

James L. Holly, M.D.

Chronobiology

By: James L. Holly, MD

Psychologically and physiologically, humans are conscious of time, dates, calendars, starting and finishing. Often, we forget what original concepts these basic ideas really are. As we approach the beginning of a new year, which itself is a novel concept, we are intensely conscious of “beginnings,” even of “new beginnings” and of timing, which in health, as in comedy, is often critical.

Circadian Rhythm

Human beings are unconsciously aware of time divisions, particularly the duration and timing of daily exposure to light. Not only is there a “circadian rhythm” in the human body, but there are seasonal adjustments to both heat and light by the body. The Circadian rhythm is the "internal body clock" that regulates the twenty-four-hour cycle of processes in animals and plants.

Not only are there daily cycles of hormone production, but there are “diurnal” (within the day) changes in bodily functions such as:

- Production of cholesterol.
- Blood pressure
- Functioning of the heart and other organs
- Among others

The effects of flight across time zones and shift work are reminders that although modern technologies can create "cities that never sleep," we cannot escape the internal, cellular clocks that regulate much of our physiology. Moreover, malfunctions in the human circadian timing system are implicated in illnesses such as:

- chronic sleep disorders in the elderly,
- manic-depression, and
- seasonal affective disorders (SAD or winter depression).

Disruption to rhythms usually has a negative effect in the short term. Many travelers have experienced the condition known as jet lag, with its associated symptoms of fatigue, disorientation and insomnia.

Regulation of the Circadian Clock

In its most basic form, circadian clocks in the cells of humans are comprised of a set of proteins that generate a self-sustaining loop with a period of about twenty- four hours. One or more of the clock components is acutely sensitive to light, resulting in the ability for the body to synchronize to local time.

Of the normal physiologic processes, the most common is the sleep-wake cycle over a twenty-four-hour period. The relationship between changes in heart rate and blood pressure and the day/night cycle has been well studied. As mentioned above, blood pressure fluctuations over twenty-four hours is well described. Blood pressure and heart rate tend to be lowest around 2:00-4:00 AM. Levels begin to increase after that and before awakening.

Chronobiology

Chronobiology is the study of naturally occurring biological rhythms and how these rhythms may interact with normal body functions as well as in disease processes. Biological rhythms become important in the management of illness, since they may define the optimal timing of therapeutic dosing.

Emphasis on the associations of biologic rhythms and the timing of treatment has occurred in several areas, including asthma and osteoporosis, but has not been widespread in the area of cardiovascular disease.

In addition to the concept of chronobiology, two other terms are important to this discuss:

- **chronotherapy** - relating therapy to circadian rhythms to increase benefit
- **chronotoxicity** - increasing disease activity or symptoms because of an incompatibility of therapy with an underlying rhythm

Chronobiologists have identified daily, monthly, and seasonal rhythms. While most studies have focused on circadian or twenty-four-hour rhythms related to the sleep-wake cycle, other rhythms such as ovulation and the menstrual cycle as well as seasonal changes have been evaluated.

Circadian Rhythm, Heart Rate and Blood Pressure

Of the normal physiologic processes which are well-known, the most common is the sleep-wake cycle over a twenty-four-hour period. The relationship between changes in heart rate and blood pressure and the day/night cycle has been well

studied. A profile of blood pressure fluctuation over a twenty-four-hour period is well described. Blood pressure and heart rate tend to be lowest around 2:00-4:00 in the morning. Levels begin to increase after that and before awakening.

Normal blood pressure pattern:

- Sharp increase in blood pressure and heart rate in the early morning prior to awakening, certainly upon awakening and upon getting up.
- The rate of rise of heart rate and blood pressure is highest in the morning compared to any other time of day; this sharp rate of increase is important in terms of cardiovascular risk.
- Blood pressure may peak in the morning and then stay at that level during the afternoon and evening.
- In some patients the blood pressure continues to rise gradually, peaking in the late afternoon.
- Blood pressure and heart rate start to decline in the evening, reaching their lowest levels in the early morning between 2:00 and 4:00 a.m.

Dipping

This decrease in blood pressure at night is referred to as "dipping." Some patients, however, are "non-dippers," that is, they do not have a reduction in blood pressure at night, or if they do, it is blunted. This has been described more consistently in:

- African-Americans with hypertension,
- Diabetics

The physiology of "non-dippers" is not well defined, but the "non-dipping" appears to increase cardiovascular risk. Increased cardiovascular risk has been associated with daytime systolic and diastolic blood pressure, but it is also probably even more closely correlated with total twenty-four-hour pressure load.

When pressure "dips" at night, the overall blood pressure load is reduced. For non-dippers, the overall blood pressure load is not decreased, thus increasing cardiovascular risk.

Other Rhythms and Cardiovascular Risk

Some other normal physiologic rhythms that have been well described are also related to cardiovascular risk. The release of pituitary-related hormones such as TSH and prolactin tend to be highest at night. Whereas, cortisol and catecholamine release tend to be highest in the morning. We tend to see a surge in norepinephrine around awakening that corresponds to the abrupt increase in blood pressure and heart rate. We also see the most abrupt increase in peripheral resistance in the morning. This increases the work the heart must do

and therefore increases the demand for oxygen; these two events undoubtedly relate to cardiovascular events.

Why are these cardiovascular events more likely to occur in the morning? As mentioned, with sharp increases in heart rate and blood pressure in the morning, there is an increase in the heart's demand for oxygen. These increases are related in large part to activity. Getting out of bed and moving around will increase blood pressure and heart rate. These increases are not exclusively associated with activity, however; since blood pressure and heart rate start to increase prior to arising.

The most abrupt increases in blood pressure and heart rate often occur with wakening and getting out of bed; as does increase in peripheral resistance. It has been recently shown that the rate of increase in these parameters is of greatest concern. Obviously, absolute levels of the blood pressure and heart rate are related to risk, but the sharp rise in blood pressure and heart rate contribute even more strongly to increased risk.

Compounding these changes are changes in platelet aggregation and blood viscosity – how easily and smoothly blood flows through the arteries. Patients are at higher risk for a thrombotic (clot) event because of this increase in platelet aggregation and the increase in blood viscosity which may be in part related to AM increases in catecholamines. It is theorized that the AM surge in catecholamines which prepares us for “getting out of bed” and starting the day, contributes to increased risk of plaque rupture or plaque destabilization.

Chronotherapy: Therapeutic Options to Minimize Cardiovascular Risk in the Morning

There are limited options available to reduce increased cardiovascular risks in the morning. Some of those which are logical as a result of our understanding of body rhythms are:

- Dose aspirin in the morning to maximize anti-platelet effect in the morning.
- Withdraw nitrates at night when the risk of angina is less.
- The secondary prevention benefit of beta-blockers is best demonstrated in the morning.
- A new formulation of Verapamil has been designed to have a peak effect on blood pressure and heart rate when dosed at bedtime, around 10 p.m.
- The same benefit of blunting sharp increases in heart rate and blood pressure cannot be obtained simply by nocturnal dosing of conventional hypertensive agents.
- Dose most medications in the morning.
- A twice-a-day dosing regimen should include a second dose between 3:00 and 4:00 p.m.

In the future, other diseases and illnesses will certainly be shown to be responsive to chronotherapy. For now, we should all be aware that our bodies function better when we have regular patterns of sleep and nutrition. Night owls, those who chronically stay up late and sleep late have more health problems than those who go to sleep earlier and awaken earlier. For those who do shift work, the longer the shift interval, the healthier. Switching shifts weekly is more stressful than shifting every month or every year.

The November 4, 2002 Your Life Your Health column discussed “Depression and Seasonal Affective Disorder.” You can read this at www.jameshollymd.com. It relates practical issues of chronobiology to seasonal depressions, particularly around holidays.

Next week, the value to your health of “new beginnings” is our subject. Remember, it is your life and it is your health; only you can make a decision to protect both.