

## **РЕЗЮМЕТА НА НАУЧНИТЕ ТРУДОВЕ**

**ЗА УЧАСТИЕ В КОНКУРС ЗА АКАДЕМИЧНА ДЛЪЖНОСТ „ДОЦЕНТ”**

**ПРИ МБАЛ ”НАЦИОНАЛНА КАРДИОЛОГИЧНА БОЛНИЦА”**

**НА Д-Р КРАСИМИРА АТАНАСОВА ХРИСТОВА, ДМ**

**КЛИНИКА ПО КАРДИОЛОГИЯ, ОТДЕЛЕНИЕ ПО НЕИНВАЗИВНА  
ДИАГНОСТИКА**

**МБАЛ ”НАЦИОНАЛНА КАРДИОЛОГИЧНА БОЛНИЦА”**

### ***IV. Реални публикации в международни медицински списания с или без импакт фактор***

**1. Daniel Barbosa , Krasimira Hristova, Dirk Loeckx, Frank Rademakers, Piet Claus and Jan D’hooge. 3D motion and strain estimation of the heart: initial clinical findings. Proceedings of the SPIE, Volume 7629, pp. 762904-762909 (2010).**

### **3D motion and strain estimation of the heart: initial clinical findings**

Daniel Barbosa ; Krasimira Hristova ; Dirk Loeckx ; Frank Rademakers ; Piet Claus ; Jan D’hooge

*Proc. SPIE 7629, Medical Imaging 2010: Ultrasonic Imaging, Tomography, and Therapy, 762904 (March 12, 2010); doi:10.1117/12.848557*

The quantitative assessment of regional myocardial function remains an important goal in clinical cardiology. As such, tissue Doppler imaging and speckle tracking based methods have been introduced to estimate local myocardial strain. Recently, volumetric ultrasound has become more readily available, allowing therefore the 3D estimation of motion and myocardial deformation. Our lab has previously presented a method based on spatio-temporal elastic registration of ultrasound volumes to estimate myocardial motion and deformation in 3D, overcoming the spatial limitations of the existing methods. This method was optimized on

simulated data sets in previous work and is currently tested in a clinical setting. In this manuscript, 10 healthy volunteers, 10 patient with myocardial infarction and 10 patients with arterial hypertension were included. The cardiac strain values extracted with the proposed method were compared with the ones estimated with 1D tissue Doppler imaging and 2D speckle tracking in all patient groups. Although the absolute values of the 3D strain components assessed by this new methodology were not identical to the reference methods, the relationship between the different patient groups was similar.

**2. Iana Simova, Tzvetana Katova, Velislava Kostova, Krasimira Hristova, Nikolay Domitrov. Reproducibility of arterial stiffness indices in different vascular territories and between different observers. Echocardiography, 14 MAR 2011 | DOI: 10.1111/j.1540-8175.2010.01365.**

**BACKGROUND:**

Increased arterial stiffness (AS) corresponds to an increase in cardiovascular risk. According to recent guidelines AS parameters can be measured on all superficial arteries.

**OBJECTIVE:**

Proceeding from the assumption that viscoelastic properties differ along the arterial tree we set ourselves the task to study the reproducibility of AS indices measured at the common carotid, brachial and femoral arteries.

**METHODS:**The initial study population included 75 patients ( $40 \pm 14.5$  years, 45% males) with a variable distribution of cardiovascular risk factors and without clinical evidence of coronary artery disease. AS parameters were measured at the common carotid, brachial and femoral arteries in all patients using echo-tracking (ET) technique. In a subgroup of 36 patients we tested the interobserver variability in the three vascular territories.

**RESULTS:**

We found that there was a significant correlation between AS indices measured at the common carotid and femoral artery (with the only exception for augmentation index) and that AS parameters measured at the brachial artery did correlate neither with common carotid nor with femoral artery indices. The interobserver variability of ET derived AS parameters was good when they were measured at the carotid or femoral artery. The values of AS indices at the brachial artery however showed considerably lower interobserver agreement.

**CONCLUSION:**

The reproducibility of ET derived AS parameters was good when AS was measured at the common carotid or femoral arteries. On the basis of our results brachial artery is probably not a reliable site for AS measurement.

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**5. Omidvar S, Pati S, Singh RB, Takahashi T, Shin HH, Lee M-K, Kim S-R, Fedacko J, Singh R, Tribulova N, Hristova K, De Meester F, Wilczynska A, Wilson DW, Martyrosyan D, Singh R B, Sharma R & Juneja LR . Association of Cocoa Consumption and**

## **Risk of Cardiovascular Diseases and other Chronic Diseases. World Heart Journal 01/2013; 5(1).**

**Background.** Antioxidant flavonoid deficiency may be risk factor for non-communicable diseases (NCDs). Further studies indicate that increased consumption of cocoa products; cocoa, and chocolates, etc. may be associated with decreased risk of NCDs; cardiovascular diseases (CVDs), coronary artery disease (CAD), stroke, hypertension, insulin resistance, memory dysfunction and cancers. In the present review, on supporting evidence for such claims.

**Methods.** Internet search and discussion with experts. Parts of meta analysis have been briefly and partly reproduced in the Results Section of the Abstract to maintain impact and impartiality throughout the paper.

**Results.** Cocoa flavonol appears to have potential beneficial effects against the risk of, metabolic syndrome, hypertension, blood lipids, stroke, coronary artery disease (CAD), cancer, cognitive function and dementia due to its antioxidant, anti-inflammatory and activation of nitric oxide effects. In a meta-analysis, epidemiological studies, comprising of 114 009 participants, The highest levels of chocolate consumption, were associated with a 37% reduction in CVD (relative risk 0.63 (95% confidence interval 0.44 to 0.90)) and a 29% reduction in stroke compared with the lowest levels. Another meta-analysis showed a significant blood pressure-reducing effect of cocoa-chocolate compared with control but it was significant only for the hypertensive or prehypertensive subgroups (SBP:  $-5.0 \pm 3.0$  mmHg;  $P = 0.0009$ ; DBP:  $-2.7 \pm 2.2$  mm Hg,  $P = 0.01$ ). BP was not significantly reduced in the normotensive subgroups. Clinical studies among subjects showed that cocoa intake can improve endothelial function by activation of nitric oxide. In a double-blind, parallel arm study in 90 elderly individuals with mild cognitive impairment, randomized to consume once daily for 8 weeks a drink containing  $\approx 990$  mg (high flavanols),  $\approx 520$  mg (intermediate flavanols), or  $\approx 45$  mg (low flavanols) of cocoa flavanols per day. The time required to complete Trail Making Test A and Trail Making Test B was significantly ( $P < 0.05$ ) lower in subjects assigned to high flavanols ( $38.10 \pm 10.94$  and  $104.10 \pm 28.73$  seconds, respectively) and intermediate flavanols ( $40.20 \pm 11.35$  and  $115.97 \pm 28.35$  seconds, respectively) in comparison with those assigned to low flavanols ( $52.60 \pm 17.97$  and  $139.23 \pm 43.02$  seconds, respectively). Similarly, verbal fluency test score was significantly ( $P < 0.05$ ) better in subjects assigned to high flavanols in comparison with those assigned to low flavanols ( $27.50 \pm 6.75$  versus  $22.30 \pm 8.09$  words per 60 seconds). Insulin resistance, blood pressure, and lipid peroxidation also decreased among subjects in the high-flavanol and intermediate-flavanol groups.

**Conclusions.** Dietary supplementation with cocoa (300-1000mg/day) in the form of dark chocolates can protect against NCDs; hypertension, stroke, atherosclerosis, insulin resistance, memory dysfunction and cancer. Further research is necessary to prove this finding.

**7. Singh R B, Takahashi T, Nakaoka T, Otsuka K, Toda E, Shin H H, Lee M-K, Beeharry V, Hristova K, Fedacko J, Pella J, De Meester F, Wilson D W, Juneja LR & Martirosyan DM (2013).**

**Nutrition in Transition from Homo sapiens to Homo economicus. The Open Nutraceuticals Journal 6(1): 6-17.**

[DOI: 10.2174/1876396001306010006]

Nutrition in Transition from Homo sapiens to Homo economicus

Ram B Singh, Toru Takahashi, Takashi Nakaoka, Kuniaki Otsuka, Eri Toda, Hyun Ho Shin, Moon-Kyu Lee, Vicky Beeharry, Krisimira Hristova, Jan Fedacko, Daniel Pella, Fabien De Meester, Douglas W Wilson, Lekh R Juneja, Danik M. Martirosyan Pp. 6-17  
(22 March 2013)

The food and nutrient intake among Paleolithic Homo sapiens, hunter-gatherers and among Asian and Homo economicus Western populations shows marked variations. Economic development and affluence may be associated with a decrease in the consumption of omega-3 fatty acids, vitamins, antioxidants and amino acids and significant increase in the intakes of carbohydrates, (mainly refined), fat (saturated, trans fat and linoleic acid) and salt compared to the Paleolithic period. The protein or amino acid intake was 2.5 fold greater (33 vs. 13%) in the Paleolithic diet Homo sapiens compared to modern Western diet consumed by Homo economicus populations. Approximately 10,000 years ago, prior to the Agricultural Revolution, our diet was based on an enormous variety of wild plants. However, today about 17% of plant species provide 90% of the world's food supply which is mainly contributed by grains produced by fertilizer based on rapidly grown crops which may result in a decrease in nutrient density and increase in energy. Wheat, corn and rice account for three fourths of the world's grain production on which humans are dependent for their food supply. Grains are high in omega-6 fatty acids and carbohydrates and low in omega-3 fatty acids and antioxidants compared to leafy green vegetables. It has been estimated that diet of Homo sapiens was characterized by higher intakes by essential and nonessential amino acids, calcium, potassium, magnesium, flavonoids and w-3 fatty acids whereas modern Western diet of Homo economicus has excess of energy-rich refined carbohydrates, w-6, trans fat and saturated fat and low in protective nutrients. The consumption of such diets in wealthy countries in conjunction with sedentary behavior is associated with increased prevalence of morbidity and mortality due to noncommunicable diseases (NCDs).

**10. Hristova K, Pella D, Singh RB, Dimitrov BD, Chaves H, Juneja L, Basu T K, Ozimek L, Singh AK, Rastogi SS, Takahashi T, Wilson DW, De Meester F, Cheema S, Garg M, Buttar HS & Milovanovic B. (2013). Sofia declaration for prevention of cardiovascular diseases and type 2 diabetes mellitus. a scientific statement of the international college of cardiology and international college of nutrition (Long version). World Heart Journal 2014, 6 , 89-106.**

On 24-26 October, 2013, the 7th International Congress on Cardiovascular Diseases and the 17th World Congress on Clinical Nutrition took place in Sofia, Bulgaria ([www.iccsk.bizpa.in](http://www.iccsk.bizpa.in)). We reiterated that treatment decisions on cardiovascular disease (CVD) and diabetes mellitus should target the overall level of risks in each patient including biological risk factors and other social and environmental determinants (1-4). In particular, behavioural and lifestyle interventions have been shown to reduce CVD risk factors in affluent countries while studies of CV preventive interventions are much needed in low and middle settings (5). Strengthening well-functioning national health systems in developing countries should be a real focus (6) since well-managing non-communicable diseases would help sustain human development capital (7). International College of Nutrition and International College of Cardiology have been emphasizing the role of

nutrition and health knowledge in the prevention strategies of CVD and diabetes in local health education since the last decade. For example, poverty may have been long blamed for its effect on risk of CVD and diabetes mellitus in the developing countries. However, we have now observed that, in fact, by offering proper health education through day-to-day clinical practice to the most deprived areas together with revisiting public health policy on a regular basis could better achieve the overall health for patients including physical, mental, social, and environmental aspects (8-10). To be specific, it is not being poor that directly causes CVD and/or diabetes (11). Rather, it is the unchanged poor environmental condition (i.e., lack of healthy foods) and unhealthy behaviors since early years (12) and the advancement of diagnostic technology to disclose the disease burden and patterns that cannot bring the number of CVD events and mortality down (13). Following this context, we propose that at the national level using tax system to regulate might be the most cost-effective way to improve local and national public health. In this way, in the long run, we believe the health care spending could be largely reduced and human development capital could be sustained in the next decades. More importantly, since nutrition has been claimed to have the positive impact throughout the life span (14,15), how to work with food industries and governments to reach the consensus on making healthy foods available at reasonable and affordable costs would be a continuous challenge for us.

**11.Hristova K, Shiue I, Pella D, Singh RB, Dimitrov BD, Chaves H, Basu TK, Ozimek L, Rastogi SS, Takahashi T, Wilson DW, De Meester F, Cheema S, Garg, M, Buttar HS, Milovanovic B, Kumar A, Handjiev S, Cornelissen G & Ivo Petrov I. Prevention strategies for cardiovascular diseases and diabetes mellitus in developing countries:World Conference of Clinical Nutrition 2013. Nutrition. 2014 Sep;30(9):1085-9.doi:10.1016/j.nut.2013.12.013. Epub 2014 Jan 8.**

On 24-26 October, 2013, the 7th International Congress on Cardiovascular Diseases and the 17th World Congress on Clinical Nutrition took place in Sofia, Bulgaria ([www.iccsk.bizpa.in](http://www.iccsk.bizpa.in)). We reiterated that treatment decisions on cardiovascular disease (CVD) and diabetes mellitus should target the overall level of risks in each patient including biological risk factors and other social and environmental determinants (1-4). In particular, behavioural and lifestyle interventions have been shown to reduce CVD risk factors in affluent countries while studies of CV preventive interventions are much needed in low and middle settings (5). Strengthening well-functioning national health systems in developing countries should be a real focus (6) since well-managing non-communicable diseases would help sustain human development capital (7). International College of Nutrition and International College of Cardiology have been emphasizing the role of nutrition and health knowledge in the prevention strategies of CVD and diabetes in local health education since the last decade. For example, poverty may have been long blamed for its effect on risk of CVD and diabetes mellitus in the developing countries. However, we have now observed that, in fact, by offering proper health education through day-to-day clinical practice to the most deprived areas together with revisiting public health policy on a regular basis could better achieve the overall health for patients including physical, mental, social, and environmental aspects (8-10). To be specific, it is not being poor that directly causes CVD and/or diabetes (11). Rather, it is the unchanged poor environmental condition (i.e., lack of healthy foods) and

unhealthy behaviors since early years (12) and the advancement of diagnostic technology to disclose the disease burden and patterns that cannot bring the number of CVD events and mortality down (13). Following this context, we propose that at the national level using tax system to regulate might be the most cost-effective way to improve local and national public health. In this way, in the long run, we believe the health care spending could be largely reduced and human development capital could be sustained in the next decades. More importantly, since nutrition has been claimed to have the positive impact throughout the life span (14,15), how to work with food industries and governments to reach the consensus on making healthy foods available at reasonable and affordable costs would be a continuous challenge for us.

**12. Singh, R B, Hristova, K, Muthusamy, V V, Basu, T K, Rastogi, S S, Toda, E, Takahashi, T Fedacko, J, Pella, D, Wilson, D W, De Meester, F, Mondal, R, Ishaq, M & Mohideen, M R (2013). The adverse effects of wealth on cardiovascular health: A scientific Statement of the International College of Cardiology. *Cardiol Angiol*,(An Int. J) 1:9- 22. URL:**

**<http://www.sciencedomain.org/journal-home.php?id=26>**

Background and Aims: Increase in economic status may be associated with increased consumption of Western type of foods and sedentary behaviour. In the present review, we discuss that increase in wealth may be associated with adverse effects on health behaviour.

Study Design and Methods: Internet search and discussion with colleagues.

Results: Review of studies indicate that with increase in wealth, there is increased consumption of high fat, ready prepared foods and decrease in physical activity in most of the countries resulting in obesity and metabolic syndrome, leading to cardiovascular diseases (CVDs) and other chronic conditions. Many experts during the United Nations High Level Meeting in Sept 2011, misinterpreted the WHO estimates and proposed that, of total deaths, 22.4 million arise in the poorest countries, and 13.7 million in high-income and upper-middle-income countries and therefore poverty may be the major cause of deaths due to non-communicable diseases (NCDs). A recent study shows that 57.0 % of deaths in adults (aged 25-64 years) were due to CVDs and other chronic diseases, 25.5% due to communicable diseases and 15.9% due to injury and accidents. The deaths due to NCDs were highly prevalent among higher social classes compared to lower social classes who had greater deaths due to communicable diseases. It is interesting to know from new data from United States, that there is 'Wealth' without cardiovascular health in America. The whole world is likely to have the same scenario in the near future.

Conclusions: Increase in wealth may be associated with altered health behaviour; greater consumption of unhealthy foods, tobacco consumption, mental load and sedentary behaviour resulting in increased risk of deaths due to CVDs and other chronic diseases which may change with knowledge about health education. Wealth may cause extension in life by buying of expensive drug therapy, intervention and surgery which are known to add income and employment in the west. See more at:

<http://www.sciencedomain.org/abstract.php?iid=221&id=26&aid=1545#sthash.dMFP99QI.dpuf>

**13. Singh,R B, Mondal,R N, Hristova,K, Takahashi,T, Pella,D, De Meester,F, Gerasimova,E & Wilson, D W (2013). Wealth Can Defeat Death and Achieve Heart Health in United States. World Heart Journal 5(2).**

**14. Hristova K, Nakaoka T, Otsuka K, Fedacko J, Singh R, Singh, R B, De Meester F, Wilczynska A & Wilson DW (2012). Editorial: Perspectives on Chocolate Consumption and Risk of Cardiovascular Diseases and Cognitive Function. Open Nutraceuticals Journal, 2012, 5 (1), pp. 207-212.**

DOI: 10.2174/1876396001205010207]

EDITORIAL: Perspectives on Chocolate Consumption and Risk of Cardiovascular Diseases and Cognitive Function

Krassimira Hristova, Takashi Nakaoka, Kuniaki Otsuka, Jan Fedacko, Reema Singh, RB Singh, Fabien De Meester, Agnieszka Wilczynska and DW Wilson Pp. 207-212

Flavonoid deficiency in the diet is a risk factor for cardiovascular diseases (CVDs) and other chronic diseases. Recent studies indicate that increased consumption of chocolates may be associated with decreased risk of CVDs and insulin resistance, inflammation and hyperlipidemia. In the present editorial, we have sought supporting evidence for such claims. It is possible that cocoa consumption (30-1000mg/day) in the form of dark chocolates can protect against hypertension, stroke, atherosclerosis, insulin resistance and memory dysfunction. Further research is necessary to prove this finding.

**15. RB Singh, Kuniaki Otsuka, Daniel Pella, Jan Fedacko, Viola Michirova, Branislav Milovanovic, Krasimira Hristova, Wilson D W, Hilton Chaves. Mini Review - Evolutionary Aspects of Circadian Rhythm and Neurocardiovascular Dysfunction. World Heart Journal 01/2013; 6(2).**

The word circadian and chronobiology, chronocardiology and chronoastrobiology were coined by Prof. F.Halberg. 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 4 th 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.

**16. NS Verma, RK Singh, RB Singh, Jan Fedacko, Krasimira Hristova, Anna Gvozdjaková, Branislav Milovanovic, Toru Takahashi, Wilson D W, NS Dhalla. Circadian Cardiomyocyte Function and Cardiomyocyte Circadian Clock. World Heart Journal 01/2013; 6(1).**

Background. Cardiomyocyte circadian rhythms and the circadian clock are known to coordinate myocardial function. In this review we discuss whether disruption of this mechanism plays a potential role in the etiology of cardiovascular diseases (CVDs), obesity and type 2 diabetes. Methods. Internet search and discussion with colleagues. Results. Circadian clock genes have been identified and characterized within almost all mammalian cell types, including cardiomyocytes, vascular smooth muscle cells, endothelial cells, and fibroblasts. Clocks are found in both prokaryotes and eukaryotes. However, a few reports suggest that specific prokaryotes may not possess functional clocks. Circadian clocks



are transcriptionally-based cell autonomous molecular mechanisms that directly coordinate cellular/biological functions at multiple temporal levels. As reported by various workers, a number of roles played by circadian clock genes within the cardiovascular system are composed of both positive and negative feedback loops, with a free-running period of approximately 24 hours. The cardiomyocyte circadian clock influences myocardial contractile function, metabolism, and gene expression and coordinates myocardial oxygen consumption and fatty acid oxidation rates. Experimental mice constitute a model of temporal suspension of the heart circadian clock at the wake-to-sleep transition, which is distinct from classic models of shift work involving manipulation of the light-dark cycle. The expression of approximately 10-15% of all myocardial genes oscillate in a time-of-day-dependent manner which is clear from hearts collected from mice under light/dark (24-hour synchronized) and constant dim light (free-running) conditions. The major fuel sources for continued contraction of the myocardium are fatty acids and glucose, which may be an integral component of the cardiomyocyte circadian clock. In the oxidative myocardial metabolism, circadian variations in the rat's heart revealed time-of-day-dependent oscillations in glucose, but not in fatty acid, oxidation. There is a greater transcriptional response when the rat's heart is challenged with fatty acids during the active phase. This response is mediated by the cardiomyocyte circadian clock, and it is potentially mediated by clock-controlled oscillations in nuclear receptors, such as PPAR $\alpha$ , Rev-erb $\alpha$ , and PGC1 $\alpha$ . The circadian system is a complex feedback network that involves interactions between the central nervous system and peripheral tissues as well as the metabolic system. It is possible that circadian coordination is intimately linked to metabolic homeostasis and that dysregulation of circadian rhythms can contribute to cardiometabolic risk. It seems that metabolic signals also feed back into the circadian system, modulating circadian gene expression and altering their behavior, resulting in an increased risk of CVDs, obesity, and diabetes.

Conclusions. Recent molecular- and genetic-based studies suggest that the cardiomyocyte circadian clock influences multiple myocardial processes, including transcription, signaling, growth, metabolism, and contractile function. In view of its physiological roles, the cardiomyocyte circadian clock has recently been linked to the pathogenesis of heart disease in response to adverse stresses, such as ischemia/reperfusion, in animal models as well as to the risk of obesity and type 2 diabetes.

**17. R B Singh, Franz Halberg, Germaine Cornelissen, Krasimira Hristova, Eri Toda, Toru Takahashi, Jan Fedacko and Kuniaki Otsuka. Personalized Circadian Timing of Exercise. World Heart Journal 2013; 5(2); 79-90.**

That exercise effect are circadian stage dependent and that exercise at the wrong circadian stage can induce Vascular Variability Disorder (VVD) has been documented earlier. Herein we show how statistically significant results can be obtained with simple individual design, that can be self -applied by everybody to optimize a desired effect by Chronobiologically –interpreted Ambulatory Blood Pressure (BP) and heart rate (HR) Monitoring C-ABPM). A 68 year old internist monitored himself at half hourly intervals with interpretation for 3 and 7 day sessions, exercise timing being kept the same within a given session and changed from one session to another. Exercise training in the morning was associated with lower BP and HR MESORs (Midline Estimating Statistic of Rhythm, rhythm –adjusted mean) as compared to exercise done at mid - day , late and in the evening. We review some of the literature, speculate about its meaning, yet do not stray beyond in single case in our conclusions for everybody : it seems

possible and desirable to exercise at a time of pertinence rather than convenience . One shoe or one timing does not fit all.

**18. Ram B Singh, Krasimira Hristova, Daniel Pella, Jan Fedacko, Adarsh Kumar, Hilton Chaves, Ratindra Nath Mondal, Branislav Milovanovic, Germaine Cornelissen, Othild Schwartzkopff, Franz Halberg, Wilson D W. Extended Consensus on Guidelines for Assessment of Risk and Management of Hypertension: A Scientific Statement of The International College Cardiology - Thank You Dr. Franz Halberg. World Heart Journal 01/2013; 6(1).**

In most of the guidelines by various agencies , a widespread belief exist that underlying usual blood pressure can alone account the benefits of antihypertensive drugs. This view may not be correct because it does not consider the total risk. Around the clock ambulatory BP monitoring is necessary for least 7 days to better assess risk related to blood pressure and BP variability. Reference limits for BP are currently based mostly on cohort studies and on controlled drug trials conducted among hypertensive patients. This must be changed. Using fixed limits for all adults 18 years old and older ( or in just 2 age groups) should be replaced by time –specified limits quantified by gender, age and clinically , to be derived from clinically healthy population as done on too small a scale with a project on BIOCOS ( the BIOSphere and the COSmos). Antihypertensive drugs with their bioavailability as well as bioactivity have to be optimized by chronotherapy to improve the benefits and reduce side effects as documented by great scientist and human being prof. Franz Halberg, an exceptional, remarkable man, the father of chronobiology, who introduced the concepts of chronopharmacology and chronotherapy.

**19. Singh RB, Darlenska TH, Hristova K, Otsuka K, Fedacko J, Pella D, Milovanovic B, Singh R. Chronocardiology and Chronotherapy. Journal of Cardiology and Therapy 2014; 1(2): 12-19**

Chrono-cardiology is the science which refers to cardiovascular function and dysfunction according to time structure. Guidelines from various agencies for the management of cardiovascular diseases (CVDs) emphasize that the necessity, choice and intensity of treatment should be determined by the individuals probability of an event (risk) within a given period which predisposes to CVD and deaths. There is little consideration to chronotherapy based on data collected, for example, during the 24 hours, which can fail to detect vascular variability disorders not yet popularly known among cardiologists. A knowledge of chronocardiology and chronotherapy may be useful in reducing the dose of the agent as well as its adverse effects while providing several fold greater benefit, thereby optimising therapeutic efficacy and toxicity.

**20. Singh, Takahashi, Tokunaga, Wilczynska, Kim, De Meester, Handjieva-Darlenska, Cheema, Wilson D W, Milovanovic B, Fedacko J, Hristova K, Chaves H. Effect of Brain Derived**

# **Neurotrophic Factor, In Relation to Diet and Lifestyle Factors, for Prevention of Neuropsychiatric and Vascular Diseases and Diabetes. The Open Nutraceuticals Journal 01/2014; 7:5-14.**

[DOI: 10.2174/1876396001407010005]

Effect of Brain Derived Neurotrophic Factor, In Relation to Diet and Lifestyle Factors, for Prevention of Neuropsychiatric and Vascular Diseases and Diabetes

Ram B. Singh, Toru Takahashi, Miki Tokunaga, Agnieszka Wilczynska, Chee J. Kim, Fabien De Meester, Teodora Handjieva-Darlenska, Sukhinder K. Cheema, Douglas W. Wilson, Branislav Milovanovic, Jan Fedacko, Krasimira Hristova and Hilton Chaves Pp. 5-14

(Published Date: 21 February 2014)

Background: Brain-derived neurotrophic factor (BDNF) is a major neurotrophin which may have promise to be a nutraceutical of this decade. It has a documented role in neurogenesis, angiogenesis, and neuronal survival. BDNF can have beneficial effects on several cardio-metabolic and neuro-psychiatric disorders, indicating that it is important in brainbody interactions. Diet and lifestyle factors may also have an influence on BDNF levels. In this review, we examine the beneficial role of BDNF on risk factors of vascular diseases, type 2 diabetes mellitus and anxiety disorders. Methods: Internet search and discussion with peer colleagues. Results: Majority of the BDNF (70-80%) is derived from dendrite of neurons but it is also present in other body tissues. BDNF controls the food intake and appetite as well as lipid and glucose metabolism. Sedentary behavior and tobacco intake may be associated with BDNF deficiency. Lower serum concentration of BDNF and higher vascular endothelial growth factor (VEGF) concentrations were associated with increased risk of incident stroke/TIA. BDNF may serve as an intermediate biomarker for subclinical vascular disease and may also have biological potential to serve as a therapeutic target for primary and secondary prevention of vascular diseases, as well as clinical and subclinical vascular brain disease. BDNF deficiency has been observed in association with anxiety, depression, insomnia, dementia, insulin resistance, type 2 diabetes and vascular diseases. The phenotypes associated with insulin resistance are at increased risk for developing cognitive decline and neuro-degeneration resulting in vascular dementia, and depression as well as diabetes mellitus and metabolic syndrome, which are risk factors for CVDs. BDNF may be administered as nutraceutical due to its protective influence on BDNF concentrations, insulin receptors and hypothalamic dysfunction leading to beneficial effects on cardiovascular risk and neuropsychological dysfunction. It is proposed that omega-3 fatty acids and moderate physical activity may enhance BDNF release. Conclusions: It is possible that circulating BDNF deficiency is a risk factor for obesity, CVDs and diabetes as well as risk factor for neuropsychiatric diseases. BDNF administration may modify the risk of clinical and subclinical stroke, depression, and dementia as well as of obesity and type 2 diabetes.

**21. Seisyou Kou, Luis Caballero, Raluca Dulgheru, Damien Voilliot, Carla De Sousa, George Kacharava, George D Athanassopoulos, Daniele Barone, Monica Baroni, Nuno Cardim, Krasimira Hristova, Alessandro Salustri, Nico Van De Veire, Ralph Stephan Von Bardeleben, Dragos Vinereanu, Jens-Uwe Voigt, Jose**

**Luis Zamorano, Erwan Donal, Roberto M Lang, Luigi P Badano, Patrizio Lancellotti. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. Eur Heart J Cardiovasc Imaging. 2014 Jun;15(6):680-90. doi: 10.1093/ehjci/jet284. Epub 2014 Jan 21.PMID: 24451180**

**ABSTRACT:** Availability of normative reference values for cardiac chamber quantitation is a prerequisite for accurate clinical application of echocardiography. In this study, we report normal reference ranges for cardiac chambers size obtained in a large group of healthy volunteers accounting for gender and age. Echocardiographic data were acquired using state-of-the-art cardiac ultrasound equipment following chamber quantitation protocols approved by the European Association of Cardiovascular Imaging. A total of 734 (mean age:  $45.8 \pm 13.3$  years) healthy volunteers (320 men and 414 women) were enrolled at 22 collaborating institutions of the Normal Reference Ranges for Echocardiography (NORRE) study. A comprehensive echocardiographic examination was performed on all subjects following pre-defined protocols. There were no gender differences in age or cholesterol levels. Compared with men, women had significantly smaller body surface areas, and lower blood pressure. Quality of echocardiographic data sets was good to excellent in the majority of patients. Upper and lower reference limits were higher in men than in women. The reference values varied with age. These age-related changes persisted for most parameters after normalization for the body surface area. The NORRE study provides useful two-dimensional echocardiographic reference ranges for cardiac chamber quantification. These data highlight the need for body size normalization that should be performed together with age-and gender-specific assessment for the most echocardiographic parameters.

**22. Patrizio Lancellotti, Luigi P Badano, Roberto M Lang, Natela Akhaladze, George D Athanassopoulos, Daniele Barone, Monica Baroni, Nuno Cardim, Jose Juan Gomez de Diego, Genevieve Derumeaux, Krasimira Hristova, Jose David Rodrigo Carbonero, Alessandro Salustri, Nico Van de Veire, Ralph Stephan von Bardeleben, Dragos Vinereanu, Jens-Uwe Voigt, Damien Voilliot, Jose Luis Zamorano, Erwan Donal, Gerald Maurer. Normal Reference Ranges for Echocardiography: rationale, study design, and methodology (NORRE Study). Eur Heart J Cardiovasc Imaging. 2013 Apr;14(4):303-8. doi: 10.1093/ehjci/jet008. Epub 2013 Jan 31. PMID: 2337683**

**ABSTRACT:**

**BACKGROUND:** Availability of normative reference values for cardiac chamber dimensions, volumes, mass, and function is a prerequisite for the accurate application of echocardiography for both clinical and research purposes. However, due to the lack of consistency in current

echocardiographic 'reference values', their use for clinical decision-making remains questionable. **AIMS:** The aim of the 'Normal Reference Ranges for Echocardiography Study (NORRE Study)' is to obtain a set of 'normal values' for cardiac chamber geometry and function in a large cohort of healthy Caucasian individuals aged over a wide range of ages (25-75 years) using both conventional and advanced echocardiographic techniques. **METHODS:** The NORRE Study is a large prospective, observational multicentre study in which transthoracic echocardiographic studies will be acquired in 22 laboratories accredited by the European Association of Cardiovascular Imaging and in one laboratory in the USA accredited by ICAEL. The final sample size has been estimated in 1100 normal subjects in whom M-mode, 2D, and 3D imaging, colour Doppler, pulsed-wave Doppler, pulsed-wave tissue Doppler, and colour tissue Doppler imaging data will be obtained. All studies will be sent to a central echocardiographic core laboratory for quantitative analysis. Multiple studies will be performed for reproducibility analysis. **CONCLUSION:** After completion of the NORRE Study, uniform reference limits according to age, gender, and anthropometric parameters will be available to standardize the quantitative interpretation of echocardiography.

**23. Ivy Shiue, Krasimira Hristova. Associated social factors of hypertension in adults and the very old: UK Understanding Society cohort, 2009-2010. Int J Cardiol. 2013 Oct 9;168(4):4563-5. doi: 10.1016/j.ijcard.2013.06.079. Epub 2013 Jul 19**

High blood pressure (HBP) is the most important risk factor worldwide for the development of cardiovascular disease and beyond [1]. It has been known that inverse associations exist between cardiovascular risk factors and socioeconomic status, whether being measured by occupation, income or education. Back in the 1980s, it was hypothesised that initiating factors for the pathogenesis of essential hypertension could be from social environment, such as weight gain and environmental stress [2,3]. Reductions in health and social inequalities could play an important role in impressive declines in cardiovascular disease-related incidence, biomarkers, and mortality [4].

**24. Ivy Shiue, Krasimira Hristova. Geographic variations in prevalent cardiovascular disease subtypes: UK Understanding Society cohort, 2009-2010. Int J Cardiol. 2014 Feb 15;171(3):e81-3. doi: 10.1016/j.ijcard.2013.11.098. Epub 2013 Dec 6**

Regional variations of cardiovascular disease (CVD) subtypes have been investigated over the last decades. Mostly, researchers focused on incidence and mortality. However, knowing the regional variations in prevalent CVD could further help medical professionals and policy makers prepare medical and social resources such as ambulance response, diagnostic acumen, and so on to be efficiently (re)allocated in the next years since rehabilitation facility will also play an important role in helping patients and family at both regional and national levels.

**25. J. Fedacko, RB Singh, A. Gupta. K. Hristova, E. Toda, A. Kumar, M.Saxena, A,Baby, R. Singh, T. Takahashi, D. Wilson. Inflammatory mediators in chronic heart failure in North India. Acta Cardiol. 2014 Aug;69(4):391-8. PMID: 25181914**

## Abstract :

**Introduction:** Recent evidence shows that pro-inflammatory cytokines may be important in the assessment of severity and prognosis in congestive heart failure (CHF). In the present study, we examine the association of cytokines with causes, grade and prognosis of CHF patients.

**Subjects and methods:** Of 127 patients with CHF, 11 were excluded and the remaining 116 patients with different aetiologies of CHF, and 250 age- and sex-matched control subjects, were evaluated in this case study. Severity of disease based on the New York Heart Association (NYHA) standards, fell within functional classes II to IV. The diagnosis of HF was based on clinical manifestations as well as on echocardiographic heart enlargement. Cytokines were measured by chemiluminescence. Causes of death were assessed based on death certificates. Multivariate logistic regression analysis was used to determine the risk factors of heart failure.

**Results:** Echocardiographic ejection fraction was  $39.1 \pm 8.2\%$  (mean  $\pm$  SD) in the study group indicating class II-IV heart failure. Laboratory data showed increase in biomarkers of oxidative stress, among HF patients compared to healthy subjects. Pro-inflammatory cytokines; IL-6 and TNF-alpha were significantly higher among HF patients compared to healthy subjects. TNF-alpha and IL-6, showed significant increase among patients with CHF due to ischaemic heart disease and cardiomyopathy compared to levels among CHF patients with valvular heart and hypertensive heart diseases. The levels of the cytokines were significantly higher among patients with class III and IV heart failure and those who died, compared to patients with class II heart failure. Multivariate logistic regression analysis revealed that CAD, cardiomyopathy, and IL-6 were strongly associated – and low ejection fraction and TNF-alpha – weakly associated with HF. Of 116 patients, 20 (17.2%) died during a follow-up of two years, and the deaths were mainly among NYHA class III and IV patients in whom the cause of CHF was CAD (10.9%) and cardiomyopathy (6.9%) which had greater levels of cytokines.

**Conclusions:** The findings indicated that pro-inflammatory cytokines may be important indicators of causes, severity of CHF and prognosis among these patients.

## 26. **K. Hristova. Hot topics in cardiology. Editorial . In J Discov Biol Med 2012,1(1):37-40**

### Hot topics in cardiology

#### LETTERS TO THE EDITOR

To the Editor: Heart disease is likely to prevail as the leading cause of death and disability in all over the world. The continued urbanization and adoption of western lifestyle given this the globally problem and in the developing world. As the INTERHEART study made clear, the same risk factors that contribute to CVD in North America also contribute to the disease elsewhere regardless of region, continent or ethnic group [1]. However, the opportunity for prevention is not an unrealistic expectation. The mortality from heart disease in the USA has steadily declined, especially within the last 10 year, where there has been over a 35% reduction of mortality from coronary heart disease (CHD). Concurrent with this reduction has been a similar reduction from death due to stroke. As researchers commented, this reduction in CVD mortality is in part related to improved therapies but also nascent efforts at disease prevention. Most notably, these efforts have included important reductions in smoking and better control of hypertension. Unfortunately, the benefits may prove to be short-lived as the burden of risk, specifically diabetes and obesity, is on rise, especially in the younger population and in developing countries.

**27. Simova I, Katova T, Nesheva A, Hristova K, Kostova V, Boyadzhiev I, Dimiktrov N. Echocardiographic predictors of early postoperative atrial fibrillation in coronary artery bypass surgery patients . World Heart J.2014, 6, (3),163-170.**

Background: Atrial fibrillation (AF) is the most common complication during the perioperative period of coronary artery bypass graft (CABG) surgery. Objective: To evaluate the predictive power of different clinical and echocardiographic parameters for the occurrence of perioperative AF (POAF). Methods: We studied 58 patients without previous history of AF undergoing elective CABG. We analyzed different demographic factors, clinical parameters, perioperative characteristics and the echocardiographic variables: left/right atrial volume index (L/RAVI), left ventricular end-diastolic diameter, ejection fraction, tissue velocities at the mitral and tricuspid annulus during early and late diastolic filling (Em, Am, Et and At, respectively) as well as interatrial asynchrony time (IAA) and global functional index. Results: Of 58 patients, 14 patients (24%) developed POAF. Demographic factors, clinical characteristics and perioperative variables didn't show a significant difference between patients with or without POAF. Patients with POAF had larger LAVI and RAVI and higher IAA. After a Linear Regression Analysis, IAA, LAVI, smoking and female gender turned out to be independent predictors for the occurrence of POAF. For IAA and LAVI we performed a ROC analysis and found that IAA values  $\geq 32$  ms had 100% sensitivity and 82% specificity, while LAVI values  $\geq 29$  ml/m<sup>2</sup> showed 86% sensitivity and 52% specificity for the occurrence of POAF. Conclusion: For a relatively small patient group without previous history of AF and undergoing CABG surgery IAA, LAVI, smoking and female gender were independent predictors for the occurrence of POAF. The strongest predictor for POAF was IAA with the cut-off value of 32.

**28. Negishi K, Negishi T, Kurosawa K, Hristova K, Popescu BA, Vinereanu D, Yuda S, Marwick TH. Practical Guidance in Echocardiographic Assessment of Global Longitudinal Strain. JACC Cardiovasc Imaging. 2014 Aug 5. pii: S1936-878X(14)00494-X. doi: 10.1016/j.jcmg.2014.06.013.**

THERE HAS BEEN INCREASING INTEREST IN THE MEASUREMENT OF GLOBAL MYOCARDIAL STRAIN because it is a sensitive and robust index to detect subclinical myocardial dysfunction, with a defined normal range. Numerous commercially-available versions of speckle tracking software are available for strain analysis, and measurement involves 6 steps that are common to different methods. Surprisingly, however, there are no standard instructions for measuring it adequately. This could be one of the causes of interobserver variation, especially in different echocardiography laboratories.

The authors developed a set of 9 cases as a step to establishing reader uniformity in an international multicenter trial of the incremental value of myocardial strain for the detection of cardiotoxicity (SUCCOUR [Strain sUrveillance during Chemotherapy for improving Cardiovascular Outcomes]: ANZ clinical trial FIGURE Steps for Myocardial Strain Measurement These steps are generic to speckle tracking techniques for the assessment of strain. ROI = region of interest.

**29. Shiue I, Hristova K. Higher urinary heavy metal, phthalate and arsenic concentrations accounted for 3-19% of the population attributable risk for high blood pressure: US NHANES, 2009-2012. *Hypertens Res.* 2014 Dec;37(12):1075-81. doi: 10.1038/hr.2014.121. Epub 2014 Jul 31. PMID: 25077919**

Hypertension Research 37, 1075-1081 (December 2014) | doi:10.1038/hr.2014.12

Abstract

The link between environmental chemicals and human health has emerged, but has not been completely examined in terms of its risk factors. Therefore, we aimed to study the relationships of different sets of urinary environmental chemical concentrations and high blood pressure (BP) in a national, population-based study. Data were retrieved from the United States National Health and Nutrition Examination Surveys, 2009–2012, including demographics, BP readings and urinary environmental chemical concentrations. Analyses included  $\chi^2$ -test, t-test, survey-weighted logistic regression models and population attributable risk estimation. Urinary cesium (odds ratio (OR) 1.52, 95% confidence interval (CI) 1.06–2.18,  $P=0.026$ ), molybdenum (OR 1.45, 95% CI 1.04–2.02,  $P=0.029$ ), lead (OR 1.49, 95% CI 1.12–1.98,  $P=0.009$ ), platinum (OR 1.66, 95% CI 1.14–2.21,  $P=0.002$ ), antimony (OR 1.44, 95% CI 1.12–1.86,  $P=0.008$ ) and tungsten (OR 1.48, 95% CI 1.22–1.79,  $P<0.001$ ) concentrations were observed to be associated with high BP. Similar results were observed for mono-2-ethyl-5-carboxypentyl (OR 1.29, 95% CI 1.04–1.59,  $P=0.024$ ), mono-n-butyl (OR 1.36, 95% CI 1.11–1.67,  $P=0.005$ ), mono-2-ethyl-5-hydroxyhexyl (OR 1.21, 95% CI 1.01–1.46,  $P=0.041$ ), mono-n-methyl (OR 1.24, 95% CI 1.01–1.46,  $P=0.014$ ), mono-2-ethyl-5-oxohexyl (OR 1.21, 95% CI 1.01–1.45,  $P=0.036$ ), mono-benzyl (OR 1.41, 95% CI 1.15–1.74,  $P=0.002$ ), dimethylarsonic acid (OR 1.38, 95% CI 1.08–1.76,  $P=0.012$ ) and trimethylarsine oxide (OR 2.56, 95% CI 1.29–5.07,  $P=0.010$ ) concentrations. Each chemical could account for 3–19% of the population attributable risk for high BP. A small sex difference was found. However, there are no associations between environmental parabens and pesticides and high BP. Urinary heavy metal, phthalate and arsenic concentrations were associated with high BP, although a causal effect cannot be established. Elimination of environmental chemical exposure in humans still needs to be pursued.

To read this article in full you may need to log in, make a payment or gain access through a site license (see right).

**30. Hristova K, Shiue I . The Role of Echocardiography for Evaluation Patients with Arterial Hypertension. *Ann Clin Exp Hypertension* 2(3): 1016, 1-6**

Arterial hypertension is a major risk factor for stroke and cardiovascular diseases, and is thus associated with significant morbidity and mortality. Hypertensive heart disease is a complex entity that involves changes to the cardiovascular system resulting from arterial hypertension; it is therefore the major cause of hypertension-related complications [1]. The development of Doppler echocardiography has offered new approaches regarding both insights into



pathophysiology and clinical implications that affect hypertensive patients[2,3] . For these reasons, it is obvious that echocardiographic assessment is very important in the clinical management of hypertensive patient. We aimed at reviewing “old” and newer data regarding the contributions of echocardiography to the evaluation of a hypertensive patient

### **31. Shuie I. Hristova K. Correspondence. Gender and outcome from acute myocardial infarction and secondary stroke. The British Journal of Cardiology, Vol. 21, issue 3, September 2014.**

Research on sex difference in mortality after myocardial infarction (MI) since the 1990s has been debated and increased. Several observational studies have shown that younger women, in particular, seemed to have higher mortality rates than men of similar age during the two-year or longer follow-up, although these studies were mainly from the USA.<sup>1-3</sup> Recent American studies have also found that, even after full adjustment for potential risk factors, excess risk for in-hospital mortality for women was still noted, particularly among those <50 years old with acute ST-segment elevation MI, leading to 98% (odds ratio [OR] 1.98, 95% confidence interval [CI] 1.26 to 3.12) greater odds of death than men.<sup>4</sup> What was additionally observed was that, in general, female patients tended to have significantly higher comorbidity scores, and were less likely to undergo revascularisation (percutaneous coronary intervention or coronary artery bypass grafting surgery) than their counterparts during hospitalisation. Moreover, during hospitalisation women were found to be less likely to have ventricular tachycardia and ventricular fibrillation, but more likely to have atrial tachycardia and atrial fibrillation, than men.

Fatal and non-fatal stroke events higher in women post-MI

In Sweden, a recent study has reported that mortality after acute MI complicated by ischaemic stroke has decreased for both men and women between 1998 and 2008,<sup>5</sup> and the authors concluded that evidence-based therapies seemed to explain the reduction of mortality post-MI. However, the proportions in females have actually increased over the last decade, from 38.2% to 42.1% in non-fatal stroke events and from 46.4% to 50.1% in all stroke events, including both fatal and non-fatal. Were those therapies better for men only? On the other hand, some concerns on the adherence to evidence-based pharmacotherapy and long-term mortality after acute MI could be of interest.

In Canada,<sup>6</sup> among statin users, compared with their high-adherence counterparts, the risk of mortality was greatest for low adherers (deaths in 261/1071 [24%] vs. 2310/14,345 [16%]; adjusted hazard ratio 1.25; 95% CI 1.09–1.42; p=0.001) and was intermediary for intermediate adherers (deaths in 472/2407 [20%]; adjusted hazard ratio 1.12; 95% CI 1.01–1.25; p=0.03). A similar but less pronounced dose-response-type adherence-mortality association was also observed for beta blockers, although mortality was not associated with adherence to calcium channel blockers.

The possibility of low-adherence to pharmacotherapy among Swedish women is, however, unclear. Another Canadian study has revealed that psychosocial factors such as post-MI depression can be a predictor of one-year cardiac mortality and the risk effect could be minimised with the advancement of social support.<sup>7</sup> In other words, by providing more social support, depression symptoms can be lessened leading to an improved prognosis for MI and a better survival, together with increasing higher adherence of pharmacotherapy. The disparity in the survival post-MI between male and female patients is continuing to widen, and we need to close the gap in survival rates among patients to prevent further unnecessary deaths in a timely manner.

**32. Singh S, Bansal M, Maheshwari P, Adams D, Sengupta SP, Price R, Dantin L, Smith M, Kasliwal RR, Pellikka PA, Thomas JD, Narula J, Sengupta PP; ASE-REWARD Study Investigators. ). American Society of Echocardiography: Remote Echocardiography with Web-Based Assessments for Referrals at a Distance (ASE-REWARD) Study. J Am Soc Echocardiogr. 2013, Mar;26(3):221-33. doi: 10.1016/j.echo.2012.12.012**

**BACKGROUND:** Developing countries face the dual burden of high rates of cardiovascular disease and barriers in accessing diagnostic and referral programs. The aim of this study was to test the feasibility of performing focused echocardiographic studies with long-distance Web-based assessments of recorded images for facilitating care of patients with cardiovascular disease.**METHODS:** Subjects were recruited using newspaper advertisements and were prescreened by paramedical workers during a community event in rural north India. Focused echocardiographic studies were performed by nine sonographers using pocket-sized or handheld devices; the scans were uploaded on a Web-based viewing system for remote worldwide interpretation by 75 physicians.**RESULTS:** A total of 1,023 studies were interpreted at a median time of 11:44 hours. Of the 1,021 interpretable scans, 207 (20.3%) had minor and 170 (16.7%) had major abnormalities. Left ventricular systolic dysfunction was the most frequent major abnormality (45.9%), followed by valvular (32.9%) and congenital (13.5%) defects. There was excellent agreement in assessing valvular lesions ( $\kappa = 0.85$ ), whereas the on-site readings were frequently modified by expert reviewers for left ventricular function and hypertrophy ( $\kappa = 0.40$  and  $0.29$ , respectively). Six-month telephone follow-up in 71 subjects (41%) with major abnormalities revealed that 57 (80.3%) had improvement in symptoms, 11 (15.5%) experienced worsening symptoms, and three died.**CONCLUSIONS:** This study demonstrates the feasibility of performing sonographer-driven focused echocardiographic studies for identifying the burden of structural heart disease in a community. Remote assessment of echocardiograms using a cloud-computing environment may be helpful in expediting care in remote areas.

**33. Ram B. Singh, Amrat K. Singh, Hideki Mori, Daniel Pella, Tapan K. Basu, Lech Ozimek, Shailendra K. Vajpeyee, Douglas W. Wilson, Fabien De Meester, Krasimira Hristova, Lekh Juneja, Sukhinder Kaur, Manohar Garg, Toru Takahashi, Adarsh Kumar, Rajiv Garg, Nirankar S. Neki, R. G. Singh and Sharad Rastogi A Tribute to Nutrio-Diabetologist Shanti S. Rastogi MBBS, MD,FRCP,FICN, FICC.The Open Nutraceuticals Journal,2014, 7,39-43**

[DOI:10.2174/1876396001407010039]

**A Tribute to Nutrio-Diabetologist; Shanti S. Rastogi MBBS, MD, FRCP, FICN, FICC**  
*Ram B. Singh, Amrat K. Singh, Hideki Mori, Daniel Pella, Tapan K. Basu, Lech Ozimek, Shailendra K. Vajpeyee, Douglas W. Wilson, Fabien De Meester, Krasimira Hristova, Lekh Juneja, Sukhinder Kaur, Manohar Garg, Toru Takahashi, Adarsh Kumar, Rajiv Garg, Nirankar S. Neki, R. G. Singh and Sharad Rastogi* Pp. 39-43

(Published Date: 28 November, 2014)

Dr. Shanti Swarup Rastogi who pioneered the Diet and Lifestyle guidelines of India was a staunch and steadfast friend who believed in the warmth of friendship.

Dr. Rastogi gave his all love to those who were his friends and hence he was affectionately called Nawab Sahib. Once I (RBS) found him worried, because he was of the opinion that his son Sharad was not that liberal with his friends.

He wanted him to be liberal and to be called at least Chhote Nawab by his friends. He was a shining light that guided us with his extraordinary enthusiasm and he would never say NO to anything. He was a visionary with 'nutritional ideas' and his work, ethos and energy were exemplary.

### **34. Krasimira Hristova, Jan Fedacko, Eri Toda, R.B. Singh, Hyun Ho Shin, and Moon-Kyu Lee. Can Aspirin Be Used in Combination with an Oral Anticoagulant in the Prevention of Thromboembolism and Bleeding in Patients with Heart Disease? World Heart Journal 2012; 4,4; 189-192**

**Introduction** — There is evidence that congestive heart failure (CHF) has become a public health problem, both in developed and developing countries, which may be due to greater prevalence of acute myocardial infarction (AMI) and hypertension and their longer survival. Further evidence showed that pro-inflammatory cytokines may be important in the assessment of severity and prognosis in CHF. However there are only a few studies indicating the association of inflammation with causes of CHF and severity and prognosis among these patients.

**Subjects and methods.** Of 127 patients of CHF, 11 were excluded and rest 116 patients with different aetiologies of CHF and 250 age and sex matched control subjects, were studied in this case study. Severity of disease was assessed according to the New York Heart Association (NYHA) standards and fell within functional classes II to IV. After written informed consent and approval from the ethics committee, patients were recruited from the Department of Cardiology, Government Medical College, Amritsar, India and Halberg Hospital and Research Institute, Moradabad, India for this study. The diagnosis of HF was based on clinical symptoms as well as

on radiological and echocardiographic heart enlargement and low ejection fraction, in presence of clinical signs of HF. Cytokines were measured by chemiluminiscence.

**Results. Echocardiographic ejection fraction was (mean±SD)39.1±8.2% in the study group indicating class II-IV heart failure. However, echocardiographic data were not available in the healthy subjects group.** Laboratory data showed that biomarkers of oxidative stress such as TBARS, MDA and diene conjugates were significantly higher among HF patients compared to healthy subjects. Pro-inflammatory biomarkers; IL-6 and TNF-alpha were significantly higher and anti-inflammatory IL-10 was significantly lower among HF patients compared to healthy subjects (normal mean(SD) value, TNF-alpha 5.3±2.5 pg/ml; interleukin-6 4.4±2.1 pg/ml.

The concentrations of both the cytokines; TNF-alpha and IL-6 show significant increase among patients with CHF due to various aetiologies; ischaemic heart disease, cardiomyopathy, valvular heart disease and hypertensive heart diseases. The trends of increase were significant for both the cytokines. The levels of the cytokines were significantly higher among patients with class III and IV heart failure compared to patients with class II heart failure.

**Conclusions** — The findings indicate that pro-inflammatory cytokines that are neurohumoural precursors related to sympathetic and parasympathetic activity, (impaired in patients with heart failure) may be important indicator of severity of CHF and prognosis among these patients.

**35. Shehab A, Elkilany G, Singh RB, Hristova K, Chaves H, Cornelissen G, Otsuka K. EDITORIAL: CORONARY RISK FACTORS IN SOUTH WEST ASIA. World Heart Journal 2015; (in press)**

The last few decades of the last century greatly increased our knowledge about the global dimensions of noncommunicable diseases (NCD), including cardiovascular diseases (CVDs) (1-3). Recent studies indicate that nutritional deficiencies coexist with appreciable overnutrition in the form of central obesity and overweight in emerging countries, and that in developed countries one-quarter of the population is obese (1-7). We proposed that overweight comes first, in conjunction with inflammation, hyperinsulinemia, increased angiotensin activity, vascular variability disorders and central obesity, followed by glucose intolerance, type 2 diabetes, hypertension, low HDL and hypertriglyceridemia (metabolic syndrome). This sequence is followed by CAD, gallstones and cancers and finally dental caries, gastrointestinal diseases, bone and joint diseases, degenerative diseases of the brain and psychological disorders, during transition from poverty to affluence.

**36. Hristova K, Cornelissen G, Fedacko J, Singh RB. Echocardiographic study of circadian myocardial function among clinically healthy subjects. World Heart Journal 2014, 6, 4.**

Background: Synchronization of organisms with their environment along the 24-hour scale is mediated by circadian clocks. This cell-autonomous mechanism has been identified within all cardiovascular-relevant cell types, including cardiomyocytes.

Subjects and Methods: The study aims to assess the circadian pattern in the contractility of the left ventricle (LV), using myocardial deformation imaging. The study involved 11 clinically healthy volunteers (mean age 38y ±10), including 4 men (mean age 30.5y ±12.4) and 7 women (mean age 42.7y ±4.8). Automated quantification of LV systolic function by measurement of LV systolic strain from speckle-tracking echocardiography was used. Echocardiography was performed with a commercially-available standard ultrasound scanner, and a 2.5-MHz transducer. All images were obtained at a rate of 50 to 70 frames/s. Strain and twist/untwist measurements were performed offline with dedicated automated software.

Results: In health, global longitudinal strain (GLS) varied from -22.35% to -22.87%, global circumferential strain (GCS) from -18.41% to -21.50%, and global radial strain (GRS) from 36.75% to 42.30%. LV twist (LVT) ranged from 8.33° to 10.77° and untwist rate (LVUR) from 87.45°/s to -71.49°/s. Overall, highest values for GLS, GRS, and LVT occurred around 06:00 and overall lowest values of GRS and LVT around 18:00. Considering results from all 6 walls as independent replications, a statistically significant circadian rhythm was found for both regional circumferential strain (P<0.001) and for radial strain (P=0.002).

Discussion and Conclusion: This study assessed global physiological consequences of the circadian clock specifically within the myocardial deformation. Apart from influences of the cardiomyocyte circadian clock on heart rate and the responsiveness of the heart to an increased workload, evidence is provided herein for the circadian stage-dependence of regional deformation, an important result pertaining to global ventricular function

**37. Krasimira Hristova, Ram B Singh, Jan Fedacko, Eri Toda, Adarsh Kumar, Manoj Saxena, Anjum Baby, Takahashi Toru, Fabien De Meester, Douglas W Wilson. CAUSES AND RISK FACTORS OF CHRONIC HEART FAILURE IN INDIA. World Heart Journal 2013,5,1.**

Introduction. Recent evidence shows that chronic heart failure (CHF) is a major cause of morbidity and mortality. The prognosis in CHF may be dependent on cause, severity and presence of risk factors and drug therapy. In the present study, we examine the causes, risk factors, class and oxidative stress among CHF patients.

Subjects and methods. Of 127 patients with CHF, 2 were excluded and the remaining 125 patients (Men 61, women 64) with different aetiologies of CHF, and 250 age and sex matched control subjects, were evaluated in this case study. Severity of disease based on the New York Heart Association (NYHA) standards fell within functional classes II to IV. The diagnosis of HF was based on clinical manifestations as well as on echocardiographic heart enlargement.

Results. The causes of CHF were; CAD (n=34, 27.2%), hypertensive heart disease (n=10, 8.0%), valvular heart disease (n=40, 32.0%) and idiopathic dilated cardiomyopathy (n=38,

30.4%). Risk factors of HF were; CAD (n=52, 41.6%), hypertension (>140/90mmHg) (n=54, 43.2%), diabetes mellitus (n=12, 9.6%), obesity (n=43, 34.4%) and albuminuria (n=12, 9.6%). Echocardiographic ejection fraction was  $39.1 \pm 8.2\%$  (mean  $\pm$  SD) in the study group, indicating class II-IV heart failure. There was a significant increase in biomarkers of oxidative stress, among HF patients compared to healthy subjects.

Conclusions. The findings indicate that HF has become a public health problem. The causes of HF appear to be CAD, cardiomyopathy and valvular heart disease. Severity of CHF, aetiology; CAD and cardiomyopathy appear to be important for increased oxidative stress among these patients.

### **38. Jan Fedacko, Viola Vargova, RB Singh, Eri Toda, Krasimira Hristova, Daniel Pella. CAN ELECTIVE PERCUTANEOUS CORONARY INTERVENTION SAFELY PERFORMED WITHOUT SURGICAL BACKUP? World Heart Journal 2013, 5, 9-12**

Emergency coronary bypass surgical grafting (CABG) over percutaneous coronary intervention (PCI) has become a rare event. This achievement of the angioplasters raises the question of whether availability of cardiac surgery on site is still necessary for the safe and effective performance of PCI?. In view of the complications such as myocardial infarction (MI) after PCI, it is important to inform clinical practice as well as to place the findings in proper perspective for the purposes of diagnostic coding, insurance and epidemiological considerations, interpretation of clinical trials, and performance "scorecards." There may be emotionally charged arguments on scorecards, because of the potentially adverse consequences for operators, if PCI in their hands is perceived as being associated with high rates of MI. It is an excoriating situation for operators who are willing to take on high-risk PCI procedures. The utility and necessity for timely access to primary PCI has justified the expansion of PCI to hospitals without on-site cardiac surgery (1,2). However, controversy exists as to whether there should be a further expansion for non-emergent PCI to these hospitals? Since the risk/benefit ratio might be different in various hospitals and the need for timely access is less important to cardiovascular outcomes, such a possibility and availability can decrease the expenses of the set up of the hospitals and therefore cost of PCI.

### **39. Teodora Handjieva-Darlenska, Krasimira Hristova, and Ram B Singh. Antioxidant Vitamins and the Heart. World Heart Journal 2014, 6, 2**

Antioxidant vitamin deficiency may be important in the pathogenesis of atherosclerosis and cardiovascular diseases (CVD). Epidemiological studies show that vitamin A, E and C and beta-carotene as well as folic acid and selenium were inversely associated with risk of morbidity and mortality due to CVDs and cancer. However, randomized, controlled intervention trials showed no evidence of benefit in CVDs and cancers; but adverse effects were observed in some of the important studies. Hence, there is no evidence to support the use of vitamins in the prevention of CVDs and cancer. Further studies are necessary to find out the role of vitamins and minerals in children, malnutrition and chronically ill people in the elderly population.

**40. Rakesh Sharma, Thakur Hemnani, Aditya K Gupta, Ram B. Singh, Teodora Handjiev-Darlenska, and Krasimira Hristova. Micro-RNA in Cardiovascular Diseases. World Heart Journal 2014, 6, 2. World Heart Journal 2014, 6, 203-208**

Cardio-enriched miRNAs play a crucial role in cardiac development and have been associated with the development of dilated cardiomyopathy. It is possible that MicroRNA binds to complementary sequences in the 3'untranslated region of mRNA and thereby facilitates down regulation of gene expression. Further studies indicate that cells release some of their miRNA content into the circulation in presence of tissue damage or stress due to acute coronary syndromes which may be used for diagnosis of cardiac damage. Majority of the microRNA species are remarkably stable and readily detectable in blood. They are, therefore, excellent candidate biomarkers for various diseases, including myocardial infarction and heart failure.

Recent studies reported that plasma microRNAs serve as biomarkers of therapeutic efficacy and disease progression in hypertension-induced heart failure, acute coronary syndrome and type 2 diabetes.

**41. Ram B Singh, Jan Fedacko, Daniel Pella, Krasimira Hristova, HiltonChaves, Branislav Milovanovic, Teodora H. Darlenska, Toru Takahashi, Fabien De Meester, Douglas W Wilson, Galal Elkilany, and Sherif Baathallah. Angiotensin Converting Enzyme: A Possible Risk during Transition from Undernutrition to Chronic Diseases of Affluence. World Heart Journal 2014, 6, 209-214**

Coronary risk factors (CRF) and coronary artery disease (CAD) have become a worldwide problem on both sides of the Atlantic [1-3]. European countries such as Slovakia, Poland, and Hungary and some in Asia such as Hong Kong, Singapore and Taiwan, that are more affluent, have greater prevalence of these adverse effects in comparison to low income countries such as The Philippines, China, India, Thailand, and Brazil [3-6]. Hypertension, diabetes and CAD are very low in the rural population of India, China, and in the African sub-continent which has less economic development [3-7]. However, in urban and immigrant populations of India and Chinese origin, the prevalence of hypertension (>140/90, 25-30%), diabetes (6-18%) and CAD (7-14%) are significantly higher than they are in some of the high income( mg/dl), obesity (5-8%) and dietary fat intake (25-30% en/day) are paradoxically not very high and do not explain the cause of increased susceptibility to CAD and diabetes in some South Asian countries [5-8]. The force of lipid-related risk factors appears to be greater in these populations due to the presence of the above factors and results in cardiovascular disease (CVD) and type 2 diabetes at a younger age in these countries. Despite decreased mortality in developed countries, these populations continue to have increased prevalence of obesity, type 2 diabetes and metabolic syndrome which are posing great threats to high income populations in these countries. It is possible that new risk factors; angiotensin converting enzyme (ACE) levels, lipoprotein(a), oxidative stress, antioxidant and omega-3 fatty acid deficiency and insulin resistance that are related to diet and lifestyle may explain the cause of variation in the risk (6-9). Diet and lifestyle factors may also explain the variations in the ACE levels in various developing

Ram B Singh, 210 Jan Fedacko, Daniel Pella et al. populations which are unlikely to be observed among Caucasians where under-nutrition and social class 5 populations have completely disappeared. ACE levels may be lower in certain other conditions; anorexia nervosa, hypothyroidism, steroid therapy, therapy of sarcoidosis and chronic liver disease. A lower level of ACE in the blood in anorexia nervosa indicates that it may be related to energy consumption which is diminished in this condition. It seems that energy intake and physical activity which is higher among lower social classes may also influence ACE levels.

**42. Teodora Handjieva-Darlenska, Ram B Singh, Krasimira Hristova, Branislav Milovanovic, Jan Fedacko, Sergey Chibisov, Sergey Shastun, Vicky Beeharry, Svetoslav Handjievi, and Chee Jeong Kim. Timing of Statin Therapy May Eliminate Its Toxicity and Increase Its Bioactivity, Said Professor Halberg, The Lord of Time. World Heart Journal 2014, 6, 1.85-88**

Halberg, the Lord of Time proposed that any adverse effects of any therapeutic agent can be eliminated or reduced in extent and bioactivity can be increased by the rescheduling the treatment along the 24-hour scale. The treatment may be modifications of routine activities, diet and/or daily exercise and/or statin or antihypertensive medication. For any non-drug or drug treatment the rescheduling in kind and/or timing of administration being gauged by hours after the habitual awakening time or by other marker rhythms such as continuous ambulatory blood pressure monitoring (C-ABPM), wrist activity or a human metabolite timetable. Cholesterol synthesis has a diurnal variation and most of it is synthesized in the night. There is evidence that statins are potent and effective agents with several pleiotropic effects for treatment of hypercholesterolemia and coronary artery disease (CAD). Statins can also decrease sympathetic activity. Statin may have adverse effects, if given in higher doses and in combinations, indicating that it may be a two edged sword. However, if the approach based on timing is used, the dosage of statins may be lowered to achieve greater therapeutic benefit without having any adverse effects of the drug.

**43. Jan Fedacko, Ram B. Singh, Teodora Handjiev Darlenska, Krasimira Hristova, Daniel Pella, and Hilton Chaves. Editorial - Antiplatelet Therapy in Heart Failure. World Heart Journal 2014, 6, 2.**

The prevalence and incidence of heart failure (HF), based on disease-specific estimates may be conservatively attributed mainly due to coronary artery disease (CCAD), hypertension, obesity, diabetes



and rheumatic heart disease. The prevalence rate range from 1.3 to 4.6 million, with an annual incidence of 491 600-1.8 million. However, the causes of HF in the Western World are CAD, cardiomyopathy, hypertension, obesity and diabetes mellitus. Although, no data are available from developing and newly industrialized countries, regarding the exact prevalence and incidence of HF, it is possible that higher propensity for CVDs and ageing of population, may enhance the burden of HF greater than that in the Western populations. There is an urgent need to have HF registries in the secondary, tertiary care centers and at the national level. The heart failure registry may help and provide us the detailed information related to incidence, prevalence, and aetiology of HF in India. In earlier studies from India, rheumatic heart disease has been the major cause of HF. In later studies, CAD and cardiomyopathy have become major causes of HF in India . The mechanisms of HF may be related to oxidative stress, mitochondrial and microRNA dysfunction, inflammation and disturbed myocardial substrate metabolism as observed in various studies.

**44. R.B. Singh, Krasimira Hristova, Galal El-Kilany, Takahashi Toru, Abdullah Shehab, Hilton Chaves, DW Wilson, Divya Rupini , Neelesh Gupta and Rajeev Gupta. LETTER TO THE EDITOR: Nutritional Modulators in Chronic Heart Failure. *The Open Nutraceuticals Journal*, 2015, 8, 1-4 ( in press)**

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## СПИСЪК НА НАУЧНИТЕ ТРУДОВЕ

на д-р Красимира Атанасова Христова , д.м..

### А. НАУЧНИ ПУБЛИКАЦИИ В ПЪЛЕН ОБЕМ / РЕАЛНИ /

#### ***I. Дисертация***

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#### **Б. УЧАСТИЯ С ДОКЛАДИ ИЛИ ПОСТЕРИ В МЕЖДУНАРОДНИ НАУЧНИ ФОРУМИ С ОТПЕЧАТАНИ РЕЗЮМЕТА ИЛИ ПРОГРАМИ**

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***В. УЧАСТИЯ С ДОКЛАДИ ИЛИ ПОСТЕРИ В БЪЛГАРСКИ НАУЧНИ ФОРУМИ  
С ОТПЕЧАТАНИ РЕЗЮМЕТА ИЛИ ПРОГРАМИ***

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