies published with the  $AT_1$ -receptor blockers, valsartan and olmesartan, which similarly reduced the blood pressure after both morning and bedtime dosing (Hermida et al., 2003; Smolensky et al., 2007). In patients with chronic renal disease olmesartan restored the nightly decline in blood pressure (Fukuda et al., 2008).

### Diuretics and other antihypertensives

Antihypertensives of other classes have rarely been studied in relation to possible circadian variation. Once-daily morning dosing with diuretics such as indapamide or xipamide reduced blood pressure in essential hypertensives without changing the 24-h blood pressure pattern (Raftery et al., 1981a; Ocon and Mora, 1990). In salt-sensitive hypertensive patients (dippers and non-dippers) an interesting study was performed with diuretics: Uzu and Kimura (Uzu and Kimura, 1999) demonstrated that diuretics did not affect the circadian blood pressure profile in dippers but transformed the non-dippers into dippers (Fig. 13).

Table 3. Effect of angiotensin converting enzyme (ACE) inhibitors and AT<sub>1</sub>-receptor-blockers on blood pressure profile in dippers, cross-over studies.

Drug	Patients (n)	Dose (mg)	Duration (days, wks)	Dosing time	Lowering of Blood Pressure			References
					Day	Night	24h-Profile	
<b>ACE-Inhibitors</b>								
Benazepril	10	10	1 d	09.00h 21.00h	↓↓↓ ↓	↓↓ ↓↓	preserved changed	Palatini et al., 1993
Enalapril	10	10	1 d	08.00h 19.00h	↓↓ ↓↓	↓ ↓↓↓	preserved changed	Witte et al., 1993
Enalapril	10	10	3 wks	08.00h 19.00h	↓↓ ↓	↓ ↓↓	preserved changed	Witte et al., 1993
Perindopril	18	2	4 wks	19.00h 21.00h	↓↓ ↓	↓ ↓↓	preserved changed	Morgan et al., 1997
Quinapril	18	20	4 wks	08.00h 22.00h	↓↓ ↓↓	↓ ↓↓	preserved preserved	Palatini et al., 1992
Ramipril	33	2.5	4 wks	08.00h 20.00h	↓ (↓)	(↓) ↓	preserved preserved	Myburgh et al., 1995
Trandolapril	30	1–2	8 wks	morning bedtime	↓↓ ↓↓	↓↓ ↓↓	no profiles shown	Koroda et al., 2004
<b>AT<sub>1</sub>-Receptor-Blockers</b>								
Valsartan	90	160	3 months	awaking bedtime	↓↓ ↓↓	↓↓ ↓↓	preserved preserved	Hermida et al., 2003
Olmesartan	18	20/40	12 wks	08.00h 20.00h	↓↓ ↓↓	↓↓ ↓↓	preserved preserved	Smolensky et al., 2007

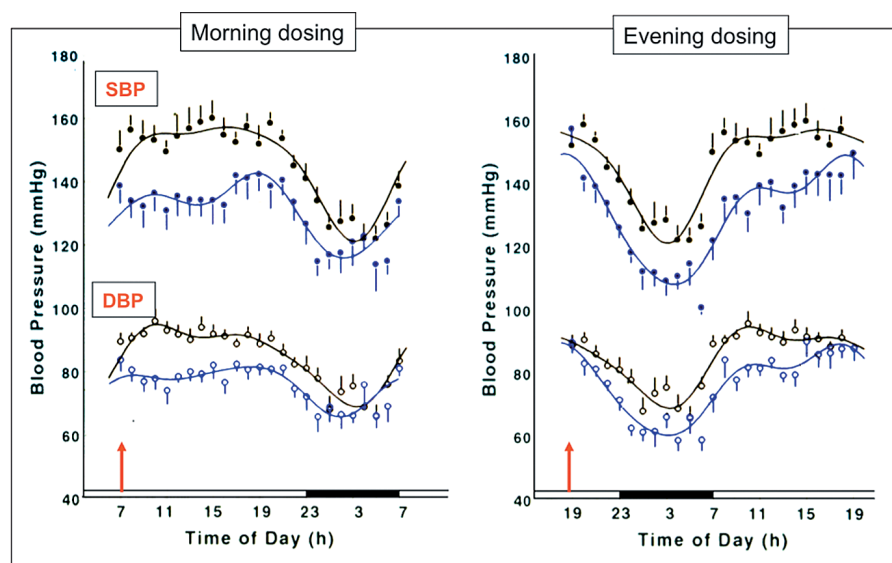


Fig. 12. Effect of the ACE-inhibitor enalapril on the 24-hour blood pressure profile of primary hypertensive patients after single morning or single evening dosing for 3 weeks each. Shown are the pre-treatment (black lines) and treatment profiles (data from Witte et al., 1993).

Twice daily dosing of the  $\alpha$ -adrenoceptor antagonists indoramin (Gould et al., 1981) or prazosin (Weber et al., 1987) did not change the blood pressure profile either. Since  $\alpha$ -adrenoceptor blockade more effectively reduced the peripheral resistance during the early morning than at

others times of the day (Panza et al., 1991) these findings point to the importance of  $\alpha$ -adrenoceptor-mediated regulation of blood pressure during this time of day. In addition, peak treatment effect after nighttime dosing of doxazosin was later than predicted from the drug's

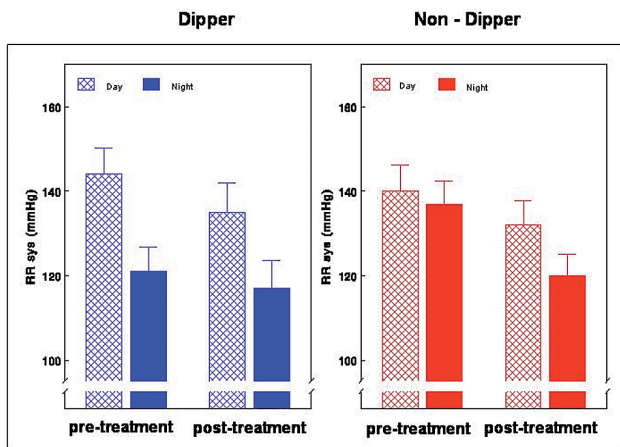


Fig. 13. Effect of diuretics on blood pressure profile as shown by the day and night values in salt-sensitive dippers and non-dippers (data from: Uzu and Kimura, 1999).

pharmacokinetics (Pickering et al., 1994), an observation which nicely supports similar findings of a circadian phase dependency in the dose-response relationship of nifedipine, enalapril and propranolol (Langner and Lemmer, 1988; Witte et al., 1993). A long-acting preparation of an  $\alpha$ -adrenoceptor-blocking drug, doxazosin-GITS, decreased the blood pressure but did not change the 24-hour profile in primary hypertensive patients (Lemmer and Nold, 2003).

### Duration of the antihypertensive effect

There may be pitfalls in restriction of blood pressure monitoring by ABPM to 24 hours when evaluating the duration of the antihypertensive effect. Chronic morning dosing of atenolol produced inadequate 24-h control of blood pressure, but the pattern of reduction persisted the next day after the drug was withdrawn as found in a 48-h blood pressure recording (Gould and Raftery, 1991). The same finding was reported after single morning or single evening dosing of enalapril (Witte et al., 1993). These reports clearly support the notion that certain regulatory mechanisms of the 24-h blood pressure profile may predominate at certain times of day and that it is worthwhile not to restrict blood pressure monitoring to 24 h in order to avoid false conclusions. These observations also support a circadian time-dependent dose-response relationship, mentioned above.

That massive antihypertensive drug treatment in the evening hours can lead to a drug-induced super-dipping – bearing the risk of stroke due to reduced cerebral perfusion – is shown in one patient in Fig. 14.

### White coat/office hypertension

“Office hypertension” or “white coat hypertension” is nowadays of increasing medical importance, as it can modify the circadian pattern in plasma norepinephrine

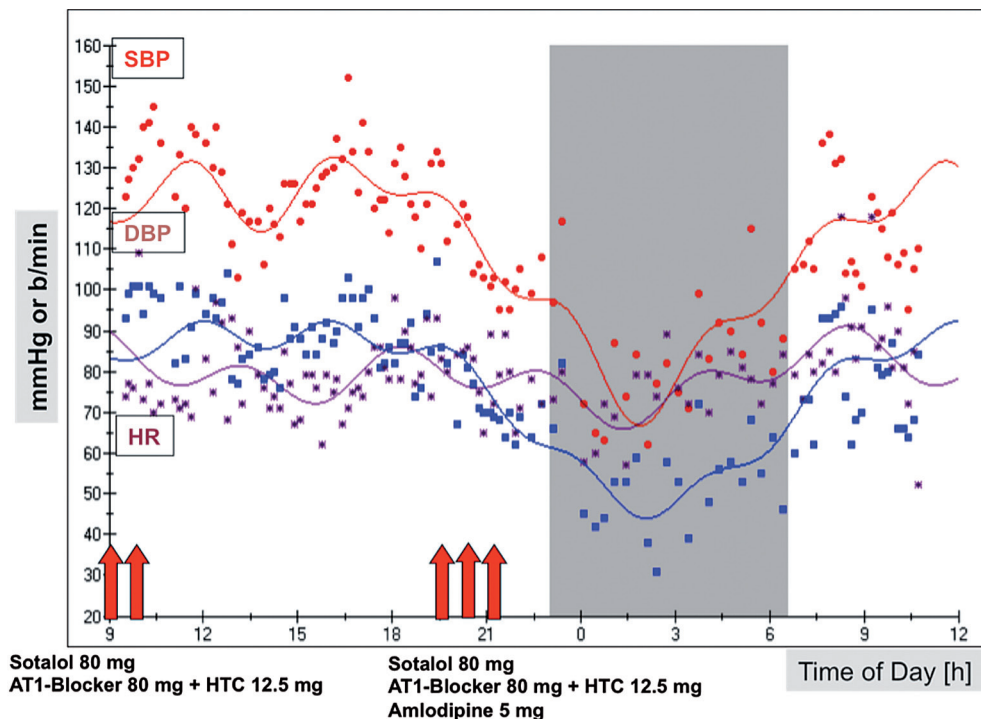


Fig. 14. Drug-induced super-dipping in one patient after evening overdosing, please note that diastolic blood pressure values at night are as low as 40–50 mmHg (from: Lemmer, 2006a).

and in the blood pressure profile. It is of interest to note that both symptoms had already been independently and precisely described more than 300 years ago by several authors (Lemmer, 1995, 2004c) (Fig. 15):

#### Joachim Targiri (1698)

“Most of all one has to have an experienced knowledge to study the pulse of the artery, the movement of which can be manifold increased, decreased, and disturbed by internal causes and external conditions. Even catching sight of the doctor and the doctor’s stepping in may not be of minor importance, ... because this, indeed, can induce changes in the movement of the pulse.”

#### Christoph Hellwig (1738)

“It is important to note that the patient’s pulse may change remarkably ... most commonly this is caused by the advent of the doctor”.

#### Théophile de Bordeu (1756)

“In order to estimate the quality of the pulse it is necessary to feel the pulse several times; it is an exception that the presence of the doctor does not lead occasionally to some changes which may *elevate* or *increase* it: the practitioners never forget to keep in mind the pulse which they call the *pulse of the doctor*.”

Early reports on the symptoms of “white coat hypertension” by (Hellwig, 1738, Targiri, 1698) and (de Bordeu, 1756) (*italics* also in the original text); in: (Lemmer, 1995, 2004c), private library, all translations by B.L).

Moreover, Hellwig proposed that the doctor should sit down and talk to the patient for a while before examining the quality of the pulse once or several (sic!) times (Hellwig, 1738), a recommendation reflecting our modern guide-lines when measuring the blood pressure. Shortly later Théophile de Bordeu, professor at the University of Montpellier, named the same observation “*le pouls du médecin*” (de Bordeu, 1756).

White “coat/office hypertension” is now of increasing interest, because a permanent hypertension can develop with its complications (Pickering, 1992; Verdecchia et al., 1992; Middeke and Schrader, 1994; Pierdomenico et al., 2002; Ben-Dov et al., 2008).

In “office/white coat hypertension” elevated blood pressure values are found by office measurement but not with ABPM (Middeke and Lemmer, 1996). Furthermore, it is interesting to note that, in comparison to normotensive subjects, the levels of norepinephrine in the blood and the vascular reactivity in patients with “office hypertension” are further increased during the early morning leading to an amplitude hypertension (Middeke and Lemmer, 1996).

### Chronopharmacology of coronary heart disease

As already outlined the onset of angina pectoris and the frequency of angina attacks both in stable angina, silent ambulatory ischemia, sudden cardiac death (Fig. 4, top right picture) and in vasospastic Prinzmetal angina (Fig. 4, top and middle left pictures) exhibit a circadian rhythm,



Fig. 15. Cover pages of early reports on white coat hypertension, see above (Targiri, 1698; Hellwig, 1738; de Bordeu, 1756), from the author’s library.

findings which have been confirmed by many authors. It is, therefore, not surprising that antianginal drugs may also exert circadian-phase-dependent effects in patients with variant (Prinzmetal) or stable angina pectoris (Lemmer and Witte, 1996; Lemmer, 2006b, 2007a; Portaluppi and Lemmer, 2007).

## Oral nitrates

Although organic nitrates are widely used in the treatment of coronary heart disease (CHD), little is known about their circadian time dependent effects, especially from cross-over studies, i.e. morning versus evening. A summary of the time-dependent incidence of ischemias in CHD is presented in Table 4.

Table 4. Effects of calcium channel blockers, nitrates and acetylsalicylic acid (aspirin) on the circadian pattern of symptoms in coronary heart diseased patients.

Drug	n	Dose [mg], & Duration	Incidence of Ischemia			Diagnosis	References
			Morning	Daytime	Night		
<b>Calcium Channel Blockers</b>							
Amlodipine	47	5-10, mean 71d	↓↓	↓↓	(↓)	CHD, AA	Taylor, 1992
Amlodipine	250	10, 7w	↓↓	↓↓		CHD, stA	Deanfield et al., 1994
Diltiazem	13	90, 2h	↓↓	↓↓		CHD, varA	Yasue et al., 1979
Diltiazem SR	60	2x180, 2w	↓↓	↓↓	↓↓	CHD, stA	Parmley et al., 1992
Diltiazem SR	50	350, 2w		↓		CHD, stA <sup>a</sup>	Andrews et al., 1993
Diltiazem SR	50	350, 2w		↓↓		CHD, stA <sup>b</sup>	Andrews et al., 1993
Nifedipine	50	79, 2w		↓		CHD, stA <sup>a</sup>	Andrews et al., 1993
Nifedipine	50	79, 2w		↓↓↓		CHD, stA <sup>b</sup>	Andrews et al., 1993
Nifedipine GITS	92	30-180m, 4w	↓↓	↓↓	↓	CHD, stA	Parmley et al., 1992
NifedipineGITS + Beta-Blockers	92 115	30-180e, 4w ?	↓↓ ↓↓	↓↓ ↓↓	↓ ↓	CHD, stA CHD, stA	Parmley et al., 1992
Nifedipine	33	3x10-20, 5d	∅	(↓)	∅	CHD, stA	Mulcahy et al., 1988
Nifedipine	10	4x10-30, 1w	↓↓↓	↓	↓	CHD, stA	Nesto et al., 1991
Nifedipine	16	3x20/30, 2-4w	↓↓	↓↓		CHD	Deedwania et al., 1991
Nifedipine	9	3x10/20, 5d		↓	↓↓	CHD <sup>c</sup>	Quyyumi et al., 1987
CC-Blockers	147	?, ?	∅	∅	∅	MI <sup>d</sup>	Willich et al., 1989b
CC-Blockers	132	?, ?	↓↓			MI <sup>d</sup>	Woods et al., 1992
<b>Organic Nitrates</b>							
ISDN SR	15	120m, 2w	↓	↓↓	∅	CHD, stA	Hausmann et al., 1989
ISDN SR	10	10m, 3w	↓↓	↓↓		CHD, stA	Wortmann & Bachmann, 1991
IS-5-MN	10	2x20, 3w	↓↓	∅		CHD, stA	Wortmann & Bachmann, 1991
IS-5-MN	187	40m, 2w	↓↓	↓↓	↓↓	CHD	Ganzinger, 1992
IS-5-MN	195	2x20, 2w	↓↓	↓↓	↓↓	CHD	Ganzinger, 1992
IS-5-MN	9	2x40, 5d		↓	↓↓	CHD <sup>c</sup>	Quyyumi et al., 1987
Glyceroltrinitrate	7	0.6 acute	↓↓	∅		CHD, varA <sup>f</sup>	Yasue et al., 1979
Nitrates	174	?, ?	∅	∅	∅	MI <sup>d</sup>	Woods et al., 1992
<b>Others</b>							
Aspirin	211	325, ?	↓↓↓	↓↓	∅	MI	Tofler et al., 1987

Rating of drug effects: “↓”, “↓↓”, “↓↓↓”, “↓↓↓↓” = effective, ∅ = no effect, “--” = worsening.

The following abbreviations are used: CHD = coronary artery/heart disease, MI = myocardial infarction, stA = stable angina pectoris, varA = variant angina, AA = angina attacks, VA = ventricular arrhythmias, VPC = ventricular premature complex, n-Q = non Q-wave infarction, SCD = sudden cardiac death.

<sup>a</sup> ischemia associated with heart rate increase,

<sup>c</sup> rhythm in ischemic threshold abolished,

<sup>e</sup> severe angina pectoris,

<sup>b</sup> ischemia not associated with heart rate increase,

<sup>d</sup> influence on rhythmic pattern,

<sup>f</sup> increase in coronary artery diameter.

The first evidence for a circadian-time-dependent effect of oral nitrates was provided in the classical paper of Yasue et al. (Yasue et al., 1979): in this study 13 patients with Prinzmetal's variant angina performed treadmill exercise tests in the early morning (05.00–08.00 h) and again in the afternoon (13.00–16.00h). Exercise-induced angina attacks as well as ECG abnormalities occurred in all patients in the morning, but in only 2 patients in the afternoon. Interestingly, glyceroltrinitrate administration in the morning prevented the angina attacks and had a greater dilating effect on the coronary vessels than when given in the afternoon, indicating temporal variations in vasomotor tone. Essentially the same results were obtained with the calcium channel blocker diltiazem, whereas propranolol aggravated the symptoms when given in the early morning. This study clearly demonstrated for the first time that exercise-induced coronary spasm was dependent on the time of the day at which the exercise challenge was performed. Supporting this hypothesis and the time-dependency of medication, the authors of the glyceroltrinitrate study demonstrated an increase in patency of the great coronary arteries, induced by this drug when taken in the morning but not when taken in the afternoon.

In 174 patients receiving organic nitrates prior to myocardial infarction the temporal distribution did not differ from untreated patients (Woods et al., 1992). In contrast, Hausmann et al. (Hausmann et al., 1989) demonstrated that in stable angina pectoris, once-daily dosing of isosorbide-dinitrate (ISDN) reduced the number of ischemic episodes exclusively during daytime with no effect during the night, resulting in a blunted circadian pattern in myocardial ischemia. Quyyumi et al. (1987) compared the anti-anginal efficacy of atenolol, nifedipine, and iso-

sorbide-5-mononitrate (IS-5-MN) and observed a similar reduction of nocturnal ischemia with all drugs, whereas daytime episodes were less affected by nifedipine and the mononitrate compared to atenolol. Similarly, Ganzinger et al. found no time-dependent difference in the effectiveness of IS-5-MN in CHD (Ganzinger, 1992). In patients with stable angina pectoris Wortmann and Bachmann (Wortmann and Bachmann, 1991) compared the effects of 20 mg IS-5-MN twice-daily and 120 mg ISDN once-daily on ergometric ST-segment depression at different circadian times (10.00h, 14.00h, and 18.00h). They observed that exercise-induced ST-segment depression depended on the circadian time, the most pronounced depression occurring in the late afternoon. The anti-ischemic effects of isosorbide-dinitrate did not differ between times of exercise testing, whereas those of isosorbide-5-mononitrate achieved statistical significance only during ergometry in the morning. The studies on oral nitrates in CHD published are summarized in Table 4.

The chronopharmacology of the oral nitrates isosorbide dinitrate (ISDN) and isosorbide-5-mononitrate (IS-5-MN) has been investigated only in studies in healthy subjects after acute dosing (Lemmer and Witte, 1989; Lemmer et al., 1991c,d; Scheidel and Lemmer, 1991) (see Table 1). ISDN-induced decrease in systolic blood pressure and the reflex-induced increase in heart rate (determined in the standing position) were more pronounced after nighttime dosing at 20.00 h, even though the bioavailability (AUC) of ISDN was significantly lower after evening than after the morning dosing at 08:00h. Daily variations were also seen in the pharmacokinetics of an immediate-release preparation of IS-5-MN with  $t_{max}$  being 0.9 and 2.1 hours at Rx of 06.30 h and 18.30 h, respectively (Fig. 16).

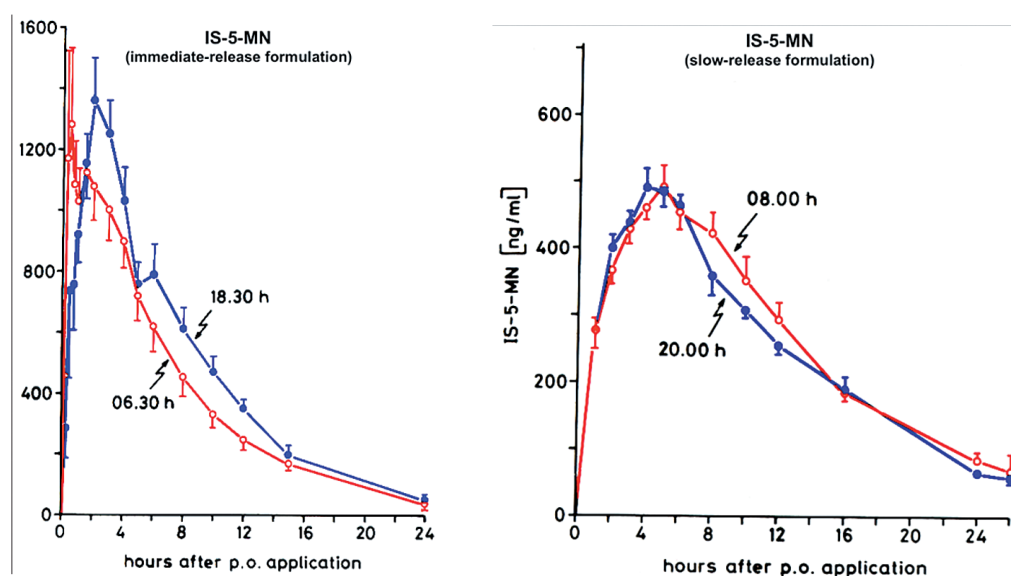


Fig. 16. Isosorbide-5-mononitrate (IS-5-MN) plasma concentrations in healthy subjects after morning or evening drug dosing of an immediate-release and a sustained-release preparation at two different times of day (data from Lemmer et al., 1990; Scheidel and Lemmer, 1991).

A decrease in standing blood pressure and increase in heart rate occurred at about 0.6–1.0 hours after drug ingestion at either dosing time, thus, providing evidence for a dissociation in time between peak drug concentrations and peak effects during the evening hours. Similar results were obtained after oral dosing of an IS-5-MN retard formulation either at 08.00 h or at 20.00 h. The maximum decrease in standing blood pressure and increase in heart rate occurred about 3 hours after drug intake at 20.00 h, but about 5–6 hours after drug intake at 08.00 h (Lemmer et al., 1991d). Most interestingly, no circadian-phase-dependency was observed in the pharmacokinetics of this retard preparation (Lemmer et al., 1991d) (see Table 1; Fig. 16); at either dosing time peak drug concentrations were found after about 6 hours. Similarly with sustained-release molsidomine no circadian phase-dependency in its pharmacokinetics were found after acute dosing (Nold and Lemmer, 1998). These

data clearly demonstrate that drug formulation may influence the pharmacokinetic profile of a drug when taken at different times of day.

### Beta-adrenoceptor antagonists

Beta-Adrenoceptor antagonists have been shown to reduce the risk of recurrent myocardial infarction. A large number of studies have addressed the question whether or not these drugs could influence the circadian pattern in myocardial infarction (see Fig. 1, Table 5). Unfortunately, there are no cross-over studies, i.e. morning versus evening, among them. A summary of the studies on the time-dependent incidence of ischemia and myocardial infarction in CHD is presented in Table 5.

In the ISAM study (Willich, et al., 1989a, Willich,

Table 5. Effects of beta-adrenoceptor antagonists on the circadian pattern of symptoms in coronary heart diseased patients. In general coronary heart disease was verified by angiography, mostly Holter-ECG was used to assess the ischemic burden, myocardial infarction was verified objectively. If available the number of patients (n), the drug dosage (after titration), the duration of treatment (h = hours, d = days, w = weeks), the time of drug dosing (m = morning, e = evening), the main diagnose and the reference are given. Though not mentioned in the studies a morning application can be assumed for drugs with once daily dosing.

Drug	n	Dose [mg] & Duration	Incidence of Ischemia			Diagnosis	References
			Morning	Daytime	Night		
<b>Beta-Adrenoceptor Antagonists</b>							
Atenolol	23	59/100m, 4w	↓↓↓	↓↓↓	↓↓↓	CHD, stA	Kostis, 1988
Atenolol	24	50/100, 2-4w	↓↓↓↓	↓↓↓↓		CHD	Deedwania et al., 1991
Atenolol	41	100, 5d	↓↓↓↓	↓↓↓	↓	CHD, stA	Mulcaey et al., 1988
Atenolol	15	100, 5d		↓↓↓	↓↓↓	CHD <sup>e</sup> , aa	Quyyumi et al., 1987
Atenolol	9	100, 5d		↓↓↓	↓↓↓	CHD <sup>e</sup>	Quyyumi et al., 1984
Atenolol /Propranolol	18	25/40 or 80, 2w	↓↓↓	↓↓↓	↓↓↓	CHD, stA <sup>c</sup>	Benhorin et al., 1993
Bevantolol	21	200, 4w	↓↓↓	↓↓↓	↓↓↓	CHD, stA	Bowles et al., 1986
Bisoprolol	13	10m, 2w	↓	↓↓↓	(↓)	CHD	Prager et a., 1989
Metoprolol	9	2x100/200, 1w	↓↓↓	↓↓↓↓	↓↓↓	CHD, stA	Imperi et al., 1987, Willich et al., 1989b
Metoprolol	10	2x200, 1w	↓↓↓	↓↓↓↓	↓↓↓	CHD	Coy et al., 1990
Metoprolol	31	2x50/100, 2w	↓↓↓	↓↓↓	(↓)	CHD, stA	Egstrup, 1991
Nadolol	23	40/80m, 4w	↓↓↓↓	↓↓↓	↓↓↓	CHD, stA	Kostis, 1988
Pindolol	15	3x5, 5d		↓	∅	CHD,aa	Quyyumi et al., 1984
Propranolol	13	60, 2h	--	--		CHD, varA	Yasue et al., 1979
Propranolol	419	?, 6w	↓↓↓	↓↓↓	(↓)	CHD, VA	Lichtstein et al., 1983
Propranolol	9	4x40, 4w		↓↓↓		CHD, stA	Joy et al., 1982
Propranolol	123	85±28, 116±56w	↓↓↓	↓↓↓	∅	MI <sup>f</sup> ,VA	Aronow et al., 1994
Propranolol LA	50	292, 2w	↓↓↓↓	↓↓↓↓		CHD, stA <sup>a</sup>	Andrews et al., 1993
Propranolol LA	50	292, 2w		↓↓↓		CHD, stA <sup>b</sup>	Andrews et al., 1993
Propranolol LA	24	80, 5d	↓↓↓↓	↓↓↓↓	↓↓↓	CHD,	Cohn et al., 1989
Propranolol	101	180/240, 6-12w	↓↓↓	(↓)	(-)	SCD <sup>d</sup>	Peters et al., 1989

Drug	n	Dose [mg] & Duration	Incidence of Ischemia			Diagnosis	References
			Morning	Daytime	Night		
Beta-Blockers	135	?, ?	↓↓	∅	∅	MI <sup>d</sup>	Muller et al., 1985
Beta-Blockers	143	?, ?	∅	∅	∅	MI, n-Q <sup>d</sup>	Kleiman et al., 1990
Beta-Blockers	206	?, ?	↓↓	∅	∅	MI <sup>d</sup>	Willich et al., 1989a
Beta-Blockers	132	?, ?	↓↓	↓↓↓	∅	MI, VPC <sup>d</sup>	Gillis et al., 1992
Beta-Blockers	185	?, ?	↓↓				Woods et al., 1992

Rating of drug effects: “↓”, “↓↓”, “↓↓↓”, “↓↓↓↓” = effective, ∅ = no effect, “--” = worsening.

The following abbreviations are used: CHD = coronary artery/heart disease, MI = myocardial infarction, stA = stable angina pectoris, varA = variant angina, AA = angina attacks, VA = ventricular arrhythmias, VPC = ventricular premature complex, n-Q = non Q-wave infarction, SCD = sudden cardiac death.

<sup>a</sup> ischemia associated with heart rate increase,

<sup>c</sup> rhythm in ischemic threshold abolished,

<sup>e</sup> severe angina pectoris,

<sup>b</sup> ischemia not associated with heart rate increase,

<sup>d</sup> influence on rhythmic pattern,

<sup>f</sup> rhythm observed with no antiarrhythmics abolished by propranolol

Muller, 1996) the morning peak in the onset of myocardial infarction was abolished by  $\beta$ -adrenoceptor blockade. This finding is supported by the majority of a large number of studies (Lichtstein et al., 1983; Quyyumi et al., 1984; Muller et al., 1985; Bowles et al., 1986; Imperi et al., 1987; Quyyumi et al., 1987; Kostis, 1988; Mulcahy et al., 1988b; Cohn and Lawson, 1989; Peters et al., 1989; Prager et al., 1989; Willich et al., 1989b; Coy et al., 1990; Deedwania et al., 1991; Egstrup, 1991; Gillis et al., 1992; Woods et al., 1992; Andrews et al., 1993; Benhorin et al., 1993; Aronow et al., 1994) (see Table 5). The number of sudden cardiac deaths between 05.00 – 11.00h was reduced by propranolol (Peters et al., 1989), whereas the occurrence of deaths at other circadian times was almost equal in untreated and treated patients. Interestingly, non-Q wave infarction did not show circadian variation, neither in untreated patients nor in those receiving  $\beta$ -adrenoceptor antagonists (Kleiman et al., 1990). In analysing the high and low frequency components it was shown that heart rate variability after acute myocardial infarction was significantly affected by either atenolol or metoprolol reducing sympathetic activation and increasing vagal tone, with the effects being more pronounced during the day (Sandrone et al., 1994). On the other hand, a worsening of the symptoms in variant angina was described for propranolol (Yasue et al., 1979).

Concerning the rhythmicity in ischemic episodes and in the incidence of angina attacks most studies demonstrated an abolition or attenuation of the morning peak by propranolol (Cohn et al., 1989) or the more selective antagonists metoprolol (Imperi et al., 1987; Egstrup, 1991) and atenolol (Mulcahy et al., 1988a; Cohn and Lawson, 1989; Deedwania et al., 1991).

In other studies with atenolol, atenolol/propranolol or bevantolol (Bowles et al., 1986) no influence on the circadian distribution of angina attacks or of ischemic episodes was observed though their total number was reduced at both times of day (Table 5). Pindolol, a  $\beta$ -adrenoceptor

antagonist with intrinsic sympathomimetic activity, even increased heart rate at night and did not reduce angina attacks (Quyyumi et al., 1984). Despite the preservation of circadian rhythmicity in silent ischemia the time-dependent variation in ischemic threshold, i.e. heart rate at the onset of ischemia, was completely abolished by treatment with  $\beta$ -adrenoceptor antagonists (Benhorin et al., 1993; Lemmer and Witte, 1996).

Whether or not influences of  $\beta$ -adrenoceptor antagonists on circadian rhythms in angina are observed may also depend on the subgroup of patients studied. A significant circadian variation, with a morning increase, was shown in the frequency of ventricular premature complexes, that was abolished by  $\beta$ -adrenoceptor antagonists (Gillis et al., 1992). However, a baseline circadian rhythm could be demonstrated only in patients with left ventricular ejection fraction [LVEF] greater than 0.30, whereas in those with more pronounced ventricular dysfunction (LVEF < 0.30) no rhythmicity was observed. Analysis of all patients without subdivisions would have obscured the circadian time-dependent effects of drug treatment of ventricular arrhythmias. In myocardial infarction, ventricular arrhythmias were also suppressed more effectively during early morning and daytime hours than during the night (Lichtstein et al., 1983). A detailed analysis of data from the ASIS study (The Angina and Silent Ischemia Study Group; see (Andrews et al., 1993) showed the importance of subclassification of ischemic events with regard to concomitant changes in heart rate. In that study propranolol markedly reduced those ischemic events which occurred while or directly after heart rate increased, whereas the proportion of episodes not related to heart rate changes was even more pronounced under  $\beta$ -adrenoceptor antagonist treatment. Since heart rate-related ischemias were shown to have a different circadian pattern than non-heart rate-related episodes, anti-ischemic treatment, affecting only one type of ischemia, can definitely be expected to show a circadian time-dependency.



Unfortunately, prospective chronopharmacological studies comparing the effects of  $\beta$ -adrenoceptor antagonists on ischemic events after dosing at different times of the day have not been performed so far.

At least in myocardial infarction and in stable angina pectoris (see Fig. 4) the attenuation of the increased sympathetic tone during the early morning and during the day seems to be an important therapeutic aspect in the use of the  $\beta$ -adrenoceptor antagonists (see Lemmer and Witte, 1996; Lemmer and Portaluppi, 1997).

In conclusion, it appears that treatment of coronary heart diseased patients by  $\beta$ -adrenoceptor antagonists effectively reduces ischemic events at any time of day.  $\beta$ -Adrenoceptor antagonists seem to be of special therapeutic value in the early morning which is the time of high risk.

### Calcium channel blockers

In patients receiving calcium channel blockers conflicting results have been reported in several studies concerning their effect on the circadian pattern in ischemic episodes or in myocardial infarction (Quyyumi et al., 1987; Mulcahy et al., 1988b; Deedwania et al., 1991; Nesto et al., 1991; Parmley et al., 1992; Taylor 1992; Woods et al., 1992; Andrews et al., 1993; Deanfield, 1994; Deanfield et al., 1994) are presented in Table 4. It was reported that nifedipine – in contrast to atenolol – did not alter the circadian profile in the episodes or in the duration of ischemia (Mulcahy et al., 1988b). However, reductions by nifedipine in the morning incidence of ischemic episodes have been observed in several other studies (Table 4).

In conclusion, calcium channel blockers – mainly short acting and non-retarded preparations – seem to be less effective than  $\beta$ -adrenoceptor antagonists in reducing ischemic events during the night and early morning. However, the role of formulation and/or subclasses of the calcium channel blockers remains to be elucidated. Finally, the early morning peak in myocardial infarction seems to be less or not greatly influenced by these drugs (Table 4).

After the observation that low-dose aspirin was able to reduce mortality in unstable angina pectoris by about 50% (Lewis et al., 1983), it was of interest to evaluate whether the morning peak in the incidence of myocardial infarction could also be influenced by inhibition of platelet aggregability, which has itself been reported to be increased in the early morning (Tofler et al., 1987). Consequently, Ridker et al. (1990) studied the preventive effects of alternate-day aspirin intake versus placebo in more than 22,000 physicians and analyzed the circadian distribution of infarction in both groups (Table 4). In the placebo group a bimodal distribution with a primary peak in the morning hours was observed, whereas in the aspi-

rin group this morning peak was reduced by about 60% resulting in a loss of circadian variation in the onset of myocardial infarction.

### Conclusion

The cardiovascular system is highly organized in time, both in health and disease. Disturbances in the physiological daily (circadian) rhythmic patterns of this system, e. g. in cardiac functions and blood pressure regulation, peripheral resistance, endothelial functions and vessel regulation by hormones and neurotransmitters can be regarded as warning signs of an increased cardiovascular risk and they can be of predictive value. There is now convincing evidence that most of these rhythms – from single cells to the highly complex human organism – are driven by biological clocks. It is, therefore, conceivable that this circadian organisation down to the level of signal transduction processes, enzyme and gene regulation may have implications for experimental and clinical pharmacological research. The aim of this paper is to review the circadian organisation of the cardiovascular system in humans and to demonstrate its impact on drug treatment in hypertension and coronary heart disease. The data presented clearly show that the circadian organisation of the human physiology and pathophysiology and the time-of-day of drug dosing has to be included in the design of clinical trials in order to better treat the patients and to avoid false conclusions on the effectiveness and side effects of drugs.



Fig. 17. A medical doctor taking into account that a drug has to be dosed at a defined time of day (picture by W. Langmandel, owned by the author).

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