Nutrition in Chronocardiology: We are Indebted Professor Franz Halberg

R.B. Singh[1,*], A.K. Singh[1], J.P. Sharma[1], R.K. Singh[2], Adarsh Kumar[3], S.S. Rastogi[1], Garima Singh[1], Kumar Kartikey[1], Sushav Singh[1], Jan Fedacko[4], Daniel Pella[4], Fabien De Meester[5], Agnieszka Wilkzynska[5] and D.W. Wilson[6]

[1]*Halberg Hospital and Research Institute, Moradabad, UP, India*

[2]*K G M C, Lucknow*

[3]*Government Medical College, Amritsar, India*

[4]*Safaric University, Kosice Slovakia*

[5]*Tsim Tsoum Institute, Krakow, Poland*

[6]*School of Medicine and Health, Durham University, Durham, UK*

Abstract: Franz Halberg had very many experiences in India. The word circadian and chronobiology, chronocardiology and chronoastrobiology were coined by him. He also discovered that in studies of single daily meals, eating breakfast was associated with weight loss compared to dinner, despite similar energy intake. The role of time-adjusted drug intake, especially in the early morning, was also known to ancient Indian physicians. In Ayurveda, drinking of large amounts of water in the early morning is advised, which appears to be in an attempt to increase vagal tone due to gastric distention. A circadian cell cycle resides in every cell, and peripheral timing mechanisms are being documented in molecular biologic terms at about 24-hour (circadian) and higher (ultradian) frequencies, with coordination, in mammals, by the adrenal and the pineal-hypothalamic-pituitary network. The suprachiasmatic nuclei (SCN) and clock gene contribute to the coordination of the circadian rhythms' phase and amplitude, in every day life. The SCN are influenced by the daily alternation between light and darkness directly *via* the eyes and by plasma melatonin concentrations secreted by the pineal gland, which is a window to both light and geomagnetics. A clinical event occurs when our neuroendocrine time structures (chronomes) are not able to cope with the adverse effects of stimuli from within or from without, acting, e.g., *via* the sympathetic nervous system. Triggering of the neuroendocrines by environmental factors may activate the pineal gland, pituitary functions and adrenal secretions, resulting in adverse effects on circadian variations, heart rate variability (HRV) and blood pressure variability (BPV). Circadian rhythm was known to ancient man from the time of Homoerectus and Homosapiens who use to have intercourse in the early morning hours, before going for hunting to forests, causing increased secretion of testosterone in the morning as a circadian rhythm. Frey considered the mean distribution of deaths along the scales of the day and the year. In one industrial population, Pell and D'Allonzo, discussed time-macroscopically the occurrence of a peak in the morning hours in a study of acute myocardial infarction (AMI), a proposition also ascertained and extended to the yearly pattern time-microscopically. The subsequent reports from other countries, the erstwhile Soviet Union and the extensive data by WHO in the report of myocardial infarction Community Registers from 19 European centers demonstrated a peak incidence of onset of chest pain due to AMI from 8.00 to 11.00 AM with a ratio of 1:2, approximately. In one study from India, in 605 AMI patients, 39% of those who had Q wave infarction (n=174) had the onset between 6.00 AM to 12.00 noon. A further study from India, among 202 AMI patients, the incidence of onset of chest pain was highest in the second quarter of the day (41.0%), mainly between 4-8 a.m., followed by the 4th quarter, usually after large meals (28.2%). Emotion was the second most common trigger (43.5%), which was commonest in the patients with onset of chest pain in the second quarter of the day (51.8%). Cold weather was a predisposing factor in 29.2% and hot temperature (40°C) was common in 24.7% of the patients. A large meal, especially large breakfast in the morning was an important trigger of AMI in this study. It is possible that modern men can prevent AMI and stroke, if they eat small super foods breakfast, containing w-3 rich egg, vegetables, fruits, walnuts, almonds, raisins and yogurt which are known to be protective against cardiovascular diseases.

Keywords: Egg, fatty acids, nutrition, nutraceuticals, circadian, chronobiology, chronocardiology, fruits, vegetables, whole grains.

*Address correspondence to this author at the Halberg Hospital and Research Institute, Civil Lines,Moradabad-10(UP)244001, India; Tel/Fax: 0091 591 2417437; E-mails: icn2005@sancharnet.in, rbs@tsimtsoum.net

INTRODUCTION

Circadian rhythms of triggers and cardiac events and their mechanisms have been described by various workers

1876-3960/12

[1-3]. It is possible that circadian rhythm could be a new target for treatment with lifestyle changes, nutrient and nutraceiticals such as w-3 fatty acids and coenzyme Q10, prayer and drug therapy in the management of non-communicable disease (NCD) including cardiovascular diseases (CVDs) [1, 2]. Dr Halberg is more accurate to prefer to write nutriceutical because, these molecules are derived from nutrients but the commonly accepted spelling is nutraceutical.

I am delighted to mention the latest letter written to me (RBS), on June 7, 2011 by Prof Franz Halberg. Dear RB: Accepting having a center named after me constitutes an obligation to serve this institute and hospital and the friend heading it. It is a dream to serve India *via* this center, if at all possible. The challenge of our day is to serve health care worldwide, if possible with you and Fabien. Please allow me to do so. Allow me first to allude to the highlights of my experience in India. On the basic side, we learned in old Delhi, on the Yamuna river, that a catfish, Heteropneustes fossilis, in tanks provided with control of lighting and temperature (specifically under conditions of standardized lighting, i.e., continuous light, continuous darkness or a fixed photofraction, an about-yearly rhythm in gonadal size persisted, perhaps synchronized by some environmental factors; but we must be cautious since an apparent circannual component of the spectrum of human 17-ketosteroid excretion of a clinically healthy man during 15 consecutive years turned out to be a set of near transyears [4]. These studies in the department of B.A. Seshachar, a past president of one of your academies of science, carried out by Dr. Bangalore Sundararaj, were made as far as possible under control of the daily temperature and lighting in specially constructed fish tanks and, to my regret, were discontinued when both Dr. Seshachar and Dr. Sundararaj died [5]. With longer series, we might have learned whether biological near- or far-transyears corresponding to spectral components reported for human 17-ketosteroid excretion as oscillations longer than 1 year, were present in catfish, in whom we showed, as in humans, the role of timing nutrition [4].

On the clinical side, we had found and reported by 1960 at a symposium at Cold Spring Harbor (Long Island, NY) a large amplitude circadian rhythm in the response of mice to whole-body irradiation gauged by computing the dose that killed 50% of the mice investigated [6]. It seemed to be of interest to extend this finding to clinical radiotherapy: Dr. B.D. Gupta achieved that feat with Dr. Akhil Deka at the Postgraduate Institute of Medical Education and Research in Chandigarh [7]. It is still the major achievement in the application of timing to the treatment of human cancer. The chronobiology of antioxidants was and is a topic of collaboration with Dr. R.K. Singh in Lucknow and continues with his daughter Ranjana. Again, cancer chronotherapy, guided by marker rhythms, is in focus, in B.D.Gupta's footsteps on patients with perioral cancers given radio-therapy and on ovarian cancer patients receiving chemo-therapy, to be possibly guided not only by tumor and body core temperature but also by biochemical markers. R.K. Singh, however, although he is a leading biochemist, has embraced blood pressure monitoring by automatic tools since at heart he is a chronobiologist. Chronobiologists in India in medical terms also have an outpost in many other locations in India. But whether basic or applied, two goals may be pursued in Moradabad that involve structures in time relating to the individual and to society. For the individual, it is cardiovascular disease prevention; for society, it is prevention of aggression, based on a history of international battles that traces events for the past 2,556 years, considered by many but as yet solved by nobody [8]. In this light and with these goals, I have prepared a revised abstract, hoping that a true cooperation will ensue with you in Poland as well as Moradabad. India has managed to avoid religious strife thus far. But long-term monitoring will be essential and Fabien should not cut corners as he did with A&D in Japan and now in a pilot study aimed at body and mind, while ignoring the fact that the mind also has a frequency structure of its own that cannot be assessed without around-the-clock mood and vigor ratings. The action items needing your support to achieve a cooperation in Poland, if not (yet?) in Moradabad, are: 1. find out the role of circadian timing of omega-3; 2. monitor mood around the clock at least 4 times a day; 3. don't advertise what you don't (yet?) have. Sincerely, affectionately and gratefully, Othild, Germaine & Franz.

VARIABILITY

Except to ascertain whether a patient is dead or alive, in all other cases the clinician may gain from assessing chronobiologically the variability of heart rate and blood pressures and other vital signs that undergo a broad spectrum of rhythmic and other changes [1-3]. Circadians account for the difference between life and death, along the scale of a day, e.g., in response to ouabain [9, 10]. These circadian rhythms, reflected also in mortality and morbidity patterns, are modulated by rhythms with yet longer periods, e.g., of a decade, that are beyond our scope, even if they also are reflected in morbidity and mortality [1-3, 11].

It has been proposed that the universe came into existence about 13.7 billion years ago after explosion of the primordial fire ball of the infinitely dense singularity. Within 3 minutes of explosion, the elementary matter particles coalesced to form the nuclei of lightest elements, which were much later under the influence of the gravitational fields were responsible for the formation of the galaxies and clusters and superclusters of galaxies. Most of the galaxies appear to recede from us with high velocities and geomagnetic forces, which has been explained by the expansion model of the universe. Rhythm and their geomagnetic activity appear to be fundamental characteristics of the galaxies in our universe. The Sun revolves around the core of the Milky Way Galaxy, rotating on its axis. The planets revolve around the Sun and the moon revolves around the planets. One season follows the other season, day follows night, tide-in follows tide-out and all the objects are rolled round. Most of the rhythms are linked to the movements of heavenly bodies. The rotation of Earth is responsible for day and night cycle, and the Moon orbiting around the Earth, for the monthly cycle.The procession (precession-26000 years) of the Earth on its axis is responsible for the four seasons and the Earth orbiting the sun for the annual cycle. Many physiological functions have to adapt to these external rhythms and geomagnetic forces, causing dysfunctions in our body resulting in development of diseases [1-3].

The universe of living creatures appears to have similar characteristics. All living cells have clock genes, life cycles and periodicity in their life function [3]. The migration of birds, the hibernation of bears, dogs and several other animals, ripening of fruits and flowering of plants are driven by the changing seasons. Similarly, other rhythms, such as sleep and wakefulness, the opening and closing of flowers, feeding and nesting are also driven by the circadian cycle. There is substantial evidence that cardiovascular events occur in the second quarter of the day and the exact pathogenesis and risk factors of circadian rhythms are not known [1-15].

THE GENES AND MEMES AND ADAPTATION

Mind and body have evolved independently in conscious species, yet they interact closely for the span of a lifetime within individuals. Whereas the mind-related memes have evolved rapidly over the past 5-10,000 years of nascent humanity, the body related genes have barely changed. Gene-wise, modern man is very much similar to his hunter-gatherer's ancestor. It is therefore no surprise that memes and genes have a difficult time cohabitating the same environment. Mind stress occurs due to variability in thoughts inducing body strain, which if not taken care of at an individual level, can induce tissue injuries and chronic degenerative diseases, The primary risk factors; diet and lifestyle, tobacco, pollutants, stress, alcohol are most important environmental factors which interact with genes, in the pathogenesis of cardiovascular disease, diabetes and cancer. The interaction of genes and memes with environment, nature and nurture is the foundation for development of disease and health. It has been shown through molecular biological techniques that genetic factors determine susceptibility to disease and environmental factors determine, which genetically susceptible individual will develop the disease [14, 15]. Despite major changes in our diet and lifestyle in the last 10,000years, our genes have not changed and hence our biological responses are unable to adapt, resulting into greater adverse effects of these factors on our circadian rhythms. The spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years. A period of 10,000 years of agricultural revolution appears to be too small to modulate our genes, causing approximately 0.005% alterations. It seems that our genes are much similar today to our ancestors of Paleolethic period 40,000 years ago, when our genetic profile was established [14]. However, it is clear, that human today live in an environment that completely differs from that, for which our genetic constitution was selected and therefore our clock gene remains as potent as several million years ago to initiate the biorhythms of our body. It is possible, that our clock gene do not allow our body, to adapt to modulate rapid changes in diet and lifestyle that have occurred after 1910, due to industrialization and urbanization, which have adverse effects on the circadian rhythms of biological functions, resulting into cardiovascular diseases in the morning.

THE EVOLUTIONARY ASPECTS OF RHYTHMICITY OF BIOLOGICAL FUNCTIONS

According to one estimate, our brain size was 1500c cc, about 200,000 years ago that has decreased to 1350cc today in 2011, which appears to be due to primary risk factors; tobacco, alcoholism, faulty diet, sedentary behavior and geomagnetic activity. It is possible that early men were drinking plenty of water and consuming high w-3 fatty acids diets, which are known to be positively associated with brain size. *Homo sapiens* along with their predecessors *Homo-habilis* were primarily vegetarians, although for more than a million years, they have been hunting. They became omnivorous, as they moved away from other primates. Environmental influences, development of social groups and increasing demands for survival, made them skillful and caused significant changes in their lifestyle and environment. They used to go to the forest in the early morning, for hunting, when the animals come out of dense forest, and were killed early in life due to accidents. It has been proposed that to preserve their progeny, the *Homo sapiens* use to have intercourse early in the morning, resulting into one of the most important physiological adaptation of increased release of testosterone in the morning, as a circadian rhythm. The increased release of testosterone occurred to coordinate the sexual activity with an aim to make the women pregnant because he was at risk of dying due to accidents at a young age. The evolution of circadian rhythm may have been due to the start of the hunting in the morning. We suggest that since hunting used to start at about sun rise, causing enormous excitement, physical and mental exertion and increased sympathetic activity, (associated with marked secretion of cortisol, catecholamines, aldosterone, angiotensin and renin in a state of low melatonin), which also became a circadian rhythm in modern man, in the second quarter of the day [1]. The ancient man was able to adapt and fight the adverse effects of testosterone, cortisol and catecholamines, due to their enormous physical activity and they had no time for breakfast but the modern men is not so, resulting in increased rhythmicity of cardiac events, in the second quarter of the day. Late night sleep, late awakening, heavy breakfast, no physical activity and no meditation in the morning, and excitement for going to the workplace, trigger a biochemical and biological environment in our body, that contribute to greater cardiovascular events and deaths between 8.00-11.00 hours [1-3]. Otsuka K (RBS personal communication) is comparing the diet and lifestyle as well as heart rate and blood pressures around the clock for 7days, in people living in tribal areas and in adverse conditions of Laddakh, with those living in Moradabad and Tokyo City to find out the pattern of circadian changes, to provide further insight in the pathogenesis of circadian rhythms [9, 15].

EVOLUTIONARY ASPECTS OF ENVIRONMENTAL FACTORS

The theory of evolution by Darwin, not forgetting contributions by Wallace, appears to have significant influence on biological sciences related to human health and disease. Recently, several scholars became interested in health and disease from an evolutionary perspective and consider whether our departure from the hunter-gatherer lifestyle may contribute to contemporary health problems [1, 2]. Foods are probably appropriate candidate for risk of diseases for any given species, especially, if they were regularly consumed thus exposing to potential toxicants and adverse effects of excess of nutrients. During most of the

prior evolution, as in case of hunter-gatherers, prehistoric human hunter-gatherers may have protected themselves by choosing plants that have low concentrations of xenobiotics and by avoiding dangerous plant species [13, 14]. The available food staples during the Palaeolithic period may have been meat, fish, shellfish, leafy vegetables, honey, fruits, nuts,seeds, insects and larvae in varying proportions. Since tubers often require cooking, for their starch to be digestible, their routine consumption may have started in the later period [11-17]. The hunter-gatherers of India are in a rapid socio-economic transition but have a long life compared to other communities of the area [14].

About 10,000 years ago, prior to the agricultural revolution, humans ate an enormous variety of wild plants. Meat, fish, green leafy vegetables, fruits, nuts, berries and honey were also the food items, available to pre-agricultural humans which shaped modern humans genetic nutritional requirements [13, 14]. Early man also managed to survive, in a wide range of environments, from the tropical rainforest to the near Arctic, each of these offering a different limited set of foods. However, all diets of ancient man lacked, breakfast foods; the milk, cheese, butter, syrups, cereals and of course refined carbohydrates, salt and sugar that is sprinkled on them, which are known to have adverse effects on our metabolisms causing insulin resistance. These foods, supply approximately 70% of energy in the diets of the Western world today. Irrespective of the specific proportions of meat and vegetables, any prehistoric hunter-gatherers diets would have been very different from those of contemporary humans with regard to their nutritional value [13, 14]. Hunting was the major part of occupational physical activity of prehistoric man which may continue throughout the whole day. After they returned from the forest in the midday or evening, they may be having late heavy lunch, and dancing and eating in the late evening which is similar to diet and lifestyle among Indian hunter-gatherers today [14]. Most experts suggest that reversion to the original Palaeolithic human lifestyle (1.5 million-10,000 years BP)may be useful in the prevention of chronic diseases of Western populations.[11-17].The main symbols of Gods of early men were Sun, fire, sea and hills, which they worshiped to decrease their mental stress.

Several biological functions, such as temperature regulation, blood circulation in the nasal mucosa, the calibre of trachea-bronchial airway, blood pressure, heart rate, cortisol and growth hormone release exhibit an intrinsic circadian rhythm [1-5]. Most physiological rhythms may be ultradian having a duration of seconds, minutes, or atmost a few hours. Circadian means 24hours, circamensual, 30days and circannual, one year. The sleep phases, heart rate, respiratory rate and the functional peaks of many enzymes, receptors and endothelial nitric oxide release show ultradian variations, depending upon triggers and clocks (Table **1**).

CIRCADIAN

The words circadian and chronobiology were used for the first time by Franz Halberg in 1950 and officially introduced to a nomenclature committee in Stockholm for the first time in 1955 [9-11]. Chonobiology developed globally, after 1969, when an article entitled Chronobiology was published in the Annual Review of Physiology and became a Current Content citation classics [18]. Body temperature shows

Table 1. Triggers of Acute Myocardial Infarction. (Reference 11)

Precursors	Healthy Subjects (n-595)	AMI (n=202)
Anxiety	88(14.8)	122(60.4)*
Depression	42(7.0)	45(22.3)*
Type A behaviour	103(17.3)	95(47.2)*
Emotional stress	147(24.2)	92(45.5)*
Sleep deprivation	42(7.0)	56(27.7)*
Cold Climate	-	59(29.2)*
Hot climate (>40 degree celcius)	-	50(24.7)*
Large Meals	147(24.7)	96(47.5)*
Physical Exertion	173(29.1)	63(31.2)*
Diabetes mellitus	70(11.7)	53(26.2)*

*=P<0.05 by Chi square test.

circadian variation; it is lowest in the morning, peaks in the afternoon and falls again during the night. In contrast, cortisol release peaks in the morning. The blood pressure varies by up to 40 mmHg over the time structure of the day with a clear-cut peak in the morning. Cholesterol is synthesized mainly in the night. An annual variation has also been reported in aldosterone secretion showing a peak during the winter. The cycle of the reproductive organs is the best known circa-menstrual rhythm. Ultradian sleep phases (up to a few hours), heart rate, respiratory rate, circadian temperature changes in the interior of the body, all have a circadian rhythm. A circannual rhythm has been observed for serum cholesterol levels, with the winter values being much higher than summers. Halberg feels that apart from circadian, circa-septan (weekly), monthly, yearly or even longer-term physiological variations occur. Otsuka proposed that the physiological chronomes such as heart rate variability have counter parts in our environment and our genetic make –up over time may have evolved from our adaptation to and integration with our cosmos [9, 15]. There is a need to examine how these phenomena in the cosmos including heliomagnetics and geomagneics, can influence physiological chronomes, especially for the heart rate and blood pressure variability [4, 8, 9, 15].

CLOCKS

The circadian rhythms enable the body to adapt in the optimum manner to changes in its environments including geomagnetics in the cosmos. These rhythms are set up endogenously in the body and the entire system of harmonized rhythms, the biological time structure can be influenced by external and internal factors, which are called clocks. It is very difficult to assess the internal factors that govern the circadian rhythms hence we know very little about internal clocks. Halberg has proposed that a circadian cycle resides in every living cell and peripheral timing mechanisms are being documented in molecular biological

terms at about 24 hour(circadian)and utradian frequencies, with coordination in mammals by the adrenal, pineal-hypothalamic-pituitary network (Fig. **1**) [15, 16]. The suprachiasmatic nucleius (SCN) is one known specific area of the brain that works an internal clock and is responsible for the regulation of central nervous functions, phase and amplitude, as it receives information from the eyes. The information from the brain is transferred to pineal gland. Melatonin released from pituitary gland during the dark hours of the days in a circadian cycle, regulates sleep and awake periods. The SCN are influenced by the daily alternation between light and darkness directly *via* the eyes and the melatonin levels. A cardiovascular event occurs, when our neuroendocrine time structures (chronomes) are not able to cope with the adverse effects of stimuli from within or without, acting eg *via* the sympathetic nervous system. It appears that two most powerful external clocks for humans are light at high intensity and social contacts. The results of initial attempts to use bright light to adapt shift workers were encouraging [19]. Most organisms from cyanobacteria to mammals, are known to use circadian clocks to coordinate their metabolism with the natural circadian light/dark cycle. The human clock gene was discovered and mapped to chromosome17p12-13.1 in 1997 [20]. It is surprising that the clock gene is similar in all life forms on Earth. In plants, several molecular components have been described for the circadian system.

TRIGGERS

Environmental factors can trigger chronomes and may activate the pineal gland, pituitary functions and adrenal secretions, causing adverse effects on circadian rhythms, heart rate variability and blood pressure variability [15-19], resulting into cardiovascular events [16-20]. The various clinical manifestations of cardiovascular events do not occur at random times, but according to time structure. It is possible that certain external activities, known as triggers, may play a major role in causing myocardial ischemia, myocardial infarction, sudden cardiac death and stroke [16-20]. The MILIS (Multicentre Investigation of Limitation of Infarct Size) study showed that half of all myocardial infarction patients reported a temporal relationship between characteristic activities and occurrence of infarction. Emotional stress, mild and heavy physical exertion, sleep deprivation and large meals were the most frequently reported triggering activities [21].

The TRIMM (Triggers and Mechanisms of Myocardial Infarction) study showed that 76% of all infarction patients reported, an unusual event shortly before the onset of infarction [22]. Emotional upset or stress was reported by 52% of the subjects and 10% reported multiple trigger activities coinciding just before the event. Morning increase in Platelet aggregation appears to be one of the most important trigger for cardiovascular events, in the second quarter of the day [23]. It seems that there is a powerful evidence for a link between these triggers and the sequences of cellular and pathophysiological events that are proposed to be responsible for coronary artery ischemia. In one study among 58 patents with AMI, large meals including large breakfast, emotional stress, cold climate and hot climate (>40^{o} C) were important triggers. A large breakfast in the morning was associated with increased concentration of pro-inflammatory cytokines; tumor necrosis factor-alpha and interleukin-6 as well as insulin and glucose in the blood [16] (Table **2**). In the MAMI (mechanism of acute myocardial infarction) study [17], large meals, sleep deprivation, emotional stress, cold climate and hot climate were quite commonly observed (Table **3**). Circadian rhythms of

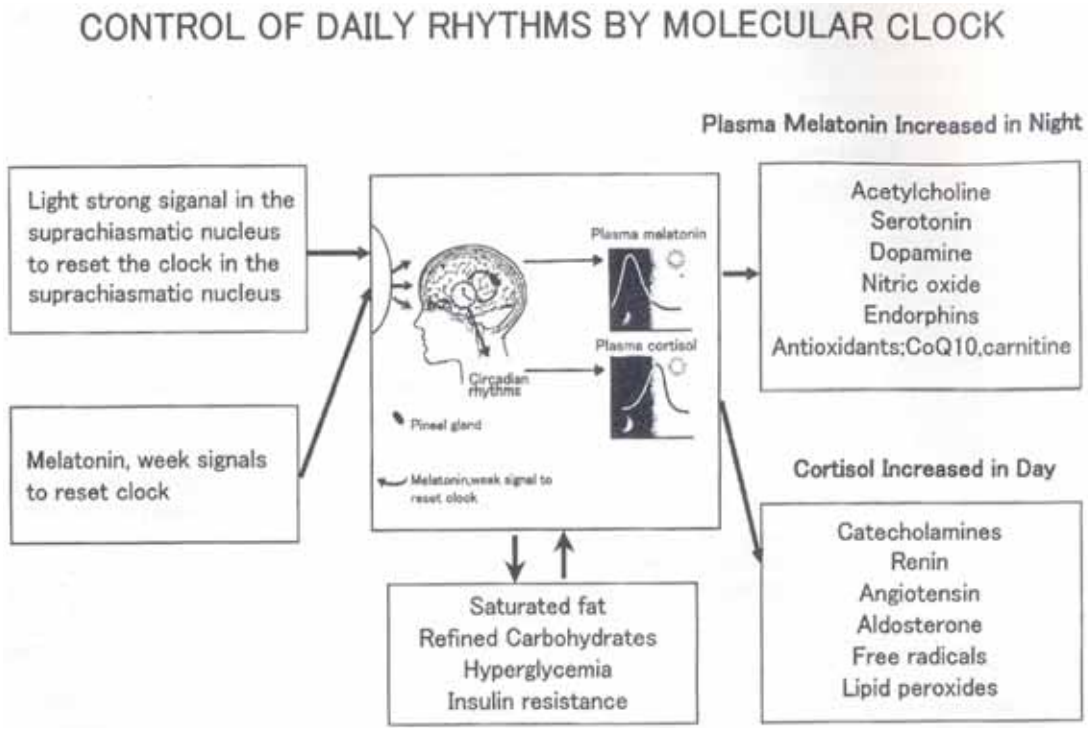

Fig. (1). Mechanism of circadian rhythm and the effects of nutrients and neurotransmitters.

Table 2. Clinical Characteristics of Subjects in Various Subgroups in Relation to Circadian Pattern

Sub Group Total n=202	**1-6 Hour 34(16.8)**	**6-12 Hours 83(41.0)**	**12-18 Hours 28(13.8)**	**18-24 Hours 57(28.2**
Male (n=160)	24(15.0)	60(37.5)*	25(15.6)	51(31.8)
Female (n-132)	10(23.8)	23(54.7)**	3(7.1)	6(14.2)
Age>60 (n=70)	12(17.1)	32(45.7)**	8(11.4)	18(25.7)
60 & less (n=132)	12(16.6)	51(38.6)*	20(15.1)	39(29.5)
History of CAD	16(30.7)	24(46.1)**	7(13.4)	5(9.6)
Known Diabetes (n=53)	10(18.8)	22(41.5)**	8(15.0)	13(24.5)
Known Hypertension (n-75) (>140/90) ----------	13(17.3)	30(40.0)**	11(14.6)	21(28.0)

Values are number (%). P value was obtained by comparison of subgroups by chi square test. *P>0.05m **=P<0.02, CAD= Coronary artery disease.

Table 3. Triggers Observed in 202 Patients of Acute Myocardial Infarction in Relation to Circadian Periods

Quarter of 24 Hrs Subjects	**1-6 Hours 34**	**6-12 Hours 83**	**12-18 Hours 28**	**18-24 Hourse 57**	**Total 202**
Trigger total	25(73.5)	70(84.3)	15(53.5)	42(73.7)	162(82.2)
Large meals	18(52.9)*	41(49.4)	12(42.8)	26(45.6)	96(47.5)
Emotional stress	15(44.1)	43(51.8)*	14(50.0)	20(35.0)	92(45.5)
Physical Exertion	12(35.3)	25(30.1)	8(28.5)	18(31.6)	63(31.2)
Sleep deprivation	8(23.5)	32(38.5)*	6(21.4)	10(17.5)	56(27.7)
Cold climate	10(29.4)	35(42.1)*	5(17.8)	9(15.5)	59(29.2)
Hot climate	8(23.5)	30(36.1)*	5(17.8)	7(12.3)	50(24.7)
(>40 celsious)					

Values are number (%) *=P<0.05, P values were obtained by comparison of subgroups by chi square test.

myocardial ischemia, angina pectoris, myocardial infarction, sudden cardiac death and stroke have been described by several experts which are triggered by environmental factors as well as biochemical and biological triggers present in every living cell.

CIRCADIAN RHYTHMS IN ISCHEMIC HEART DISEASE

In the decade since the 1985 observation by Muller *et al.*, indicated that the frequency of onset of myocardial infarction peaks at 9 a.m., numerous publications have supported this observation for myocardial infarction, as well as for sudden cardiac death, transient myocardial ischemia, and stroke. Refinement of these epidemiological observations has led to the conclusion that the morning peak in disease onset is due in part to the physical and mental stressors associated with morning awakening and activity and that stressors such as heavy physical activity and anger can trigger acute cardiovascular events [23, 24].

A circadian rhythm peaking in the morning is also found for so-called silent myocardial ischemia (SMI), which occurs in more than 20% of patients with arterial hypertension, and can be regularly detected in combined 24-h-ABPM/ EKG examinations. Comparative studies have shown that hypertensives with SMI suffer more cardiac events than those with no SMI. It has further been demonstrated that an elevated blood pressure amplitude, which is considered an independent risk factor for cardiac events, is associated with an increased incidence of SMI in patients with micro- or macro-angiopathy [25].

MECHANISMS INVOLVED IN MYOCARDIAL ISCHEMIA

Ambulatory ST segment monitoring, can detect transient myocardial ischemia which is also unevenly distributed during the day. The pathophysiology and the mechanism [5] underlying these variations are the focus of much investigation, while it is not currently fully understood. Heart rate, blood pressure, neural and humoral vasoactive factors such as plasma nor-epinephrine concentrations, coronary constriction, platelet aggregation, coagulation and renin activity, and probably also contractility are increased in the morning hours, indicating that increase in myocardial oxygen demand contribute importantly to the increased prevalence of ischemia in the morning. A study found that circadian rhythm of ischemic threshold detected by repetitive exercise treadmill tests in patients with chronic coronary artery disease is also apparently associated with levels of plasma endothelin-1 [26]. Li JJ *et al.* demonstrated that endothelin-1 values were higher in the morning hours as compared to afternoon hours. Circadian variation of plasma levels of endothelin-1 are likely to be one of the most likely mechanisms involved in reduction in the ischemic threshold in the morning hours [27]. Coronary spasm is induced by acetylcholine (ACh), which causes vasodilation when the endothelium is functioning normally, and the spasm is promptly relieved by nitroglycerin (NTG), which causes vasodilation through its direct action on the smooth muscle. The frequency of ischemic attacks displays diurnal variation in patients with vaso-spastic angina (VA). The number of attacks increase in the early morning and decrease in the afternoon. It seems that these neurohumoral dysfunctions are associated with oxidative stress, hyperglycemia and increase in free fatty acids, insulin and lipoprotein (a), with endothelial dysfunction in the morning compared to evening. Eating a heavy breakfast or meal during this period, particularly with high w-6/w-3 ratio of fatty acids and refined carbohydrates, is likely to enhance all the biochemical and biological factors in the body predisposing rhythmicity of cardiovascular events [7, 16, 18].

In one study [28] data were collected every 4 hourly for 24 hours, showing 8 hour component, instead of the anticipated 24-hour rhythm. These findings were confirmed in another study conducted in Austria [29].

In patients with coronary spasm, coronary dilation caused by endothelium-dependent vasodilators is reported to be impaired. In addition, antioxidants, such as vitamin C and glutathione, attenuate the constrictor response to acetylecholine. The plasma concentrations of vitamin E, a natural antioxidant, are decreased in coronary arteries of patients with variant angina exhibiting a circadian variation in tone [7]. As the endothelial function of the brachial artery and that of the coronary artery are closely related [27], the fluctuation of endothelium-dependent dilation in the brachial artery most likely takes place in the coronary arteries as well. It is known that the day/night pattern in the intensity of physical activity causes diurnal variation of hemodynamics. In the evening and afternoon, peripheral blood flow to the skeletal muscle is increased through local regulation in proportion to its need for oxygen and nutrients. Endothelial nitric oxide synthase is known to be upregulated by increased blood flow or shear stress. Therefore, it is possible that the variation in baseline blood flow may upregulate nitric oxide synthase and contribute to the fluctuation of the flow-mediated, endothelium dependent vasodilation in patients with variant angina. Diurnal fluctuation of endothelial function may play an important role in the occurrence of ischemic episodes in patients with variant angina [30]. Incidence of sudden cardiac death peaks during the early morning hours when there is a rapid withdrawal of vagal and an increase of sympathetic tone. The rate of autonomic change could be of prognostic importance. Wennerblom B *et al*., showed that during the night/morning hours, healthy controls demonstrated faster high frequency maximum velocity and higher high frequency gradient than in angina patients. The authors concluded that rapid vagal withdrawal seemed to be a sign of a healthy autonomic nervous system in the control group but was significantly slower in angina patients. IS-5-MN and metoprolol tended to normalise vagal withdrawal and metoprolol slowed down the rapid increase in sympathetic predominance in the morning in these patients [31].

CIRCADIAN RHYTHM OR PERIODICITY IN MYOCARDIAL INFARCTION

Although impressive strides in the diagnosis and management of AMI have developed over the past three decades, it continues to be a major public health problem in the industrialized world and is becoming an increasingly important problem in developing countries [16-18]. About 50 percent of the deaths associated with AMI occur within 1 hour of the event and are attributable to arrhythmias, most often ventricular fibrillation. Because AMI may strike an individual during the most productive years, it can have profoundly deleterious psychosocial and economic ramifications. The classical manifestations of coronary artery disease (CAD), such as angina pectoris, silent ischemia, myocardial infarction (MI) and sudden cardiac death, have a pronounced circadian rhythmicity, tending to cluster in the second quartile (6.00-12.00 hours) of the day. This increase in the rate of cardiovascular events in the morning may be due to a hypercoagulable state, consisted of increased platelet aggregation, increased tPA inhibitor levels, and rapid metabolism of heparin in the morning [7, 16-18]. In addition, the morning hours are associated with a decrease in vagal tone and increase in sympathetic activity, resulting in lower levels of acetylecholine and melatonin and increased concentrations of cortisol, aldosterone, catecholamines and angiotensin, which make the atherosclerotic plaques more vulnerable to rupture and thrombosis. These circadian manifestations are associated with a decreased heart rate variability (HRV), which is an independent risk factor for cardiovascular events. An analysis of a large number of patients hospitalized with MI, studied as a part of the Multicenter Investigation of Limitation of Infarct Size (MILIS), revealed a pronounced circadian periodicity for the time of onset of AMI, with peak incidence of events between 6 a.m. and 12 p.m. About 20% of myocardial infarctions occur between midnight and 6 AM. The circadian distribution of acute myocardial infarction has a morning peak, especially during the first few hours after awakening [32, 33]. In a review, Cornelissen *et al.* reported circadian, circaseptan and circaannual rhythms in myocardial infarction, stroke and other CVDs [34] and in another compared

Table 4. Circadian Pattern of Acute Myocardial Infection in Relation to Drug Therapy

Subgroups " "	**1-6 Hours** **34**	**6-12 Hours** **83**	**12-18 Hours** **28**	**18-24 Hourse** **57**	**Total** **202**
Beta-blockers Calcium	10	8	6	6	30
Blockers	2	2	2	6	12
ACE-inhibitor	4	4	-	6	14
Fish oil Coenzyme	5	2	-	2	9
Q10	8	2	12	4	26
No Drug Therapy	(4.3)	64(54.7)**	10(8.5)	37(31.6)**	117
Drug Therapy Total	29(34.1)*	19(22.3)	18(21.2)	20(23.5)	85

Values are number (%) out of totals * = P<0.05, **P=P<0.01m O value were obtained by comparison of sub-groups by Chi square test.

acrophases of circadian rhythms in different cardiovascular conditions [35] Tables (**4**-**8**).

PATHOGENESIS

Circadian rhythms affect many physiological and biochemical parameters; the early morning hours are associated with rises in plasma catecholamines and cortisol and increases in platelet aggregability. At this time, sympathetic activation is thought to disrupt atherosclerotic plaque through coronay vasoconstriction and an increase in blood pressure. In addition, early morning changes in hemostatic activity may lead to thrombosis. In contrast, sleep may be protective, both because of the absence of external triggers and the decline in sympathetic activity during non–rapid eye movement (REM) sleep, which accounts for about 80% of total sleep time. However, about 20% of myocardial infarctions occur between midnight and 6 AM. REM sleep, which is characterized by sympathetic surges, might be involved—as it is in vasospastic angina but REM sleep constitutes less than 20% of total sleep time in adults [36]. The pathogenesis of nocturnal myocardial infarctions may differ from those that occur during the daytime, since they may not be related to sympathetic activation or triggering events. Other sleep-induced cardiovascular changes that affect the coronary circulation or cardiac function may be involved. For example, sleep-induced variations in flow patterns in coronary arteries might be involved, or shifts in blood volume might affect the dimensions and hemodynamic function of the right ventricle [37, 38].

Table 5. Clinical Characteristics of Subjects in Patients with Heart Attack

	Acute Myocardial Infarction (n=54)	**Controls (n=85)**
Sex- males	45 (83.3)	76(89.4)
Mean age (years)	49.5± 4.2	52.1± 5.2
Body mass index (kg/m2)	23.7± 3.2	22.4±3.4
Hypertension (>140/90 mmhg)	25(46.3)*	25(29.4)
Glucose intolerance	12(22.2)*	10(11.8)
Diabetes mellitus	14(25.9)	--
Smoking	24(44.4)*	28(32.9)
Higher transfattyacids (>5g/day) Large meals(>1000 Kcal) Large breakfast(>1000 Kcal)	27(50.0)** 27(50.0)** 22(40.7)**	-- 25(29.4) 10(11.8)

*=P <0.05 P value was obtained by z score test for proportions by comparison of two groups.Values are number (%) and mean(Standard deviation), **=P<0.02.

CIRCADIAN VARIATION IN THE BIOLOGY OF PLAQUE DISRUPTION

Pathological studies have revealed that plaque rupture is one of the major causes of AMI. One large-scale multicenter study has demonstrated that AMI is 1.28 times more likely to begin between 6:00 A.M. and 12:00 P.M. than during the other three 6-hour intervals of the day. Pathologic studies have revealed that plaque rupture and subsequent thrombosis is one of the major causes of AMI. Therefore, the hypothesis that increased physiological and stressful activities in the morning hours may trigger plaque disruption has been proposed [39]. Tanaqa *et al.*, demonstrated that in the plaque rupture group, a morning increase (6:00 A.M. to 12.00 noon) was observed, whereas in the non-rupture group there was a nocturnal nadir (from 12 to 6:00 A.M) and no significant morning increase was detected. About 53% of the patients in

Table 6. Circadian Rhythm of Cardiac Events in Patients with Acute Myocardial Infarction

Quarters of the Day	**Number of Subjects (%)**
1-6 Hours	10(18.5)
6-12 Hours	20(40.7)**
12-18 Hours	7(12.9)
18-24 Hours	15(27.7)*

*=P <0.05, **=P>0.02, P value was obtained by Z score test for proportions.

Table 7. Laboratory Data in Patients with Acute Myocardial Infarction at Baseline and after 4 Weeks in Relation to Meal Size

Data	Large Breakfast,n=22)		Small Breakfast,n=32)	
	Baseline	**After4 Weeks**	**Baseline**	**After 4 Weeks**
Lipoprotein(a)mg/dl	23.1±5.4	20.1±4.2*	22.5+4.6	19.7+4.1*
Triglycerides (mmol/L)	1.88±0.61	1.70±0.38*	1.81+0.60	1.64+0.32*
Bloodglucose(mmol/l	7.7±1.6	6.0±1.2*	6.6+1.4*	5.5+0.30*
Plasma insulin(mg/dl)	47.5+11.3	36.3+5.6**	43.2+8.8*	27.6+3.5*
TBARS(pmol/l)	1.87+0.46	1.32+0.33*	1.77+0.42	1.30+0.31*
MDA(pmol/l)	2.68+0.34	2.02+0.21*	2.66+0.33	2.01+0.21*
Dieneconjugate(OD)	27.5+4.2	24.6+4.0*	26.2+4.1	24.2+3.5*
CoenzymeQ10(ug/m)	0.21+0.02	0.32+0.23*	0.23+0.03	0.45+0.24*
Interleukin-6(pg/ml)	32.6+6.2	22.5+4.3*	27.5+5.2*	20.6+0.22*
TNF-alpha(ug/dl)	42.5+12.8	23.6+4.1*	38.2+10.6*	19.6+0.18*

* = P < 0.05,**=P<0.002, TNF=Tumour necrosis factor,MDA=malonaldehyde.

Table 8. Circadian Distribution of Cases in Relation to 4 Hourly Period

Periods	Men	Women	Total
0-4 hours	6(3.7)	2(4.7)	8(3.9)
4-8 hours	58(36.2)*	22(51.7)*	80(39.6)*
8-12 hours	25(15.6)	4(9.4)	29(14.3)
12-16 hours	8(5.0)	---------	8(3.9)
16-20 hours	40(25.2)*	10(23.5)*	50(24.7)*
20-24 hours	23(14.3)	4(9.4)	27(13.3)

Values are numbers (%) *=P<0.05 P values are obtained by comparison of subjects in various sub groups of periods.

the non-rupture group had pre-infarction angina and only 31% of patients had an AMI at rest. This circadian pattern was not detectable in non-rupture group. This morning increase in the incidence of plaque rupture accounts for the characteristic circadian rhythm of AMI [40]. Various physiological studies have highlighted the fact that systemic physiologic processes increase in intensity in the morning, such as an arterial pressure surge accompanied by an increase in heart rate [41] and increased vascular tone [42]. Serum cortisol concentrations also decrease during the period of increased plaque disruption, because the Japanese population of patients with AMI compared with Caucasians shows a higher incidence of spasm and greater vaso-constriction of non-spastic segments after acetylcholine [43]. This decrease in serum cortisol concentrations could enhance the sensitivity of the coronary arteries to the vasoconstrictive effects of catecholamines. Such physiologic alterations may, alone or in combination, account for the morning increase in plaque rupture. When plaque rupture occurs, the contents of the lipid core that form the most thrombogenic components of the plaque may be released into the lumen and precipitate a cascade that produces thrombosis. Increased platelet activity, increased blood viscosity, and the minimal level of fibrinolytic activity may further contribute to thrombosis in this setting during the morning hours. These physiological variations may play an etiologic role in plaque disruption and resultant thrombosis because, efficacy of β blockers and aspirin in preventing AMI indirectly lends support to this idea [31]. Several studies have shown that in many instances, MI may occur without any obvious precipitating events and may occur at rest. Grines *et al*., [44] reported that one independent predictor of a higher frequency of onset during the morning hours was the absence of a history of angina.

Q-WAVE VERSUS NON-Q WAVE MYOCARDIAL INFARCTION

There is evidence that both AMI types show a non-uniform daily distribution of onset with a night nadir (0 to 4 A.M.), and Q-wave AMI also showed a late morning peak (8 A.M. to noon) [45]. The study demonstrated that wakeful patients with Q-wave infarction were more likely to have AMI onset in the presence of a possible external trigger than

those with non–Q-wave AMI. It is consistent with the hypothesis that powerful hemodynamic stresses may produce more extensive plaque rupture, often leading to complete occlusion of the coronary lumen and Q-wave infarction. Non–Q-wave infarction is more likely to result from a shorter occlusion of a major coronary artery, with earlier and more frequent reopening than from firm occlusion of a small branch. An acceptable explanation of a diverse circadian pattern in 2 AMI types, with late morning peak only in Q-wave AMI, is that, hemodynamic, prothrombotic, and vasoconstrictive forces resulting from a morning rise in sympathetic activity and cortisol concentrations contribute to the formation of sustained coronary occlusion and Q-wave infarction. A lower incidence of both infarction types during the early morning hours corresponds to the time when most patients would be expected to be asleep, so hemodynamic and other triggering forces may be reduced in patients with both types of AMI.

It is possible that pain at different body areas and other relevant symptoms more frequently follow Q-wave infarction. Both sympathetic and vagal afferent fibers can transmit cardiac pain to remote body areas due to convergence of visceral and somatic fibers on the same neurons within the central nervous system. Accordingly, a greater area of myocardial damage and more extensive stimulation of afferent fibers could induce pain sensation in a greater number of somatic regions and cause a higher frequency of other symptoms in patients with Q-wave AMI. Study also demonstrated that dyspnea was more associated with non–Q-wave infarction [36]. A similar frequency of pulmonary congestion in 2 AMI type subsets, even in the presence of lower left ventricular ejection fraction among patients with Q-wave infarction, has been attributed to acute transient myocardial ischemia associated with non–Q-wave infarction, whereas irreversible ischemia could be the dominant mechanism of ventricular dysfunction in patients with Q-wave AMI [46].

CIRCADIAN PERIODICITY AND THE SITE OF MYOCARDIAL INFARCTION

Moruzzi P and colleagues [36] demonstrated that 55% of the infarctions were anterior or anterolateral and 45% were inferior, including posterior or involving right ventricle. They found that there was a slight peak in the incidence of myocardial infarction between 6 AM and noon. Anterior infarctions were more common from 6 AM to midnight, whereas inferior infarctions were more common between midnight and 6 AM.

Coronary involvement varied by the time of symptom onset among patients with inferior infarctions: right coronary artery involvement was much more common than left circumflex artery involvement among those with symptom onset from midnight to 6 AM. Among those with right coronary artery involvement, the proximal segment was more common as the site of the culprit lesion between midnight and 6 AM than between 6 AM and midnight. The right coronary artery, which maintains its large caliber down to the crux, is characterized by slow flow velocity [46-48]. It is possible that, by decreasing the pressure gradient across a coronary artery stenosis, sleep-induced reduction in aortic pressure increases distal stasis, thereby facilitating thrombosis. This may be more of a problem in the right coronary artery than in the left coronary artery because the pressure gradient is inversely related to the fourth power of the minimum lumen diameter [36]. If the rhythmic biochemical mechanisms, that drive the circadian rhythm of myocardial-infarction onset can be identified, their modification may delay or prevent the occurrence of infarction.

CIRCADIAN PERIODICITY AND SUDDEN CARDIAC DEATH

Sudden cardiac death (SCD) is natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms, in a person with or without known preexisting heart disease, but in whom the time and mode of death are unexpected. The worldwide incidence of SCD is difficult to estimate but estimates for United States range from 300,000 to nearly 400,000 SCDs annually [49].

Biologic functions of mammals vary according to a circadian rhythm of about 24 hours which is governed by the hypothalamus. These rhythms can be altered by disease and the actions of drugs can be affected by the time of day at which they are administered. Several important physiological parameters such as heart rate, blood pressure, vascular reactivity, cardiac contractility, and various hemostatic factors all demonstrate a circadian pattern similar to that described for cardiovascular disorders. Circadian patterns have been observed for several supraventricular arrhythmias, premature ventricular beats, ventricular tachycardias including sudden cardiac death [50].

Sudden cardiac death has a circadian pattern, with the peak incidence occurring from 7 to 11 A.M. [51], from 7 to 9 A.M., with more sudden cardiac deaths occurring between 6 A.M. and 12 noon than during the other quarters of the day [52]: from 9 A.M. to 12 noon [53], and from 6 A.M. to 12 noon [54]. A study by Aronow *et al.*, [55] showed that there was a circadian pattern in the number of deaths per hour in patients with congestive heart failure after prior myocardial infarction. The primary peak occurred between 6 A.M. and 12 noon, with 39% of deaths occurring in that 6-hour period.

Flack and Yunis [56] indicate that the morning peak from 6 am to 12 noon of such occurrences as MI, thrombotic stroke, transient myocardial ischemia, and SCD is due to the high levels of coronary vasomotor tone, plasma catecholamines, and platelet aggregability, and the low levels of coronary blood flow and plasma fibrinolytic activity. At this same time, there is a rapid increase in blood pressure during the early morning hours. He also feels that it is important to maintain control of blood pressure throughout the early morning to try to avoid adverse events. A study in Auckland, New Zealand, by Van der Palen *et al.*, [57] had some slightly different findings on circadian rhythm. They report an afternoon peak in SCD (32.5%) and a secondary morning peak (27.6%). Also, they found a Saturday high (18.6%) for SCD. Peckova and colleagues [49] showed a similar pattern of cardiac arrest: a low incidence at night, a sharp increase between 8 AM and noon with peaking at '10 a.m., a relatively high incidence during the day, and another

peak between 5 and 8 a.m. Both morning and evening peaks were of a similar magnitude. Young patients had a relatively higher incidence at night than older patients and also exhibited a higher incidence in the morning than in the evening. Patients in the age category 41 to 65 years had a higher evening peak. Elderly patients maintained a rather high incidence during the daytime hours, with less pronounced peaks.

MECHANISMS UNDERLYING SUDDEN CARDIAC DEATH

In a study on chronomic approach to SCD, circadian and circaannual components were also observed [58]. The non-photic components were also associated with SCD [59]. Cardiac arrest occurs due to a acute precipitating trigger and the chronic electrical instability of the myocardium. It may have either a cardiac or a non-cardiac etiology and may present with a variety of arrhythmias, including ventricular tachycardia, ventricular fibrillation, asystole, and electro-mechanical dissociation. The likelihood of a "sudden death" episode occurring and being witnessed is not constant throughout the day. A few studies [60, 61] observed that there were three major time periods when a cardiac arrest was most likely to occur—an *early* peak in the morning around 1100 hours, a *late* peak in the evening around 2200 hours, and, for those whose arrest was from a cardiac disease, a third time period—around 1600 hours—also seemed to be critical. In Seattle [62] and Berlin [63], the most important times for a cardiac arrest seemed to be around 1000 and 1800 hours. Ventricular fibrillation was most frequent around 2000 hours in the series by Peckova *et al*. [60, 64], while Arntz and associates found that ventricular fibrillation occurred most often around 1000 hours, with the exception of ventricular fibrillation, the circadian variation of the arrest rhythm in both cardiac and non-cardiac groups appeared to be identical. The triggers for a cardiac arrest in both groups are likely to be similar when the arrhythmia is something other than ventricular fibrillation, irrespective of the etiology of arrest [65]. It is possible that association of size of meals with occurrence of SCD of two peaks in a day should have been examined in these studies to find out if large meals can explain this controversy [16, 17].

There may be multifactorial mechanisms underlying sudden cardiac death probably and in some patients, primarily electrical factors or an interaction between electrical abnormalities and myocardial ischemia may be responsible for sudden cardiac death. Ambulatory recordings at the moment of sudden death have shown that ventricular tachycardia degenerating into ventricular fibrillation is a common terminal rhythm and often occurs in the absence of antecedent ischemic ST segment shifts [66]. In addition, the frequency of complex ventricular ectopy and the occurrence of sustained monomorphic ventricular tachycardia as well as ventricular asystole also are greatest in the early morning hours when the incidence of sudden death is greatest. Thus, a circadian variation in cardiac electrophysiological parameters may be an alternate mechanism contributing to the circadian variation in sudden death [67]. The distribution of ventricular fibrillation events followed the general pattern except that the evening peak is substantially higher than the morning peak. Peckova and colleagues [60] suggest the evening peak to be of approximately the same magnitude as the morning peak of incidence. They found that the bimodal pattern is mainly an attribute of ventricular fibrillation and that patients with asystole or pulseless electrical activity have a less pronounced evening peak. There was no difference in circadian variation between sexes, races, or days of the week. The analysis suggested that differences between the age categories are probably explicable by different rhythm distributions and thus are more likely due to sociodemographic factors than to biological differences.

CIRCADIAN PERIODICITY AND REFRACTORINESS

The variability in the time of onset of ventricular fibrillation appears to be main cause for circadian variation in the incidence of sudden cardiac death [64]. The triggers may also have independent influence on such variations [11-18]. Evidence has provided confirmation of the traditional hypothesis that ventricular fibrillation is due to multiple functional reentrant circuits, which change over time [65, 66]. Shorter refractory periods promote reentry by allowing reentrant circuits to be maintained in a smaller mass of tissue and by decreasing the length of lines of block, leading to the variability in reentry observed during ventricular fibrillation. Experimental studies also have demonstrated that shortening of refractory periods under a variety of conditions may be proarrhythmic [67]. In the present study [67], maximal shortening between hourly refractory periods as well as the shortest absolute refractory periods were observed around the hour of waking, raising the possibility of a close relation between these findings and the increased morning incidence of arrhythmic sudden death. Although not measured in this study, an increased dispersion of refractoriness, which has been shown to promote ventricular arrhythmias [68], might be expected when overall ventricular refractoriness is rapidly changing. The circadian variation in refractory periods may be associated with a circadian variation in other electrophysiological properties, such as conduction velocity, which also may promote the emergence of reentrant circuits and arrhythmias. Fluctuations in sympathetic tone are mainly responsible for temporal changes in ventricular refractoriness [64]. There is evidence that acute cardiac events are temporally linked to waking [69]. In the Physicians' Health Study [70], 25% of myocardial infarctions occurred within 3 hours of waking, and the relative risk of infarction during this time interval was almost twice that during any other 3-hour period during the day. In another study [64], the most pronounced changes in ventricular refractoriness were also more closely linked to the hour of waking than to the absolute time of day. Results of the study therefore suggest that the time around waking is characterized by marked electrophysiological changes and possibly an increased vulnerability to arrhythmias which may due to disturbance in the chronocardiovascular dysfunction under influence of environmental factors like geomagnetic forces.

CIRCADIAN PERIODICITY AND REPOLARIZATION

The QT interval as measured on the surface electro-cardiogram (ECG) reflects global ventricular myocardial repolarization [71]. It has been found to be longest during sleep and shortest during the waking hours. However, the relevance of these observations to a potential circadian

variation in ventricular refractoriness is not completely clear because the refractory period and action potential duration (as reflected globally by the QT interval) may be dissociated in some situations [72, 73]. A circadian variation in the QT interval has been described previously [72] and has been attributed to a circadian variation in ventricular repolarization. In addition, evaluation of the QT interval at different times of the day requires a correction for heart rate, which could limit the accuracy of the analysis of circadian changes in the QT interval. Finally, unlike refractory periods that were generally reproducible to within 4 ms with the methodology used in the study by Kong *et al*. [64], estimation of the QT interval may be somewhat less reproducible. Despite these potential differences, the results of the study suggest that the circadian periodicity in ventricular refractoriness qualitatively parallels the previously described circadian variation in the QT interval. Yi *et al*., [73] examined circadian variation of the QT interval in post MI patients and normal controls and its relation to SCD. They found the SCD victims did not show a significantly longer QT interval at night when compared to day as the normal subjects and MI survivors did, and the SCD victims did show a significantly longer QTc averaged over 24 hours. Thus, the circadian variation of the QT interval did vary when compared to normal subjects and those who survived the year following a MI.

SERUM POTASSIUM, MAGNESIUM AND PLASMA CATECHOLAMINE LEVELS

We observed a low levels of magnesium and potassium as well as coenzyme Q10, vitamine E and C and higher levels of thiobarbituric acid reactive substances(TBARS) and melondialdehyde(MDA), that are indicators of oxidative damage, in the second quarter of the day compared to evening values [7, 16, 17] Table **9**. Kong *et al*., [64] demonstrated a significant circadian variation in mean serum potassium levels, with the highest levels observed during the waking hours and the lowest levels during sleep. In eight of nine subjects, the minimum potassium levels were observed between the hours of 1:00 AM and 4:00 AM; the ninth subject had a minimum level at 2:00 PM. A significant circadian periodicity was also observed in mean levels of plasma epinephrine and norepinephrine. Mean levels of each were highest during the day and lowest during sleep. A single harmonic model with a peak at 3:00 PM provided the best fit for epinephrine levels, and a double harmonic model with peaks at 9:00 AM and 9:00 PM provided the best fit for norepinephrine levels.

Some of the circadian variability in the incidence of sudden death may be due to a morning increase in myocardial ischemia [74-77]. However, ischemic events do not account for all instances of sudden cardiac death, as autopsy studies of sudden death victims have failed to demonstrate acute coronary lesions in up to 42% of cases [78]. Furthermore, the occurrence of sustained monomorphic ventricular tachycardia, which is not generally a consequence of acute ischemia [79], also demonstrates a substantial variation [80]. Therefore, a circadian variation in cardiac electrophysiological parameters could potentially contribute to the increased morning incidence of sudden cardiac death.

CIRCADIAN PERIODICITY AND STROKE

There is a specific temporal pattern for onset of stroke [81-90], characterized by a higher frequency in winter and in the mornings. Stroke is classified in a heterogeneous group of vascular diseases, unlike myocardial ischemia, with different etiopathogenic mechanisms. Arterial pressure, and other factors, may play an important role, favoring an increase in morning stroke onset. But these same factors, such as lower arterial pressure and heart rate during the night may contribute, through a hemodynamic mechanism, to a stroke onset during the sleeping hours, particularly in thrombotic stroke. Results of study by Lago *et al*., [90] show that thrombotic and lacunar strokes have a higher onset during sleeping hours when compared with embolic stroke, circadian rhythm of arterial blood pressure could be disturbed in patients who have suffered from stroke. According to a meta-analysis of more than 11,000 patients, an estimated 37% of strokes occurred during morning hours [82]. A circaseptan rhythm, with a significant peak on Monday was observed for all strokes and for ischemic strokes. Data from a Norwegian study [83] suggested that

Table 9. Biochemical Data in Patient with Acute Myocardial Infarction Compared to Healthy Subject

Data	Healthy Subjects (n=595)	Acute Myocardial Infarction (n-202)
Serum magnesium (m EQ/L)	1.64(0.25)	1.51(0.23)*
Serum potassium (m EQ/L)	4.3(0.96)	3.7(0.82)*
Vitamin C (mmol/l)	37.5(6.8)	18.6(4.3)*
Vitamin E(mmol/l)	20.1(3.7)	14.5(2.5)*
Vitamin A(mmol/l)	2.25(0.19)	1.86(0.15)*
Interleukin-6 (pg/ml)	15.6(3.2)	30.5(5.7)*
Tumour necrosis factor-alpha (pg/dl)	18.8(4.5)	41.6(8.4)*
Insulin (mg/dl)	17.6(4.2)	48.8(12.8)*

*=P<0.05, Values are mean (Standard deviation).

biochemical factors associated with cardiovascular risk—such as measures of hematosis and carbohydrate and lipid metabolism—were less favorable on Mondays compared with other days of the week. Thus, similar to the association between increased thrombophilia in the mornings [84] and the circadian pattern of other thrombotic disease such as myocardial infarction [85] and limb ischemia [86], the Monday risk of ischemic stroke may reflect an increased thrombogenic condition [87] which may worsen due to heavy breakfast.

The cause of circadian periodicity of stroke has been related to the circadian rhythm of fibrinolysis, platelet aggregability [88] and mainly, arterial blood pressure, with its minimum value during sleep and maximum value in the early hours in the morning, in both normotensive and hypertensive patients [89]. However, it has been suggested that an increase in morning stroke onset could be due to patients awakening with neurological deficits as a result of a stroke that could have occurred during the night [90]. Lago *et al*., [90] found a higher frequency of stroke during the day and a lower frequency between 6:01 PM and 12:00 midnight, obvious in all the different types of ischemic stroke viz. lacunar, thrombotic, embolic stroke. Circadian and circaseptan variations in the onset in stroke incidence have been reported by Halberg group in relation to circadian hyperamplitude tension [91, 92]. In acute myocardial ischemia, the time of onset is easily determined [93, 94] corresponding with the onset of thoracic pain and does not occur when the patient with ischemic stroke is discovered on awakening; the onset may have occurred at any time during sleep. Unfortunately, at present there is no marker that indicates the time of stroke onset.

The risk of stroke is directly related to elevations of blood pressure. Jain *et al*., [95] showed a pathologically reduced or abolished circadian BP variation after stroke. Absence of normal dipping results in a higher 24 hour blood pressure load and may have more target organ damage than those with normal diurnal variation of blood pressure. Epidemiology of acute stroke is different in developing countries from that in developed world. The age at stroke, risk factors, subtypes of stroke and prognosis are different in developing countries. In India, ischemic strokes constitute 70-75% while hemorrhagic strokes account for 20-25% of total cases [95]. However, hypertension remains a dominant risk factor and prognostic indicator in patients with stroke in all communities.

The accurate measurement of blood pressure after an acute stroke is important because antihypertensive therapy may be considered in some patients. However, blood pressure may be falsely elevated or depressed immediately after a stroke depending on the level of consciousness, severity of neurological deficit and physical activity.

The normal diurnal variation in blood pressure i.e. night time dipping was abolished in 88% patients in study by Jain and colleagues [95]. This non-dipping was seen equally in both hemorrhagic and ischemic subgroups without any statistically significant difference.

In studies of patients with stroke, abnormal pattern of circadian rhythm of blood pressure using ambulatory blood pressure monitoring (ABPM) has been reported [96-99]. The circadian amplitude-acrophase pair works better than the day night ratio. In a study, Dawson *et al*., [99] found a significant reduction in diurnal variation in systolic blood pressure in cortical infarct and intracerebral hemorrhage subgroups, compared with control subjects. The subcortical infarct subgroup demonstrated only minimal reduction in normal circadian variation. Fujishima *et al*., [100] reported that blood pressure was elevated in the acute phase of a single lacunar infarction and it declined with time. No night time fall was noted in acute phase, but the circadian periodicity in blood pressure normalized in the subacute and chronic phase of stroke.

CONTROVERSIES IN THE CIRCADIAN PERIODICITY OF STROKE

Early studies of the timing of acute stroke, indicated that many afflicted patients reported awakening with new neurologic deficits, and several reports indicated that acute strokes tended to occur either during the evening hours or during sleep which were contradicted in later studies [101-104]. The highest risk is found between 8:01 a.m. and noon; the lowest is found between midnight and 4 a.m. Because there are some reports from Japan [103], especially regarding hemorrhagic stroke [104], which suggest that there may be differences in circadian variation of stroke timing according to the subtype of stroke of interest, meta-analyses of ischemic and hemorrhagic stroke (including subarachnoid and intracerebral bleeds), and transient ischemic attack were also carried out. Results of the study by Elliott WJ and colleagues [102] suggest that for each subtype of stroke studied, there is an increase in risk during the early morning hours. The data are remarkably consistent across the various subtypes of stroke, and indicate, for ischemic stroke, hemorrhagic stroke, and even transient ischemic attacks, that the excess risk during the 6 a.m. to noon time period is significantly higher than would be expected by chance: 89%, 52%, and 80%. Similarly, there was a significantly lower risk of stroke during the nighttime hours (midnight to 6 a.m.) for each stroke subtype: 30%, 54%, and 81%.

The finding that the early morning hours (and not the nighttime hours) have the highest risk of the onset of stroke symptoms has two broad implications. The first is that patients should no longer be told that stroke symptoms are not a medical emergency. Although this may have been sound public policy when acute treatments for stroke were not available, there is now some evidence that acute emergent treatments for cerebral ischemia can be delivered in a timely fashion and result in improved long-term outcomes. Meta-analysis indicates that irrespective of the type of stroke, most patients will be awake when the onset of stroke symptoms occurs. The recognition of new neurologic deficits should prompt afflicted patients and their families to consider these as a medical emergency (or “brain attack”). The second implication has to do with some modalities useful in stroke prevention. Blood pressure is often considered one of the most powerful risk factors for stroke and has a circadian variation that essentially parallels the circadian variation in stroke onset. Antihypertensive agents administered in the morning ought to have a long duration of action to still have an effect on the early morning rise in blood pressure. It is tempting to speculate that

antihypertensive agents that specifically target the early morning rise in blood pressure and heart rate, without reducing blood pressure severely during the night, might be more advantageous in controlling the 20% rise in blood pressure during the hours around awakening. This appears also to be the time of day associated with an increased risk of stroke, myocardial infarction, and sudden cardiac death [102]. It is possible that eating dinner rich in protective nutrients that can modulate vascular biology and increase blood pressure may be protective in the morning against stroke. There is evidence that CHAT carries several fold greater risk of stroke than MESOR hypertension [91, 92]. A recent study showed that increased intake of alphalinolenic acid by eating 50-10g/day of walnuts can inhibit CHAT and decrease blood pressures. In this case nuts (50-60g/day) were given while continuing exercise and pranayama regularly. After about 8 weeks, in March first week 2010, his blood pressure record by mercury manometer showed decrease in mean systolic and diastolic blood pressures but blood pressures were on the higher side of normal range. These changes in blood pressures were associated with body weight 70.3 Kg, waist circumference 96 cm, blood pressure by mercury manometer 130/85 mm Hg, pulse rate 80 min. On March 29, his blood pressures record showed 128 mm Hg systolic and 75 mm Hg diastolic blood pressures recorded by mercury manometer as well as by automatic blood pressure instrument. His physical activity and pranayam breathing were continued twice daily without change, with increased consumption of fruits, vegetable (450g/day) including nuts (56g/day), whole grains and legumes (350g/day), lower intake of refined carbohydrates (150g/day). Visible fat intake (25-35g/day) and salt intake (5-6g/day) were similar during the last 6 months of the follow up. It is clear that one most significant change in the food consumption pattern was that the nuts intake was doubled and the increase was mainly in the walnuts. The consumption of alpha-linolenic acid which is rich in walnuts, whole grains, leafy vegetables and mustered oil increased from 1.2g/day to 2.6g/day, as assessed by 3 days food intake records and with the help of nutrient composition of Indian foods tables. There was a significant decrease in blood pressures and reversal of CHAT to normal blood pressures [105].

CIRCADIAN PERIODICITY OF BRAIN HEMORRHAGE

The occurrence of cerebral infarction has been reported to vary with the time of day; cerebrovascular ischemic events predominantly occur in the early morning and late afternoon [91,101,106-109]. Subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) are associated with a high morbidity and mortality, and they represent about 20% of all strokes [106]. Seasonal variation in the incidence of this disorder also has been detected, the peak occurrence being in the winter and autumn [110]. The occurrence of SAH in individuals with a history of hypertension has been reported to vary also with time of day [110-113]. Nyquist *et al*., [110] reported that the occurrence of ICH and SAH combined was increased during the winter. However, when the hemorrhage subtypes were evaluated, the main trend for seasonal differences was noted in SAH but not in ICH.

The circadian variation of blood pressure seems to mirror the time of onset of hemorrhagic stroke in that daily increases in blood pressure occur in the morning and early afternoon and lower levels occur at night [101, 112, 114]. Some investigators have hypothesized that this increase in blood pressure may be responsible for the increase in hemorrhagic stroke frequency in the early morning and afternoon. In addition, others have noted that normotensive individuals who experience SAH or ICH may have a late-afternoon locus of onset instead of an early morning locus of onset [112]. Other authors have suggested that the occurrence of SAH and ICH during the working hours may suggest an activity precipitant for SAH or ICH [115]. Factors that might contribute to an increased risk during the winter are uncertain. However, cardiovascular stresses occur during the winter, particularly in climates with extremes of seasonal climate, which may result in fluctuations in blood pressure, blood coagulability, and cardiovascular performance. These stresses include deconditioning, stress of physical activity in temperature extremes, types of activity required in a cold climate, and more specific effects of abrupt temperature changes and temperature extremes on the blood pressure and vascular system. Inflammatory factors such as cytokine levels and cortisol levels fluctuate with circadian and circannual rhythmicity. These factors may play a role in priming the vasculature to respond in a manner predisposing the endothelium to rupture [110].

CIRCADIAN PERIODICITY AND TRANSIENT ISCHEMIC ATTACK

A metaanalysis of 31 publications reporting the circadian timing of 11 816 strokes found a 49% increase in stroke of all types between 06 00 and 12 00 [116]. Possible explanations for the circadian pattern of cerebrovascular events have focused on circadian or postural changes in platelet aggregation, thrombolysis, blood pressure, heart rate, and catecholamine concentrations that occur after awakening with resumption of physical and mental activities. In a minority of cases, which varies in the literature from less than 10% to as much as 44%, stroke occurs at night [101,107,116]. This suggests that sleep, although "protective" for most cerebrovascular events, may represent a vulnerable state for a subset of patients at risk for stroke. Nocturnal blood pressure swings, cardiac arrhythmias, and sleep disordered breathing have been suggested as possible explanations for the nocturnal onset of stroke. Not only acute ischemic stroke but also transient schaemic attack have a circadian pattern with a peak of onset between 0600 and 1200 and about 20% of events occurring at night time [117-119]. Furthermore, it is shown for the first time that patients with daytime and night time onset of transient ischemic attack/stroke are similar in most cardiovascular risk factors; clinical and polysomnographic sleep characteristics; and stroke parameters. Findings by Bassetti *et al*., [120] suggests that low diastolic blood pressure values may predispose to night time onset of cerebrovascular events enhancing the sleep related fall in blood pressure.

Sleep apnoea, while being a risk factor for stroke [121-125], may only rarely represent the immediate cause of transient ischemic attack or stroke. Rather, respiratory events during sleep may cause haemodynamic and haematological changes which increase the risk of cerebrovascular events at the transition from sleep to wakefulness and during the subsequent few hours.Sleep disordered breathing is present

in about 50% of patients with acute cerebrovascular diseases [121,122]. It is nevertheless conceivable that in a patient with severe sleep apnoea swings in blood pressure, decreased cerebral blood flow, and cardiac arrhythmias produced by respiratory events may trigger cardiovascular and cerebrovascular events during sleep [120]. In a study of 1233 patients [90], it was reported a higher frequency of all types of stroke during the day and a higher night time onset in macroangiopathy and microangiopathy compared with other stroke subtypes. Macroangiopathic and micro-angiopathic strokes may be particularly susceptible to nocturnal haemodynamic changes and decreased cerebral perfusion. Although yet to be proved, it is possible that intrathoracic pressure variations related to sleep apnoea may also predispose to cardioembolic strokes secondary to right-left shunt (for example, patent foramen ovale). Bassetti *et al*. [121] have thus proven that night time and daytime transient ischemic attack/ stroke are similar in sleep and stroke characteristics, and [94, 95] diastolic hypotension may predispose to night time cerebrovascular events.

CHRONO-PHARMACOTHERAPY AND CHRONO-KINETICS

The concept of homeostasis in biology postulates that there is constancy of the intern milieu. Thus is assumed the risk and exacerbation of disease are invariable and independent of the time of day, day of month, and month of year as are the responses of patients to diagnostic tests and medications. Findings from the field of chronobiology, the study of biological rhythms, challenge the concept of homeostasis and the many assumptions and procedures of clinical medicine based on it. It is now recognized that human functions have daily, weekly, monthly and yearly biological rhythms. Plants, animals, and insects also have chronobiological rhythms. Circadian patterns have been observed for variety of cardiovascular disorders, including cardiac arrhythmias, sudden cardiac death, cerebrovascular events, episodes of stable angina, unstable angina and acute myocardial infarction. The morning predominance of these events has been well documented in a number of large population studies. It is now recognized that circadian and other rhythms of the gastrointestinal tract and vital organs are capable of significantly affecting the pharmacokinetics and dynamics of cardiovascular and other medications. This means that the effects of therapeutic interventions administered in identical doses in the morning versus the evening may not be equivalent. The prevention and treatment of cardiovascular disease must take into account chronobiological factors [125].

CHRONOTHERAPEUTICS AND CHRONOKINETICS

Chronotherapeutics is the delivery of interventional or otherwise treatment in levels that match the body's changing needs at certain times of day or night. Chronotherapy links the effects of a disease to time, and the timing of treatment delivery. The main objective of chronotherapy for heart disease would be to deliver needed drugs in higher concentrations during the time they are needed the most (early morning after-waking period); and at reduced drug levels when the need is less (during the middle of the sleep cycle) [126]. Although, the agent may be highly bioavailable in the blood at a particular time of the day however, the bioactivity of the agent may be highest at different time when the drug level is lower which is dependent on the chronokinetics of the agent. The goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed [127].

Many drugs or nutraceuticals, display normal, reproducible daily variations in pharmacokinetics and pharmacodynamics. Lemmer identified more than 100 drugs that display significant variation in concentrations or effects, or both, over 24 hours. Perhaps the best example is heparin. Even when it is administered at a constant infusion rate, the activated partial thromboplastin time and the risk of bleeding vary significantly according to the hour of the day and are higher at night [128]. The narrower the therapeutic window (i.e., risk-benefit ratio) for a specific drug, the more important is the implication of the circadian variation in plasma concentrations [124].

In selecting the most appropriate treatment for diseases that can be managed with chronotherapy, clinicians should understand that pharmacodynamic profiles of chrono-therapeutic formulations are often different from those of traditional homeostatic formulations, even when the active drug itself is the same. Such differences may have important clinical consequences. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hours, chronotherapeutic formulations may use various release mechanisms (eg, time-delay coatings, osmotic pump mechanisms, matrix systems) that provide for varying levels throughout the day [129]. Cornelissen *et al*., reanalyzed data in the Physicians study [130], and reported a 12 hour component in patients taking aspirin or placebo, the only difference being a decrease in mean in the aspirin group. A circadian stage dependent effect of low dose aspirin in relation to blood coagulation has also been observed [130, 131].

ACE-inhibitors [132] and calcium channel blockers [133], provide greater protection if given in the evening by preventing morning rise in blood pressures. The Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of alternate-day aspirin intake (325 mg) among 22,071 US male physicians, afforded the opportunity to assess this circadian pattern and examine whether it is altered by aspirin therapy. During a 5-year period of follow-up, 342 cases of nonfatal myocardial infarction were confirmed, of which the time of onset was available in 211 (62%). In the aspirin group, circadian variation was minimal, due primarily to a marked reduction in the morning peak of infarction. Specifically, aspirin was associated with a 59.3% reduction in the incidence of infarction during the morning waking hours, compared with a 34.1% reduction for the remaining hours of the day. The greater reduction was observed during the 3-hour interval immediately after awakening, a period with a risk of infarction twice that of any other comparable time interval. Aspirin intake was associated with a mean reduction in the incidence of

infarction of 44.8% over the entire 24-hour cycle. Aspirin reduces the risk of infarction by inhibiting platelet aggregation during the critical periods [134, 135]. Drugs may suppress diurnal variation, specifically beta-blockers [136, 137], antiarrhythmic drugs, and aspirin. The fact that b-blockers suppress circadian variation of myocardial infarction was already noted in several studies. If beta-blockers also suppress circadian variation of cardiac arrests, we would expect that the interval between the times of day of the two arrests would widen, because the expected difference between the arrest times if no circadian variation is present is larger than in the presence of circadian variation [137]. Cornelissen *et al*., have proposed that chronobiology predicts actual and proxy outcomes when dipping fails [138]. Dipping appears to be a protective mechanism of the body to control blood pressures in the night. Beta- blockers prevent dipping as well as morning rise in blood pressures so the total effect is beneficial. The reasons underlying the superiority of the cosinor approach are the fact that time specified references values are used that are qualified by gender and age and the fact that the day-night ratio does not take into consideration the changing waveform with age that includes a more pronounced post-prandial dip with advancing age [131].

NONPHARMACOLOGICAL TREATMENT

Nonpharmacological management of circadian rhythm with yoga, physical activity, moderate alcohol intake, functional foods such as almonds, walnuts, rape seed oil, and neutraceuticals eg coenzyme Q10and w-3 fatty acids appear to be protective against circadian rhythms of cardiovascular events. The brain is quite rich in w-3 fatty acids, hence function of certain areas of the brain, responsible for circadian rhythm and neurotransmetters release may be altered by supplementation of these agents [139-146].

The Indo-Mediterranean Diet Heart Study was a single blind randomized study that assessed the effect of a diet rich in alpha-linolenic acid, the parent n-3 fatty acid, on the occurrence of myocardial infarction and sudden cardiac death [139, 140]. One thousand subjects took part in the Indo-Mediterranean Diet Heart Study, and115 patients from both control and intervention groups had cardiac events [139]. The timing of cardiac events throughout the day was compared between the intervention and control groups. The distribution of cardiac events along the four quartiles of the day was compared between groups as well as against equal distribution. The risk ratio for a cardiac event was lowest between 4:00 and 8:00 hours in the morning for the intervention group. The control group had a higher rate of events in the second quartile of the day, which deviated from an equal distribution, as expected (P=0.013). In the intervention group events were equally distributed along the day. No statistically significant difference was found in daily event distribution between the groups. The findings indicated that a diet rich in alpha-linolenic acid may abolish the higher rate of cardiac events, normally seen in the second quartile of the day. This alteration in the circadian rhythm of cardiac events appears to be due to beneficial effects of w-3 fatty acids on brain function as well as on cardiovascular function. The beneficial effects of Mediterranean diets have also been demonstrated in the Indian Experiment of Infarct Survival [141] and the Lyon Heart Study [145, 146]. A diet comprising of low w-6/w-3 ratio of fatty acids appears to be protective, whereas a high ratio of these fatty acids in the neurons, endothelial cells, liver cells and cardiomyocytes can predispose metabolic syndrome as well as circadian rhythm of cardiovascular events [141-146].

We are indebted to Professor Franz Halberg for enlightening us with this new science of Chronocardiology, Chronoastrocardiology and Chronomics as well as with Nutrio-chronocardiology, which helps us in finding out the relation of environmental factors in general, nutrition in particular with mind-body interactions which is proposed as a Tsitm Tsoum concept by Fabien De Meester [147, 148]. In this issue of the journal, Fabien De Meester, Douglas Wilson shed further light on the Chronomics study as well as on the Tsim Tsoum concept.

However, this is not the end, Prof Franz Halberg has also demonstrated that consuming the same amount of energy as breakfast can cause decrease in weight compared to weight gain in the evening, despite similar intake of energy at breakfast and dinner [149-153].

A recent study by Arble *et al*., [153-155] provides added evidence that feeding at the "wrong time" can lead to weight gain. These recent findings on mice were extended to humans in 1973 [151], as shown on top of Fig. (**2**). As seen at the bottom of Fig. (**1**) in the mouse, the timing of food intake can contribute to the difference between death and survival, as is also documented for other agents [152]. A circadian rhythm in SBP and DBP was invariably demonstrated during each of the 12 weeks of study ($P<0.001$). As compared to the reference span, Q-Gel was associated with a reduction of the circadian double amplitude of both SBP (from 40.5 to 30.9 mm Hg; Student $t = 5.005$; $P < 0.001$) and DBP (from 24.8 to 18.5 mm Hg, Student $t = 4.725$, $P < 0.001$) (15, cf. 16). This effect was circadian stage-dependent (SBP: $P = 0.043$; DBP: $P = 0.012$), the largest reduction in circadian amplitude being associated with CoQ10 supplementation in the evening (around 14 h after awakening) A start with nutriceuticals indicates that in a person investigated by varying the administration times of Coenzyme Q10 (CoQ10), the circadian stage played an important role. If and only if the observation in this case can be extended to more subjects, CoQ10 supplementation may serve as a nutriceutical intervention to treat a circadain blood pressure overswing or CHAT, short for circadian hyper-amplitude-tension, a risk of stroke greater than a high blood pressure. Notably in the absence of MESOR-hypertension, an active nutriceutical may be preferred as anti-hypertensive medication [152-157]. Clinical trials should be set up to see whether the results obtained by this great scientist are more generally applicable. A chronobiologic design such as the one used herein is advocated so that any individual differences in response can be assessed. For so doing, the chronomically-assessed longitudinal monitoring of BP is critical. Automatic monitors can be obtained with a large reduction in price, with analyses, by participating in a project on the BIOsphere and the COSmos (BIOCOS) (by writing to corne001@umn.edu) in exchange for the data.

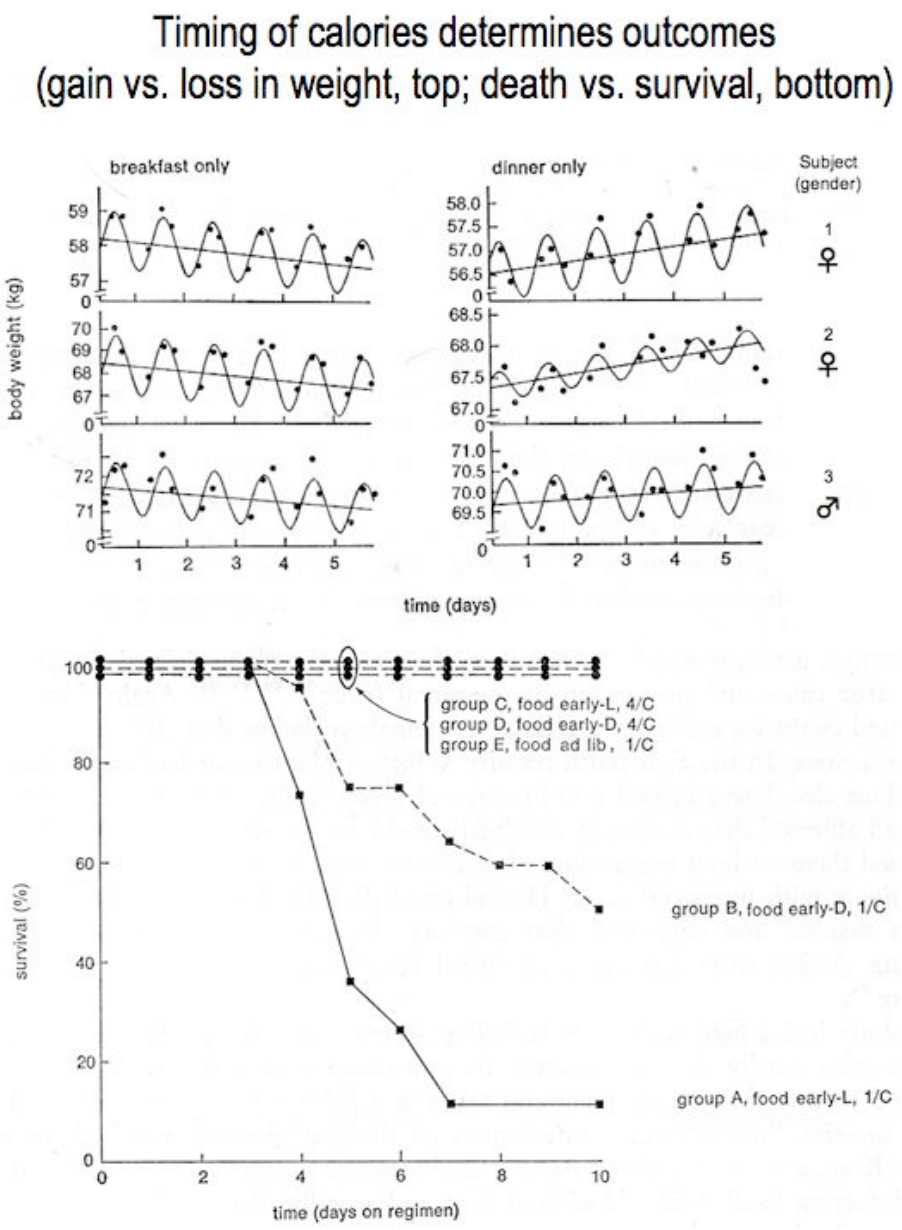

Fig. (2). Effect of feeding in the wrong time on weight gain in men and bottom on death or survival in mice.

In brief, our understanding of circadian rhythms of cardiovascular events in association with variability in other biomarkers in both normal human biologic function as well as in disease has heightened the awareness that the timing of therapeutic regimens may have an important impact on effectiveness of treatment. Outcomes in several diseases that have predictable circadian variations have been improved by matching the timing of medication use to the circadian rhythm of the illness. Cardiovascular events have a circadian rhythmicity, clustering more in the second quartile of the day. Low w-6/w-3 fatty acid diet reduces the rate of cardiac events, but its effect on their circadian rhythmicity has not been examined [158, 159]. Additional studies are needed to identify the underlying mechanism.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

Acknowledgements are due to International College of Nutrition, India; International College of Cardiology, Slovakia and The Tsim Tsoum Institute, Poland, for providing logistic support for writing this article.

REFERENCES

[1] Singh RB, Gupta A, Pella D, Circadian cardiology. World Heart J 2008; 1: 101-26.

[2] Singh, RB, Weydahl K, Otsuka K, *et al*. Can nutrition influence circadian rhythm and heart rate variability? Biomed Pharmacother 2001; 55: 115-24.

[3] Singh RB, Kartik C, Otsuka K, Pella D, Pella J. Brain-heart connection and the risk of heart attack (Editorial).Biomed Pharmacother 2002; 56: 257-65.

[4] Halberg F, Cornélissen G, Schwartzkopff O. Quovadis chronomics 2008: Measuring variability in us, among us and around us. In: Halberg F, Kenner T, Fiser B, Siegelova J, (eds.

Proceedings, Noninvasive Methods in Cardiology; October 4-7, Brno, Czech Republic, 2008; pp. 16-25.
[5] Sundararaj BI, Vasal S, Halberg F. Circannual rhythmic ovarian recrudescence in catfish, *Heteropneustes fossilis.* Int J Chronobiol 1973; 1: 362-3.
[6] Halberg F. Temporal coordination of physiologic function. Cold Spr Harb Symp quant Biol 1960; 25: 289-310.
[7] Halberg F, Gupta BD, Haus E, *et al.* Steps toward a cancer chronopolytherapy. In: Proc. XIV International Congress of Therapeutics. Montpellier, France: L'Expansion Scientifique Française 1977; pp. 151-96.
[8] Halberg F, Cornélissen G, Otsuka K, Katinas G, Schwartzkopff O. Essays on chronomics spawned by transdisciplinary chronobiology: Witness in time: Earl Elmer Bakken. Neuroendocrinol Lett 2001; 22: 359-84.
[9] Otsuka K, Cornelissen G, Halberg F.Circadian rhythms and clinical chronobiology. Biomed Pharmacother 2001; 55: 7-18.
[10] Halberg F, Stephens AN. Susceptibility to quabain and physiologic circadian periodicity. Proc Minn acad Sci 1959; 27: 139-43.
[11] Halberg F, Visscher MB. Regular diurnal physiological variation in eosinophil levels in five stocks of mice. Proc Soc Exp Biol (NY)1950; 75: 846-7.
[12] Singh RB, Niaz MA, Cornelissen G, *et al.* Circadian rhythmicity of circulating vitamin concentrations. Scripta Medica (BRONO) 2001; 74: 93-6.
[13] Eaton SB, Strassman BI, Nesse RM, *et al*. Evolutionary health promotion. Prev Med 2002; 34: 109-18.
[14] Singh RB, Reddy KK, Fedacko J, De Meester F, Wilkzynszka A, Wilson DW. Ancient concepts of nutrition and the diets in hunter-gatherers. Open Nutra J 2011; 130-5.
[15] Otsuka K, Shohgo M, Kozo M, *et al.* Chronomes,aging and disease.In: Furukawa H, Nishibuchi M, Kono Y, Kaida Y, Eds. Ecological destruction, health and development: advancing asian paradigms. Australia: Trans Pacific Press 2004; pp. 367-94.
[16] Singh RB, Pella D, Rastogi S, *et al.* Increased concentrations of lipoprotein(a),circadian rhythms,and metabolic reactants evoked by acute myocardial infarction in relation to large breakfast. Biomed Pharmacother 2004; 58: 116-22.
[17] Singh RB, Pella D, Neki NS, *et al.* Mechanism of acute myocardial infarction(MAMI) study. Biomed Pharmacother 2004; 58: 111-5.
[18] Halberg F. Chronobiology. Annu Rev Physiol 1969; 31: 675-725.
[19] Czeisler CA, Johnson MP, Duffy JF, Brown EN, Rondo JM, Kronauer RE. Exposure to bright light and darkness to treat physiologic maladaptaion to night work. N Engl J Med 1990; 18: 1253-9.
[20] Tei H, Okamura H, Shigeyoshi Y, *et al.* Circadian oscillation of a mammalian homologue of the Drosophila period gene. Nature 1997; 389: 512-6.
[21] Tofler GH, Stone PH, Maclure M, *et al*. Analysis of possible triggers of myocardial infarction (The MILIS Study). Am J Cardiol 1990; 66: 22-7.
[22] Willich SN, Loewel H, Lewis M, *et al*. Association of wake time and the onset of infarction. Z Kardiol 1991; 80(Suppl. 3): 105-10.
[23] Tofler GH, Brezenski D, Schafer AI, *et al.* Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987; 316: 1514-8.
[24] Kozak M. Circadian rhythms in cardiovascular diseases,ischemic heart disease. Vnitr Lek 2003; 49(4): 302-7.
[25] Un S, Baulmann J, Weisser B, Dusing R, Vetter H, Mengden T. Circadian rhythm of silent myocardial ischemia. Why morning is so risky for hypertensive patients. MMW Fortschr Med 2003; 145(47): 34-8.
[26] Li JJ. Circadian variation in myocardial ischemia: the possible mechanisms involving in this phenomenon. Med Hypotheses 2003; 61(2): 240-3.
[27] Li JJ, Huang CX, Fang CH, *et al.* Circadian variation in ischemic threshold in patients with stable angina: relation to plasma endothelin-1. Angiology 2002; 53(4): 409-13.
[28] Tarquini B, Perfetto F, Tarquini R, Cornélissen G, Halberg F. Endothelin-1's chronome indicates diabetic and vascular disease chronorisk. Peptides 1997; 18: 119-32.
[29] Herold M, Cornélissen G, Loeckinger A, Koeberle D, Koenig P, Halberg F. About 8-hourly variation of circulating human endothelin-1 (ET-1) in clinical health. Peptides 1998; 19: 821-5.
[30] Kawano H, Motoyama T, Yasue H, *et al*. Endothelial function fluctuates with diurnal variation in the frequency of ischemic episodes in patients with variant angina. J Am Coll Cardiol 2002; 40(2): 266-70.
[31] Wennerblom B, Lurje L, Karlsson T, Tygesen H, Vahisalo R, Hjalmarson A. Circadian variation of heart rate variability and the rate of autonomic change in the morning hours in healthy subjects and angina patients. Int J Cardiol 2001; 79(1): 61-9.
[32] Antman ME, Braunwald E. Acute myocardial infarction. In: Braunwald E, Eds. Heart disease. A textbook of cardiovascular medicine. 6th ed. Philadelphia: W. B. Saunders Company 2001; p. 1114.
[33] Muller JE, Stone PH, Turi ZG, *et al*. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985; 313: 1315-22.
[34] Cornélissen G, Breus TK, Bingham C, *et al*. Beyond circadian chronorisk: worldwide circaseptan-circasemiseptan patterns of myocardial infarctions, other vascular events, and emergencies. Chronobiologia 1993; 20: 87-115.
[35] Cornélissen G, Tamura K, Tarquini B, *et al*. Differences in some circadian patterns of cardiac arrhythmia, myocardial infarction and other adverse vascular events. Chronobiologia 1994; 21: 79-88.
[36] Moruzzi P, Marenzi G, Callegari S, Contini M. Circadian distribution of acute myocardial infarction by anatomic location and coronary artery involvement. Am J Med 2004; 116(1): 24-7.
[37] Kirby DA, Verrier RL. Differential effects of sleep stage on coronary hemodynamic function. Am J Physiol 1989; 256: H1378-83.
[38] Verrier RL, Dickerson LW. Autonomic nervous system and coronary blood flow changes related to emotional activation and sleep. Circulation 1991; 83(suppl II): 81-9.
[39] Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989; 79: 733-43.
[40] Tanaka A, Kawarabayashi T, Fukuda D, *et al*. Circadian variation of plaque rupture in acute myocardial infarction. Am J Cardiol 2004; 93(1): 1-5.
[41] Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978; 1: 795-7.
[42] Fujita M, Franklin D. Diurnal changes in coronary blood flow in conscious dogs. Circulation 1987; 76: 488-91.
[43] Pristipino C, Beltrame JF, Finocchiaro ML, *et al*. Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction. Circulation 2000; 101: 1102-8.
[44] Grines CL, Booth DC, Nissen SE, *et al*. Mechanism of acute myocardial infarction in patients with prior coronary artery bypass grafting and therapeutic implications. Am J Cardiol 1990; 65: 1292-6.
[45] Culic V, Miric D, Eterovic D. Different circumstances, timing, and symptom presentation at onset of Q-wave versus non-Q-wave acute myocardial infarction. Am J Cardiol 2002; 89(4): 456-60.
[46] Benhorin J, Moss AJ, Oakes D, *et al.* Multicenter Diltiazem Post-Infarction Group. The prognostic significance of first myocardial infarction type (Q wave versus non-Q wave) and Q wave location. J Am Coll Cardiol 1990; 15: 1201-7.
[47] Ofili EO, Labovitz AJ, Kern MJ. Coronary flow velocity dynamics in normal and diseased arteries. Am J Cardiol 1993; 71: 3D-9D.
[48] Anderson HV, Stokes MJ, Leon M, Abu-Halawa SA, Stuart Y, Kirkeeide RL. Coronary artery flow velocity is related to lumen area and regional left ventricular mass. Circulation 2000; 102: 48-54.
[49] Myerburg JR, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, Eds. Heart disease: A textbook of cardiovascular medicine. 4th ed. Philadelphia: W. B. Saunders Company 2001; p.756.
[50] Kozak M. Circadian rhythms in cardiovascular diseases-arrhythmias. Vnitr Lek 2003; 49(4): 297-301.
[51] Muller JE, Ludmer PL, Willich SN, *et al.* Circadian variation in the frequency of sudden cardiac death. Circulation 1987; 75(1): 131-8.
[52] Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. Am J Cardiol 1987; 60(10): 801-6.

[53] Willich SN, Goldberg RJ, Maclure M, Perriello L, Muller JE. Increased onset of sudden cardiac death in the first three hours after awakening. Am J Cardiol 1992; 70(1): 65-8.

[54] Levine RL, Pepe PE, Fromm RE Jr, Curka PA, Clark PA. Prospective evidence of a circadian rhythm for out-of-hospital cardiac arrests. JAMA 1992; 267(21): 2935-7.

[55] Aronow WS, Ahn C. Circadian variation of death from congestive heart failure after prior myocardial infarction in patients >60 years of age. Am J Cardiol 2003; 92(11): 1354-5.

[56] Flack JM, Yunis C. Therapeutic implications of the epidemiology and timing of myocardial infarction and other cardiovascular diseases. J Hum Hypertens 1997; 11(1): 23-8.

[57] Van der Palen J, Doggen CJ, Beaglehole R.Variation in the time and day of onset of myocardial infarction and sudden death. N Z Med J 1995; 108(1006): 332-4.

[58] Cornélissen G, Halberg F, Rostagno C, Otsuka K. A chronomic approach to cardiac arrhythmia and sudden cardiac death. The Autonomic Nervous System 2007; 44: 251-4.

[59] Halberg F, Cornélissen G, Otsuka K, *et al*. Incidence of sudden cardiac death, myocardial infarction and far- and near-transyears. Biomedicine & Pharmacotherapy 2005; 59(Suppl. 1): S239-S2.

[60] Peckova M, Fahrenbruch CE, Cobb LA, Hallstrom AP. Circadian variations in the occurrence of cardiac arrests: Initial and repeat episodes. Circulation 1998; 98: 31-9.

[61] Soo LH, Gray D, Young T, Hampton JR. Circadian variation in witnessed out of hospital cardiac arrest. Heart 2000; 84: 370-6.

[62] Arntz HR, Willich SN, Oeff M, *et al*. Circadian variation of sudden cardiac death reflects age-related variability in ventricular fibrillation. Circulation 1993; 88(5 Pt 1): 2284-9.

[63] Leclercq JF, Maisonblanche P, Cauchemez B, Coumel P. Respective role of sympathetic tone and of cardiac pauses in the genesis of 62 cases of ventricular fibrillation recorded during Holter monitoring. Eur Heart J 1988; 9(12): 1276-83.

[64] Kong TQ Jr, Goldberger JJ, Parker M, Wang T, Kadish AH. Circadian variation in human ventricular refractoriness. Circulation 1995; 92: 1507-16.

[65] Cha YM, Birgersdotter-Green U, Wolf PL, Peters BB, Chen PS. The mechanism of termination of reentrant activity in ventricular fibrillation. Circ Res 1994 ; 74(3): 495-506.

[66] Frazier DW, Wolf PD, Wharton JM, Tang AS, Smith WM, Ideker RE. Stimulus-induced critical point. Mechanism for electrical initiation of reentry in normal canine myocardium. J Clin Invest 1989; 83(3): 1039-52.

[67] Sheridan DJ, Culling W. Electrophysiological effects of alpha-adrenoceptor stimulation in normal and ischemic myocardium. J Cardiovasc Pharmacol 1985; 7 (Suppl. 5): S55-60.

[68] Kuo CS, Atarashi H, Reddy CP, Surawicz B. Dispersion of ventricular repolarization and arrhythmia: study of two consecutive ventricular premature complexes. Circulation 1985; 72(2): 370-6.

[69] Goldberg RJ, Brady P, Muller JE, *et al*. Time of onset of symptoms of acute myocardial infarction. Am J Cardiol 1990; 66(2): 140-4.

[70] Ridker PM, Manson JE, Buring JE, Muller JE, Hennekens CH. Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. Circulation 1990; 82(3): 897-902.

[71] Bexton RS, Vallin HO, Camm AJ. Diurnal variation of the QT interval--influence of the autonomic nervous system. Br Heart J 1986; 55(3): 253-8.

[72] Rozanski GJ, Jalife J, Moe GK. Determinants of postrepolarization refractoriness in depressed mammalian ventricular muscle. Circ Res 1984; 55(4): 486-96.

[73] Yi G, Guo XH, Reardon M, *et al*. Circadian variation of the QT interval in patients with sudden cardiac death after myocardial infarction. Am J Cardiol 1998 ; 81(8): 950-6.

[74] Tofler GH, Brezinski D, Schafer AI, *et al*. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987; 316(24): 1514-8.

[75] Muller JE, Stone PH, Turi ZG, *et al*. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985; 313(21): 1315-22.

[76] Willich SN, Linderer T, Wegscheider K, Leizorovicz A, Alamercery I, Schroder R. Increased morning incidence of myocardial infarction in the ISAM Study: absence with prior beta-adrenergic blockade. ISAM Study Group. Circulation 1989; 80(4): 853-8.

[77] Fujita M, Franklin D. Diurnal changes in coronary blood flow in conscious dogs. Circulation 1987; 76(2): 488-91.

[78] Roberts WC. Qualitative and quantitative comparison of amounts of narrowing by atherosclerotic plaques in the major epicardial coronary arteries at necropsy in sudden coronary death, transmural acute myocardial infarction, transmural healed myocardial infarction and unstable angina pectoris. Am J Cardiol 1989; 64(5): 324-8.

[79] Davies MJ, Bland JM, Hangartner JR, Angelini A, Thomas AC. Factors influencing the presence or absence of acute coronary artery thrombi in sudden ischaemic death. Eur Heart J 1989; 10(3): 203-8.

[80] Lampert R, Rosenfeld L, Batsford W, Lee F, McPherson C. Circadian variation of sustained ventricular tachycardia in patients with coronary artery disease and implantable cardioverter-defibrillators. Circulation 1994; 90(1): 241-7.

[81] Manfredini R, Gallerani M, Portaluppi F, Salmi R, Fersini C. Chronobiological patterns of onset of acute cerebrovascular diseases. Thromb Res 1997; 88(6): 451-63.

[82] Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 1998; 29(5): 992-6.

[83] Urdal P, Anderssen SA, Holme I, *et al*. Monday and non-Monday concentrations of lifestyle-related blood components in the Oslo Diet and Exercise Study. J Intern Med 1998; 244(6): 507-13.

[84] Brezinski DA, Tofler GH, Muller JE, *et al*. Morning increase in platelet aggregability. Association with assumption of the upright posture. Circulation 1988; 78(1): 35-40.

[85] Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997; 79(11): 1512-6.

[86] Manfredini R, Gallerani M, Portaluppi F, Salmi R, Zamboni P, Fersini C. Circadian variation in the onset of acute critical limb ischemia. Thromb Res 1998; 92(4): 163-9.

[87] Manfredini R, Casetta I, Paolino E, *et al*. Monday preference in onset of ischemic stroke. Am J Med 2001; 111(5): 401-3.

[88] Kelly-Hayes M, Wolf PA, Kase CS, Brand FN, McGuirk JM, D'Agostino RB. Temporal patterns of stroke onset. The Framingham Study. Stroke 1995; 26(8): 1343-7.

[89] Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978; 1(8068): 795-7.

[90] Lago A, Geffner D, Tembl J, Landete L, Valero C, Baquero M. Circadian variation in acute ischemic stroke: a hospital-based study. Stroke 1998; 29(9): 1873-5.

[91] Johansson BB, Norrving B, Widner H, Wu J, Halberg F. Stroke incidence: circadian and circaseptan (about-weekly) variations in onset. Prog Clin Biol Res 1990; 341A: 427-36.

[92] Jiang Z, Li W, Liu Y, *et al*. Circadian blood pressure and heart rate characteristics in haemorrhagic vs ischaemic stroke in Chinese people. J Hum Hypertens 2010; 24: 165-74.

[93] Quyyumi AA. Circadian rhythms in cardiovascular disease. Am Heart J 1990; 120(3): 726-33.

[94] Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989; 79(4): 733-43.

[95] Jain S, Namboodri KK, Kumari S, Prabhakar S. Loss of circadian rhythm of blood pressure following acute stroke. BMC Neurol 2004; 4(1): 1.

[96] Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. Br Med Bull 1994; 50(2): 272-98.

[97] Sander D, Klingelhofer J. Changes of circadian blood pressure patterns after hemodynamic and thromboembolic brain infarction. Stroke 1994; 25(9): 1730-7.

[98] Yamamoto Y, Akiguchi I, Oiwa K, Satoi H, Kimura J. Diminished nocturnal blood pressure decline and lesion site in cerebrovascular disease. Stroke 1995; 26(5): 829-33.

[99] Dawson SL, Evans SN, Manktelow BN, Fotherby MD, Robinson TG, Potter JF. Diurnal blood pressure change varies with stroke subtype in the acute phase. Stroke 1998; 29(8): 1519-24.

[100] Fujishima S, Abe I, Okada Y, Saku Y, Sadoshima S, Fujishima M. Serial changes in blood pressure and neurohormone levels after the onset of lacunar stroke. Angiology 1996; 47(6): 579-87.

[101] Marshall J. Diurnal variation in occurrence of strokes. Stroke 1977; 8(2): 230-1.

[102] Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 1998; 29(5): 992-6.

[103] Hayashi S, Toyoshima H, Tanabe N, Miyanishi K. Daily peaks in the incidence of sudden cardiac death and fatal stroke in Niigata Prefecture. Jpn Circ J 1996; 60(4): 193-200.

[104] Vermeer SE, Rinkel GJ, Algra A. Circadian fluctuations in onset of subarachnoid hemorrhage. New data on aneurysmal and perimesencephalic hemorrhage and a systematic review. Stroke 1997; 28(4): 805-8.

[105] Vargova V, Mechirova V, Fedacko J, *et al*. Can nut consumption modulate cardiovascular diseases. Report of a case and review of literature. Open Nutra J 2011; 4: 88-96.

[106] Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke 1996; 27(3): 373-80.

[107] Van der Windt C, Van Gijn J. Cerebral infarction does not occur typically at night. J Neurol Neurosurg Psychiatry 1988; 51(1): 109-11.

[108] Wolf PA, Caplan LR, Foulkes MA. Morning increase in onset of ischemic stroke. Stroke 1989; 20(4): 473-6.

[109] Argentino C, Toni D, Rasura M, *et al*. Circadian variation in the frequency of ischemic stroke. Stroke 1990; 21(3): 387-9.

[110] Nyquist PA, Brown RD Jr, Wiebers DO, Crowson CS, O'Fallon WM. Circadian and seasonal occurrence of subarachnoid and intracerebral hemorrhage. Neurology 2001; 56(2): 190-3.

[111] Sloan MA, Price TR, Foulkes MA, *et al*. Circadian rhythmicity of stroke onset. Intracerebral and subarachnoid hemorrhage. Stroke 1992; 23(10): 1420-6.

[112] Kleinpeter G, Schatzer R, Bock F. Is blood pressure really a trigger for the circadian rhythm of subarachnoid hemorrhage? Stroke 1995; 26(10): 1805-10.

[113] Gallerani M, Manfredini R, Ricci L, *et al*. Chronobiological aspects of acute cerebrovascular diseases. Acta Neurol Scand 1993; 87(6): 482-7.

[114] Rautaharju PM, Manolio TA, Furberg CD, *et al*. Ischemic episodes in 24-h ambulatory electrocardiograms of elderly persons: the Cardiovascular Health Study. Int J Cardiol 1995; 51(2): 165-75.

[115] Vermeer SE, Rinkel GJ, Algra A. Circadian fluctuations in onset of subarachnoid hemorrhage. New data on aneurysmal and perimesencephalic hemorrhage and a systematic review. Stroke 1997; 28(4): 805-8.

[116] Chamorro A, Vila N, Ascaso C, Elices E, Schonewille W, Blanc R. Blood pressure and functional recovery in acute ischemic stroke. Stroke 1998; 29(9): 1850-3.

[117] Marsh EE 3rd, Biller J, Adams HP Jr, *et al*. Circadian variation in onset of acute ischemic stroke. Arch Neurol 1990; 47(11): 1178-80.

[118] Wroe SJ, Sandercock P, Bamford J, Dennis M, Slattery J, Warlow C. Diurnal variation in incidence of stroke: Oxfordshire community stroke project. BMJ 1992; 304(6820): 155-7.

[119] Haapaniemi H, Hillbom M, Juvela S. Weekend and holiday increase in the onset of ischemic stroke in young women. Stroke 1996; 27(6): 1023-7.

[120] Bassetti C, Aldrich M. Night time versus daytime transient ischaemic attack and ischaemic stroke: a prospective study of 110 patients. J Neurol Neurosurg Psychiatry 1999; 67(4): 463-7.

[121] Bassetti C, Aldrich MS, Chervin RD, Quint D. Sleep apnea in patients with transient ischemic attack and stroke: a prospective study of 59 patients. Neurology 1996; 47(5): 1167-73.

[122] Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB. Investigating the relationship between stroke and obstructive sleep apnea. Stroke 1996; 27(3): 401-7.

[123] Palomaki H, Partinen M, Erkinjuntti T, Kaste M. Snoring, sleep apnea syndrome, and stroke. Neurology 1992; 42(7 Suppl. 6): 75-81.

[124] Partinen M. Ischaemic stroke, snoring and obstructive sleep apnoea. J Sleep Res 1995; 4(S1): 156-9.

[125] Kozák M. Use of chronobiology findings in therapy of cardiovascular diseases. Vnitr Lek 2003; 49(4): 308-13.

[126] Sica DA,White W. Chronotherapeutics and Its role in the treatment of hypertension and cardiovascular disease. J Clin Hypertens 2000; 2(4): 279-86.

[127] Elliott WJ. Timing treatment to the rhythm of disease: a short course in chronotherapeutics. Postgrad Med 2001; 110(2): 119-29.

[128] Reinberg AE. Concepts of circadian chronopharmacology. Ann N Y Acad Sci 1991; 618: 102-15.

[129] Singh RB, DeMeester F, Pella D, Basu TK, Watson RR. Globalization of dietary wild foods protect against cardiovascular disease and all cause Mortalities? A scientific satement from the International College of Cardiology, Columbus Paradigm Institute and the International College of Nutrition. Open Nutra J 2009; 2: 42-5.

[130] Cornélissen G, Halberg F, Prikryl P, Dankova E, Siegelova J, Dusek J, International womb-to-tomb chronome study group: Prophylactic aspirin treatment: the merits of timing. JAMA 1991; 266: 3128-9.

[131] Cornélissen G, Halberg F, Otsuka K, Singh RB. Separate cardiovascular disease risks: circadian hyper-amplitude-tension (CHAT) and an elevated pulse pressure. World Heart J 2008; 1(3): 223-32.

[132] White WB, Black HR, Weber MA, *et al*. Comparison of effects of controlled onset extended release verapamil at bedtime and nifedipine on gastrointestinal therapeutic system on arising on early morning blood pressure, heart rate, and the heart rate-blood pressure product. Am J Cardiol 1998; 81: 421-31

[133] Frishman WH, Glasser S, Stone P, *et al*. Comparison of controlled-onset extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. Am J Cardiol 1999; 83: 507-14.

[134] Ridker PM, Manson JE, Buring JE, Muller JE, Hennekens CH. Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. Circulation 1990; 82(3): 897-902.

[135] Willich SN, Linderer T, Wegscheider K, Leizorovicz A, Alamercery I, Schroder R. Increased morning incidence of myocardial infarction in the ISAM Study: absence with prior beta-adrenergic blockade. ISAM Study Group. Circulation 1989; 80: 853-8.

[136] Kupari M, Koskinen P, Leinonen H. Double-peaking circadian variation in the occurrence of sustained supraventricular tachyarrhythmias. Am Heart J 1990; 120(6 Pt 1): 1364-9.

[137] Peckova M, Fahrenbruch CE, Cobb LA, Hallstrom AP. Circadian variations in the occurrence of cardiac arrests: Initial and repeat episodes. Circulation 1998; 98: 31-9.

[138] Cornelissen G, Halberg F, Otsuka K, Singh RB, Chen CH. Chronobiology predicts actual and proxy outcomes when dipping fails. Hypertension 2007; 49: 237-9.

[139] Gal D, Pella D, Singh RB. The effect of an alpha-linolenic acid rich diet on the circadian rhythm of cardiac events. World Heart J 2008; 1: 49-56.

[140] Singh RB, Dubnov G, Niaz MA, *et al*. Effect of an Indo-Mediterranean diet on progression of coronary disease in high risk patients: a randomized single blind trial. Lancet 2002; 360: 1455-61.

[141] Singh RB, Rastogi SS, Verma R, Bolaki L, Singh R. An Indian experiment with nutritional modulation in acute myocardial infarction. Am J Cardiol 1992; 69: 879-85.

[142] Singh RB, Pella D, Otsuka K. Can brain dysfunction be a predisposing factor for metabolic syndrome? Biomed Pharmacother J 2004; 58: 58-68.

[143] Singh RB, DeMeester F, Mechirova V, Pella D, Otsuka K. Fatty acids in the causation and therapy of metabolic syndrome. In: De Meester F, Watson RR, Eds. Wild type foods in health promotion and disease prevention. NJ: Humana Press 2008; pp. 263-84.

[144] De Meester F. Wild-type land based foods in health promotion and disease prevention: the LDL-CC:HDL-CC model. In: De Meester R, Watson RR, Eds. Wild type foods in health promotion and disease prevention. NJ: Humana Press 2008; pp. 3-20.

[145] de Lorgeril M, Renaud S, Mamelle N, *et al*. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994; 343: 1454-9.

[146] Renaud S, de Lorgeril M, Delaye J, *et al*. Cretan Mediterranean diet for prevention of coronary heart disease. Am J Clin Nutr 1995; 61(6 Suppl): 1360S-67S.

[147] Singh RB, De Meester F, Wilczynska A. The Tsim Tsoum approaches for prevention of cardiovascular diseases. Cardiol Res Prac 2010; 2010: 824938.doi:10.4061/2010/824938.

[148] De Meester F. Impact of research conducted by Dr Ram B Singh on modern concepts of nutrition and lifestyle in mind-body diseases. Open Nutra J 2011; 4: 31-3.

[149] Cornélissen G, Halberg F, Schwartzkopff O, *et al*. Coenzyme-Q10 effect on blood pressure variability assessed with a chronobiological study design. In: Noninvasive Methods in Cardiology, Brno, Czech Republic: Masaryk University. September 14, 2005, p. 10.

[150] Halberg F, Cornélissen G, Singh RB. Timing nutriceuticals? Open Nutra J 2010; 3: 100-11.

[151] Halberg F, Haus E, Cornelissen G. From biologic rhythms to chronomes relevant for nutrition. In: Marriott BM, Ed. Not eating enough: overcoming Underconsumption of military operational rations. Washington DC: National Academy Press 1995; pp. 361-72. Available at: http://books.nap.edu/books/0309053412/html/361.html#pagetop

[152] Halberg F. Protection by timing treatment according to bodily rhythms: an analogy to protection by scrubbing before surgery. Chronobiologia 1974; 1(Suppl. 1): 27-68.

[153] Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. Circadian timing of food intake contributes to weight gain. Obesity 2009; 17: 2100-2.

[154] Arble DM, Goldschmidt C, Vitaterna MH, Turek FW. Circadian eating and sleeping patterns in the night eating syndrome. Sleep 2009; 32: A61.

[155] Kovac M, Mikulecky M. Secular rhythms and Halberg's paraseasonality in the time occurrence of cerebral stroke. Bratisl Lek Listy 2005; 106(2): 423-7.

[156] Rohde RA, Muller RA. Cycles in fossil diversity. Nature 2005; 434: 208-9.

[157] Sothern RB, Yamamoto T, Cornélissen G, Takumi T, Halberg F. Central and peripheral circadian clock genes, their statistical analysis for rhythms, and relationship to health and disease. Scripta Medica(Brno) 2009; 82: 133-63.

[158] Simopoulos AP. Genetic variation and dietary response: Nutrigenetics/nutrigenomics. Asia Pac J Clin Nutr 2002; 11(S6): 117-28.

[159] Singh RB, Cornelissen G, Weydahl A, *et al*. Circadian heart rate and blood pressure variability considered for research and patient care. Int J Cardiol 2003; 87: 9-28.

Received: January 07, 2012 Revised: January 25, 2012 Accepted: January 27, 2012