NONINVASIVE METHODS IN CARDIOLOGY 2019

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100 years of Masaryk University 2019

100th Anniversary of Masaryk University in Brno, Czech Republic

Jarmila Siegelova

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The history of Masaryk University closely reflects the history of the Czech nation. The independent Czechoslovak Republic was founded in October 1918.

The second Czech university in the country was established with the aim to promote the scientific and cultural development and to create a center of academic life in Moravia. The university was named after T.G. Masaryk, the first Czechoslovak president, whose continuous and strong support played a decisive role in the establishment of the university.

In 1919, the Faculty of Law and the Faculty of Medicine started their teaching program, in 1921 followed the Faculty of Arts and the Faculty of Science. In the First Republic (1919-1939), the university achieved high pedagogic and scientific recognition in many areas, in medicine in the fields of physiology, anatomy, histology, surgery and internal medicine. During the Second World War, the Masaryk University was closed and many personalities of the university staff and students were imprisoned and lost their lives.

In 1945, teachers and students resumed immediately their work. The political development in Czechoslovakia after 1948 caused the change of the name of the University. The university bore the name of J.E.Purkyně, a famous Czech physiologist, between the years 1960-1989.

The history of the long lasting international cooperation started in the Physiological Department in the sixties, when under the famous teacher Prof. MUDr. Vladislav Kruta, DrSc. Prof. MUDr. Bohumil Fiser, CSc. and Prof. MUDr. Jarmila Siegelova, DrSc. started their professional careers as young teachers and scientists in physiology. The Department of Physiology in University of J.E. Purkyne (Masaryk University) was very well known all over the world; the head of the department was Prof. MUDr. Vladislav Kruta, DrSc. who cooperated with the physiologists from England, France, Netherlands, Switzerland and other countries. With the team of his younger coworkers, some of them becoming in the future professors, Prof. Vladislav Kruta with the staff of Department of Physiology organized also International Congresses: in 1969 in Prague to the honour of Prof. Jan Evangelista Purkyne and in 1970 Annual Congress of French Physiological Society in Brno.

Professor Kruta sent his coworkers from the Dept. of Physiology abroad. Prof. MUDr. Jan Penaz, CSc., was in the Netherlands, Prof. MUDr. Pavel Braveny, CSc. was in the USA, Prof. MUDr. Milos Kukleta, CSc. was in France, Prof. MUDr. Borivoj Semrad, CSc. was in Germany, Prof. MUDr. Bohumil Fiser, CSc. was in the Netherlands, Prof. MUDr. Jarmila Siegelová, DrSc. was in Germany, Doc. MUDr. Josef Sumbera, CSc. was in Switzerland, MUDr. Zdenek Franz, CSc. was in France. Prof. Vladislav Kruta did not agreed with the political situation in the Czech Republic in 1968 and signed the proclamation of 2000 words against the political situation. That is why he had to leave the Dept. of Physiology and with him also Prof. P. Braveny, Doc. J. Sumbera and Prof. J. Siegelova had to leave.

The revolution in November 1989 marked a landmark in the life of the Czech country. The university in Brno resumed its original name Masaryk University in 1990.

After the velvet revolution in 1989, it was possible to renew the international scientific activities between the foreign universities. Prof. Siegelova from Dept. of Third Dept. Medicine of Medical Faculty Masaryk University (later from 1996 Dept. of Functional Diagnostics and Rehabilitation, Medical Faculty, Masaryk University) started to organize, together with Prof. Fiser, from Dept of Physiology Medical faculty, Masaryk University and Dr. Jiri Dusek, every year international Congresses, Symposia and Workshops in Masaryk University, two times or three times per year. There was established the chronobiological scientific group in Brno under the leadership of Prof. Siegelova, which was composed from members of Masaryk University, and enlarged in the 90th of Prof. Petr Dobsak, CSc., Mgr. Leona Dunklerova, Mgr. Alena Havelkova, Ph.D. and others. These congresses and symposia were visited every time by famous scientific personalities - Prof. Franz Halberg and Prof. Germaine Cornelissen from University of Minnesota, USA, Prof. Thomas Kenner, Rector of University and Dean of Medical Faculty, University of Graz, Austria and Prof. Jean-Paul Martineaud, Medical Faculty, Hopital Lariboisiere, Paris, France.

One of the Congresses was held also in Masaryk University, Medical Faculty in the year 1994 at the occasion of 75th Anniversary of Masaryk University. In the year 2009 we celebrated the Anniversary of 90 years of Masaryk University together with cooperating scientists from University of Minnesota, USA, from University of Graz, Austria, from Medical Faculty, Hopital Lariboisiere, Paris and University of Dijon, France, from Tohoku University, Sendai, Japan, namely with Prof. Dr. Franz Halberg, M.D. and Prof. Dr. Germaine Cornelissen-Guillaume, University of Minnesota, USA, Prof. Dr. Thomas Kenner, Karl-Franzens-University Graz, Austria, Prof. Dr. Jean-Paul Martineaud, Hopital Lariboisiere, University Paris, France, Prof. Dr. Etienne Savin, Hopital Lariboisiere, University Paris, France, Professeur Jean-Eric Wolf, C.H.U. du Bocage, Dr. Jean-Christophe Eicher, C.H.U. du Bocage, University Dijon, France, Professor Kou Imachi, M.D., Ph.D., T.U.B.E.R.O., Tohoku University, Sendai, Japan, Professor Masahiro Kohzuki, M.D. Ph.D., Tohoku University, Sendai, Japan, Professor Yambe Tomoyuki, M.D. Ph.D., Tohoku University, Sendai, Japan.

In the last 30 years the chronobiologic staff of Masaryk University presented scientific results in USA, France, Italy, Austria, Japan, Canada and other countries.

In the 21th century the Masaryk University became a modern institution promoting the advanced teaching in the fields of medicine and chronobiology, philosophy, law, natural sciences, economics and administration, education and informatics, and providing research in all the above mentioned fields. The Masaryk University contributed to the cultural and scientific development of chronobiology and noninvasive methods in cardiology during the last 30 years with the international cooperation all over the world.

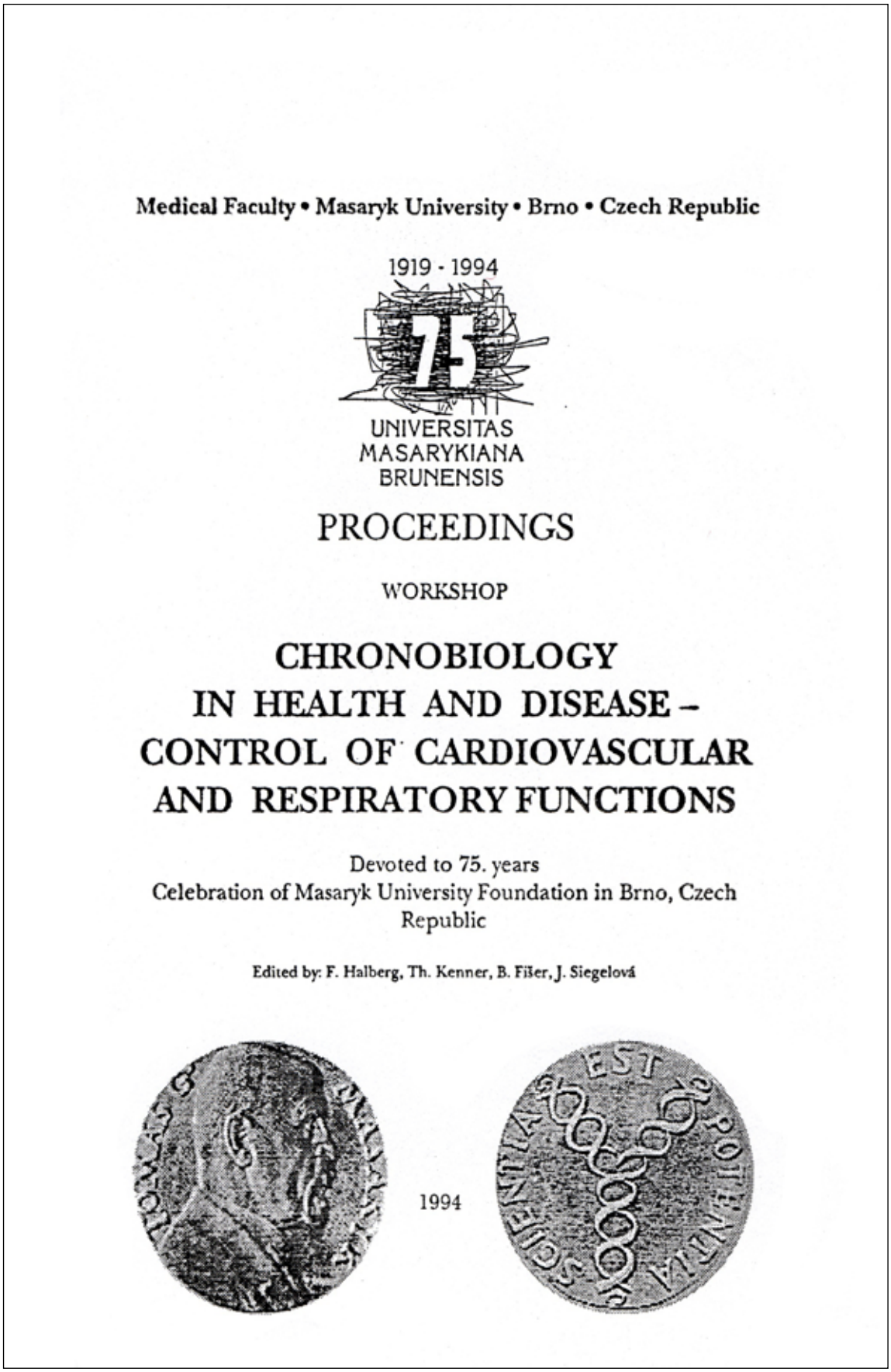


Figure 1: *Proceedings from the Workshop, devoted to 75 years of Masaryk University in 1994*

Figure 2: *Professor Thomas Kenner, Dr. h. c. mult., Austria, presentation devoted to 75 years of Faculty of Medicine, Masaryk University in 1994*

Figure 3: *In the second row is Professor Thomas Kenner, Dr. h. c. mult., Austria, Brigitte Kenner, Ing. Jiri Moudr, Professor Jan Penaz, CSc., Professor Jarmila Siegelova, DrSc., Dr. Jiri Dusek, CSc., Workshop, devoted to 75 years of Faculty of Medicine, Masaryk University in 1994*

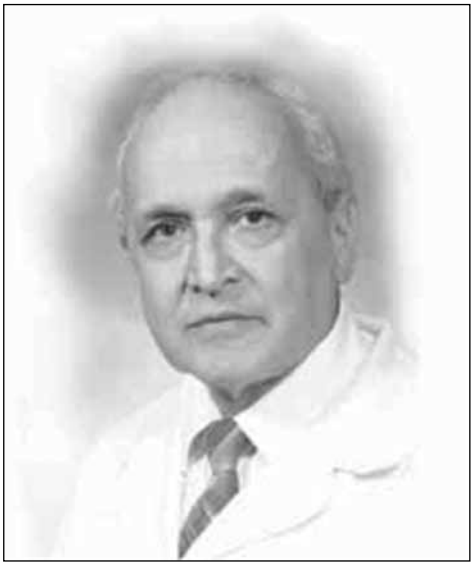
Figure 4: *Prof. Franz Halberg, Dr. h.c. mult., USA, Professor Jarmila Siegelova, DrSc., Professor Jan Penaz, CSc. in Masaryk University, Brno, 1994*

Figure 5: *Professor Thomas Kenner, Dr. h. c. mult., Austria, Professor Jarmila Siegelova, DrSc., MEFA Workshop, 2000*

100th Anniversary Celebration of the Birth of Franz Halberg

Germaine Cornelissen

Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA and the Project on the BIOsphere and the COSmos (BIOCOS)



Prof. Dr. Franz Halberg, 5.7.1919 -9.6.2013

July 5, 2019 marked the centenary of Franz Halberg, the father of chronobiology and chronomics. The event was celebrated worldwide. His work leading to the birth of chronobiology as a discipline in its own right, and his lifetime achievements were presented on May 31, 2018, at the Russian Section of the International Academy of Sciences [1]. It is also commemorated this year in the first issue of the new "Journal of Chronomedicine" by its editor-in-chief, Professor Denis Gubin [2]. Tyumen State Medical University indeed decided to develop its former "Tyumen Medical Journal" in the direction of one of this University's oldest scientific schools, chronobiology and chronomedicine, the study of dynamical and rhythmic processes in our body and in the environment, in conjunction with human health.

On June 21, 2019, Professor Max Moser kindly honored Halberg's legacy and represented Franz's international team upon the kind invitation of Professor Nandu Goswami at a meeting he organized in Graz, Austria, to remember the late Professor Thomas Kenner who regularly lectured at the Brno workshops organized by Professor Jarmila Siegelova. On July 3-5, 2019, while in Minnesota some of us remembered Franz over dinner and discussed the future direction of his Center at the University of Minnesota, the International Society for Chronobiology held its 30th international meeting in Warsaw, Poland. Our lecture and those of several other speakers were dedicated to Franz. Its former President, Professor Francesco Portaluppi, had also agreed to present a few slides highlighting the history of the Society and the critical role Franz Halberg played in the transformation of the Society for Biological Rhythms into the International Society for Chronobiology [3, 4]. On October 16, 2019, Franz was remembered at the Noninvasive Methods in Cardiology workshop organized in Brno, Czech Republic by Professor Jarmila Siegelova.

Franz Halberg (1919—2013) was a remarkable man and an exceptional scientist. He earned his reputation as the "father" of modern chronobiology from realizing the critical importance and far-reaching implications of biological rhythms. Not only did he undertake the tasks of documenting their ubiquity at all levels of organization, he developed methods for their objective and quantitative characterization. Moreover, he uncovered their rules of behavior and mapped a broad time structure of interacting multi-frequency rhythms. He provided the nomenclature and paved the way for important applications in medicine and biology more generally. By adding "time" to the existing body of knowledge, Halberg raised the homeostatic curtain of ignorance (Figure 1), thereby fundamentally changing our view of physiology. By insisting on an inferential statistical foundation, a microscopy in time was born. By adding a telescopy in time with a methodical scrutiny of non-photic and environmental influences on biota, chronomics flourished under his leadership (Figure 2).

The fact that circadian rhythms persist in the absence of known synchronizers when they assume a period slightly but statistically significantly different from exactly 24 hours led Franz to realize the importance of circadian rhythms. The existence of free-running was the third in a series of puzzles that had to be solved [5, 6]. The first puzzle consisted of making sense of confusing variability and characterizing the underlying rhythmic variation, thereby documenting the reproducibility of changes along the 24-hour scale. Another puzzle that needed solving relates to the role played by competing environmental synchronizers: Franz showed that the phase of circadian rhythms can be reversed by switching the lighting regimen from LD12:12 to DL12:12. He demonstrated that time-restricted feeding to a single daily "meal" greatly alters the phase of some variables (insulin, glucagon, growth hormone) whereas the phase of other variables is barely affected (cortisol).

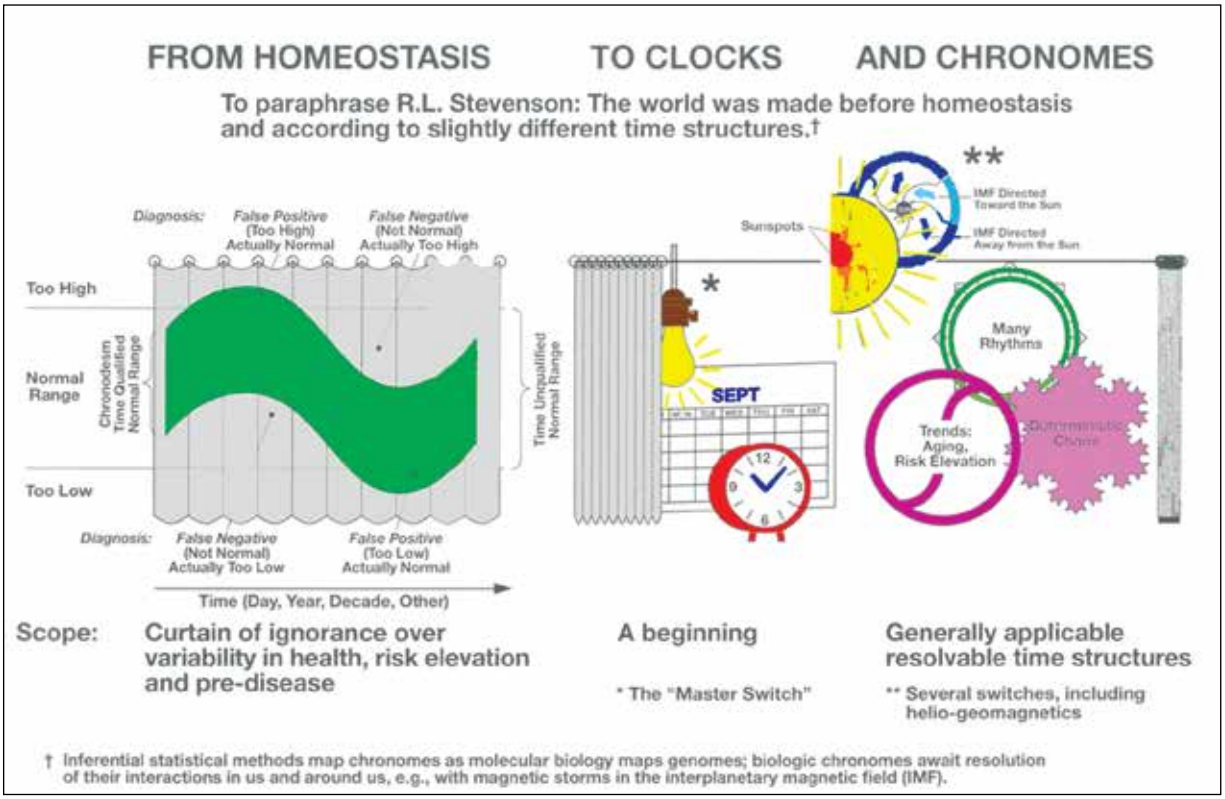


Figure 1: *By adding "time" as the fourth dimension in biology, Franz Halberg raised the homeostatic curtain of ignorance, thereby fundamentally changing our view of physiology.* © Halberg Chronobiology Center

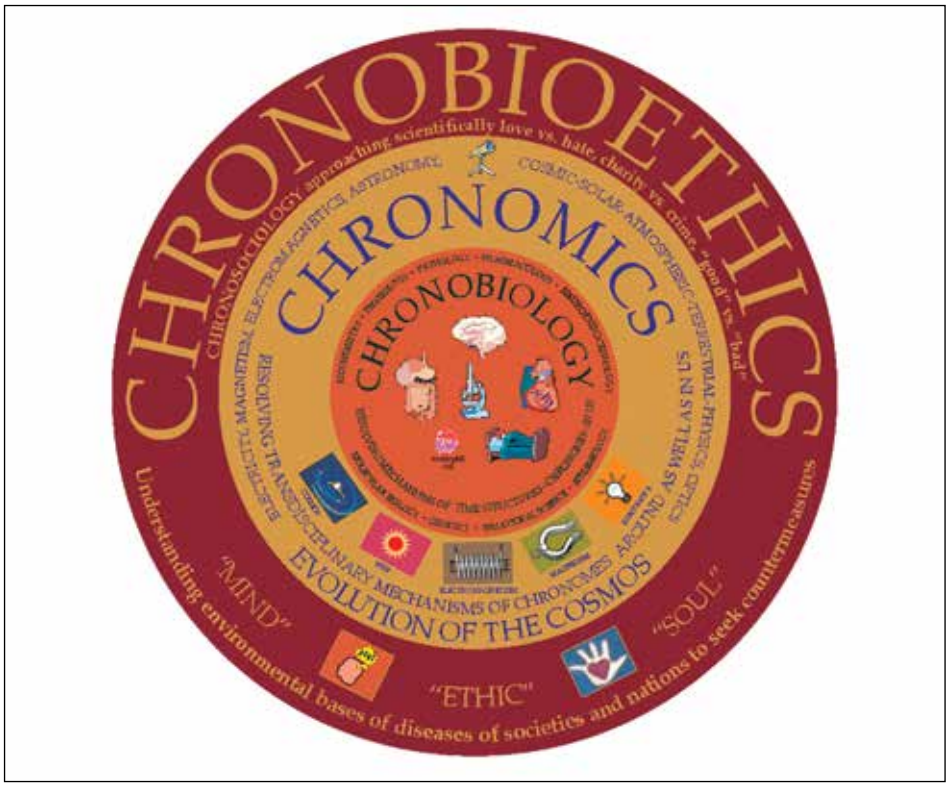


Figure 2: *Franz Halberg's vision is now his Chronobiology Center's logo: transdisciplinary sciences spawned by chronobiology (center), complemented by the study of non-photic and environmental influences on biota as chronomics (inner circle), and yet-to-be-developed chronobioethics (outer circle) aim to serve the health of individuals, the well-being of nations, and the integrity of the cosmos.* © Halberg Chronobiology Center

From the demonstration that DNA and RNA are circadian periodic at a time well before clock genes were discovered, to the development of personalized marker-rhythm guided chronotherapy, based on the circadian rhythm in mitosis in the case of cancer and on the hours of changing resistance more generally, important milestones were reached throughout his career. [1, 6]. Their impact was so great that Franz lived to see how his work and vision -- gained from looking at the data without any preconceived ideas -- became fully vindicated since underlying mechanisms could be scrutinized in more detail once a molecular basis for circadian rhythms was established. Halberg's concepts of feedsidewards and collaterally hierarchical cellulo-neuro-endocrine mechanisms are slowly becoming recognized as work at the molecular and cellular level uncovers the intricacy of pathways affected by core clock genes in the SCN and in the periphery [7, 8].

The lifetime accomplishments of Franz Halberg are summarized in over 3,600 publications in cooperation with colleagues around the world, listed on the website of the Halberg Chronobiology Center. In particular, Franz and his team in Minnesota enjoyed close and long-lasting cooperation with colleagues in Brno, documented in the yearly Proceedings on Noninvasive Methods in Cardiology. Halberg's work earned him many awards and other recognitions [4]. In India, a hospital has been named after him, Figure 3. The breakthroughs in his long and fruitful career have also been reviewed in a series of laudatios and review articles [1, 7-13].

Figure 3: *Halberg Hospital and Research Institute, Moradabad, India.* © Halberg Chronobiology Center

We remember his incredible legacy. Halberg's lifetime work helped change the world, and he was fortunate to witness the impact it made. It now falls upon us to follow in his footsteps and teach the next generations the lessons learned with Franz throughout our lifetimes.

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Prof. Dr. Franz Halberg, 5.7.1919 -9.6.2013: Chronobiological research of Halberg University Center, University of Minnesota, USA

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Franz Halberg, M.D., Dr. h.c. (Montpellier), Dr. h.c. (Ferrara), Dr. h.c. (Tyumen), Dr. h.c. (Brno), Professor of Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral Medicine, Director, Halberg Chronobiology Center, University of Minnesota, Minneapolis Campus
420 Delaware Street SE, Minneapolis, MN 55455, USA

Franz Halberg was a great scientist and founder of modern chronobiology.

Prof Halberg was an exceptional scientist, who was a founder of biological rhythms in humans and other animals and also in cells. He started his scientific work after the Second World War and continued it until 2013. His enormous scientific activities are demonstrated by the list of his scientific papers counting over 3 600 publications. Prof. Halberg dedicated almost 70 years of his life to chronobiological research.

Chronobiology, the study of mechanisms underlying diversity in time, and chronomics, the mapping of chronomes - time structures, could complement genetics. It is the study of mechanisms underlying diversity in space and also genomics, the mapping of the genomes. Halberg focused on the chronobiologic-chronomic assessment of blood pressure and heart rate variability as the alternative to the spotcheck of the blood pressure advocated by official current guidelines. Chronobiology allows us to approach risks, diagnosis and treatment dependent on appointment time, especially of the dynamics of time, gender, age, ethnicity and geographical location.

His chronobiological studies represent a new original Minnesotan branch of science based upon resolving the chronome and its mapping from womb to tomb. Womb -to- tomb chronome initiative consists in extension of a unique existing data archive and reference standard bank on variables of biomedical interests: heart rate, blood pressure in animal studies and especially in humans in health and in pathology, body temperature, a host of chemical determinations on blood, saliva and urine in healthy subjects and also in oncology.

Prof. Franz Halberg was also a very good organiser. He founded the Halberg Chronobiology Center at the University of Minnesota, USA, he was very active and was able, in cooperation with other scientists all over the world, to found International Society of Chronobiology.

For his chronobiological studies he was able to create cooperation with a lot of scientists all over the world in many fields of biology and medical sciences as it is documented in coauthorship in his scientific papers. Prof. Franz Halberg work and influence was renowned internationally and he collaborated with groups around the world, particularly the USA, Japan, India and European states, such as Germany, Austria, Czech Republic, Slovakia, Romania, Hungary, Russia, France, Italy, Belgium, England. Prof. Franz Halberg generous hospitality was manifested in the organisation of workshops and symposia in University of Minnesota, and he and his chronobiology group in Minnesota and his family invited a lot of scientists all over the world also to his home, where he prepared also lunch parties. Prof Franz Halberg believed that friendship, collaboration and endeavour pushed the frontiers of knowledge. One of the symposia was held in 2009 at the occasion of 90th anniversary of Prof. Franz Halberg.

Let me to introduce some of the important scientific personalities from Minnesota, USA, who are close friends from Prof. Franz Halberg.

Dr. h.c. mult. Earl Elmer Bakken, 1924-2018, Minnesota, USA, first described device a battery-operated pacemaker in 1957 in University of Minnesota and later was Medtronic‘s Chief Executive Officer and Chairman until 1975 and was a global leader in medical electronic technology. He was one of the best friends of Prof. Franz Halberg and took part every year in Chronobiology Symposia and Workshops organized by Prof. Franz Halberg at the University of Minnesota.

Dr. Betty Sullivan, Phd., 1902-1999, studied chemistry in Paris, France under professor Marie Sklodowska-Curie and at the University of Minnesota, USA and in 1935 got the Ph.D. at University of Minnesota. She was Chief chemist in Russel Miller Milling Company, later vice-president and director of research until 1955, later President of Peavey Co.Flour Mills. She admired chronobiology studies of prof. Franz Halberg and discussed some possibilities in analysis of chemical substancies in humans.

Prof. Spector Herbert Novera discussed and published together with Prof. Franz Halberg some chronobiological aspects in neuromodulation and endocrinology.

A very important cooperator of Prof Franz Halberg in University of Minnesota was professor Germaine Cornelissen.

Prof. Cornelissen is a long-time cooworker of Prof. Franz Halberg in the Halberg Chronobiology Center, University of Minnesota, USA.

Prof. Germaine Cornelissen studied physics at the University of Brussels, Belgium, where she graduated in 1971 (M.S. in Physics and M.Ed., University of Brussels). She continued her studies and in 1976 she obtained her Ph.D. degree in physics at the University of Brussels.

Prof. Cornelissen started studies in her main scientific task, chronobiology, in 1976 in the Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, headed by Prof. Franz Halberg, founder of modern chronobiology. As a fellow (1976-1982) she admired all new scientific approaches and findings in chronobiology; she used her knowledge in physics and mathematics and applied it to chronobiology. At that time Prof. Cornelissen was a very hard working scientist who in the team of Prof. Halberg cooperated with scientists in many countries and summarized chronobiological data, covering practice and theory of chronobiology in humans, animals and in astronomy. She was awarded for her intensive scientific work in chronobiology in 1983 with Hoechst Foundation Chronobiologia Award. She was also Member of the board in International Society for Chronobiology (1985-1995).

In 1990 Prof. Halberg and Prof. Cornelissen visited Masaryk University in Brno for the first time and presented chronobiological results in cardiovascular parameters in man in Masaryk University in Brno Symposium. Immediately, an intensive cooperation started between the Brno team, consisting of Prof. Jarmila Siegelova and Prof. Bohumil Fiser (emeritus head of the Physiology Department, Czech Minister of Health and executive board member of WHO); Dr. Jiri Dusek, with Prof. Halberg and Prof. Cornelissen, University of Minnesota, USA. In Brno at that time we carried out the beat-to-beat noninvasive measurement of blood pressure, developed by Prof. Jan Penaz and young scientist subject Prof. Fiser, as well as measurements of baroreflex sensitivity and heart rate variability and Prof. Jarmila Siegelova had the equipment for ambulatory 24-h blood pressure monitoring for adults. The University of Minnesota lent us equipment for oscillometric measurement of blood pressure in newborn children. We started common scientific work while our data of blood pressure and heart rate collected on the Czech population were at first faxed, later on line sent via e-mail to Chronobiological laboratories in Minnesota, Halberg Chronobiology Center and analyzed in the University of Minnesota, USA. Then for 29 years until now the ambulatory monitoring of blood pressure and heart rate data from Brno were immediately analyzed by Prof. Cornelissen and the results of these analyses served not only for scientific work, but also for therapy of the Czech population. Between the years 2000 and 2008 the Brno team consisting of Prof Jarmila Siegelova, Prof. Fiser, Dr. Dusek and me collected 73 888 sets of blood pressure and heart rate measurements and all data were analyzed by Prof. Cornelissen the following day. The daily data exchange and analysis continues until now.

Very important chronobiological findings of blood pressure control were made on newborn children's blood pressure, on blood pressure changes after the timed administration of low dose aspirin, on baroreflex sensitivity in healthy subjects and patients with essential hypertension, and on groups of normotensive subjects and hypertensive patients given antihypertensive therapy and without therapy. The cooperation resulted in many common publications.

From 1990 every year, sometimes twice a year, common meetings were organized in Brno, such as MEFA Congress or chronobiological congresses of Noninvasive methods in cardiology, presenting a lot of latest findings in chronobiology of ccarčdiovascular parameters in scientific lectures. This scientific meetings were organized with the participation of Prof. Cornelissen and Prof. Halberg from Minnesota; USA, Prof. Thomas Kenner, former president of the University of Graz, Austria; and Prof. J.P. Martineaud, Hopital Lariboisiere, Medical Faculty, Paris, France. Prof. Cornelissen prepared a lot of publications for every year congresses and symposia in Brno.

The Brno team visited USA, Franz, Austria many times.One chronobiology study was undertaken in University in Minnesota in 1995, where Prof. Cornelissen and the Brno team- Prof. Siegelova, Prof. Fiser and Dr. Dusek evaluated two Japanese ambulatory blood pressure monitors. The scientists measured themselves day by day two weeks. The scientific team placed blood pressure cuffs on both arms and worn them for fourteen days. The results were evaluated using cosinor analysis and Prof. Cornelissen published them.

In 1987 Prof. Cornelissen was appointed the secretary of the North American branch of the International Society for Research on Civilization Diseases and the Environment (SRMCE). She summarized and published numerous papers on risks of civilization diseases and on morbidity and mortality of cardiovascular diseases. In 1994 Prof. Cornelissen became coordinator of international chronobiology project Womb-to-Tomb Study, now BIOCOS (The BIOsphere and the COSmos). The Brno team is a member of both international projects.

On November 22, 1994 BIOCOS was described for the first time. The Biosphere and the Cosmos, BIOCOS, as the task of building a novel transdisciplinary spectrum was pursued, and further periods of decades, centuries, and thousands and millions of years were documented. Much of the evidence was provided very successfully by Germaine Cornelissen, PhD, Professor of Integrative Biology and Physiology at the University of Minnesota, so that the new periodicities were dubbed the Cornélissen-series at an international meeting in Ekaterinburg, Russia.

Prof. Cornelissen's scientific capabilities were appreciated by a number of awards, citations and membership in scientific organizations. She has been a member of the Sigma Xi Society since 1988, of the Editorial Board of Chronobiologia from 1989 to1991 and of the Editorial Board of Il Policlinico from 1991 to 1996; has contributed to Neuroendocrinology Letters since 1999, Geronto-Geriatrics since 1999, the Journal of Applied Biomedicine since 2006, the World Heart Journal since 2007, and the Journal of Experimental Therapeutics and Oncology since 2010. She was co-editor of Chronobiologia from 1991 to 1994, guest editor of Psychophysiology (1992), Neuroendocrinology Letters (2003) and The Open Nutriceuticals Journal (2012), was on the Board of Directors of the Underlab Project (Ancona, Italy) (1993-1996), and has been a member of the book committee of the National Chapters of Phi Beta Kappa since 2000. She was nominated as an honorary member of the Cardiff Scientific Society (2002), a member of the advisory board of the International College of Nutrition and International College of Cardiology, MYODEA, Moradabad, India (2005), of which she is a fellow Royal Scientist; a foreign member of the Problem Commission on Chronobiology and Chronomedicine of the Russian Academy of Medical Sciences (2006); a member of the Leibniz Society (the former Academy of Science of the German Democratic Republic) (2009), and of the International Academy of Science (2010).

Prof. Cornelissen participated in many international Congresses and Symposia and workshops. In 2008 she was appointed full Professor in the Department of Integrative Biology and Physiology, and co-Director of the Halberg Chronobiology Center, University of Minnesota, Minneapolis, USA. In 2013 Prof. Cornelissen become the director of Halberg Chronobilogy Center until today.

Prof. Cornelissen crossed from physics to biomedicine and added a lot of transdisciplinary information. In chronobiology one of her most important challenges remains, in all zones on earth and beyond, the exploitation of vascular variability disorders in man for a universal preventive health care based on cyber-implemented self-help. She has collected time series of chronobiological measurement for multiple purposes; the time series of biological data may serve in health care to minimize cardiovascular events such as stroke, myocardial infarction and other serious diseases first and foremost.

Benefit from her many chronobiological analyses of data from all over the world relates both to medical and transdisciplinary research. Medically, by her analyses of data, she compares the relative merits of harbingers of risk. In addition, she seeks an understanding of the effects of the sun in dealing with aggression and other diseases of society. The many reported effects of the sun on living organisms and human beings are now documented, apparently for the first time in inferential statistical terms, by Prof. Cornelissen in many chronobiological and chronomic papers. She is now building an atlas of the time structure of the human mind, the chronousphere, based on the Cornélissen-series, so named by an international consensus.

I thank Prof. Germaine Cornelissen, director of Halberg Chronobiology Center who in the last 6 years replaced prof. Franz Halberg and continues the broad international cooperation all over the world very successfully.

The cooperation between Halberg Chronobiology Center and Dept.of Physiotherapy and Dept. of Sports Medicine and Rehabilitation, Medical faculty, Masaryk University will continues in the future.

Figure 1: *Fom the right side Prof. Earl Elmer Bakken, Dr. h.c. mult., USA, Prof. Germaine Cornelissen, USA, Prof. Franz Halberg, Dr. h.c. mult., USA, Dr. Yuji Kumagai, Japan, Dr. Othild Schwartzkopff, Prof. Jarmila Siegelova, DrSc. in Minnesota, USA, 2001*

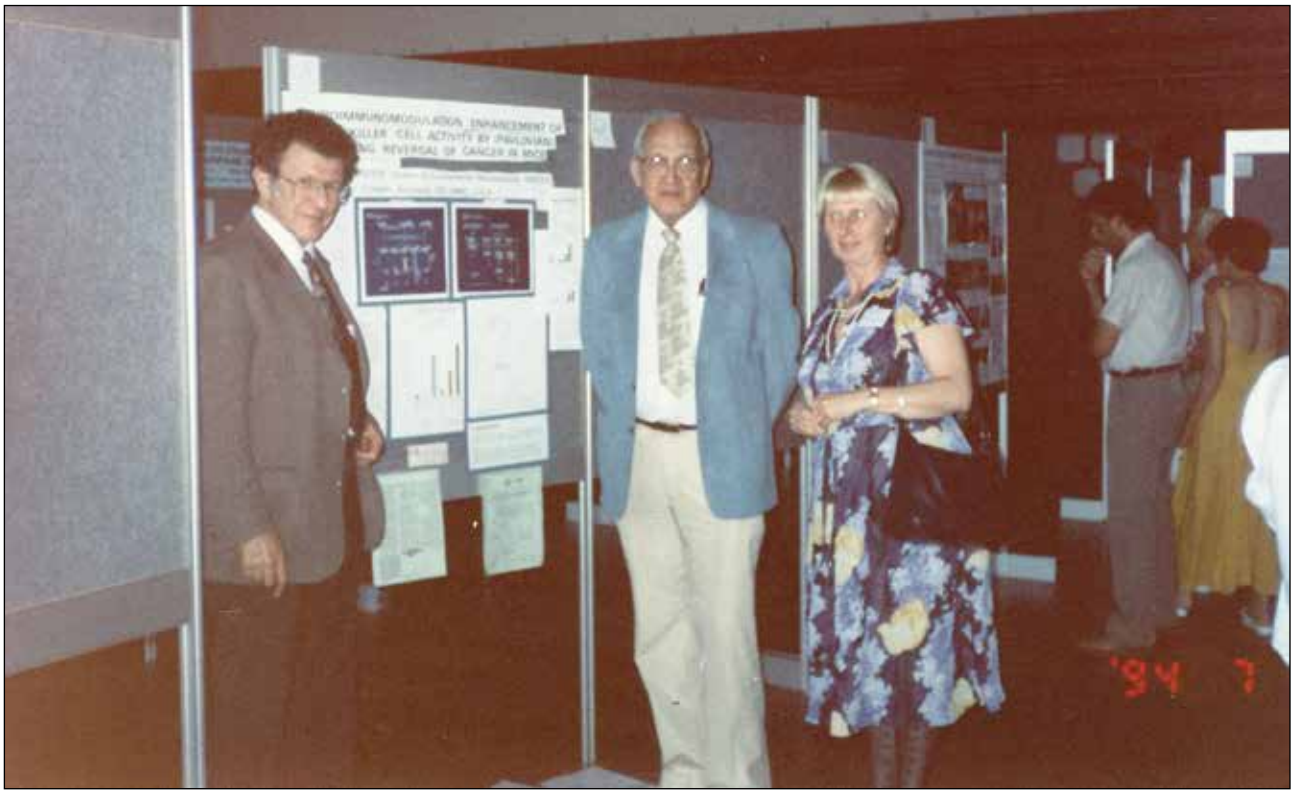

Figure 2: *From the right side Prof. Jarmila Siegelova, DrSc., Prof. Franz Halberg, Dr. h.c. mult., USA, Prof. Spector Herbert Novera, USA, Prague, 1994*

Figure 3: *From the right side Prof. Jarmila Siegelova, DrSc., Prof. Germaine Cornelissen, USA, Prof. Franz Halberg, Dr. h.c. mult., Prof. Keiko Uezono, Kyushu University in Fukuoda, Japan, Paula Lofstrom an Dr. Denis Lofstrom, USA, 2001 at the University of Minnesota*

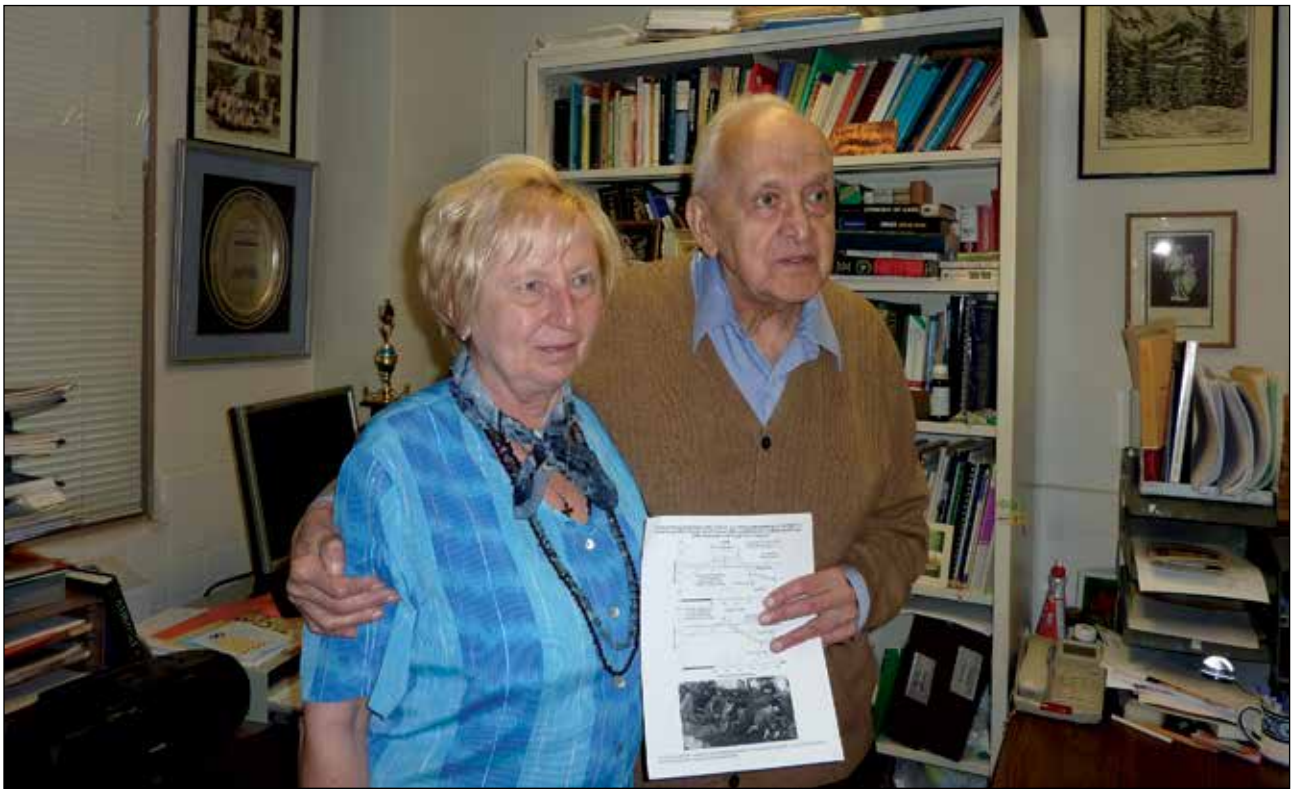

Figure 4: *Prof. Franz Halberg, Dr. h.c., mult., USA, Prof. Jarmila Siegelova, DrSc., University of Minnesota, 2009*

Figure 5: *Prof. Germaine Cornelissen, University of Minnesota, 2009*

Figure 6: *From the right side Dr. Julia Halberg Julia's husband, Mark Chatterton and Prof. Jarmila Siegelova, DrSc., Minnesota, USA, 2009*

Figure 7: *On the left of the picture is Dr. Francine Halberg, M.D. and her husband Terry Kessler, Dr. Jiri Dusek, Prof. Jarmila Siegelova, DrSc., Prof. Fabien DeMeester, Belgium, behind the lady from the restaurant the La Casita, a restaurant in Roseville, USA, next Dr. Pavel Homolka, M.D., Prof. Franz Halberg, Dr.h.c. mult., Othild Schwartzkopff, M.D., in front of them is the Russian translator, next Prof. R.B. Singh, India, Prof. Sergey Chibisov, Russia, nad Prof. Germaine Cornelissen, Minnesota, USA, 2009*

Figure 8: *On the left part above of the picture Prof. Jarmila Siegelova, DrSc., Tomoyuki Yambe, Professor, Ph.D, MD, Sendai, Japan, Prof. MUDr. Petr Dobsák, CSc., MU, Masaryk University, Dr. Jiri Dusek, Yusuke Inoue, Assistan Professor, Ph.D., Sendai, Japan, Kazumasu Sasaki, D.V.M., Ph.D., Sendai, Japan, Mitsuya Maruyama, Fukuda Denshi, Tokyo, Japan.*

On the right part above of the picture is Brigitte Kenner and Prof. Thomas Kenner, Dr. M.D., Dr. h. c. mult., University Graz, Austria, Prof. Dieter Platzer, Dipl.-Ing. Dr.techn., Institut für Biophysik, University Graz, Austria.

On the right part down of the picture is Prof. Germaine Cornelissen, Dr., University of Minnesota, USA, Cathy Gierke, Univerzity of Minnesota, USA

Five major determinants for peak VO_2

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Chronic obstructive pulmonary disease (COPD) is an important and growing cause of morbidity and mortality worldwide. Cardiovascular, musculoskeletal, metabolic, and mental comorbidities are considered to be part of the frequently prevalent non-pulmonary sequelae of the disease [1,2]. Increasing evidence suggests that extra-pulmonary effects of COPD and airflow limitation are only poorly correlated [3]. Waschki et al. found that objectively measured physical activity is the strongest predictor of all-cause mortality in patients with COPD [4]. The association between physical inactivity and poor outcomes is well established for patients with pulmonary disease, cardiac disease, chronic kidney disease [4-6]. Patients with pulmonary disease, cardiac disease, or renal disease typically engage in a lower level of physical activity than do the general population, which can induce a catabolic state including reduced neuromuscular functioning, reduced exercise tolerance and reduced cardiorespiratory fitness (CRF). CRF is an important consideration, in addition to physical activity, as it is a strong predictor of mortality [7,8]; low CRF presents a particularly high risk of death compared to other common risk factors, such as diabetes, high cholesterol or hypertension [9]. CR fitness is defined as the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity and is usually expressed as maximal oxygen uptake (VO_2max) during maximal exercise testing [10]. In 2016, the American Heart Association published a scientific statement [11] recommending that CRF, quantifiable as VO_2 max, be regularly assessed and utilized as a clinical vital sign. This statement was based on mounting evidence that lower CRF levels are associated with high risk of cardiovascular disease, all-cause mortality, and mortality rates stemming from various types of cancers. VO_2 max is expressed either as an absolute rate in (for example) liters of oxygen per minute (L/min) or as a relative rate in (for example) milliliters of oxygen per kilogram of body mass per minute (e.g., mL/(kg·min)). The latter expression is often used to compare the performance of endurance athletes and patients.

Figure 1 shows gas transport mechanisms for coupling cellular (internal) to pulmonary (external) respiration. The gears represent the functional interdependence of the physiological components of the system. Cardiac output, pulmonary diffusion capacity, oxygen carrying capacity, renal function and other peripheral limitations like muscle diffusion capacity, mitochondrial enzymes, and capillary density are all examples of VO_2 max determinants [12].

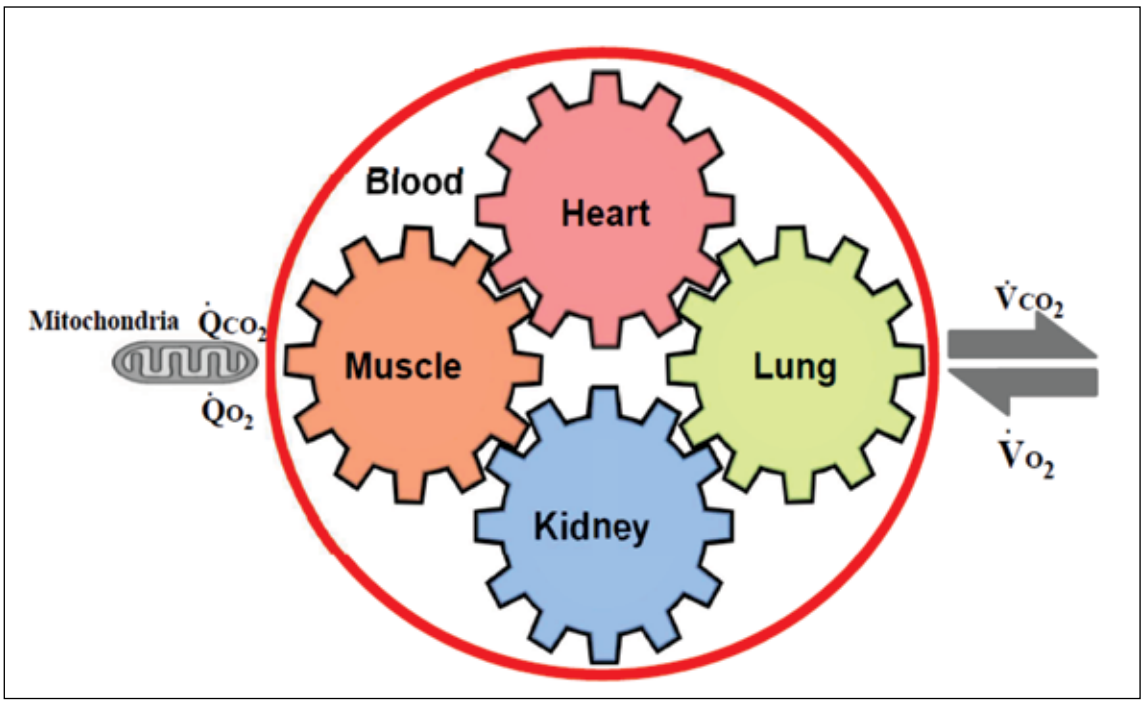

Figure 1: *Gas transport mechanisms for coupling cellular to pulmonary respiration: five major determinants for peak VO2 [12]*

The large increase in O_2 utilization by the muscles (QO_2) is achieved by increased extraction of O_2 from the blood perfusing the muscles, the dilatation of selected peripheral vascular beds, an increase in cardiac output (stroke volume and heart rate), an increase in pulmonary blood flow by recruitment and vasodilatation of pulmonary blood vessels, and finally, an increase in ventilation. O_2 is taken up (VO_2) from the alveoli in proportion to the pulmonary blood flow and degree of O_2 desaturation of hemoglobin in the pulmonary capillary blood. Metabolic acidosis in chronic kidney disease (CKD) patients promotes muscle protein wasting and protein-energy wasting (PEW) by increasing protein degradation [13] and reducing protein synthesis [14]. As a result, maintenance of muscle mass is impaired in CKD patients with altered protein turnover rates [15]. Adding to sarcopenia, metabolic acidosis, protein-energy wasting, angiotensin II, myostatin overexpression in uremia contribute the etiology in muscle wasting in CKD [16]. Moreover, the drug erythropoietin (EPO) can boost VO_2 max by a significant amount in both humans and other mammals [17]. COPD often coexists with other diseases (comorbidities such as heart disease, CKD, osteoporosis) that may have a significant impact on prognosis. Thirty-three percent of elderly patients with heart failure had COPD and 25% of elderly patients with COPD also had heart failure [18]. This risk of comorbid disease can be increased by the sequelae of COPD; e.g., reduced physical activity. As super-aged society has come, the number of persons with multimorbidity and multiple disabilities (MMD) [19] and their needs of rehabilitation have increased rapidly more than we have expected [19]. Peak VO_2 offers the investigator the unique opportunity to study simultaneously the cellular, cardiovascular, ventilatory and metabolic systems' responses under conditions of precisely controlled stress. This is of significant practical importance because Peak VO_2 measured by cardiopulmonary exercise testing, provides what is probably the most

sensitive assessment of the effect of new therapy on function of any diseased organ system whose major function is to couple pulmonary gas exchange to cellular respiration. For example, it is important to determine whether new medical, surgical, and rehabilitative procedures can effectively intervene to improve the gas transport capability of a diseased organ system.

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Figure 2: *Tohoku University Graduate School of Medicine, Sendai, Japan*

Figure 3: *Professor Masahiro KOHZUKI, Chairman and his team from Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan*

Effect of shift-work on the circadian rhythm of blood pressure

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Abstract

Shift work and the circadian disruption it creates have been implicated in the increased risk of a number of disease conditions, cardiovascular disease in particular. Ambulatory blood pressure monitoring is well suited to assess deviations from norms indicative of a heightened cardiovascular risk. Herein, we report on a case-control study comparing circadian rhythm characteristics of 10 clinically healthy nurses working shifts with those of 10 clinically non-shifting healthy peers selected from the same Brno 7-day/24-hour ABPM database to match shift workers by sex, age, and body mass index. On average, shift-workers were found to have a higher blood pressure MESOR than their non-shifting counterparts. Analysis of separate 24-hour spans of records from the shift-workers corresponding to different shift schedules (daytime, nighttime, or free day) also indicates that night shift is associated with a weaker circadian variation in blood pressure. These results confirm those of previous studies. Their implication of a weakened circadian rhythm on night shifts may underlie the increased cardiovascular disease risk observed in relation to shift work.

Introduction

More than 21 million Americans or nearly 20% of the U.S. workforce are shift workers. Work falling outside of 6 am-6 pm can lead to poor diet, exercise, and sleep habits that lead to decreased productivity, increased workplace accidents, and a variety of negative health outcomes [1]. Shift workers are 32-36% more likely to fall asleep at work at least once per week and their risk of occupational

accidents is about 60% higher than that of day workers [2]. Poor health outcomes associated with non-standard shift work schedules include increased risks of diabetes mellitus, dyslipidemia, hypertension, heart disease, peptic ulcer disease, and depression [1], as well as cancer [3]. Epidemiologic findings on female-specific health consequences of shift work indicate that women, who represent a sizable part of the workforce, have a lower tolerance to shift work as compared to men, which may be accounted for by sex differences in the circadian timing system [4].

Specifically, shift work has been reported to increase the risk of overweight and obesity, along with a number of additional metabolic diseases, including metabolic syndrome and type 2 diabetes [5]. Shift workers typically have shorter sleep durations; short sleep duration has been associated with metabolic disease and shown to elicit a physiological stress response. Both physiological and psychological stress disrupt the healthy functioning of the intestinal gut microbiota. Altered intestinal microbial communities and dysbiosis of the gut microbiota have indeed been observed in circadian disrupted mice and jet lagged humans [5]. Altered gut microbiota related to sleep and circadian disruption likely contributes to an inflammatory state and metabolic disease associated with shift work [5]. Shift work has also been associated with cardiovascular disease risk through several interrelated psychosocial, behavioral, and physiological mechanisms [6]. Plausible physiological and biological mechanisms are related to the activation of the autonomic nervous system, inflammation, changed lipid and glucose metabolism, and related changes in the risk for atherosclerosis, metabolic syndrome, and type II diabetes [6].

Cardiovascular health can be assessed in part by monitoring blood pressure (BP) and heart rate (HR). These variables undergo large-amplitude circadian rhythms, characterized by lower values during rest. BP starts increasing during mid-sleep and is followed by a sharper increase in association with awakening. BP remains high during the active span and starts declining slowly before bedtime. The circadian variation itself changes as a function of age, the post-prandial dip in early afternoon becoming more accentuated in older individuals [7].

Circadian rhythms are synchronized by the environment, notably by the light-dark schedule and the rest-activity schedule. Not all circadian rhythms adjust to a change in 24-hour routine at the same rate. Whereas BP and HR adjust relatively fast, it takes much longer for other variables [8]. It has been reported that in shift workers the circadian rhythm in BP adjusts rapidly [9] but the circadian rhythm of body temperature may remain unaltered and fail to completely reverse even after 21 consecutive night shifts [10]. It has been suggested that such internal desynchronization resulting in circadian disruption may be an important factor contributing to transport accidents [11]. Circadian disruption has also been implicated in poorer health quite generally [12].

Herein, any circadian disruption associated with shift work is examined in records of BP and HR of nurses working different shifts, compared to those of non-shifting clinically healthy peers matched by sex, age, and body mass index (BMI).

Subjects and Methods

Ten nurses working shifts automatically measured their BP and HR around the clock for one week by ambulatory monitoring (7-day/24-hour ABPM) in Brno, Czech Republic [13]. Within the week of monitoring, they worked day shifts on some days, night shifts on other days, and some other days were free. There were 6 women (age 33 ± 12 years, body weight 70 ± 21 kg, mean height 165 ± 5 cm) and 4 men (age 28 ± 7 years, body weight 93 ± 11 kg, mean height 185 ± 5 cm). Similar 7-day/24-hour records within the Brno database from 10 clinically healthy non-shifting individuals matching the 10

shift workers by sex, age, and BMI served as controls in this case-control study. The TM-2421 ABPM (A&D, Tokyo, Japan) was programmed to take measurements every 30 minutes from 06:00 to 22:00 and every 60 minutes from 22:00 to 06:00. There were occasional interruptions in monitoring.

The circadian variation was assessed by cosinor [14] using a 2-component model of 24- and 12-hour cosine curves fitted to the entire 7-day record and to each day separately. Results were summarized by population-mean cosinor [14] for systolic (S) and diastolic (D) BP and HR. Population-mean parameter tests [15] were used to compare the circadian parameters of BP and HR assessed based on the entire 7-day records between the shift workers and the controls. Circadian rhythm parameters were also compared among the three shift schedules (day shift, night shift, free day) based on results obtained on separate daily spans from the 10 shift workers, pooled across study participants since records were not sufficiently long for analyses to be performed individually.

Results

Analysis of the entire 7-day/24-hour records

Overall, analyses of the entire 7-day records showed that shift workers had a higher MESOR of systolic (S) BP as compared to controls (126.5 vs. 118.5 mmHg, F=4.388, P=0.051) and a slightly advanced acrophase of the 12-hour component of SBP (F=3.742, P=0.069). Reconstructed circadian profiles are illustrated in Figure 1A. The MESOR of diastolic (D) BP was also higher (76.5 vs. 71.4 mmHg, F=5.745, P=0.028), Figure 1B. The 12-hour amplitude-acrophase pair of HR differed between the two populations, shift workers having a smaller amplitude and an advanced acrophase (F=6.344, P=0.005), Figure 1C.

In relation to the bathyphase, the magnitude of HR of shift workers was smaller than that of controls (8.3 vs. 11.3 beats/min, F=4.058, P=0.059). When expressing the magnitude as a percentage of the MESOR, the difference reached statistical significance (11.1 vs. 15.6%, F=4.561, P=0.047).

Analyses of separate 24-hour spans

In the absence of a difference in SBP MESOR, the 24-hour amplitude of SBP was found to be larger on day shifts (D) than on night shifts (N) or free days (F) (D: 14.0, N: 8.8, F: 7.9 mmHg, F=3.157, P=0.049). The 24-hour acrophase was found to occur later on night shifts (F=3.564, P=0.034). The difference in 24-hour amplitude-acrophase pair was found to be statistically significant (F=4.125, P=0.004). Results for the pairwise day vs. night comparison yielded differences in amplitude (F=4.007, P=0.053), acrophase (F=9.068, P=0.005), and amplitude-acrophase pair (F=5.463, P=0.006). The 12-hour amplitude of SBP was somewhat smaller on night shift than on day shift (3.0 vs. 7.2 mmHg, F=3.185, P=0.083). The reconstructed circadian profiles on each work schedule are illustrated in Figure 2A.

Considering the model as a whole in relation to the bathyphase, the magnitude was again found to be larger on day shift than on night shift or free days (D: 40.8, N: 21.5, F: 20.1 mmHg, F=4.161, P=0.020). The bathyphase was found to be delayed on night shifts by about 5 hours (F=5.987, P=0.004), with a significant difference in magnitude-bathyphase pair (F=5.387, P<0.001). A pairwise comparison between day and night shift found differences in magnitude (F=7.684, P=0.009), bathyphase (F=13.588, P=0.001), and magnitude-bathyphase pair (F=7.838, P=0.001).

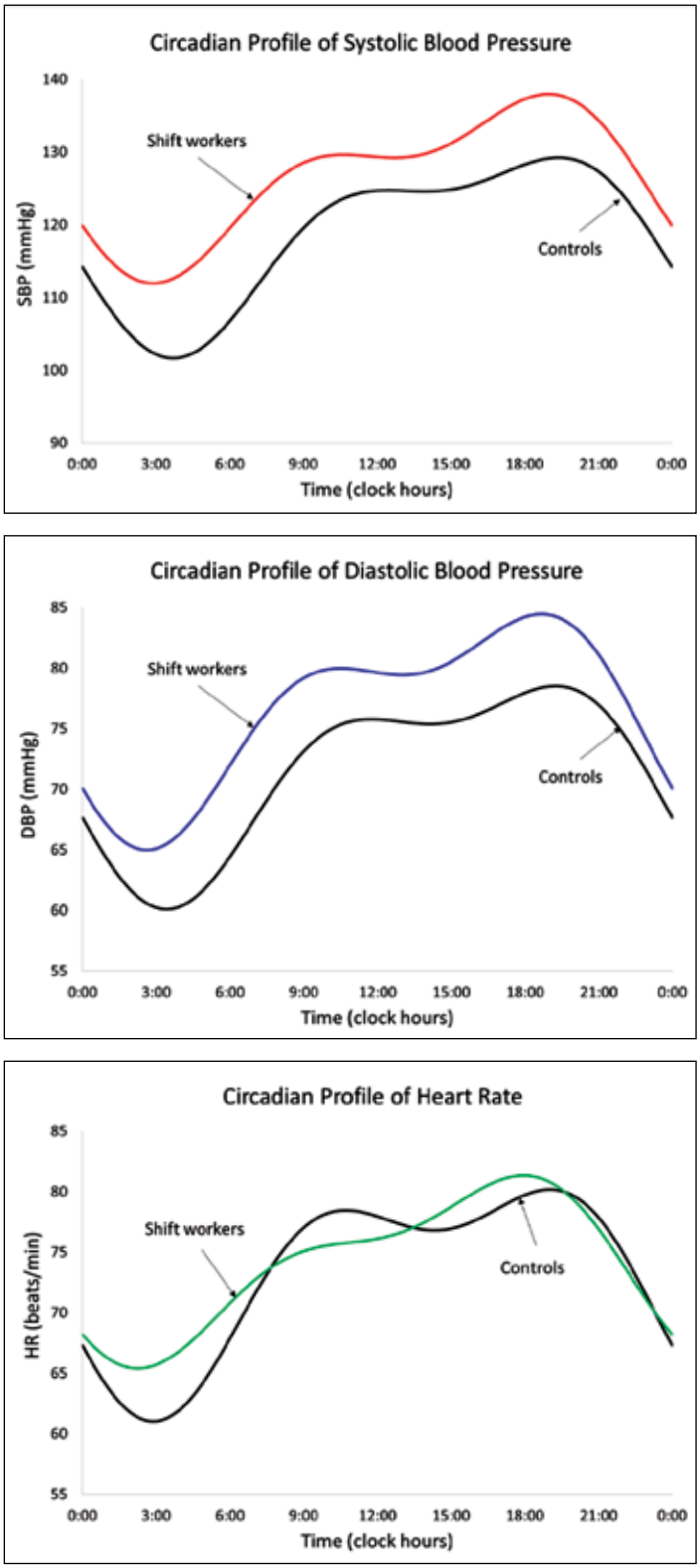

Figure 1: *Circadian profiles of SBP (A, top), DBP (B, middle), and HR (C, bottom) of shift workers as compared to controls, reconstructed based on population-mean cosinor results of the 24- and 12-hour components.* **© Halberg Chronobiology Center**

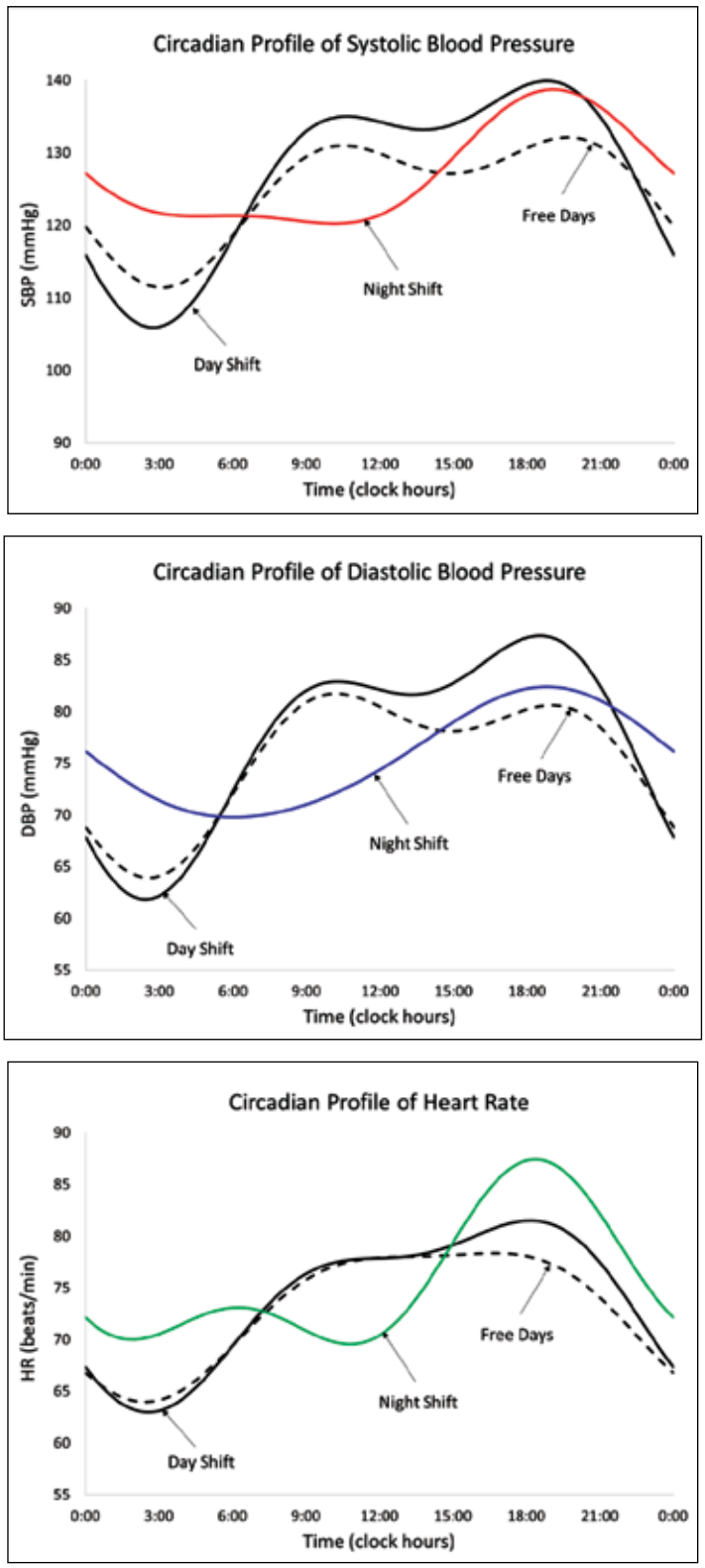

Figure 2: *Circadian profiles of SBP (A, top), DBP (B, middle), and HR (C, bottom) of night shifts compared to day shifts and free days, reconstructed based on population-mean cosinor results of the 24- and 12-hour components.* **© Halberg Chronobiology Center**

Similar results were found for DBP, Figure 2B. Specifically, the 24-hour amplitude was smaller on night shift than on day shift (6.3 vs. 10.3 mmHg, F=3.678, P=0.063), the 24-hour acrophase was delayed by about 3.5 hours (F=6.871, P=0.013), and their amplitude-acrophase pair differed with statistical significance (F=4.526, P=0.014). The 12-hour amplitude was smaller on night shift than on day shift (0.6 vs. 5.4 mmHg, F=7.023, P=0.012). In relation to the bathyphase, the magnitude was smaller on night shift than on day shift (14.7 vs. 27.0 mmHg, F=4.691, P=0.037), and the bathyphase was delayed by about 4.5 hours (F=9.265, P=0.004), yielding a difference in magnitude-bathyphase pair (F=6.057, P=0.004).

No difference was found in the 24-hour or 12-hour amplitude of HR. As in the case of BP, the 24-hour acrophase of HR was delayed by more than 3 hours (F=9.114, P=0.005), but the 12-hour acrophase was advanced by almost 2 hours (F=5.413, P=0.026), Figure 2C.

Discussion and Conclusion

Phase differences could be anticipated since they relate to differences in the rest-activity schedule, which obviously differs between day and night shift. The consistently smaller circadian amplitude, primarily observed in SBP and DBP, reflects the fact that shift work disrupts the circadian system. As such, it may be detrimental to health.

Results herein obtained in a small case-control study of only 10 shift workers and 10 sex-, age-, and BMI-matched clinically healthy non-shifting controls are in agreement with two prior studies also using ABPM. One study was performed on air traffic controllers in Bulgaria [16, 17]. The smaller amplitude of BP on night shift was statistically significant in an interim analysis carried out on 33 of the 52 study participants, Figure 3A. As in our study, the circadian acrophase of BP was delayed in association with night shift, Figure 3B.

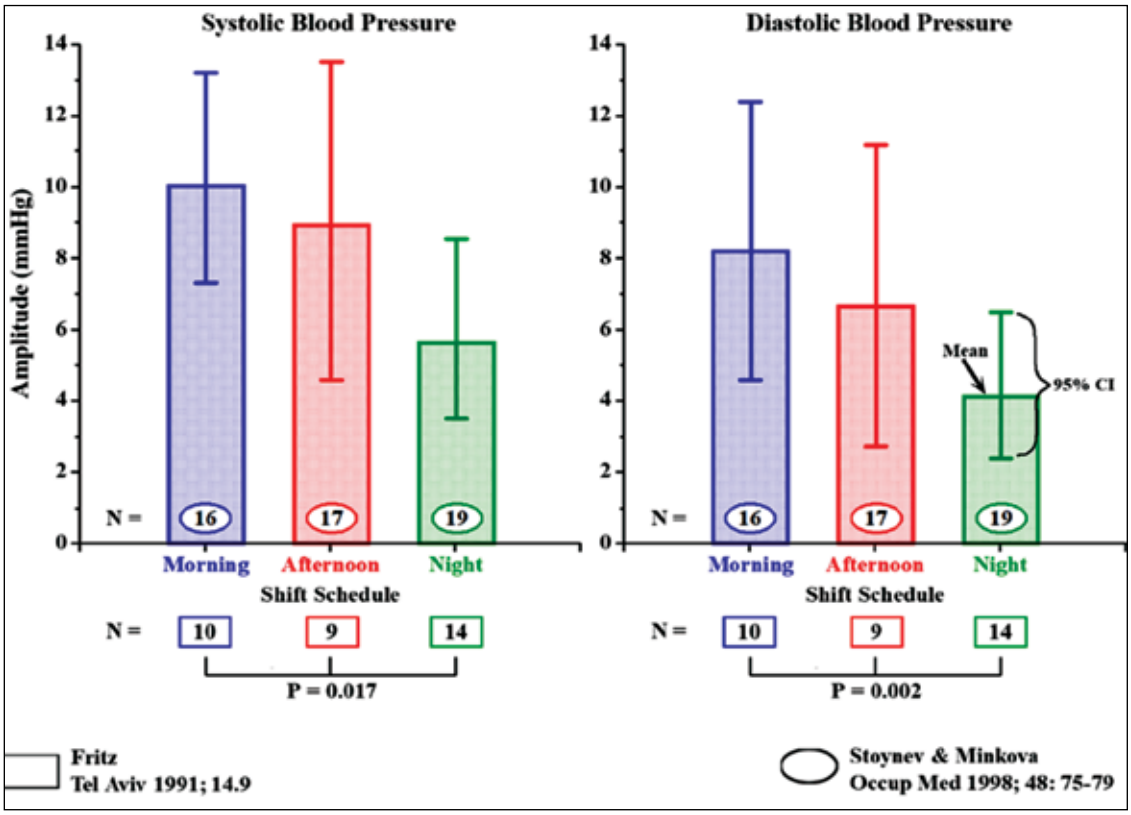

Figure 3A:. *In a study of air traffic controllers, night shift work was associated with a reduced circadian amplitude of BP.* **© Halberg Chronobiology Center**

Similar results were also found in a study of Minneapolis police officers on an advancing or delaying rotating shift, as shown in Figure 4 [18].

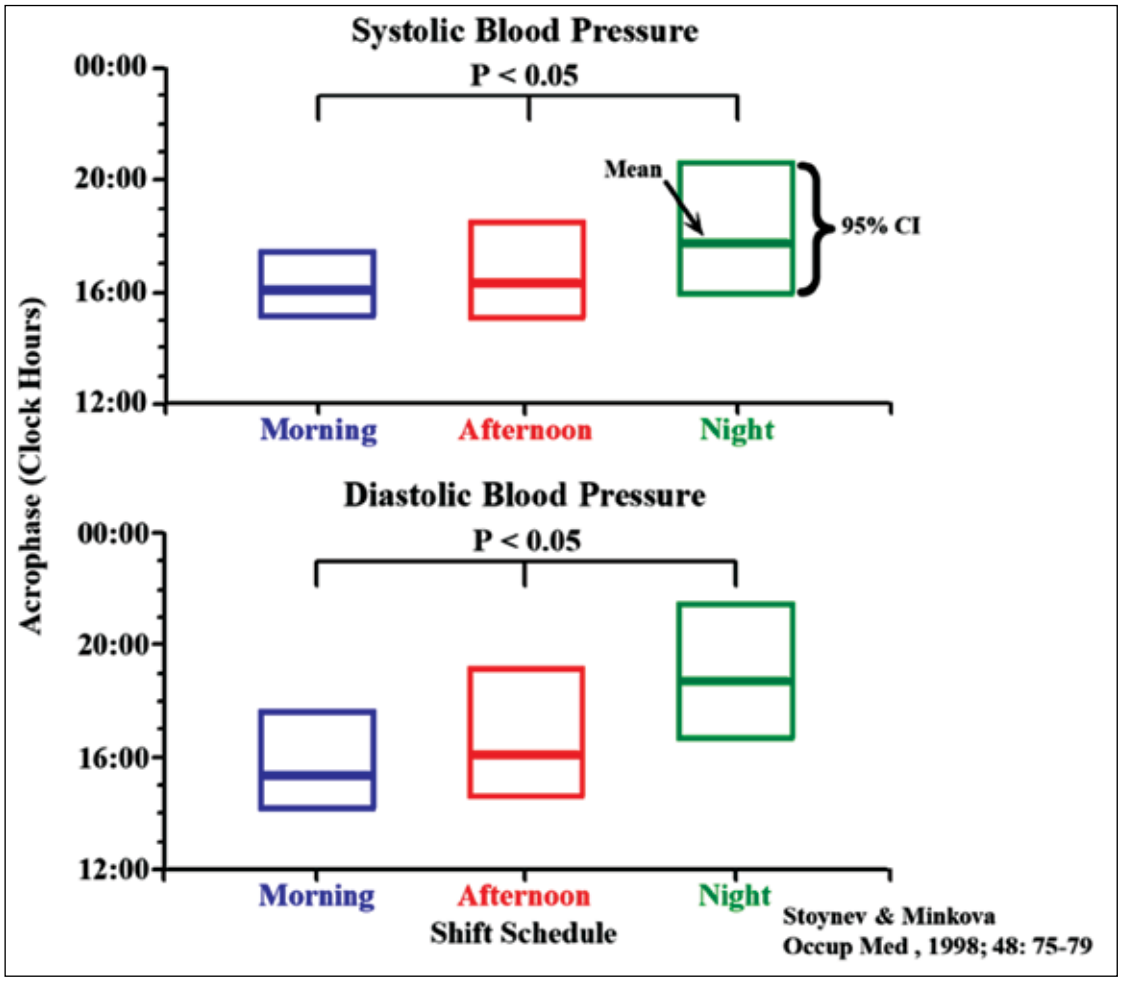

Figure 3B: *In a study of air traffic controllers, night shift work was associated with a delayed circadian acrophase of BP as compared to morning or afternoon shifts.* **© Halberg Chronobiology Center**

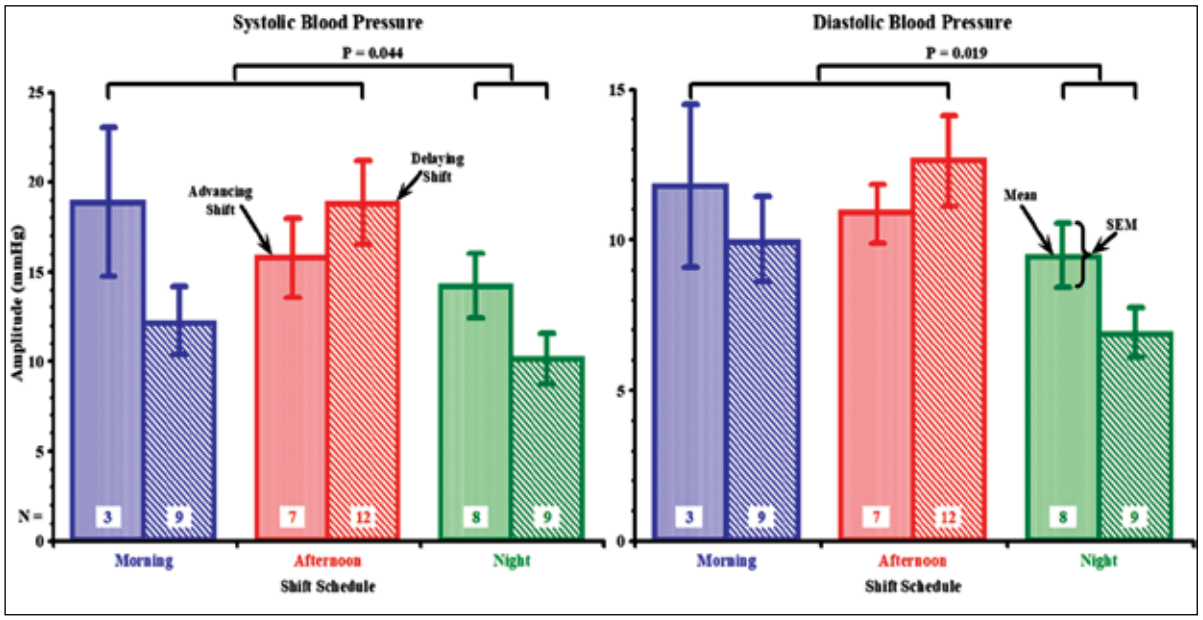

Figure 4: *Night shift is associated with a smaller circadian amplitude of BP in Minneapolis police officers on an advancing or delaying rotating shift [18].* **© Halberg Chronobiology Center**

Chronobiological outcome studies have not found an increased cardiovascular disease risk associated with a reduced amplitude of BP in the absence of a deviant circadian acrophase [19]. Taking these results together suggests that any increased cardiovascular disease risk may stem from the internal circadian desynchronization among multiple physiological variables rather than from the reduced circadian amplitude of BP itself.

Longitudinal monitoring, as done herein, could be implemented more generally to assess inter-individual responses to shift work. A better understanding of individual workers' tolerance to shift work by examining their response to variations in their sleep-wake patterns may help identify those shift workers who may be more vulnerable to unhealthy consequences from their work schedule. The health risk of shift workers needs to be considered by suggesting possible dietary or lifestyle changes that may help minimize the vascular risk factors they face working odd shifts [2]. Melatonin supplementation and optimizing environmental light are currently being considered as countermeasures to minimize ill health effects related to shift work [20-24]. Further work is also needed to determine whether there may be shift work schedules that are less detrimental than others.

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Day-to-day variation in day-night ratio of blood pressure

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Abstract

Ambulatory blood pressure monitoring (ABPM) is too often limited to only 24 hours. Too often, the data thus collected are analyzed by computing daytime, nighttime, and 24-hour means rather than assessing the circadian variation by cosinor. The day-night ratio (DNR) based on these mean values is then used for a classification in terms of "dipping". Earlier work showed the large day-to-day variability in the circadian pattern of blood pressure (BP) observed in both normotensive and hypertensive individuals. Using data from the Brno database of 7-day/24-hour ABPM records, the extent of reproducibility of a classification in terms of "dipping" is examined herein by comparing results obtained on a daily basis versus those based on the entire record, used as reference. The percentage agreement for systolic (S) and diastolic (D) BP averaged (mean ± SE) 54.43 ± 1.37% and 59.09 ± 1.74%, respectively. Individually, the range in daily DNR values averaged 19.85 ± 0.58 and 26.48 ± 0.87 for SBP and DBP, respectively. These results suggest that the DNR computed from a 24-hour ABPM is not sufficiently reliable.

Introduction

Blood pressure (BP) varies greatly, mostly because it is influenced by a host of different factors. Personal modifiers include sex; body height, weight and body mass index; age; ethnicity and personal

genetic polymorphisms. Dynamic modifiers include sleep; physical activity; endogenous circadian rhythm; diet (food, water, salt, alcohol); ambient light; darkness; ambient temperature; noise; smoking; load ("stress"); emotions [1]. Emotions can have a larger impact on BP than exercise [2-4]. As a consequence, the circadian variation in BP varies greatly from one day to another, in hypertension as well as in normotension.

Earlier, we assessed the extent of day-to-day variability in estimates of the circadian characteristics of SBP of 42 clinically healthy men and women, 20-41 years of age, by means of the Bland-Altman plot [5]. The records were part of the Brno database of 7-day/24-hour ABPM records. Results indicated that the bias on the MESOR of SBP was small, whereas the precision was consistently around 4 mmHg. The precision on the 24-hour amplitude of SBP was about 4.5 mmHg for men and 3.5 mmHg for women, with a positive bias stemming from larger estimates derived from 1-day than from 7-day records [4]. The day-to-day variability in the MESOR and 24-hour amplitude of SBP in men and women is illustrated in Figure 1.

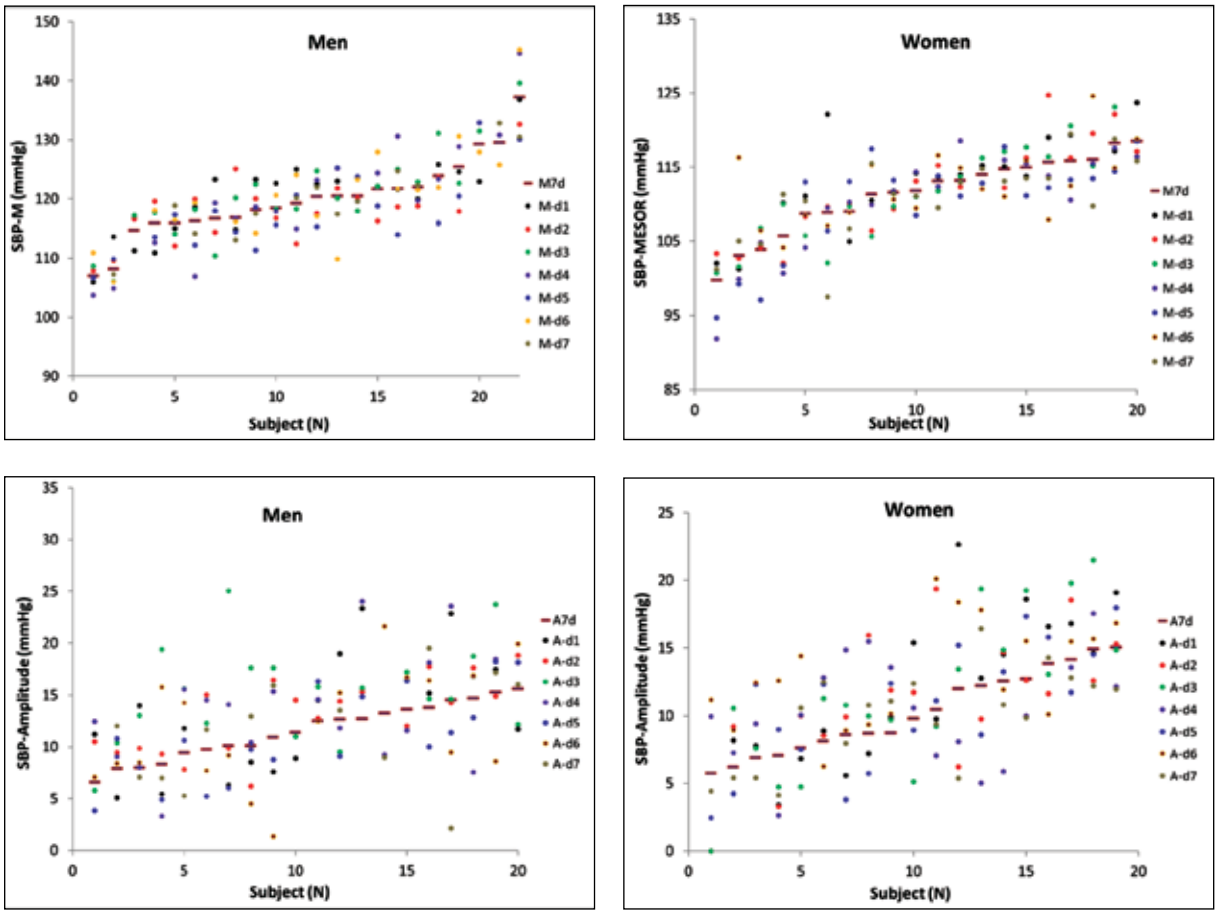

Figure 1: *Day-to-day variability in the MESOR (top) and 24-hour amplitude (bottom) of SBP in men (left) and women (right). Bars are estimates based on 7-day records; dots are estimates based on separate 24-hour spans. Spread of dots are an indication of the large day-to-day variability in circadian characteristics of SBP.*
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Using data from the Brno database of 7-day/24-hour ABPM records, the extent of reproducibility of a classification in terms of "dipping" is examined herein by comparing results obtained on a daily basis versus those based on the entire record, used as reference.

Subjects and Methods

The Brno database used herein currently consists of 267 ABPM records, obtained with the TM-2430 monitor from A&D (Tokyo, Japan). Most of them cover 7 days, with measurements of SBP, DBP and heart rate (HR) at 30-minute intervals from 06:00 to 22:00 and at 60-minute intervals from 22:00 to 06:00. There are 142 records from women 20 to 82 years of age and 125 records from men 20 to 80 years of age.

The circadian variation was assessed by sphygmochron [6, 7] using a 2-component model of 24- and 12-hour cosine curves fitted to the entire record and to each day separately. The day-night ratio (DNR) was also computed over the entire record and for each day separately, using the following formula [8]:

DNR = 100 x (Day mean – Night mean)/24-hour mean

where Day is defined as the span starting 3 hours after the time of awakening and ending 3 hours before bedtime, and Night is defined as the span starting 1 hour after bedtime and ending 1 hour before the time of awakening, disregarding data during times when BP varies more rapidly. Default values for the time of awakening and bedtime are 07:00 and 23:00, respectively.

The DNR is used for a classification in terms of dipping [8]: the desired dipping (DP) pattern corresponds to DNR values between 10 and 20%. DNR values less than 10% define non-dipping (ND). Negative DNR values correspond to reverse dippers (RD), and DNR values above 20% correspond to extreme dippers (ED), Figure 2.

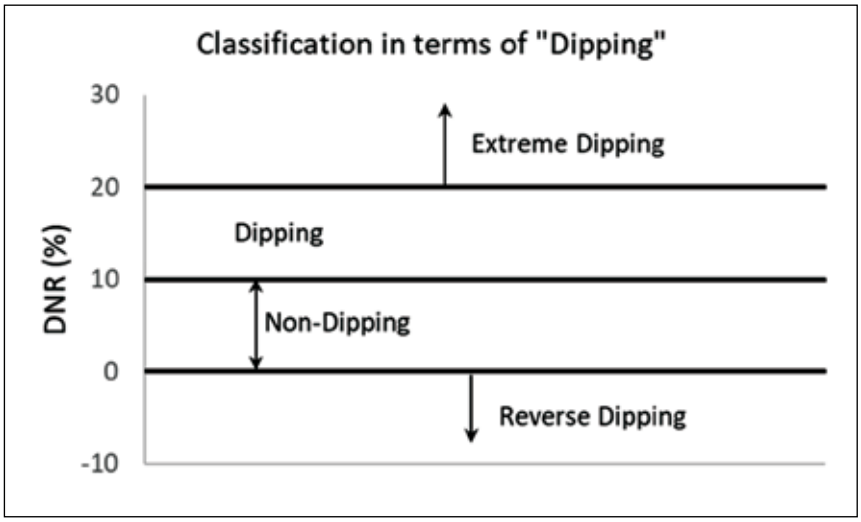

Figure 2: *Classification in terms of "dipping" based on the DNR.* **© Halberg Chronobiology Center**

The extent of agreement was determined as the percentage of diagnoses made on a daily basis that matched the diagnosis based on the entire record, used as reference.

Results

In order to obtain a reliable estimate of the DNR, the data were preprocessed. Each "day" had to have at least 20 measurements covering at least 18 hours. Sufficient data needed to be available during the day (N>5) and night (N>2) span. Only records that covered at least 5 days were considered to compute the percentage of agreement, defined as the percentage of "dipping" classification made on a daily basis that matched the classification made based on the entire record.

Of the 267 records, 259 covered at least 2 days. There were 1, 2, and 8 records spanning 2, 3, and 4 days, respectively. A few additional records from patients under rehabilitation (N=10) or from shift workers (N=10) were not considered either. There were 14, 55, and 160 records spanning 5, 6, and 7 days, respectively. Overall, 229 records were available for analysis.

The large day-to-day variability in BP is illustrated for the case of a 24-year old man in Figure 3. Estimates of the DNR for SBP and DBP of this study participant, and the corresponding classification in terms of dipping are shown in Table 1. Based on the 7-day record, this 24-year old man is found to be a dipper in relation to SBP and an extreme dipper in relation to DBP. On a daily basis, a dipping pattern of SBP was found on 3 of 7 days, yielding a percentage agreement of 42.86%, and an extreme dipping pattern of DBP was found on 5 days, yielding a percentage agreement of 71.43%.

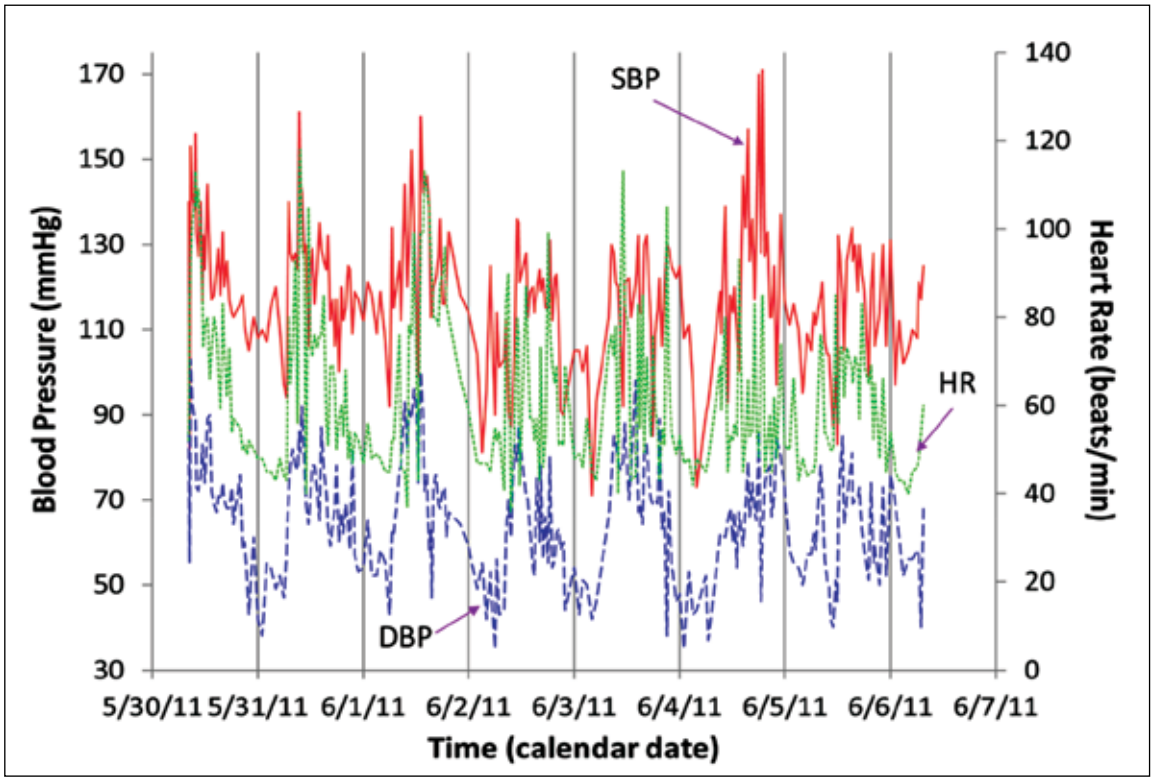

Figure 3: *Example of a 7-day/24-hour ABPM record illustrating the large day-to-day variability in BP. Data from a 24-year old man.* **© Halberg Chronobiology Center**

Overall results for all records spanning 5-6 and/or 7 days are illustrated in Figure 4. Whether the entire record spans 5-6 or 7 days, the percentage agreement for the classification in terms of dipping based on the DNR from a 24-hour ABPM record is less than 60%. This performance is only slightly better than flipping a coin (50%). On an individual basis as well, the range in DNR values computed from separate 24-hour records averages about 20%, as shown in Figure 5. Since a 10% change in DNR corresponds to the width of a dipping category, an about 20% range in daily DNR means that from one day to another most people following their regular daily routine can be classified one day as a dipper and another day as an extreme dipper, or one day as a reverse dipper and another as a dipper.

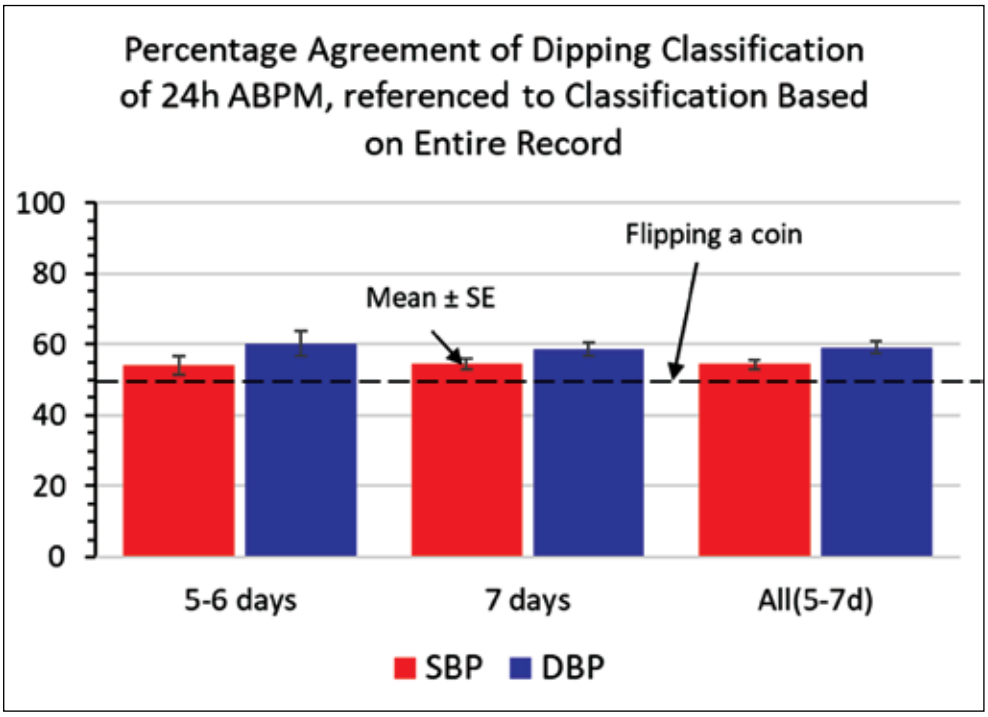

Figure 4: *For both SBP (left, red) and DBP (right, blue), the percentage agreement for the classification in terms of dipping based on the DNR from a 24-hour ABPM record is less than 60%, whether the entire records spans 5-6 days or 7 days.* **© Halberg Chronobiology Center**

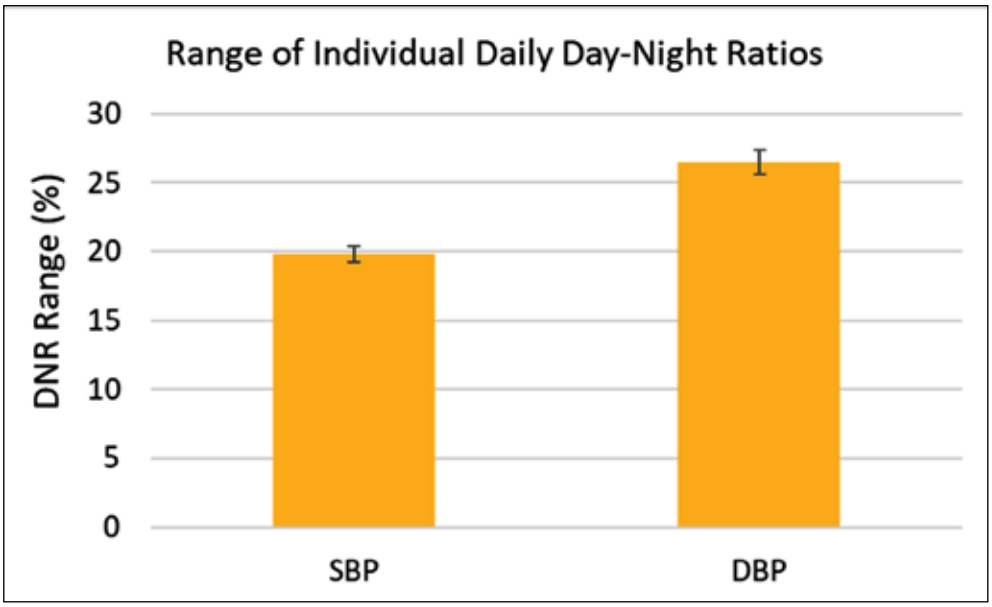

Figure 5: *Individually, the DNR based on 24-hour ABPM varies on average by about 20% within a week, thus spanning 2 to 3 dipping categories.* **© Halberg Chronobiology Center**

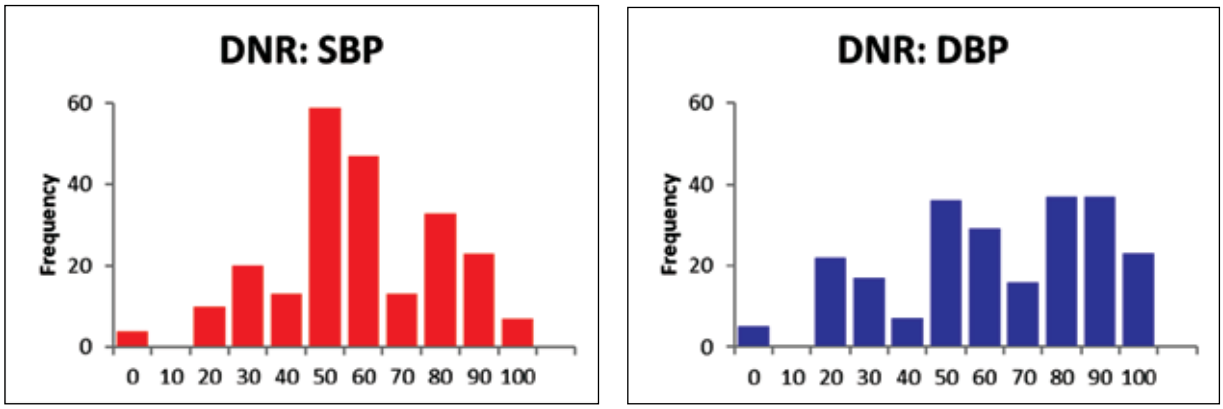

Figure 6: *Histograms of individual estimates of the percentage agreement in dipping classification based on the DNR computed from 24-hour ABPM records (using classification based on entire record as reference). Abscissa is percentage agreement in 10% bins; ordinate is number of study participants.* **© Halberg Chronobiology Center**

The poor performance of the classification in terms of dipping based on the DNR computed from a 24-hour ABPM record affects a large portion of individuals who contributed a 7-day/24-hour ABPM record to the Brno database, as illustrated by histograms of the individual agreement percentages, Figure 6. Whereas there are very few cases for which agreement was 20% or less, agreement of at least 80% is found for fewer than 50% of the study participants.

Discussion and Conclusion

Similar results are obtained for another database of 7-day/24-hour ABPM records contributed by citizens of Tosa City, Japan. Details of this data set and results obtained on their basis have been summarized elsewhere [9]. Among its 371 records, only 5 were shorter than 5 days or had otherwise insufficient data to obtain a reliable estimate of the DNR; there were 7, 20, and 339 records covering 5, 6, and 7 (or longer) days, respectively. The percentage agreement for the classification in terms of dipping averaged (mean ± SE) 59.05 ± 1.25% and 61.08 ± 1.23% for SBP and DBP, respectively. Individual ranges of the daily DNR over the weekly records exceeded 20%, namely averaging (mean ± SE) 22.45 ± 0.45% and 24.16 ± 0.48% for SBP and DBP, respectively. The fact that similar results are found in two countries on two different continents, representing two different ethnic populations attests to the generality of the limitations of the dipping classification derived from 24-hour ABPM records.

Herein, we used the original definition of the DNR [8]. Slightly different formulae have been used since [10, 11], which suffer from the same shortcomings. Several factors account for the poor performance of the DNR used for a classification in terms of dipping. First and foremost is the large variability in the circadian variation of BP from one day to another noted earlier [5], which accounts for the poor reliability of the DNR based on a single 24-hour ABPM record. Another limitation of the classification in terms of dipping based on the DNR relates to the threshold values chosen for the DNR to delineate the four dipping categories. These limits do not account for gender differences or changes in the circadian BP variation as a function of age. In particular, an accentuating post-prandial BP dip in early afternoon in older persons can greatly affect the daytime mean, and hence the DNR [12].

Addressing the foregoing caveats, a chronobiologically-interpreted 7-day/24-hour ABPM for all has been advocated at a consensus meeting held at St. Anna Hospital, Masaryk University, Brno,

Czech Republic, on October 6, 2008 [13]. The proposed guidelines served to rule out the presence of abnormal BP and/or HR variability, the so-called Vascular Variability Disorders (VVDs). If a VVD is detected, continued monitoring is advised. Abnormal BP variability can be present in the absence of an elevated BP. As such, it is not diagnosed in current clinical practice, even though several outcome studies have documented the increased cardiovascular disease risk it is associated with [14].

The merit of a chronobiologic approach has been illustrated in two different outcome studies. This approach relies on the estimation of the circadian amplitude and acrophase of BP, based on fitting a model consisting of cosine curves with periods of 24 and 12 hours to the data to approximate the non-sinusoidal circadian waveform of BP. In one study [15, 16], 297 normotensive and treated hypertensive men and women free of any cardiovascular problem contributed a 48-hour ABPM record before being followed-up at 6-month intervals for 6 years, during which time 39 adverse events (coronary artery disease, cerebral ischemic event, nephropathy, and/or retinopathy) were recorded. Whereas the relative risk of adverse cardiovascular event associated with non-dipping was not statistically significant, that associated with an excessive circadian amplitude of BP (one of the VVDs) was: the relative risk [95% CI] was 3.253 [1.798 – 5.888] for SBP and 4.274 [2.431 – 7.517] for DBP.

In another study, the left ventricular mass index (LVMI), considered as a proxy outcome measure, was determined for 1,179 untreated patients who each contributed a 24-hour ABPM. In this study, based on DBP, there was no difference in LVMI between dippers and non-dippers. LVMI was only slightly elevated in reverse dippers and in extreme dippers, but the difference only barely reached statistical significance for women ($P=0.043$), but not for men ($P=0.664$), or overall ($P=0.186$) [17]. By contrast, both an excessive circadian amplitude and an odd timing of the circadian acrophase of DBP (two VVDs) were associated with a much larger elevation in LVMI, which was statistically significant for both men ($P=0.011$) and women ($P<0.001$), as well as overall ($P<0.001$) [17]. The better performance of the chronobiologic approach as compared to a classification in terms of dipping stemmed largely from the fact that VVDs were more specific than the DNR.

In view of the large day-to-day variability in the circadian BP pattern, it would be ideal if BP could be automatically monitored around the clock longitudinally and data analyzed as-one-goes [18]. While BP monitors using an arm cuff are generally not well tolerated for long-term use, recent advances in technology and wireless communication may soon make continuous monitoring possible. Miniaturized sensors communicating with wearables such as watches and smart phones are increasingly being used for self-surveillance by ordinary citizens interested in their own health and performance. Wrist devices available for home BP monitoring could be made ambulatory but would need to incorporate a correction for position [19]. Devices based on the analysis of the BP waveform also require calibration. Photo-plethysmography has recently been used to measure BP on the wrist [20], but the accuracy of devices based on this technique remains questionable. As algorithms and technology further improve, it may soon be possible to measure BP effortlessly and to derive information about the heart's function itself [21]. This represents a unique opportunity to integrate chronobiological methods and concepts into these evolving systems to make sure that massive data collection does not happen at the expense of quality data analyses.

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Spaceflight, Aging and Bedrest confinement

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Human systems have been shaped to a large extent by gravitational forces. For example, a healthy musculoskeletal system requires gravitational loading for its maintenance. Gravity also influences the way we interact with the environment because it provides a strong reference to align multimodal information such as vision and proprioception, critical for balance. On the other hand, gravitational forces can cause a shift of up to half liter of fluid to the lower extremities within 20 seconds of standing. This, in turn, can compromise the venous return, cardiac preload, and lead to a to drastic reduction in mean arterial blood pressure and cerebral blood flow, and consequently result in falls. Luckily for us, rapid autonomic nervous responses to postural changes occur, leading to maintenance of mean arterial pressure and prevention of orthostatic intolerance. Therefore, in our daily life, we do not realize the impact of gravity on our physiological systems.

The impact of (lack of) gravity can be seen readily when one enters into spaceflight-induced microgravity environment. In addition to becoming weightless, there is a massive cephalad (headward) shift of fluid resulting in puffiness of the face and engorgement of the neck vessels. Different systems react differentially to the microgravity environment but, within six weeks of being in space, homeostatic responses occur in each of these systems leading to their adaptation in the new 0-g environment. The microgravity environment of spaceflight affects specifically the musculoskeletal, cardiovascular, and neurovestibular systems. Some of the physiological effects of microgravity include bone loss, muscle atrophy and plasma volume losses; these physiological changes lead to deconditioning and impaired responses to gravitational loading upon return to Earth.

The changes seen in spaceflight share important common features with age-associated deconditioning and impairment of functions. For instance, a greater incidence of orthostatic intolerance, and consequently falls, occur both in older persons and in astronauts upon return to Earth from the microgravity environment of spaceflight. In older persons, falls can be associated with fracture of bones and/or head injuries. Such fractures and injuries are often associated with prolonged bedrest confinement, which, in turn, leads to more deconditioning. Therefore, prolonged bedrest confinement may lead to greater incidence of orthostatic intolerance and/ or fear of falls, and patients may prefer to stay further in bed. Many bedrest confined persons enter this vicious cycle and they may not be able to recover.

As the number of astronauts that go annually into space is rather limited, understanding spaceflight-induced deconditioning often requires the use of ground-based analogs such as bedrest confinement. Such bedrest confinement studies – carried out mostly in young healthy persons - provide unique insights into the role of short (up to a week), intermediate (up to three weeks) and long-term (greater than three weeks) bedrest confinement on physiological responses. While the space agencies routinely pay young adults to lie in bed for these bedrest confinement studies, older persons on their own spend quite a substantial time lying in bed! Bed confinement is a paramount problem in older persons as they spend long periods in bed either due to chronic diseases, pain, weakness, pre-and post-surgeries, etc. Hence, data from bedrest studies in young healthy adults are useful for understanding the deconditioning effects of bedrest confinement in older persons, which is a rapidly growing segment of the overall population. It has been shown that bedrest confinement can lead orthostatic hypotension

and/or postural control deficiencies, both of which are major contributors to falls in the elderly upon change in posture from supine to upright.

The knowledge gained from bedrest confinement is important for developing countermeasures against deconditioning induced by spaceflight and aging. Indeed, it can be expected that integrating information inherited from space environments and ground-based models of deconditioning will provide novel perspectives and innovative approaches for expanding knowledge – and for developing novel countermeasures – that can be used for astronauts and older persons.

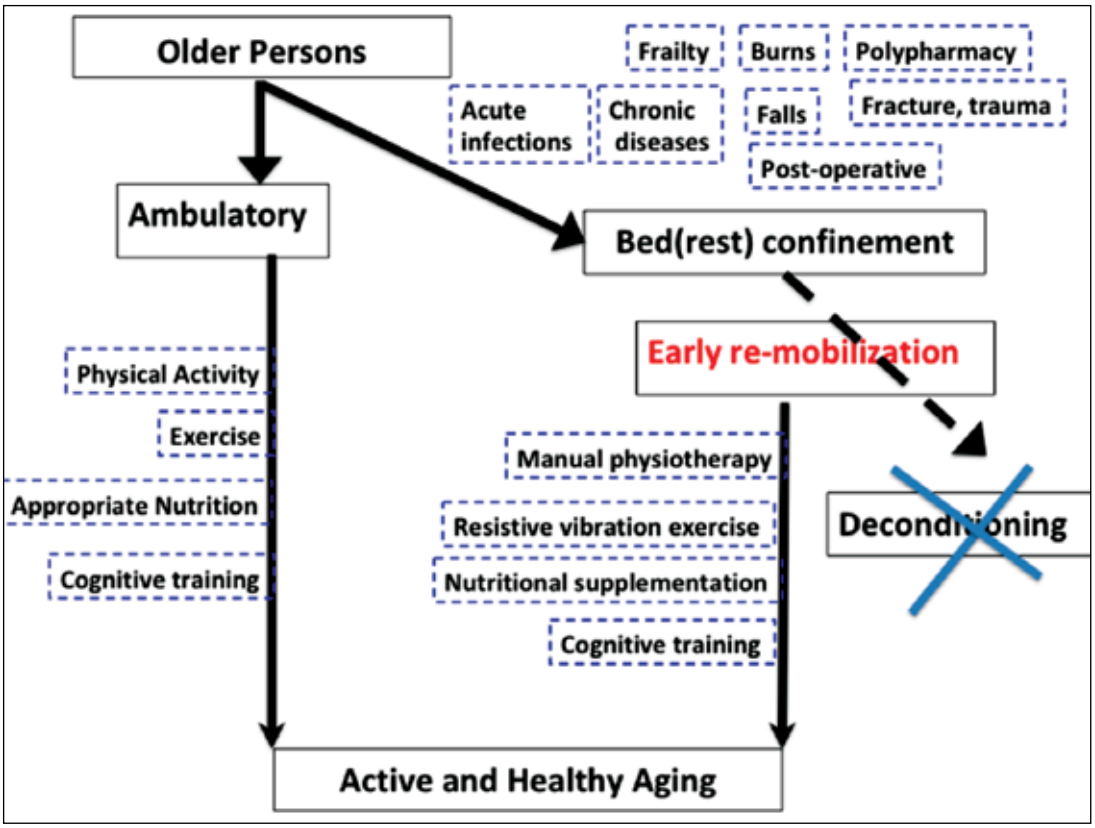

Figure 1: *Early Re-mobilization*

1. Goswami N. (2018). Spaceflight meets Geriatrics!. *Front. Physiol.* Conference Abstract: 39th ISGP Meeting & ESA Life Sciences Meeting.doi: 10.3389/conf.fphys.2018.26.00022

Bedrest and Geriatrics

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Institute of Physiology, Medical University of Graz, Austria

Physiological deconditioning similar to that seen in spaceflight also occurs on Earth, especially as a consequence of the aging process and also due to bedconfinement and/ or immobilization. Illness or injury in older persons frequently requires hospitalized based care. However, the immobilization that occurs during hospitalisation is itself a major factor in physiological deconditioning and functional decline and in older persons can further contribute to a downward spiral of increasing frailty, dizziness upon standing up (orthostatic intolerance) and increased risk and incidence of falls.

Bedrest is used as a ground-based analog for studying the effects of weightlessness on physiological systems as seen during space flight. As older persons spend up to 80% of their time in hospital bed-confined, bedrest studies can also help in furthering our understanding of the deconditioning process during hospitalization in older persons.

This presentation discusses how knowledge obtained from space research can provide guidance towards optimising health care strategies to tackle bed-confined deconditioning, especially in older persons (”Spaceflight meets Geriatrics!”).

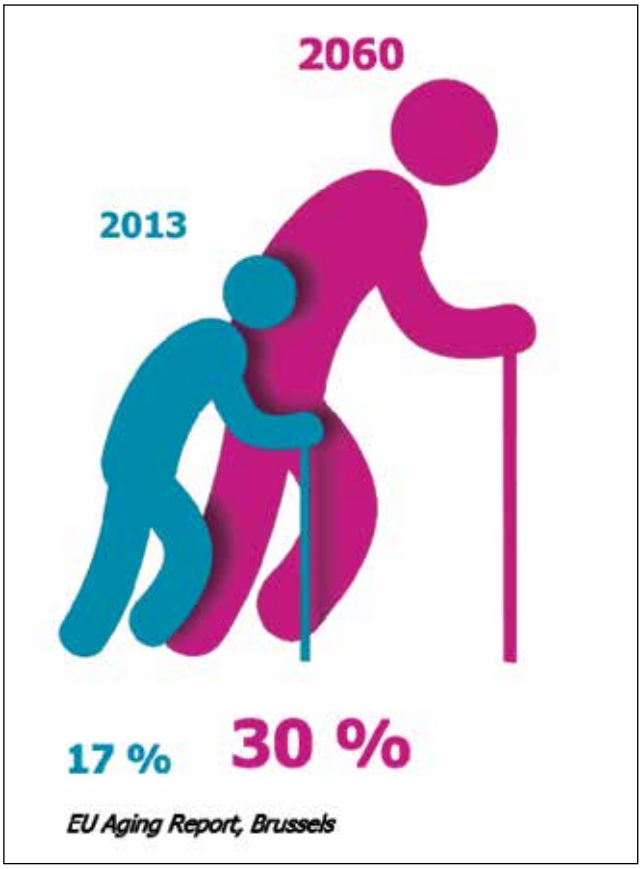

Figure 1: *Aging and Healthcare Costs Trends in 21st century*

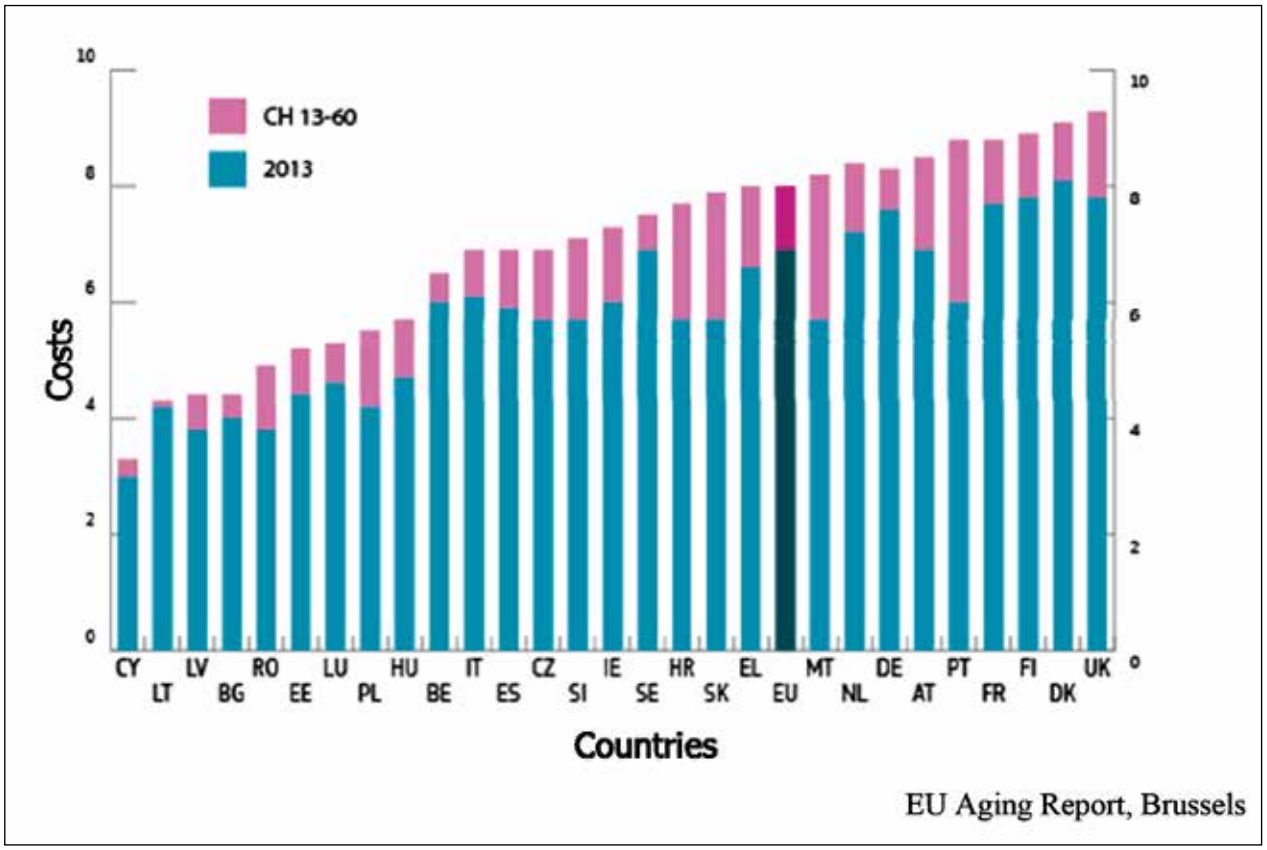

Figure 2: *European´s future*

Effects of resistive vibration exercise on cardiovascular parameter

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Blood pressure regulation is essential in the transition from a sitting to a standing position. A large number of falls occur during this transition of standing up. This can have tremendous effects, such as injuries, especially in the eldery. Orthostatic intolerance is a multifaceted condition with serious consequences. Resistive vibration could be a suitable countermeasure that proved its efficiency against the plethora of major health concerns for the elderly: muscle atrophy, bone mineral density loss, and insulin insensitivity. The aim of this pilot study is to assess how resistive vibration exercise affects the cardiovascular parameters during orthostatic loading (supine-to-stand test).

This study under the ethical approval of Medical University of Graz conducted two consecutive stand tests, before and after 15 minutes of 13 Hz sinusoidal vibration on the Galileo vibration platform attached to the foot of a bed tilted up by 15°; the intervention was preceded and proceeded by baseline and recovery recordings. Selected cardiac parameters were analyzed for five young healthy individuals (1 female, four males; mean age 25.6 years ± 2.245). Repeated measures one-way ANOVA revealed that both heart rate and diastolic blood pressure showed significantly different values following the vibration intervention ($p=0.0022$ and $p=0.0288$ respectively), even though it was passively performed at low frequency and on the tilted bed.

It is concluded that vibration is a promising method to improve cardiopostural response to orthostatic stress, with benefits available to patients confined to bedrest. Further detailed analysis of the data and further research is needed to ensure that the countermeasure's full capacity for the future benefit.

Seven day/24-h ambulatory blood pressure monitoring in night shift workers: Excessive Pulse Pressure

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Introduction

Franz Halberg and Germaine Cornelissen together with Brno chronobiological team using ambulatory blood pressure monitoring showed the need to account for day-to-day changes of blood pressure and heart rate and the necessity to circadian assessment of the hour-to- hour variability in cardiovascular parameters. Together with the Chronobiology Center of Minnesota we participate in the international project BIOCOS. The presentation in 2018 adds new results to this project BIOCOS (1,2 ,3,4,5,6,15,17,18,19,23,24,27). Franz Halberg in Brno Consensus 2008 proclaimed vascular variability disorders and included excessive pulse pressure (3,4).

Excessive pulse pressure is defined by a difference between systolic and diastolic blood pressure record more than 60 mmHg (25,28). Acceptable pulse pressure is below 60 mmHg. According to vascular variability disorders, an excessive pulse pressure increases the risk of cardiovascular morbidity and mortality.

Shift work schedule involving irregular or unusual hours, is becoming popular among people because of the high demand for flexibility and productivity in the workforce in modern society (7). It is reported that 15-30% of workers in America and Europe are engaged in different degrees of shift work, and the trend is increasing rapidly (8,9,10).

Aim

The aim of the study was to compare the 7-day/24-h blood pressure monitoring in healthy subjects and nurses working in day and night work shifts and to determine pulse pressure by means of seven day/24h ambulatory BP monitoring showed increased variability of pulse pressure in every subject day by day and the seven day mean value of pulse pressure could show us the real risk of this parameter.

Methods

We examined 297 healthy subjects including shift workers - 6 women (age 33 ± 12 years, body weight 70 ± 21 kg, mean height 165 ± 5 cm) and 4 men (age 28 ± 7 years, body weight 93 ± 11 kg, mean height 185 ± 5 cm).

The monitoring week in nurses was composed from the days with day work, days with night work and free days. During the monitoring we evaluate the sleep time in different days in every nurse.

The subjects and nurses were recruited for seven-day ambulatory blood pressure monitoring.

Medical Instruments TM2431 (A&D, Japan) were used for ambulatory blood pressure monitoring (oscillation method). The regime of measurement of blood pressure was done for 7 days repeatedly every 30 minutes from 5 to 22 h during the day time and once in an hour from 22 to 5 h at night.

One-hour means of systolic and diastolic blood pressure were evaluated. We calculated mean systolic and diastolic blood pressure for seven days and every 24-hour profile and variability of pulse pressure in every subject day by day and the seven day. We also used the evaluation according to cosinor-based rhythmometry (20).

Results

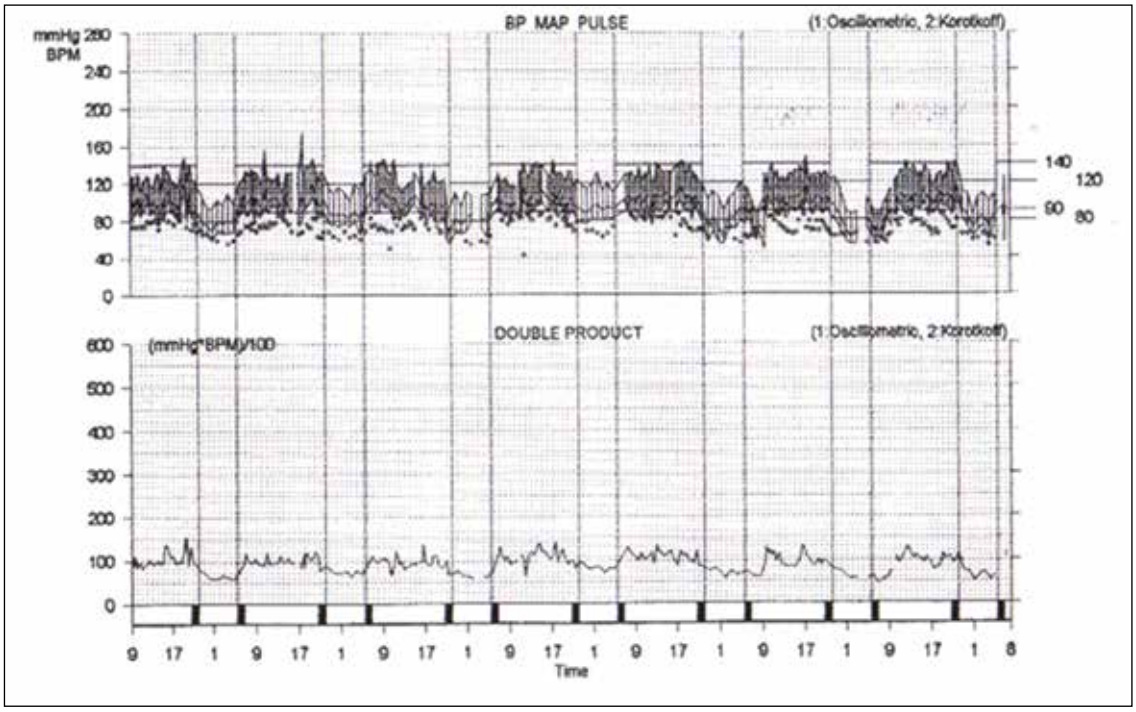

Figure 1: *Seven day /24-h blood pressure profile in healthy subject is shown in Fig. 1 and we can see circadian rhythm in blood pressure and double product*

In Figure 1 is presented the record from seven day/24-h blood pressure monitoring in healthy subject with regular sleep. In the upper part we can see blood pressure (mmHg) and heart rate (b.p.m.), in the lower part double product (mmHg.bpm/100). In both parts of the record in one week (time in h) we can see the presence of circadian rhythm in cardiovascular parameters, increase during daytime and decrease at night.

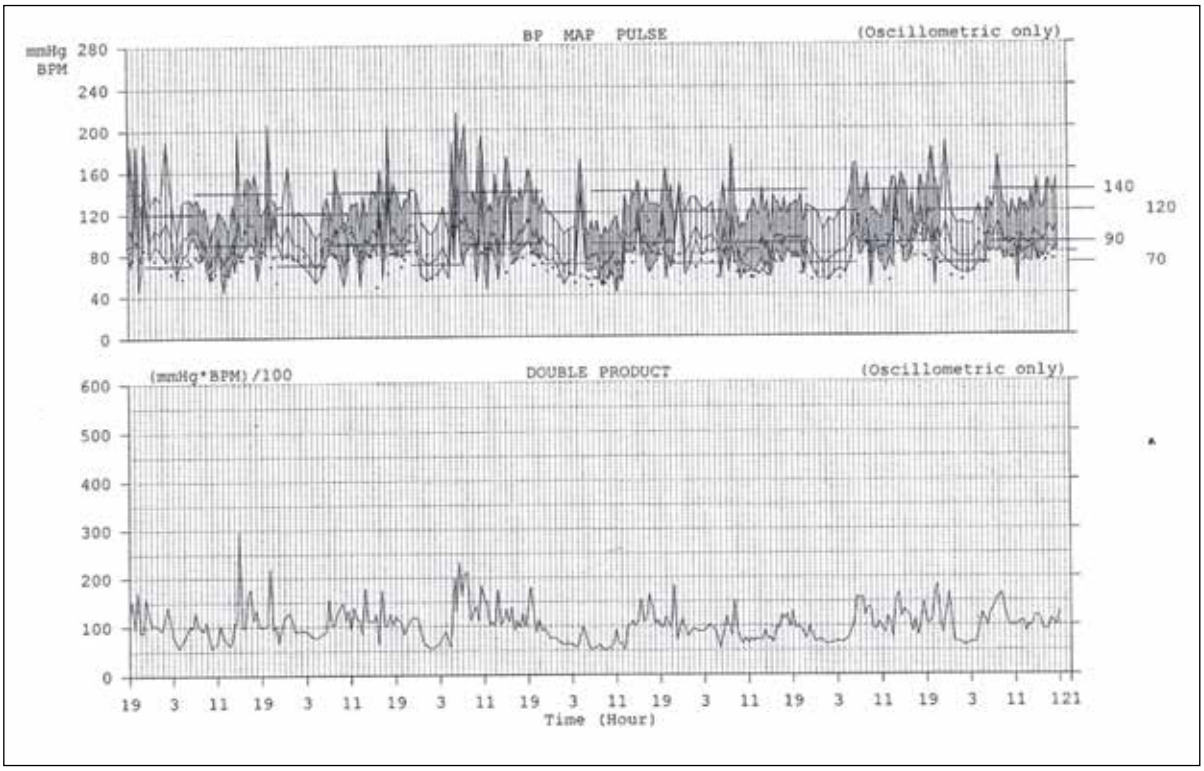

Figure 2: *Seven day /24-h blood pressure profile in nurse. We cannot see circadian rhythm in blood pressure and double product*

Figure 2 is showing record from seven day/24-h blood pressure monitoring in nurse (woman) with shift work with irregular sleep. In the upper part we can see blood pressure (mmHg) and heart rate (b.p.m.), in the lower part double product (mmHg.bpm/100). In both parts of the record in one week (time in h) we can see the impairment of circadian rhythm in cardiovascular parameters.

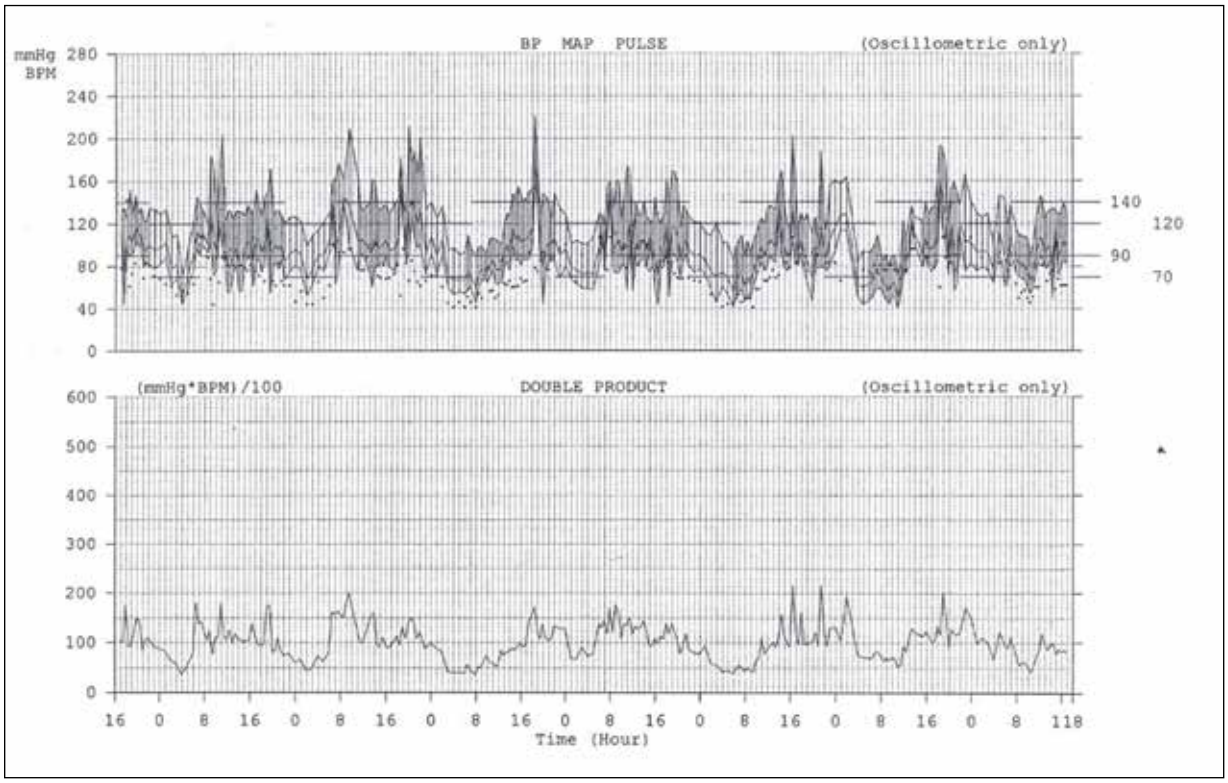

Figure 3: *Seven day /24-h blood pressure profile in nurse (man) in shift work. We cannot see circadian rhythm in blood pressure and double product*

In Figure 3 is presented the record from seven day/24-h blood pressure monitoring in nurse (man) with shift work with irregular sleep. In the upper part we can see blood pressure (mmHg) and heart rate (b.p.m.), in the lower part double product (mmHg.bpm/100). In both parts of the record in one week (time in h) we can see the impairment in circadian rhythm of cardiovascular parameters.

Shift workers were ordered according to mean 7-day SBP (from subject No: 1 - 110 mmHg to subject No: 10 - 138 mmHg) variability of one-daytime SBP values during 7-day monitoring is seen in Figure 4. According to guidelines for hypertension diagnosed from 24 h ambulatory blood pressure monitoring (16,21,22,26) 24 h systolic blood pressure was in 6 shift workers increased about 135 mmHg one to three times and 7-day mean profile of SBP was increased in three shift workers.

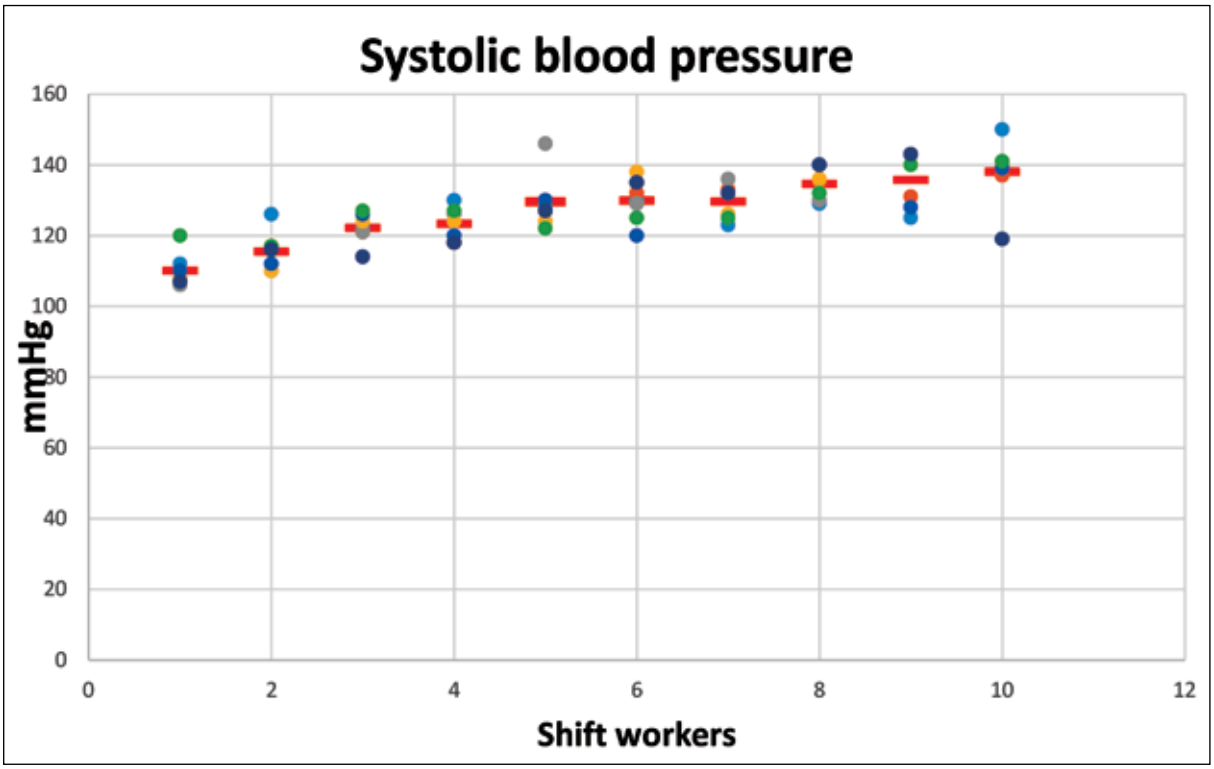

Figure 4: *Variability of 24 h systolic blood pressure profile (colored points) and 7-day mean systolic blood pressure (red line) in 10 shift workers*

Diastolic blood pressure in shift workers was ordered according to mean 7-day SBP; variability of one-daytime DBP values during 7-day monitoring is seen in Fig. 5. According to guidelines for hypertension diagnosed from 24 h ambulatory blood pressure monitoring (16,21,22,26) 24 h diastolic blood pressure was in 4 shift workers increased about 85 mmHg one to six times and 7-day mean profile of DBP was increased in one shift worker.

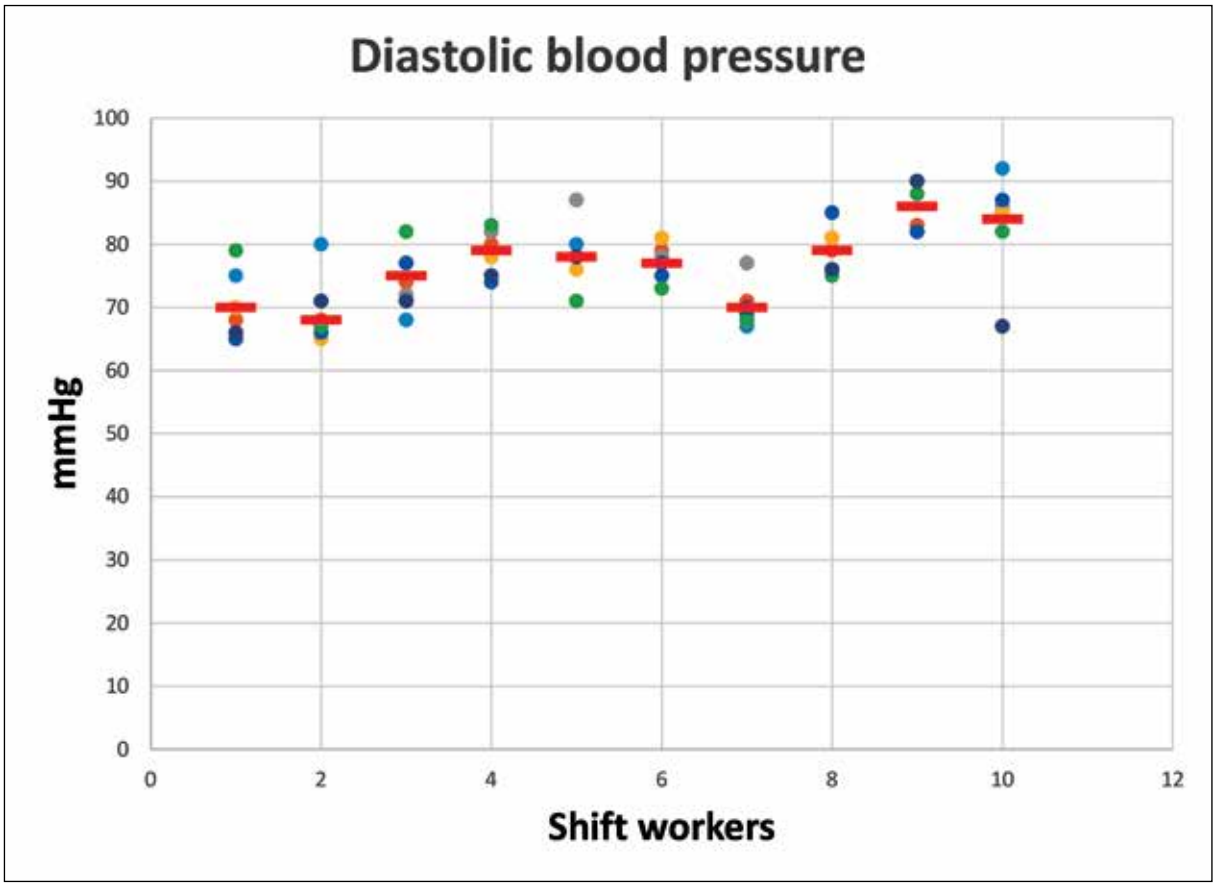

Figure 5: *Variability of 24 h diastolic blood pressure (colored points) and 7-day mean diastolic blood pressure (red line) in 10 shift workers*

Pulse pressure in shift workers was ordered according to mean 7-day SBP; variability of one-daytime PP values during 7-day monitoring is seen in Figure 6. According to vascular variability disorders for increased pulse pressure diagnosed from 24 h ambulatory blood pressure monitoring (3,4,25,28) 24 h pulse pressure about 60 mmHg was in two shift workers increased; 7-day mean pulse pressure was increased in one shift worker.

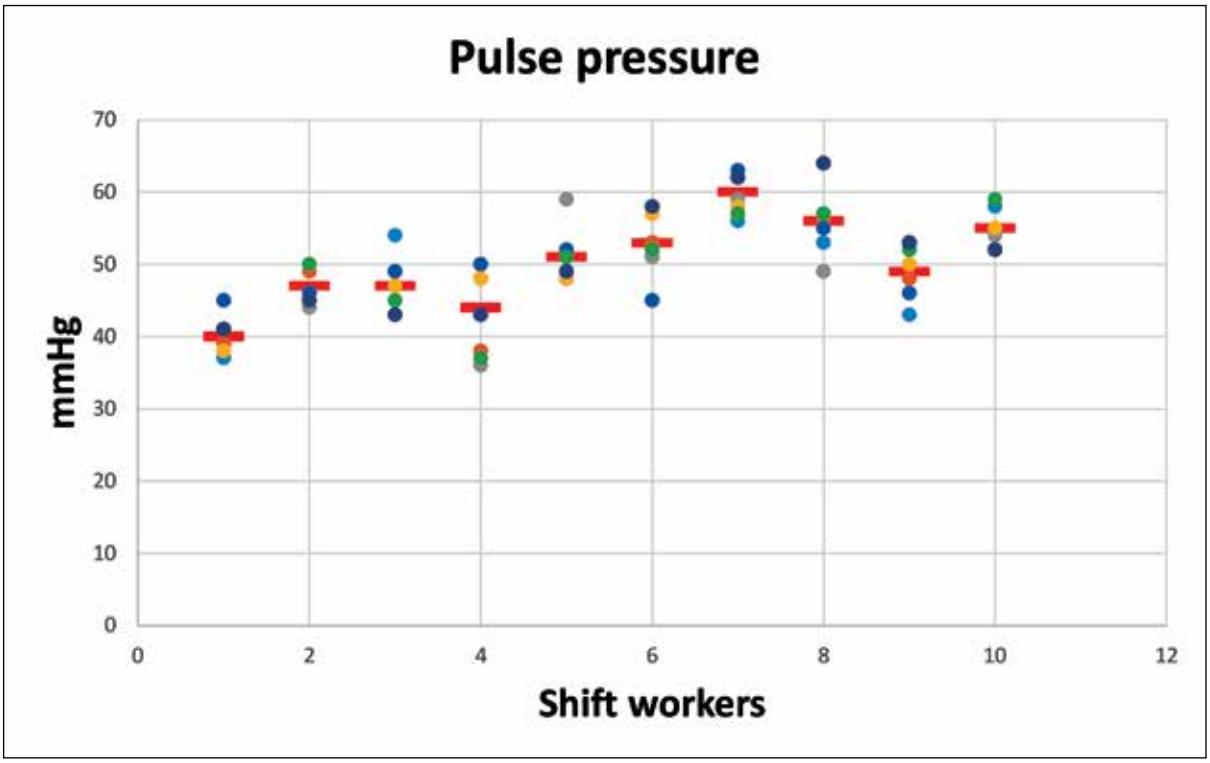

Figure 6: *Variability of 24 h pulse pressure (colored points) and 7-day mean pulse pressure (red line) in 10 shift workers*

In healthy subjects the SBP and DBP variability in 24 h blood pressure profile and in 7-day mean SBP and DBP is similar to our group of our shift workers.

Discussion

Shift work evokes circadian disruption, which disturbs the function of the intrinsic clocks in our body. Our body clocks tend to delay every day and require time to fully adjust after abrupt changes in any schedule that misaligns the external day length with the length of the bodily day. Work at night also means light at night (10,11).

Shift work shows in Wang (7) study that each five years in shift work increases the risk of cardiovascular disease events by 5%. Each five years in shift work increases cardiovascular morbidity by 6% (13,14).

Night-time workers are prone to cancer. Shift work is also known to present risk of insufficient sleep, insufficient physical activity, unhealthy diet, overweight, obesity, hypertension and diabetes mellitus type II. All risk factors in nurses aged 45 – 64 years increase the risk of ischemic heart disease (10,12).

Conclusion

Seven day/24-h ambulatory blood pressure monitoring in night shift workers – nurses shows impairment of circadian rhythm depending on different working shifts.

The timing of working shifts in our study group is very irregular, in seven days are the days with day work shift, night work shift and free days.

Pulse pressure variability in the present study showed the appearance of the excessive pulse pressure in shift workers who were monitored for seven-day/24 hour ambulatory blood pressure under usual conditions of their daily life. The excessive pulse pressure appeared in daily blood pressure profiles and also in mean seven-day/24 hour ambulatory blood pressure.

For the determination of excessive pulse pressure value in individual subjects is important to use long lasting, preferably seven day, ambulatory blood pressure monitoring.

The seven day/24-hour systolic blood pressure profiles vary from 110 to 140 mmHg and we can not use reference values for 24-h ambulatory blood pressure monitoring, while there is impairment in circadian rhythm because of irregular night work. The similar condition is valid for diastolic blood pressure.

The circadian amplitudes vary in every nurse according to the working conditions.

The study in our nurse group, using the 7-day/24-h blood pressure monitoring, showed great impairment of circadian rhythm in blood pressure and heart rate.

Further studies should show the necessity to improve the working conditions to lower the circadian rhythm impairment.

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EM. UNIV.-Prof. DR. MED. UNIV. Thomas Kenner, D.h.c. mult. 29.9.1932 – 22.12.2018

Jarmila Siegelova

Dept. of Physiotherapy and Rehabilitation, Dept. of Sports Medicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Anna´s Teaching Hospital, Brno

Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult.
Dr. h. c. Universität Jena, 1990
Dr. h. c., Semmelweis University Budapest, 1998
Dr. h. c., Masaryk University Brno, 2000
Head, Dept. of Physiology, Karl-Franzens-Universität Austria, 1972-1997
Rektor (president) Karl-Franzens-Universität, Austria, 1989-1991
Dean of Medical School, Karl-Franzens-Universität, Austria, 1991-1997

Prof. Thomas Kenner was exceptional physiologist who focused primarily on physiology of cardiovascular system, covering diverse areas such as aerodynamic properties of arteries, chronobiology of cardiovascular system, pathophysiology and incidence of sudden infant death syndrome, physiology and monitoring of physiological functions in space.

The life story of exceptional scientist we have described in book Noninvasive Methods in Cardiology 2017 at the occasion of his 85th anniversary of birth.

It is very difficult to describe the outstanding scientific, educational and organizational activities of Prof. Thomas Kenner in physiology. The Dept. of Physiology in the University of Graz under

his guidance flourished and attracted many researchers from different countries. His outstanding capabilities to carry out physiological experiments were presented and published particularly in the area of cardiovascular physiology and cardiovascular pathology and in clinical disciplines, where his students continued in the experimental scientific work.

Prof. Thomas Kenner cooperation with Faculty of Medicine, Masaryk University, Brno, Czech Republic started in 1991. Prof. Thomas Kenner was known in our University as a scientist from the publication about the dynamic of arterial pulses from the year 1968. We met personally for the first time in Prague in 1991 on International Physiological Congress, he was also accompanied by his wife Brigitte Kenner. Then he went to Masaryk University and at the meeting we signed an agreement of cooperation and since this time we were meeting every year once or twice in Brno, where we organized every year one Symposium about Chronobiology at Faculty of Medicine and one Symposium during Medical Trade Fair in Brno.

We have had a great luck to cooperate with Prof. Thomas Kenner from nineties in the last century, he visited Brno every year two or three times, presented every time one or two lectures and dicussed with me, late Prof. Bohumil Fiser, CSc, Dr. Jiri Dusek,CSc, Prof. Petr Dobsak, CSc, late Prof. Jan Penaz, CSc, late Profesor Zdenek Placheta, DrSc., Prof. Pavel Braveny, CSc., Masaryk University and our other excelent scientist from abroad Prof. Dr. Franz Halberg, D.h.c, father of chronobiology, Prof. Dr. Germaine Cornelissen, University Minnesota, Halberg Chronobiology Center, USA, late Prof. Dr. Jean Paul Martineaud, Medical Faculty, University Paris, France, Prof. Jean Eric Wolf, University Dijon, France, Dr. Jean Christoph Eicher, University Dijon France and other cooperating visitors from Japan Prof. Masario Kohzuki University Sendai and Prof. Kohji Shirai, Toho University, Chiba. The presentations were published in Scripta Medica, Masaryk University Brno (included in SCOPUS database), in Abstracts books and in Noninvasive methods of Cardiology 1996, 1999, 2002, 2003, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016 and it is possible to find then on Masaryk University, CZ web sides and on web sides of University Minnesota USA.

In honor of excellent scientific work of Professor Thomas Kenner, new head of Dept. of Physiology, Medical University of Graz, Assoc. Prof. Dr. Nandu Goswami, secretary Austrian Physiological Society organized Quadrilateral Physiology Symposium 2019 with the international participation prom Austria, Slovakia, Slovenia, Croatia, also with us from Brno "Vascular Physiology, Physiological Techniques and Medical Education" in Medical University of Graz on 21st of June 2019.

Professor Thomas Kenner will remain in the memory as a great scientist and a great man. We and his pupils will always remember him with gratitude for what he has done for their working life, above all by his physiological research, which he thought should always benefit of the mechanistic attitude derived from experience in basic research.

Eccentric Training in Ambulatory Rehabilitation Program of Patients with Chronic Heart Failure: a Pilot Study

[1,2]Petr Dobsak, [1,2]Leona Mifkova, [2]Michal Pohanka, [1,2]Alena Havelkova, [1]Radka Latalova, [1]Pavel Homolka, [3]Veronika Mrkvicova, [3]Petra Palanova, [1,2]Michaela Sosikova, [1,2]Jarmila Siegelova

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[3]Institute of Public Health, Faculty of Medicine, Masaryk University Brno, CZECH Republic

Excellence Award

This award is conferred to

Prof. Petr Dobsak

for the excellent presentation in the event

QUADRILATERAL PHYSIOLOGY SYMPOSIUM 2019
"Vascular Physiology, Physiological Techniques and Medical Education"

Austria - Slovakia - Croatia - Slovenia
Quadrilateral Physiology Symposium 2019

21st June 2019, Medical University of Graz, Austria

On the behalf of the organizing committee

Assoc. Prof. Nandu Goswami


Medical University of Graz
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Petr Dobsak
for actively participating in the event
Quadrilateral Physiology Symposium 2019
"Vascular Physiology, Physiological Techniques and Medical Education"
A joint initiative between:
Austrian Physiological Society
Croatian Physiological Society
Slovenian Physiological Society
Slovakian Physiological Society
LBI for Vascular Lung Research
21st of June 2019
On behalf of the scientific committee:
Assoc. Prof. Nandu Goswami
21st June 2019
Medical University of Graz, Austria

Abstract

In the last two decades, the interest in eccentric training (ECT) has increased in rehabilitation medicine due to number of specific physiological and biological effects on muscle mass. Based on clinical experience to date, ECT programs can be used not only in healthy people, but also in subjects with varying degrees of physical limitations, including patients with chronic heart failure (CHF). Patients and methods. Twenty-nine patients with mild form of CHF (NYHA I-II); 22 men; 7 women; mean age 63.8 ± 8.9 years, mean body weight 89 ± 17.4 kg. All the patients had 8 weeks of CV-RHB program and the ECT was included as a part of aerobic endurance phase of one training session. Training was performed 3 times/week; duration of one training session was 60min. At baseline and after the end of training period, peak oxygen uptake (VO_{2peak}), peak workload (Wpeak) and muscle power of knee flexors and extensors (using isokinetic dynamometer) were measured for evaluation of overall performance and the setting of training workload. Results. The mean eccentric muscle power increased significantly in both extensors and flexors: in extensors, the peak torque (PT) increased from 114.2 ± 54.6 to 158.6 ± 58.0 Nm (P<0.002) and PT of flexors from 81.1 ± 30.4 to 118.9 ± 29.5 Nm (P<0.003). Compared to concentric muscle power, the studied type of RHB program with ECT seems to be more effective on eccentric muscle power in both knee extensors and flexors. Eight 8 weeks of ECT increased significantly also the mean value of VO2peak/kg (from 20.1 ± 5.1 to 21.6 ± 5.3 ml O_2/kg/min; P<0.05). Conclusion. The results of this preliminary study suggest that ECT can be used safely in patients with CHF (mild grade of the disease) to perform high-load exercise with minimal cardiovascular stress (fairly lower systemic activation, blood pressure, HR, etc.). According to current information from scientific databases, this study is very likely one of the first attempts to include ECT in the rehabilitation of patients with CHF.

Key words

rehabilitation – exercise training – spiroergometry – isokinetic dynamometry – eccentric training

Introduction

Eccentric contractions (ECC) of large muscle groups of the lower limbs are involved in locomotor activities of daily living (ADL), but without intensity that would increase muscle power. Eccentric training (ECT) is usually applied in training programs of professional and amateur athletes with the main goal to increase muscle strength and performance. In the last two decades, the interest in ECT has increased in rehabilitation medicine due to number of specific physiological and biological effects on muscle mass (1). Eccentric muscle work can be mainly performed using isotonic, isokinetic, and also (more generally) ECC-based exercise modalities. Due to its specific physiological properties and specific cardiovascular/metabolic responses, there is an increasing interest in employing ECC muscle work for rehabilitation and clinical purposes (2). In concentric (CON) contraction the muscle exerts motor actions, produce body movements such as locomotion, whereas in ECC the muscle bears an external load, and exerts anti-gravity and braking actions. For example, ECC muscle exercise can be performed by walking or running downhill. The eccentric load can be realized either by special training methods or by using special devices, especially eccentric bicycle ergometers. Based on clinical experience to date, ECT programs have been studied up to the present not only in healthy people but also in subjects with varying degrees of physical limitations, with the main aim to improve fitness, reduce dependence and improve quality of life. Already in 1971 Knuttgen et al. demonstrated that

cardiac output (Q) and heart rate (HR) are about twofold lower during ECT than CON cycling at the same mechanical power (3). On the other hand, if both types of muscle exertion are performed at the same value of peak oxygen uptake (VO_{2peak}), a greater cardiovascular activation is present in ECT (4). One of the most important contributions of ECT in clinical medicine is very likely the possibility to apply quite high workload to target muscles with considerably lower energy demands, and at a lower level of systemic sympatho-adrenergic activation. This is an interesting circumstance, especially in patients with cardiovascular diseases (5, 6).

Aim

Only few previously published reports suggested that ECT training might be particularly suitable for improving body composition and muscle power in disabled populations, mainly in patients with coronary artery disease. The present study aimed to evaluate the effects of 8 weeks supervised endurance training combined with eccentric exercise using special bicycle ergometers in group of patients with mild grade of chronic heart failure (CHF).

Patients and methods.

Twenty-nine patients with mild form of CHF (NYHA I-II; 22 men; 7 women; mean age 63.8 ± 8.9 years, mean body weight 89 ± 17.4 kg) participated in the study. All the patients had 8 weeks of CV-RHB program and the ECT was included as a part of aerobic endurance phase of one training session. Training scheme was designed as follows: a) warm-up period (10min), b) aerobic/concentric endurance training (15min) + aerobic/eccentric training (15min), c) resistance training (10min), and d) period of cool-down (10min). Training was performed 3 times/week; duration of one training session was 60min (Fig. 1).

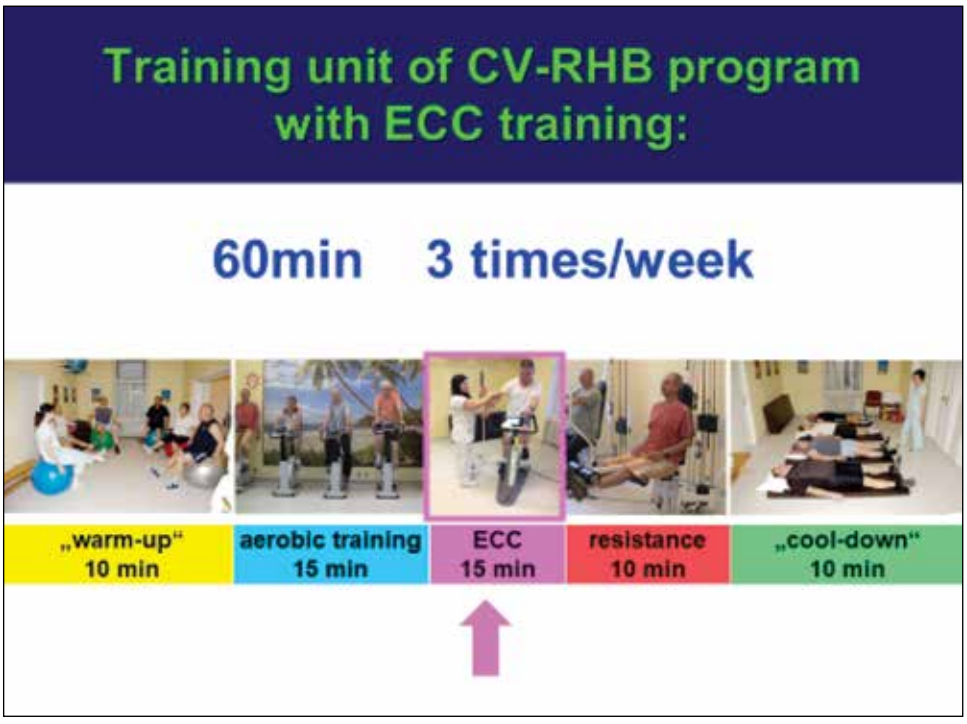

Figure 1: *Design of training unit (Center of Cardiovascular Rehabilitation, Department of Sports Medicine and Rehabilitation, St. Anne´s Faculty Hospital Brno)*

An isokinetic bicycle ergometer (Corival Lode®; Groningen, Netherlands) which generates constant angular movement velocity was used for the ECT (Fig.2). However, ECT performed at high intensity and/or for a long duration, can induce muscle damage and delayed pain, so-called ‘‘delayed onset muscular soreness’’ (DOMS). So, in order to prevent overloading or even damage of the muscle fibers, the workload of the ECC training was set according the results of the entrance spiroergometric test and gradually increased for each patient individually (according to muscle pain). At baseline and after the end of training period, spiroergometric test was performed in all patients to assess cardiopulmonary performance and the setting of training workload. Based on actual recommendations (7), peak oxygen uptake was measured during gradual workload (s.-c. ramp protocol) on bicycle ergometer (Ergoselect 200, Ergoline, Bitz, Germany) using spiroergometric system (Power Cube, Ganshorn Medizin Electronic, Niederlauer, Germany) with integrated 12-lead ECG (AT-104 PC, Schiller, Baar, Switzerland). The test was realized until the maximum according to individual functional abilities of the examined patients. Patients were instructed to keep stable rate of pedaling (60/min) and workload was automatically increased, gradually from 0 until the tolerated maximum (Wpeak/kg). Heart rate (HR) was automatically recorded during the whole test and blood pressure (BP) was measured manually every 2 minutes. Standard ventilation and respiratory parameters of blood gasses exchange (VO_2, VCO_2, ventilation) were measured by “breath-by-breath” method. Peak oxygen consumption (VO_{2peak}) was expressed as the highest reached value of O_2 in last 30 seconds of workload.

Figure 2: *Eccentric ergometer Corival Lode (Groningen, Netherlands).*

Analogically, peak heart rate (HRpeak) and peak workload (Wpeak) were assessed. After the test both ventilatory thresholds (VT-1 and VT-2) were determined. All equipment were always calibrated individually for each patient. Isokinetic dynamometry is considered as valid instrument for assessing muscle power, and it is often used to monitor progress during rehabilitation (8, 9). For this reason, an

isokinetic dynamometer was used in this study to assess muscle function with an accommodating resistance, at a constant angular velocity, thereby enabling maximum force production throughout a prescribed range of motion. Concentric/eccentric muscle power of knee flexors and extensors was measured using Humac NORM isokinetic dynamometer (CSMi, Stoughton, MA, USA) equipped by special software (Humac 2009, v.9.7.1; Fig.3 and 4).

Figure 3: *Isokinetic muscle power measurement (Humac NORM; CSMi, Stoughton, MA, USA).*

Prior to muscle power testing, all the participants performed 5 min of warm-up (70–80 revolutions per minute) on bicycle ergometer (Life-Fitness). For familiarization with the dynamometric test procedure, all the subjects performed three submaximal trial repetitions prior to each test. During the whole test the subject was seated in an upright position, with the backrest at 85°. To minimize compensatory trunk movements during testing the subject was fixed by stabilizing straps, according to the manufacturer's manual. The rotational axis of the knee was placed in line with the dynamometer axis of rotation, and 0° was determined as 0° knee extension. The dynamometer was calibrated before the start of each test according to the operating manual.

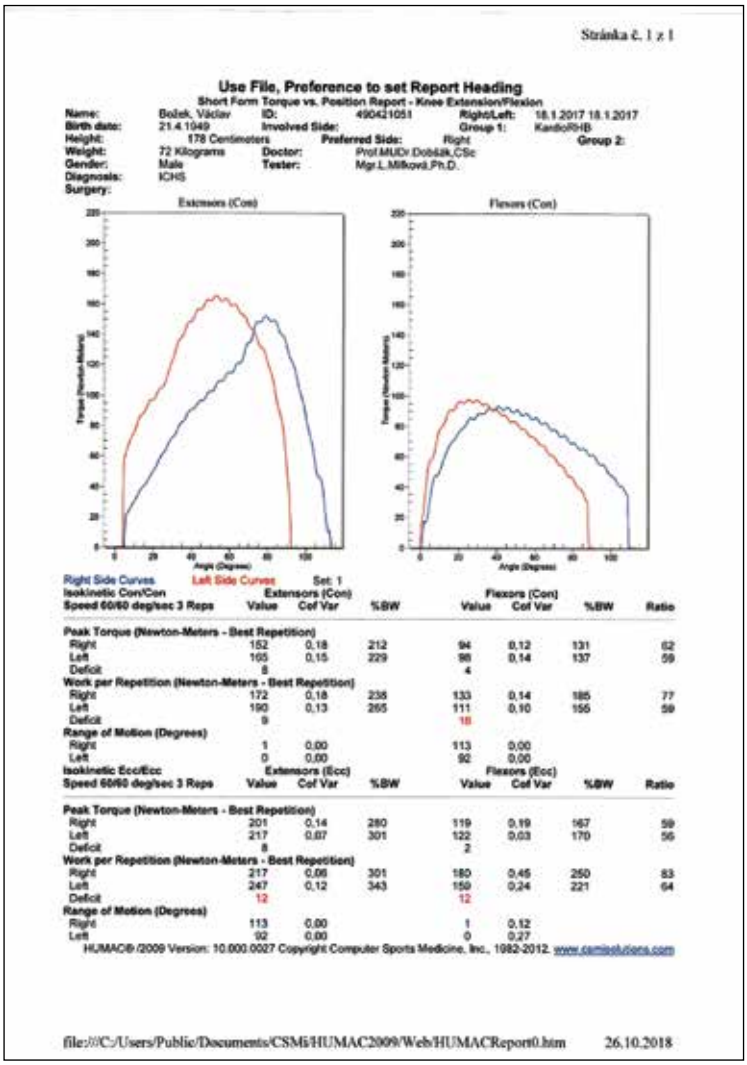

Figure 4: *Example of a peak muscle power (peak torque) testing by isokinetic dynamometer (Humac NORM; CSMi, Stoughton, MA, USA).*

The study was approved by local ethics committee and all included patients signed informed consent based on the "World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects" (updated in Fortaleza, Brazil 2013) and orders of GCP European community.

Results

During the last 4-5 weeks of CV-RHB program most of the patients achieved the workload intensity in ECT corresponding to the ventilatory threshold 2 (VT-2) determined by spiroergometric test at entrance (!). After 8 weeks of RHB training the mean concentric muscle power of knee extensors increased significantly: from 125.8 ± 45.1 to 142.6 ± 46.6 Nm ($P<0.03$).

ECCENTRIC MUSCLE POWER	At baseline (x ± s) [Nm]	After the end of training (x ± s) [Nm]	% of change	*P* value
Knee joint extensors	181 ± 57.5	199 ± 58.9	+ 9.9	p < 0.01
Knee joint flexors	116 ± 35.8	119 ± 31.1	+ 2.6	NS
CONCENTRIC MUSCLE POWER	**At baseline (x ± s) [Nm]**	**After the end of training (x ± s) [Nm]**	**% of change**	***P* Value**
Knee joint extensors	128 ± 45.5	143 ± 45.5	+ 11.7	p < 0.01
Knee joint flexors	81 ± 27.5	91 ± 28.5	+ 12.3	p < 0.01

Table 1: *Results of the measurement of concentric and eccentric muscle power of knee extensors and flexors by isokinetic dynamometry.*

There was also a clear improvement of the PT of flexors (from 79.6 ± 26.7 to 90.3 ± 28.1 Nm; NS) but without statistical significance. In contrast, the mean eccentric muscle power increased significantly in both extensors and flexors: in extensors, the PT increased from 114.2 ± 54.6 to 158.6 ± 58.0 Nm (P<0.002) and of flexors from 81.1 ± 30.4 to 118.9 ± 29.5 Nm (P<0.003). Compared to concentric muscle power, the studied type of RHB program with ECT seems to be more effective on eccentric muscle power in both knee extensors and flexors. Eight 8 weeks of ECT increased significantly also the mean value of VO_{2peak}/kg (from 20.1 ± 5.1 to 21.6 ± 5.3 ml O_2/kg/min; P<0.05). We observed also an improvement of the mean value of peak workload (from 153.2 ± 50.1 to 158 ± 47.8 W; NS), but this result was not statistically significant.

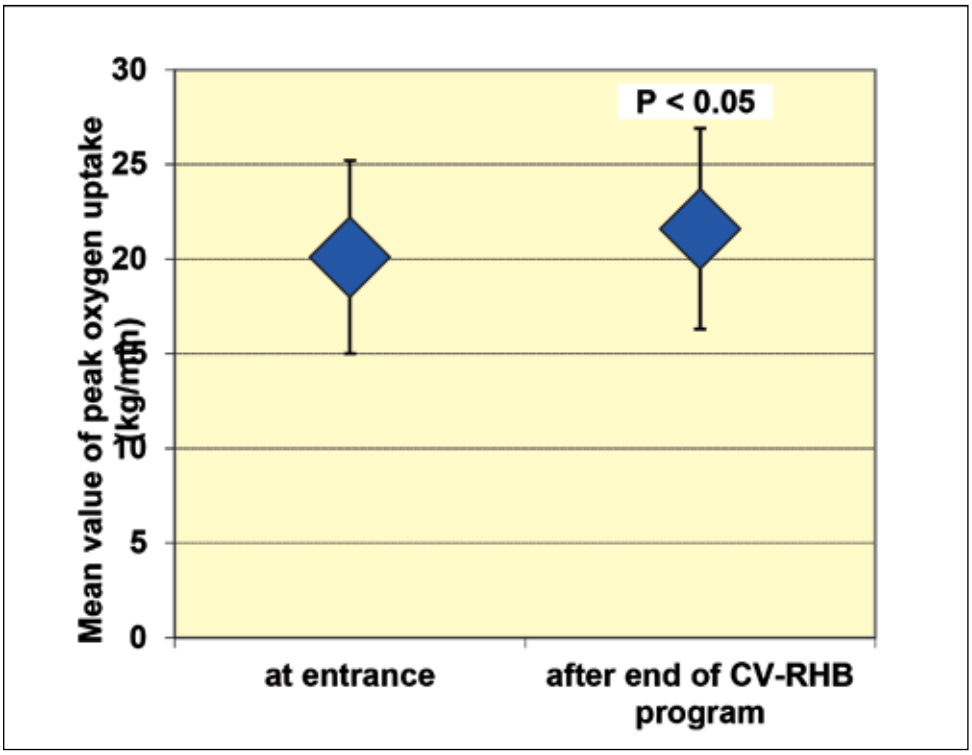

Figure 5: *Significant increase of the mean value of peak oxygen uptake after 8 weeks of CV-RHB program with ECT.*

Similarly, the mean value of HR_{peak} (spiroergometric test) improved only slightly after the end of RHB period (from 127 ± 22.8 tom 129 ± 21.6; NS).

Discussion

Eccentric training is still used only rarely in cardiovascular rehabilitation because most training protocols are traditionally based on concentric exercises (5, 6, 10). Compared to training on classic bicycle ergometers, the same mechanical load on eccentric ergometer elicits much lower metabolic and cardiovascular activation, so it is possible to use much higher workload intensity, which is a significant stimulus to increase muscle power of the lower limbs (11). The workload generated by the eccentric bicycle ergometer activates several lower limb muscle groups, especially the knee extensors braking the pedal return. This fact could (at least partly) explain why the peak muscle power (both concentric and eccentric) of the knee extensors significantly increased after 8 weeks of supervised training. The eccentric training was well tolerated by all the patients; there were no adverse effects or acute health troubles. It is quite interesting that during the last half (4 weeks) of CV-RHB program most of the patients tolerated without any negative signs or symptoms the workload intensity in ECT corresponding to the VT-2 determined at the entrance spiroergometric test. This fact is particularly important from the point of view of possible better improvement of functional performance in patients with cardiovascular diseases in comparison with standard (concentric) training. However (as mentioned above), in eccentric training the involved muscle groups are more easily overloaded compared to concentric training. Based on our own experiences and observations it is strongly recommended to start the RHB program with a shorter eccentric training of low intensity and - using the ability of relatively fast adaptation of muscles to repeated eccentric load - gradually (step-by-step) increase the intensity of the workload. This is the only proper way, how to prevent muscle damage manifested by DOMS

that could temporarily exclude the patient from eccentric training. Eight weeks of ECT led also to weaker but significant improvement of the mean peak oxygen uptake (VO_{2peak}/kg). However, this result was - very likely - influenced by a shorter (8 weeks only) period of CV-RHB program (according to the actual ESC and CSC guidelines the recommended length of supervised RHB program for cardiac patients is 12 weeks). Few previously published reports suggest that ECC training could be used in patients with coronary insufficiency to increase their muscle strength and obtain functional gains (5). ECC bicycle training also improved the mean left ventricular EF compared with CON cycle training (6). In patients with type II diabetes mellitus, the addition of ECC exercises to the classical aerobic training program improved their glucose tolerance and decreased the glycosylated hemoglobin values (12). In older individuals (mean age 80 years), ECC cycle training can lead to better improvement of the quadriceps isometric strength compared with a traditional resistance training program (13). It seems that ECC training might be particularly suitable for improving body composition and muscle strength in disabled populations, possibly via still unclear specific factors involved in muscle growth, repair and remodeling. Therefore, ECT needs to be further explored in order to broaden our understanding of the underlying physiology to provide better assistance to athletes, patients and clinicians to take full advantage of the eccentric training benefits. Several areas deserve particular attention, including the optimization and individualization of training protocols for patients, as well as the systemic, cellular and molecular events involved in the skeletal muscle and nervous system responses to acute and chronic ECC exercise.

Conclusion

The results of this preliminary study suggest that ECT can be used safely in patients with CHF (with mild grade of the disease) to perform high-load exercise with minimal cardiovascular stress (fairly lower systemic activation, blood pressure, HR, etc.). According to current information from scientific databases, this study is one of the still rare attempts to include ECT in the rehabilitation of patients with CHF. However, more extensive use of ECT in clinical practice is still limited by quite high costs of eccentric bicycle ergometers.

Declaration

No conflict of interest.

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Chronobiology research: Brno-Graz collaboration

Prof. MUDr. Jarmila Siegelova, DrSc.

Department of Physiotherapy, Department of Sports Medicine and Rehabilitation, Faculty of Medicine, Masaryk University, St. Anna Teaching Hospital, Brno, CZ

Prof. Dr. Thomas Kenner, M.D., Dr. h.c. mult.
Dr. h. c. Universität Jena, 1990
Dr. h. c., Semmelweis University Budapest, 1998
Dr. h. c., Masaryk University Brno, 2000
Head, Dept. of Physiology, Karl-Franzens-Universität Austria
Rektor (president) Karl-Franzens-Universität, Austria, 1989 - 1991
Dean of Medical School, Karl-Franzens-Universität, Austria, 1991 - 1997

Prof. Thomas Kenner was exceptional physiologist who focused primarily on physiology of cardiovascular system, covering diverse areas such as aerodynamic properties of arteries, chronobiology of cardiovascular system, pathophysiology and incidence of sudden infant death syndrome, physiology and monitoring of physiological functions in space.

Excellence Award

This award is conferred to

Prof. Jarmila Siegelova

for the excellent presentation in the event

QUADRILATERAL PHYSIOLOGY SYMPOSIUM 2019

"Vascular Physiology, Physiological Techniques and Medical Education"

Croatia - Austria - Slovakia - Slovenia
Quadrilateral Physiology Symposium 2019

21st June 2019, Medical University of Graz, Austria

On the behalf of the organizing committee

Assoc. Prof. Nandu Goswami

Certificate of Participation

This certificate is awarded to

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for actively participating in the event

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21st of June 2019

On behalf of the scientific committee:

Assoc. Prof. Nandu Goswami

21st June 2019

Medical University of Graz, Austria

Prof. Thomas Kenner cooperation started with Faculty of Medicine, Masaryk University, Brno, Czech Republic in 1991.Prof. Thomas Kenner was known in our University as a scientist from the publication about the dynamic of arterial pulses from the year 1968. We met personally for the first time in Prague in 1991 on International Physiological Congress, he was also accompanied by his wife Brigitte Kenner. Then he went to Masaryk University and we signed an agreement of cooperation and since this time. Every year he came to Brno twice, where I organized a congress on chronobiology every year at the Faculty of Medicine and one symposium at the Medical Fair in Brno.

Usually we presented latest scientific discoveries together with Prof Thomas Kenner, Austria, Prof. Franz Halberg, Prof. Germaine Cornelissen, both USA, Prof. Jean-Paul Martineaud, Paris, France and Brno team - Prof. Bohumil Fiser, Dr. Jiri Dusek and me. Sometimes Prof. Thomas Kenner, everytime accompanied by his wife, took also with him his pupils to Brno who presented at Masaryk University their scientific lectures. Prof. Thomas Kenner published his lectures in the scientific papers. Brno chronobiological team visited also some scientific meetings in Graz and presented results in the area of cardiovascular control in man in health and diseases in Austria.

We have a great luck to cooperate with Prof. Thomas Kenner from nineties in the last century. Prof. Thomas Kenner discused with Brno team, with me and late Prof. Bohumil Fiser, CSc., Dr. Jiri Dusek, CSc. and also from Brno Prof. Petr Dobsak, CSc., late Prof. Jan Penaz, CSc., late Profesor Zdenek Placheta, DrSc., late Prof. Pavel Braveny, CSc., Masaryk University and our other excellent scientist from abroad Prof. Dr. Franz Halberg, D.h.c, mult., father of chronobiology, Prof. Dr. Germaine Cornelissen, University Minnesota, Halberg Chronobiology Center, USA, late Prof. Dr. Jean Paul Martineaud, Medical Faculty, University Paris, France, Prof. Jean Eric Wolf, University Dijon, France, Dr. Jean Christoph Eicher, University Dijon France and other cooperating visitors from Japan Prof. Masario Kohzuki University Sendai, Japan and Prof. Kohji Shirai, Toho University, Chiba, Japan.

The chronobiological presentations from Brno scientific meetings were published in Scripta Medica, Masaryk University Brno (included in SCOPUS database), in Abstracts books and in Noninvasive methods of Cardiology 1996, 1999, 2002, 2003, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016 and it is possible to find then on web sides of Masaryk University, CZ and on web sides of University Minnesota, USA and Masaryk University Brno, CZ (http://www.med.muni.cz/index.php?id=1376).

Chronobiology, studied by Franz Halberg, started in 1947, in University of Minnesota countinued unitl now and showed broad spectrum of rhythms in us and around us; they are being marched up by the dozens but have not yet been recognized in terms of their pertinence to everyday life. Brno scientific meetings and congresses included the studies in the periond form 1990 and summarized all knowledge of chronobiology not only from the participants but also other scientist all over the world with whom the main personality Professor Kenner, Professor Halberg and Professor Cornelissen publisched results.

Brno Concensus 2008 summarized chronobiologically interpreted blood pressure and heart rate monitoring under the leading personality of Prof. Franz Halberg which detects prehypertension, prediabetes and a premetabolic syndrome in vascular variability disorders, that interact with a reliably diagnosed as MESOR hypertension that can carry a risk greater than a high blood pressure alown and that can coexist to form vascular variability syndromes, unrecognized in a conventional health care, but some of them already treatable.

Figure 1: *Professor Bohumil Fiser, As. Professor Michal Pohanka, Professor Thomas Kenner, Brigitte Kenner, Dr. Othild Schwartzkopff , Professor Franz Halberg, Dr. Jiri Dusek, Professor Jarmila Siegelova, Brno Congress Noninvasive Methods in Cardiology 2008 (Brno Consensus)*

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Bohumil FISER (*22.10.1943-†21.03.2011): Chronobiologist, Emeritus Head of the Physiology Department at Masaryk University (Brno, Czech Republic), Czech Minister of Health, and Executive Board Member of the World Health Organization: His Legacies for Public and Personalized Health Care

Franz Halberg[1], Germaine Cornélissen[1], Thomas Kenner[2], Jiri Dusek[3], Brigitte Kenner[2], Othild Schwartzkopff[1], and Jarmila Siegelova[4]

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[3]Health Medical Center, South Moravia Region, Brno, Czech Republic
[4]Department of Functional Diagnostics and Rehabilitation, St. Anna Teaching Hospital, Brno, Czech Republic

In 2003, one of us (JS) dedicated a special volume of papers dealing with non-invasive cardiology [1] to Bohumil Fiser, MD, our dear friend, Figure 1, and, his relatively young age notwithstanding, our mentor and supporter. In that volume, GC and JS laid the basis for a chrononeonatology. Another of us (OS) emphasized the need for long-term, preferably lifetime monitoring of blood pressure and heart rate as a concern for everybody and hence for government and ethics committees.

Figure 1. Bohumil Fiser (1943-2011).

Figure 2:

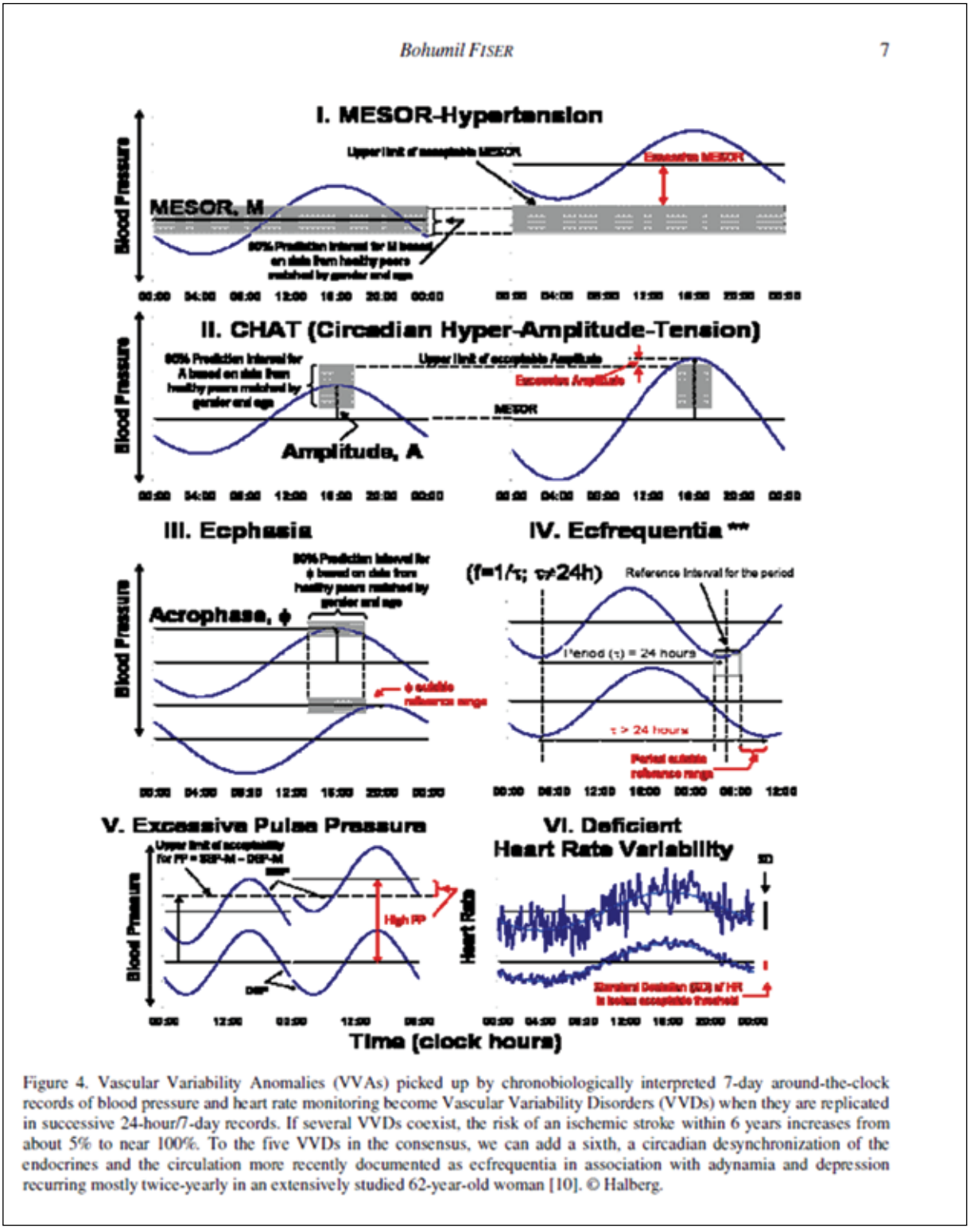
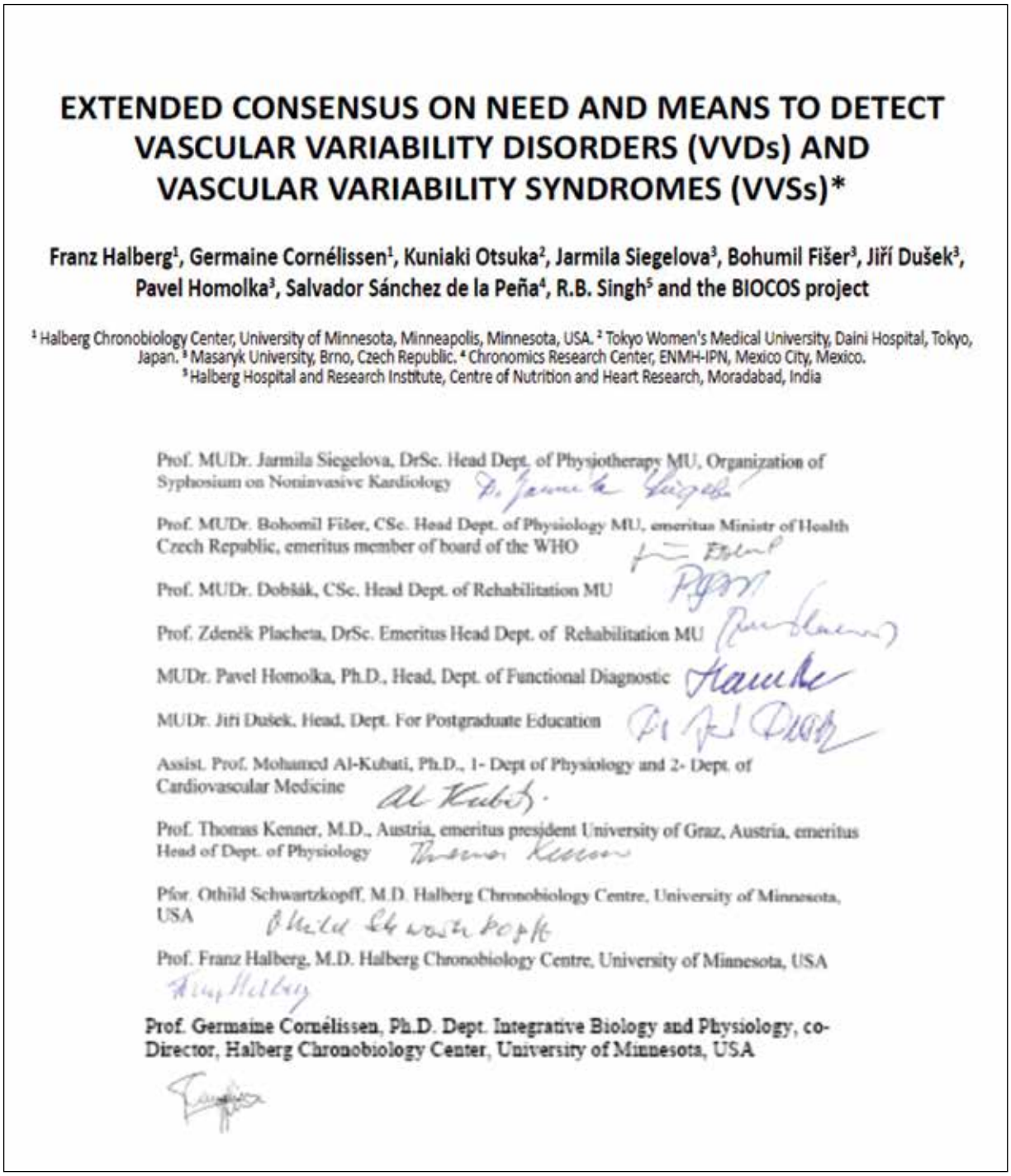


Figure 4. Vascular Variability Anomalies (VVAs) picked up by chronobiologically interpreted 7-day around-the-clock records of blood pressure and heart rate monitoring become Vascular Variability Disorders (VVDs) when they are replicated in successive 24-hour/7-day records. If several VVDs coexist, the risk of an ischemic stroke within 6 years increases from about 5% to near 100%. To the five VVDs in the consensus, we can add a sixth, a circadian desynchronization of the endocrines and the circulation more recently documented as ecfrequentia in association with adynamia and depression recurring mostly twice-yearly in an extensively studied 62-year-old woman [10]. © Halberg.

Figure 3:



EXTENDED CONSENSUS ON NEED AND MEANS TO DETECT VASCULAR VARIABILITY DISORDERS (VVDs) AND VASCULAR VARIABILITY SYNDROMES (VVSs)*

Franz Halberg[1], Germaine Cornélissen[1], Kuniaki Otsuka[2], Jarmila Siegelova[3], Bohumil Fišer[3], Jiří Dušek[3], Pavel Homolka[3], Salvador Sánchez de la Peña[4], R.B. Singh[5] and the BIOCOS project

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Assist. Prof. Mohamed Al-Kubati, Ph.D., 1- Dept of Physiology and 2- Dept. of Cardiovascular Medicine

Prof. Thomas Kenner, M.D., Austria, emeritus president University of Graz, Austria, emeritus Head of Dept. of Physiology

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Prof. Germaine Cornélissen, Ph.D. Dept. Integrative Biology and Physiology, co-Director, Halberg Chronobiology Center, University of Minnesota, USA

Figure 4: *Brno Consensus in: Intl. J. of Geronto-Geriatrics, 11 (14) 119-146, December 2008*

Brno Consensus: Vascular Variability Disorders. Excessive Pulse Pressure

Excessive pulse pressure is defined by a difference between systolic and diastolic blood pressure record more than 60 mmHg. Acceptable pulse pressure is below 60 mmHg. According to vascular variability disorders excessive pulse pressure increase risk of increased cardiovascular morbidity and mortality.

The study is aimed to determine of pulse pressure by means of seven day/24h ambulatory BP monitoring showed increased variability of pulse pressure in every subject day by day and the seven day mean value of pulse pressure could show us the real risk of this parameter.

Subjects

From our Brno database of 496 patients with ambulatory monitoring of blood pressure for seven day/24 hours, thirty healthy subjects were recruited for seven-day blood pressure monitoring. One-hour means of systolic and diastolic blood pressure were evaluated, when night-time was considered from midnight to 0600 h and day time from 1000 to 2200 h, avoiding the transitional periods. Mean day-time and mean night-time systolic and diastolic pressures were evaluated every day, and from this data we calculated pulse pressure.

7-day monitoring of blood pressure was made by means of the instrument TM – 2421 of Japanese firm A&D operating on the principle of oscillometric analysis. The instrument measured blood pressure for 7 days repeatedly every 30 min from 5 to 22 o'clock and once an hour from 22 to 5 o'clock. We calculated the 7-day mean for pulse pressure and every day mean for pulse pressure.

The study was approved by local ethics committee and the patients signed the informed consent.

The subjects were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg).

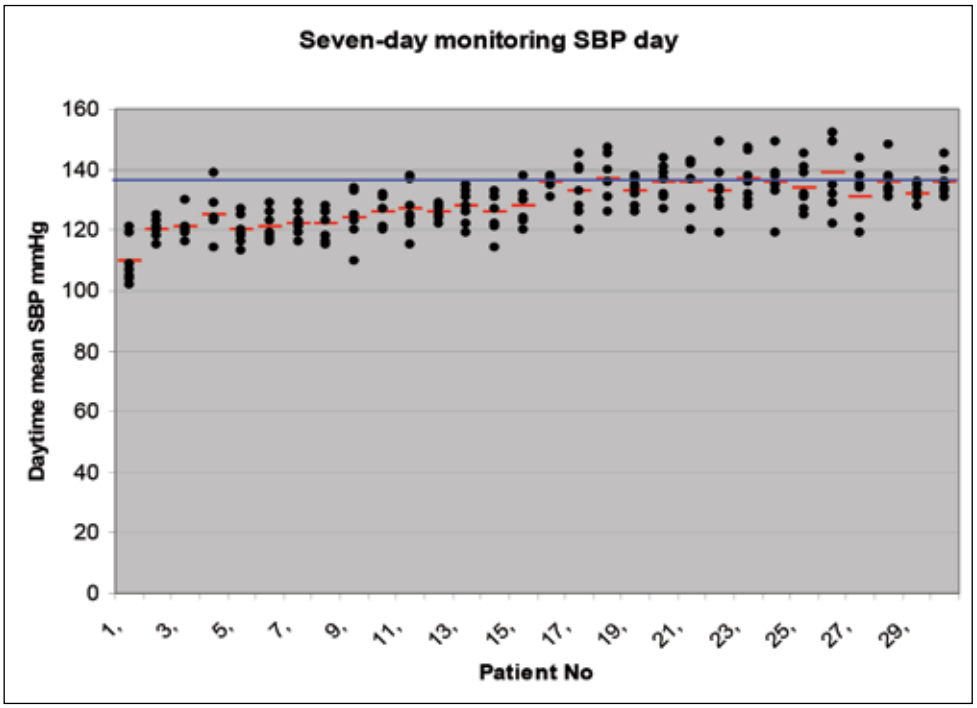


Figure 5: *The variability of one-daytime SBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

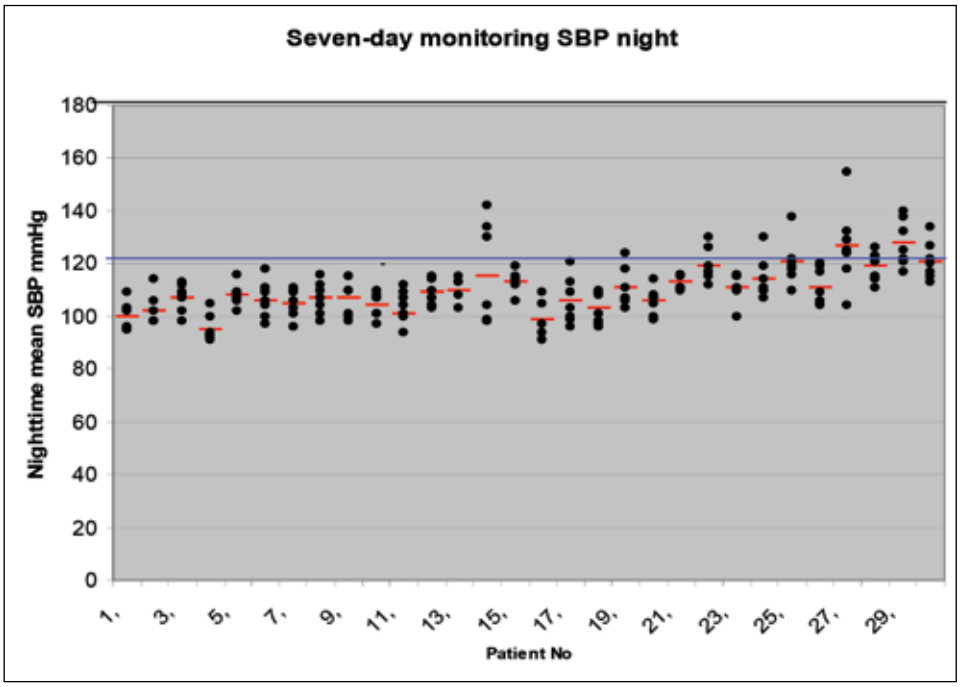


Figure 6: *The variability of one-nighttime SBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

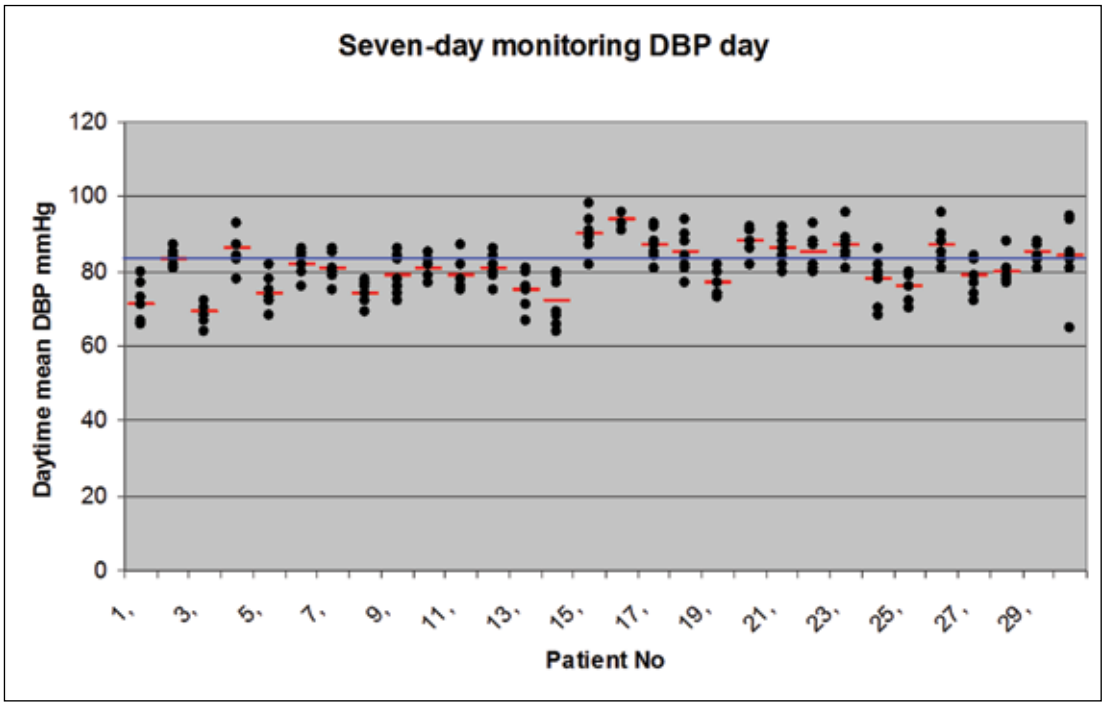


Figure 7: *The variability of one-daytime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

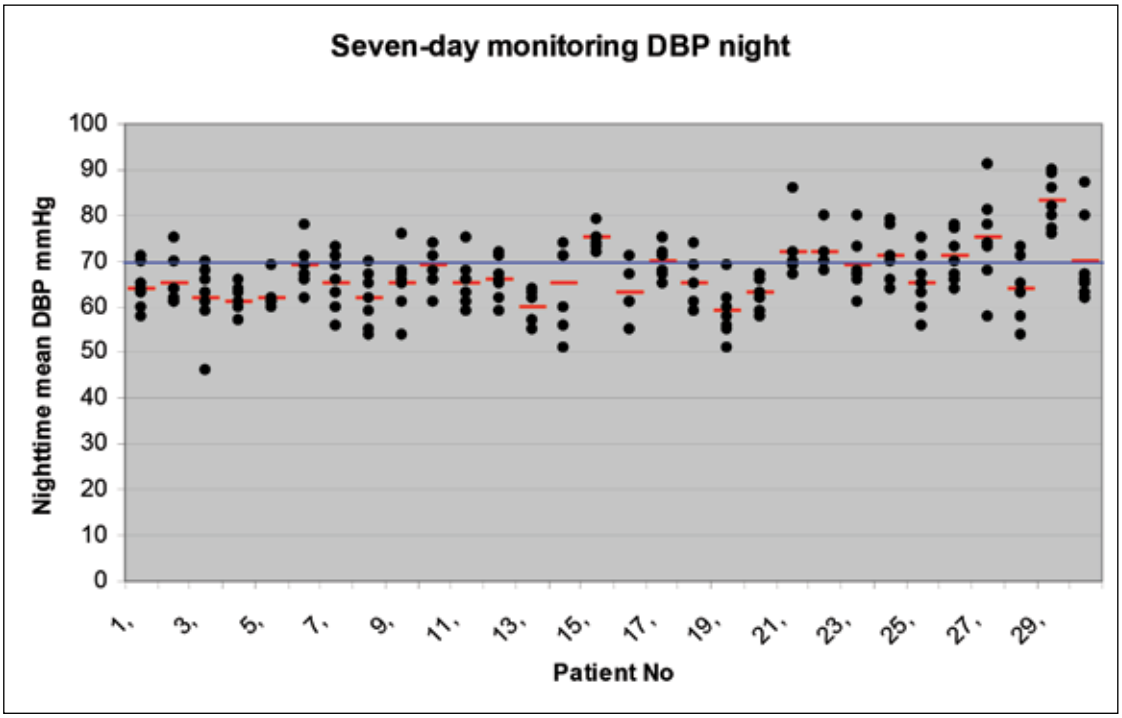


Figure 8: *The variability of one-nighttime DBP values during 7-day monitoring. The patients were ordered according mean 7-day SBP (patient No 1: 107 mmHg, patient No 30: 131 mmHg; median value: 123 mmHg). One-day mean values (point) and 7-day mean values (dash) are indicated.*

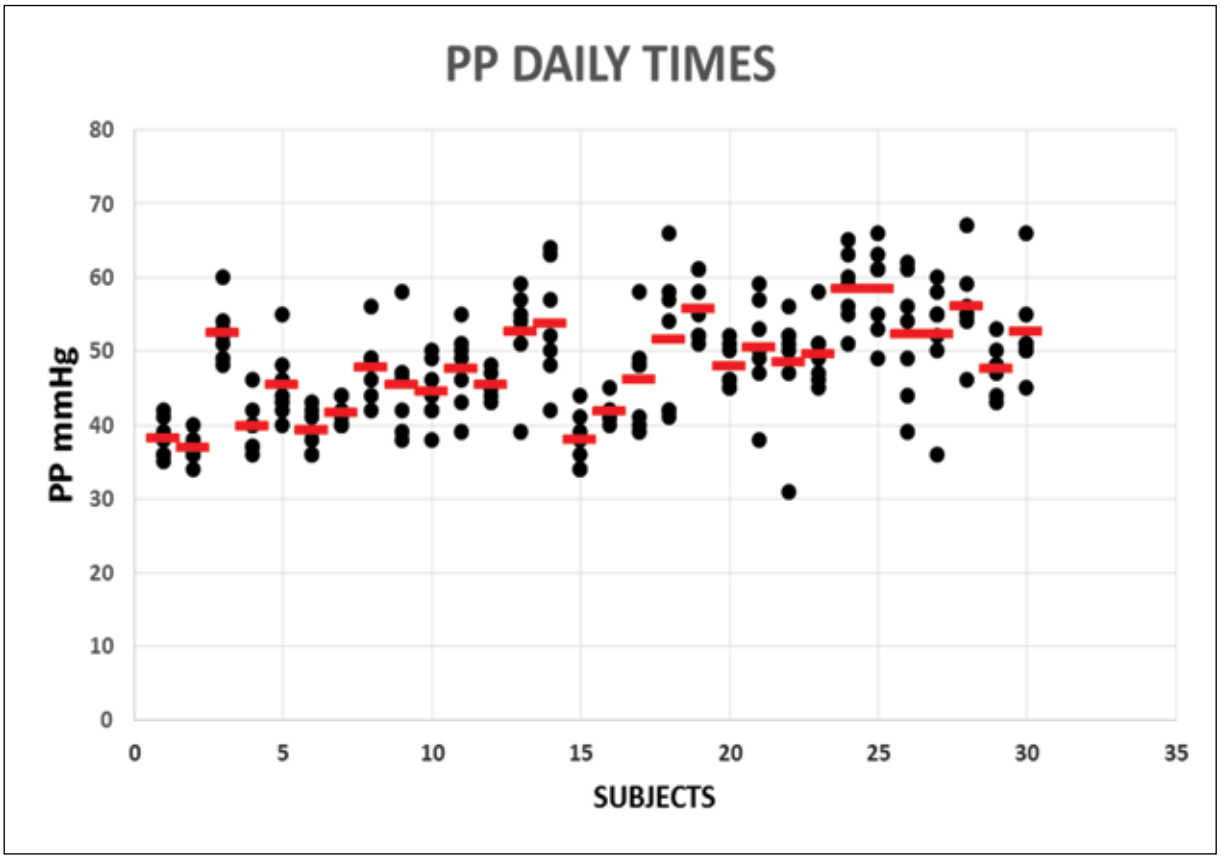


Figure 9: *The variability of pulse pressure daily times during 7-day monitoring. The subjects were ordered according mean 7-day SBP. One-day mean values of pulse pressure (point) and 7-day mean values (red dash) are indicated.*

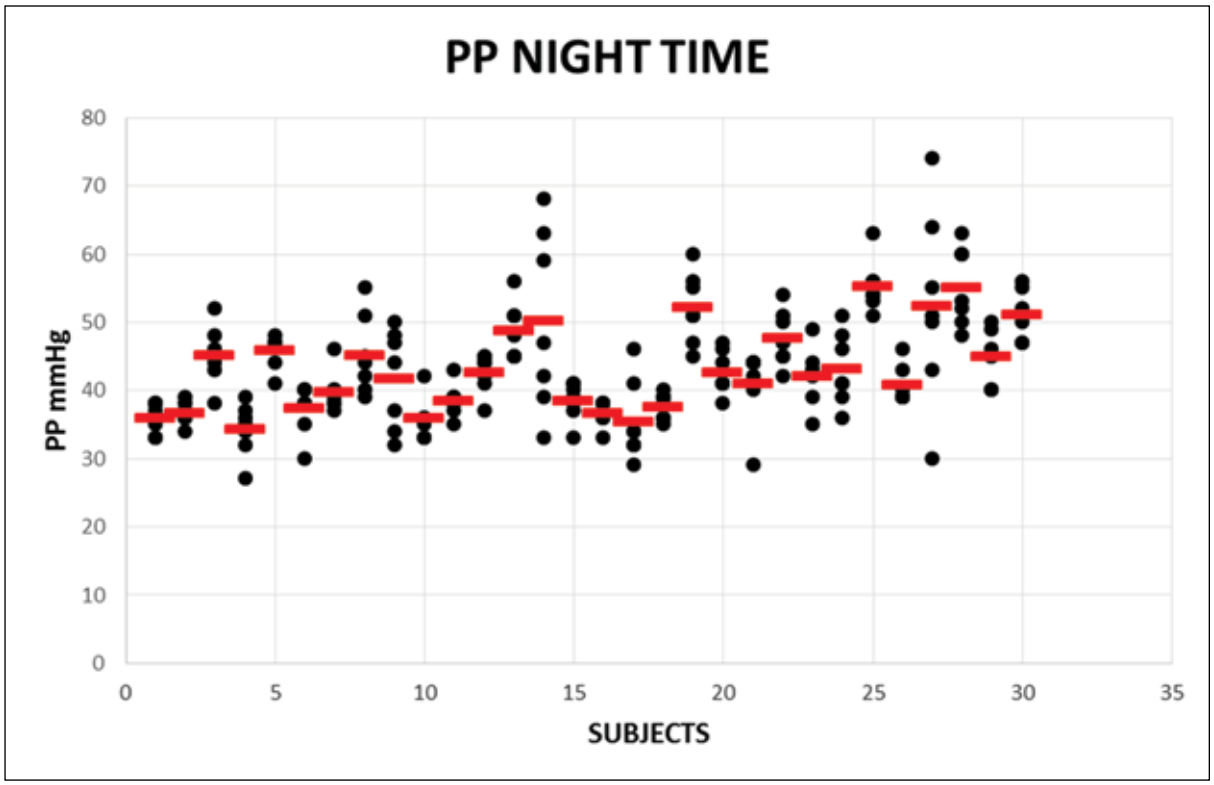


Figure 10: *The variability of pulse pressure night time during 7-day monitoring. The subjects were ordered according mean 7-day SBP. One-day mean values of pulse pressure (point) and 7-day mean values (red dash) are indicated.*

Pulse pressure variability in the present study showed the appearance of the excessive pulse pressure in subjects who monitored seven day/24 hour ambulatory blood pressure under usual conditions of daily life. The excessive pulse pressure appeared more often in the daily times hours than at night.

The seven day lasting blood pressure monitoring in our studied group of subjects have not found in any time excessive pulse pressure if calculated as seven day mean values for daytime hours or at night.

For the determination of excessive pulse pressure value in individual subjects is important to use long lasting, preferably seven day, ambulatory blood pressure monitoring.

Figure 11: *Professor Franz Halberg, Professor Pavel Bravený, Brigitte Kenner, Professor Thomas Kenner, Professor Jarmila Siegelová, Professor Jan Peňáz, Professor Bohumil Fišer in 1996*

Figure 12: *Professor Germaine Cornélissen, Brno Congress Noninvasive Methods in Cardiology 2003*

Figure 13: *Dr. Jiri Dusek, Professor Franz Halberg, Dr. Othild Schwartzkopff, Professor Thomas Kenner, Brno International Congress MEFA 2005*

Figure 14: *Prof. Dr. Thomas Kenner, Dr.h.c.mult. Austria and Prof. Dr. Kohji Shirai, Japan, Congress Noninvasive Methods in Cardiology, Brno 2012.*

Figure 15: *Professor Franz Halberg, Dr. Othild Schwartzkopff, Professor Germaine Cornélissen in Halberg Chronobiolgy Center University Minnesota on May 3-4, 2013 during Symposium (videoconference) in Masaryk University Brno, with Professor Thomas Kenner, Professor J. Siegelova and Brigitte Kenner (small picture right down).*

Figure 16: *Prof. Dr. Germaine, Cornelissen, Caty Gierke, University of Minnesota, USA, Prof. Thomas Kenner, D.h.c. mult., Assoc. Prof. Dieter Platzer, University Graz, Austria, Prof. MUDr. Jarmila Siegelova, DrSc., Prof. MUDr. Petr Dobsak, CSc., Masaryk University, Videoconference, Workshop Brno, 2016.*

Figure 17: *Anita Ertl, Professor Jarmila Siegelova, Professor Thomas Kenner, Brigitte Kenner, Graz 2016*

Photo documentation of Prof. P. Dobsak, CSc. and Prof. MUDr. J. Siegelova, DrSc. lectures in "Quadrilateral Physiology Symposium 2019", held in Medical University of Graz on 21.6.2019 in Graz

Picture 1: *Quadrilateral Physiology Symposium 2019 was done as a celebration of the life and work of Prof. Thomas Kenner, M.D., Dr. h.c. mult.*

Picture 2: *The lectures of Prof. MUDr. Petr Dobsak, CSc., Masaryk University, Brno, CZ*

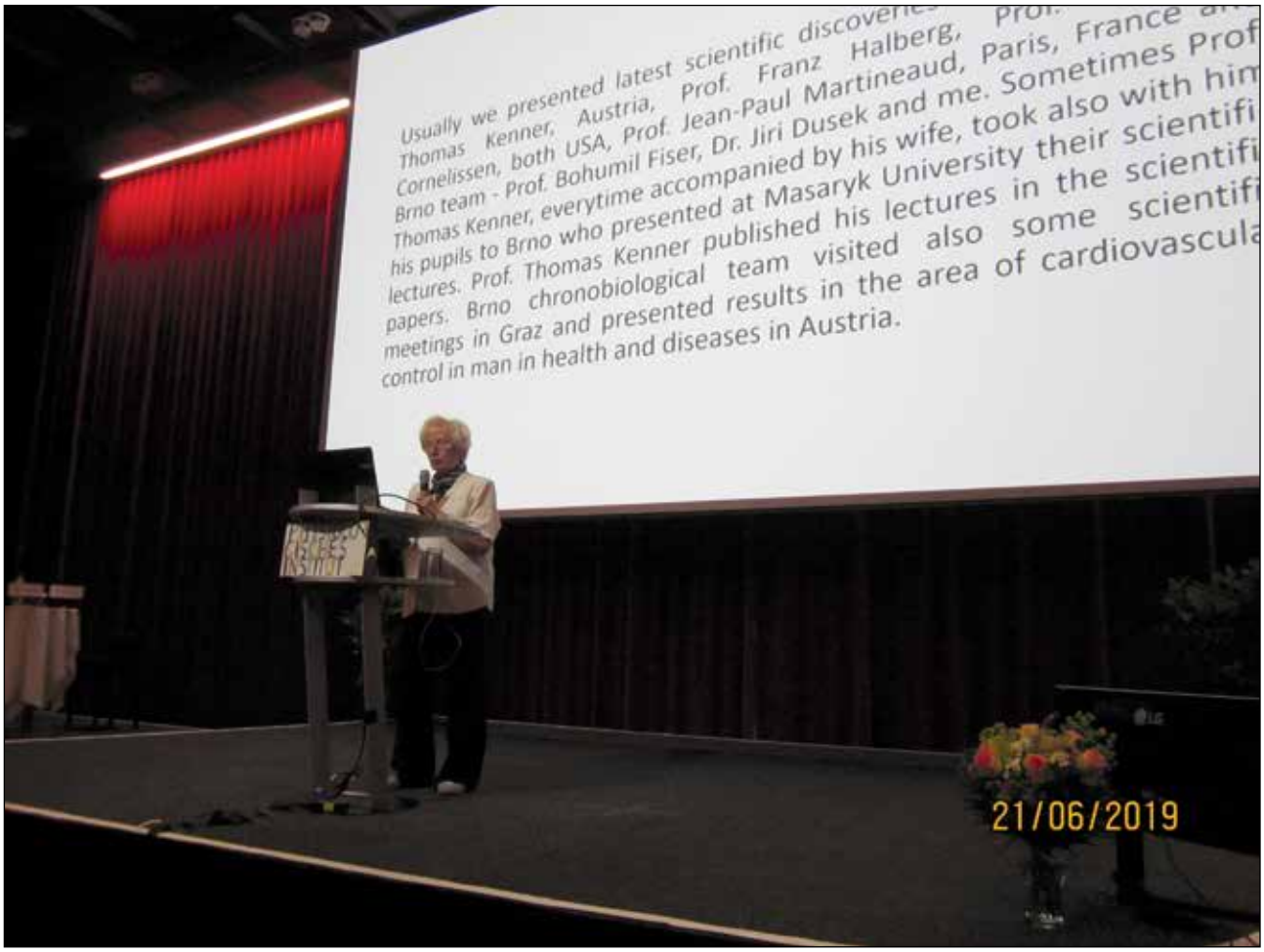
Picture 3: *Assoz. Prof. Nandu Goswami, Priv.-Doz. Dr. med. MMedSci PhD., University Graz, Dr. Carmen Possnig, European Space Agency, Prof. M. Geiger, Medical University of Vienna, Prof. MUDr. J. Siegelova, DrSc., Masaryk University, Brno, Prof. P. Dobsak, CSc., Masaryk University, Brno, Prof. Ines Drenjancevic, Osijek, Croatia, Assoc. Prof. J. Bakos, Comenius University, Bratislava, Slovakia, Prof. Bostjan Simunic, Koper, Slovenia*

Picture 4: *Prof. Erik Grasser, Switzerland, Prof. MUDr. Jarmila Siegelova, DrSc., Prof. Dieter Platzer, University Graz, Austria, Prof. Daniel Schneditz, University Graz, Austria, Brigitte Kenner, Graz, Austria*

Picture 5: *Assoz. Prof. Nandu Goswami, Priv.-Doz. Dr. med. MMedSci PhD., University Graz, Austria*

Picture 6: *Prof. Jarmila Siegelova, DrSc., Masaryk University, Brno, Brigitte Kenner, Graz*

Picture 7: *Prof. Petr Dobsak, CSc., Masaryk University, Brno, Prof. MUDr. Jarmila Siegelova, DrSc., Masaryk University, Brno, Prof. Dieter Platzer, University Graz, Brigitte Kenner, Graz*



Picture 8: *Prof. MUDr. Jarmila Siegelova, DrSc, Masaryk University, Brno*

Picture 9: *Prof. Daniel Schneditz, University Graz, Austria*

Picture 10: *Prof. Maxmilian Moser, University Graz, Austria – presented the lecture from Prof. G. Cornelissen, University of Minnesota, USA*

Picture 11: *Assoz. Prof. Nandu Goswami, Priv.-Doz. Dr. med. MMedSci PhD., University Graz, Austria, B. Kenner, Graz, Austria*

A different response of the upper and lower limb beat-to-beat pulse wave velocity to the orthostatic challenge

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Introduction

Pulse wave velocity (PWV) is a non-invasive parameter of the arterial stiffness: lower arterial stiffness leads to the higher PWV. Aortic PWV is an independent predictor of future cardiovascular events (coronary events, stroke) and all-cause mortality.[1–4] However not only aortic PWV, but also peripheral PWV can be used as an parameter of vascular damage. [5]

The main factor influencing PWV is a class of artery. Aortic compliance is higher than in peripheral arteries due to structural and functional differences. Peripheral (muscular) arteries contain smooth muscle layer controlled by sympathetic nervous system as well as vasoactive hormones (catecholamine, angiotensin, local substances, etc.), which change compliance of arterial wall. Production of local vasoactive substances is dependent on endothelial function. Blood pressure and blood volume are variable strongly influencing PWV: increased blood pressure and filling of artery lead to arterial distension and as a consequence in decrease of the compliance. Therefore PWV is increased in hypertonics and it is also influenced by short-term blood pressure variability.[2] Aortic stiffness clearly increases with structural changes caused by age.[6]but the mechanics of the progression of arterial stiffness along with age is not fully explored. We aim to investigate the age-related progression of arterial stiffness through the examination of 4659 healthy subjects aged from 20 to 75. Methods: The cardio-ankle vascular index (CAVI In a summary, PWV is a variable concentrating effect of many factors associated with vascular function.

Diabetes mellitus affects PWV by several ways. Endothelial dysfunction and structural arterial changes are caused by long lasting hyperglycaemia and hyperinzulinemia. Diabetic autonomic neuropathy impairs sympatho-vagal balance toward sympathetic predominance over the muscular arteries.[7] Diabetes is also accompanied by a hypertension, atherosclerotic process and associated complications.

The aim of this preliminary study was to analyse the effect of the orthostatic challenge to the lower and upper limb PWV in diabetics and healthy controls.

Methods

Subjects

Diabetic group contained 15 patients with diabetes mellitus II (7 male / 8 female, age 68 ± 10 years, blood pressure 158/90 ± 19/9 mmHg). No specific selection of diabetics was made in this study. Control group was consisted of 11 healthy young volunteers (5 male / 6 female, age 23 ± 2 years, blood pressure 117/76 ± 9/5 mmHg).

Pulse wave velocity recording

Multichannel bioimpedance monitor (MBM, developed by the Institute of Scientific Instruments of The Czech Academy of Sciences) was used for beat-to-beat recording of PWV.[8–10] Method was based on bioimpedance principle. Basically, transient blood flow increase caused by pulse wave passing between two electrodes induces impedance change. PWV can be evaluated from distances between electrodes and times of pulse wave passage. Simultaneously ECG was recorded. This method is able to evaluate beat-to-beat PWV in various body parts separately (fig 1). In this study, sequences of PWVs were recorded in the left arm and left leg.

Protocol

PWVs were recorded in two phases: 6 minute in supine and 6 minutes of 45° head-up-tilt.

Data analysis

Mean arm, leg and ratio arm/leg PWV were evaluated for each subject and phase. Mann-Whitney test was used for evaluation of difference between diabetics and controls. Wilcoxon pair test was used for evaluation of difference phases and limbs.

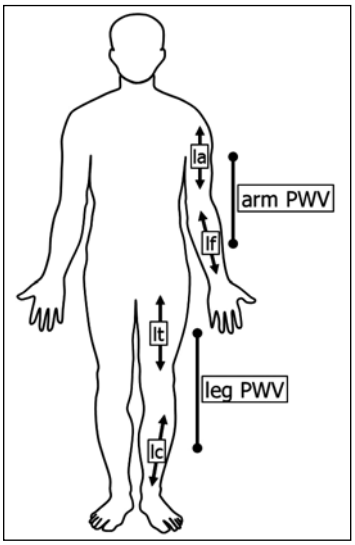

Figure 1: *Multichannel bioimpedance method: position of electrodes. PWV is measured from leg and arm.*

Results

Example of beat-to-beat PWV for one diabetic and control is shown in fig 2. Supine PWV was higher in diabetics than in controls (fig 3). Head-up-tilt led to increase of leg PWV in diabetics. PWV ratio arm/leg significantly decreased during hut in diabetics in compare to controls during hut as well as in compare to supine diabetics.

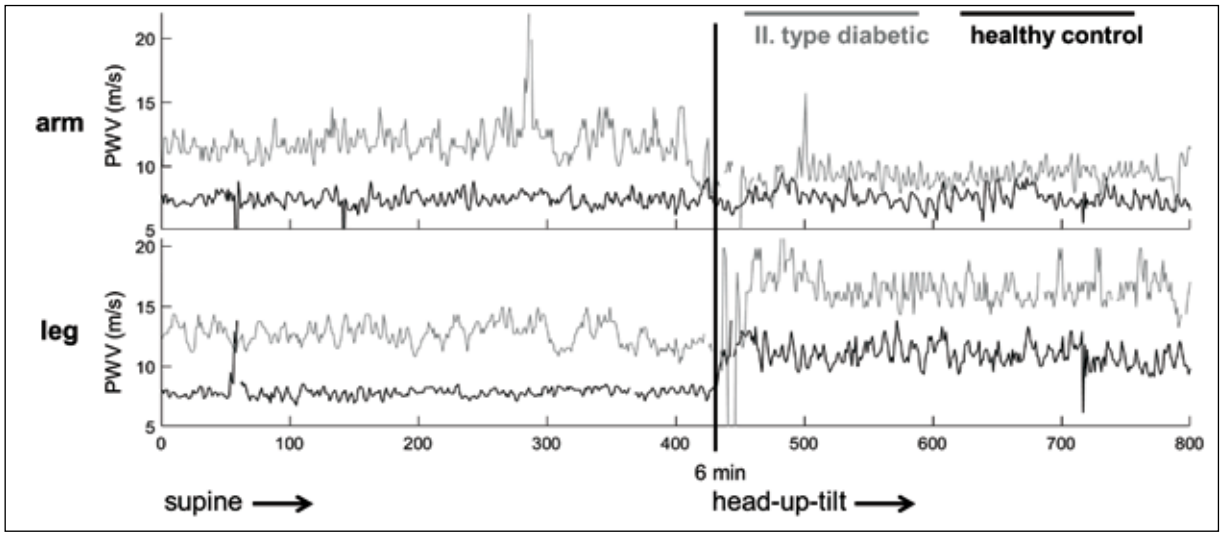

Figure 2: *An example of beat-to-beat PWV in leg and arm in a diabetic and a healthy control*

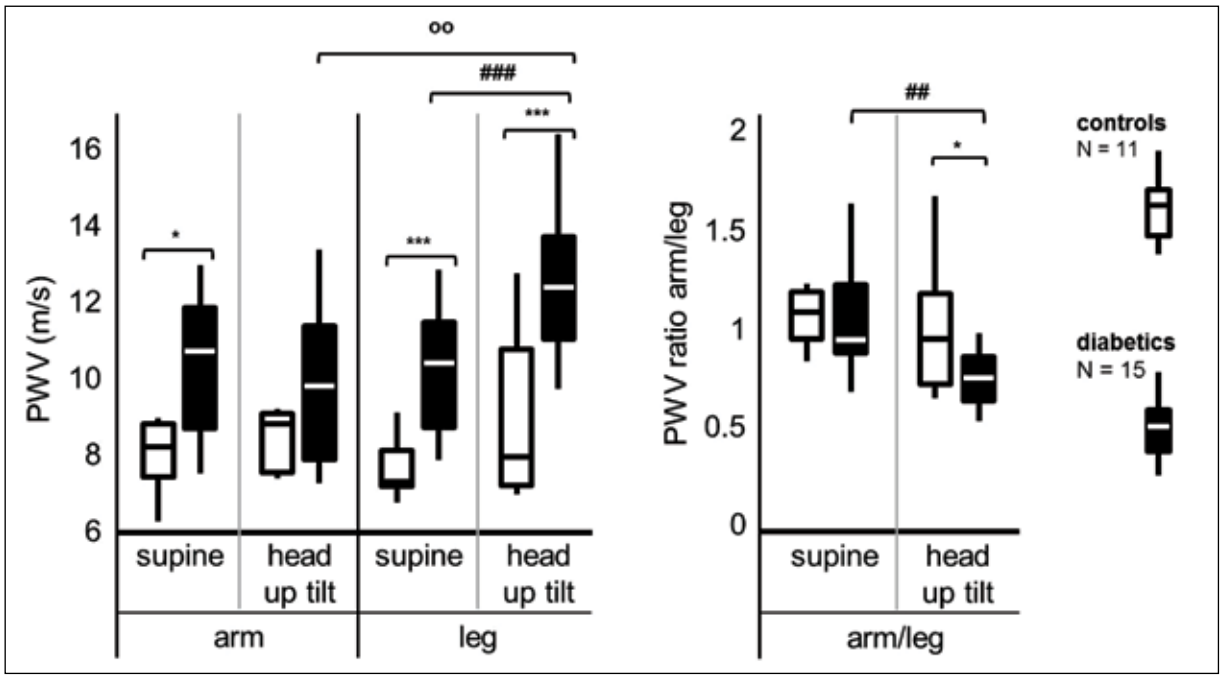

Figure 3: *Distribution of PWV and ratio PWV arm/leg. Subjects: 11 healthy controls: (5 male / 6 female) and 15 diabetics type II (7 male / 8 female). Diabetics vs. controls (Mann-Whitney test): *p<0.05; **p<0.01; ***p<0.001. Supine vs. head-up-tilt (Wilcoxon test): #p<0.05; ##p<0.01; ###p<0.001. PWV arm vs. PWV leg (Wilcoxon test): °p<0.05; °°p<0.01*

Discussion

PWV in diabetics was higher than in controls, different between arm and leg and it was influenced by postural changes. We supposed that diabetes in patient group negatively influenced endothelial function and led to the structural changes of arterial wall, both increasing arterial stiffness. Arterial stiffness also increased with higher age and hypertension presented in diabetics.[6]but the mechanics

of the progression of arterial stiffness along with age is not fully explored. We aim to investigate the age-related progression of arterial stiffness through the examination of 4659 healthy subjects aged from 20 to 75. Methods: The cardio-ankle vascular index (CAVI All these factors led to the higher resting PWV. These results were consistent with the conclusions of previous studies: increased arterial stiffness was proved in elastic (aortic) as well as in peripheral (muscular) arteries.[11]whether peripheral muscular artery stiffness is equally affected by the disease remains sparsely examined. Moreover, the association between pulse wave velocity (PWV

Increase of the leg PWV during orthostatic challenge was caused by blood redistribution and increased hydrostatic pressure and volume in lower limbs. However diabetics showed stronger increase of leg PWV than controls. It could be explained by changed autonomic control over the vessels and dysregulation of blood redistribution. Moreover arterial response to the sympathetic activation can be worsened.[12]"container-title":"BMC Endocrine Disorders","volume":"17","source":"PubMed Central","abstract":"Background\nIncreased carotid-femoral pulse wave velocity (PWV

Innovative method of bioimpedance PWV measurement used in this study had several advantages. It was able to detect beat-to-beat PWV in various parts of body. Therefore not only mean PWV, but also changes of PWV in response to orthostatic challenge in particular arteries could be possible interesting parameter reflecting arterial condition.[9]

Limitation

Analysis was made on small group of subjects and both groups were strongly different. However the aim was to prove how impedance is able to detect these clear changes in arterial stiffness. For better understanding of PWV changes, correlation with diabetic parameters such as duration of diabetes, glucose tolerance, fasting plasma glucose, glycated haemoglobin etc. should be made.[11,12]"container-title":"BMC Endocrine Disorders","volume":"17","source":"PubMed Central","abstract":"Background\nIncreased carotid-femoral pulse wave velocity (PWV And normotensive non-diabetics should be used as a control group.

Conclusion

Method of multichannel bioimpedance PWV measurement is simple, non-invasive and able to simultaneously measure PWV in various parts of body. PWV ratio arm/leg seems to be interesting variable for clinical implementation and evaluation of arterial stiffness in people at higher cardiovascular risk.

Acknowledgement

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Non-invasive assessment of arterial stiffness in cardiovascular diseases

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Introduction

The vascular effect of cardiovascular medications is today possible by studying characteristic parameters of the arterial structure and/or function, the determination of which is non-invasive, simple, rapid and reproducible. The changes observed clinically also have an epidemiological importance, because the degree of alteration of these parameters integrates the deleterious effect of "cardiovascular maligners" (i.e. atherogenesis, dyslipidemia, hypertension, diabetes, smoking, plasma homocysteine, genetic factors, etc.) on the years of exposure. In addition, it has been clearly shown that the level of impairment of these parameters is closely related to the incidence of fatal cardiovascular events (1). Thus, it is possible to envisage their important predictive value on the cardiovascular risk, higher than that of the measurement of one or more "classical" risk factors.

Role of the arterial system

The arterial system has two separate functions: 1) a transport function to bring nutrients and oxygen to tissues; and, 2) a damping function on blood pulsations generated by intermittent ventricular ejection. The damping function, from a hemodynamic point of view, is needed by the pulsatile nature of flow and pressure. The large arteries receive the volume of blood ejected from the left ventricle, store one portion of the blood bolus during systole and drain the other part during diastole, thus allowing the continuous perfusion of organs and tissues. This "Windkessel" effect is due to the visco-elastic properties of the arterial walls (2).

The elevation of aortic pressure at the time of the systolic peak depends on the left ventricular function and the distensibility (elasticity) of the ascending aorta. Thus, the peak pressure is higher if the wall of the aorta is more rigid. On the other hand, after the closure of the aortic valve, the arterial pressure falls gradually - at the same time the blood flow reaches the periphery. The end-diastolic pressure depends on the duration of the diastole and the speed of the blood pressure drop. The speed of the blood pressure fall depends on both the size of the arterioles, and the visco-elastic properties of the large arteries (2).

Endothelial dysfunction and medial degeneration are the main cause of loss of arterial elasticity. Vascular tone is influenced by a number of vasodilator (nitric oxide or prostaglandins), and vasoconstrictor substances (endothelin or angiotensin II). In particular, the role of nitric oxide (NO) is essential for maintaining physiological vascular stability. On the endothelium NO exhibits anti-

inflammatory and anti-thrombogenic effects, stimulates vasodilatation, blocks adhesion of leukocytes and proliferation of smooth muscle cells. Disrupted or reduced NO secretion due to endothelial dysfunction increases mechanical stress in the arterial wall. This causes gradual intima-media thickening and other structural changes in the vessel wall. As this chronic process intensifies, the arterial peripheral resistance increases (3). The elasticity of the arterial walls is a crucial determining factor of the speed of propagation of the pulse wave (different from the rate of propagation of blood flow). In fact, in addition to the elevated speed of propagation of the pulse wave, the increased arterial stiffness will lead to an earlier return of the reflected pressure waves, contributing to the rise of systolic and pulse pressures (4).

At the myocardial level, these abnormalities increase the myocardial oxygen consumption, left ventricular hypertrophy and drop in coronary reserve. The term "arterial compliance" meets the calculated ratio between variations of volume and variations of the distension pressure measured in the given arterial segment (5).. The slope of the pressure-volume curve corresponds in every point to the value of arterial compliance (Fig. 1). The curvilinearity of this pressure-volume curve is secondary to the histological composition of the arterial wall. Elastin fibers (that are easily distensible) are stretched at low pressures, while more stiffer collagen fibers are involved only at high pressures (6). Thus, when blood pressure rises, the arterial compliance decreases (and stiffness increases). Therefore, any interpretation of changes of arterial compliance requires knowledge of concomitant changes in blood pressure.

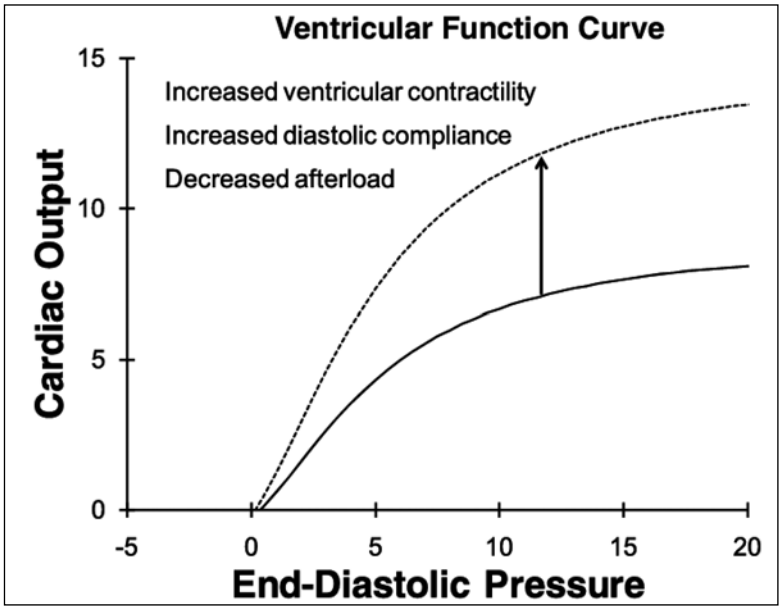

Figure 1: *This classic ventricular function curve relates input of the heart (end-diastolic pressure in mmHg) to output of the heart (cardiac output in liters per minute). The ventricular function curve shifts up and to the left when ventricular systolic contractility increases. However, increased diastolic compliance and decreased afterload can also shift the ventricular function curve up and to the left (5).*

Methods for arterial stiffness measurement

The most accurate index for measuring the rigidity of an arterial segment is the elastic model of Young, but the complexity of its calculation, which requires the measurement of the thickness and the diameter of the arteries, makes it usable only in research conditions. Thus, the simplest and widely

used method of non-invasive evaluation of systemic arterial stiffness is based on the recording of the velocity of the pulse wave (PWV). Indeed, the speed of propagation of the pulse wave measures the distensibility of the artery - an index that reflects compliance and arterial stiffness. The interpretation of the velocity of the PWV is simple because it increases with increasing arterial stiffness (6; 7). This technique involves recording an arterial signal ("mechanogram") at two arterial sites separated by a known distance. The time between these two records is related to the distance traveled by the signal. Thus, a speed value is calculated which corresponds to the celerity of the pressure wave along the arterial segment (Fig. 2).

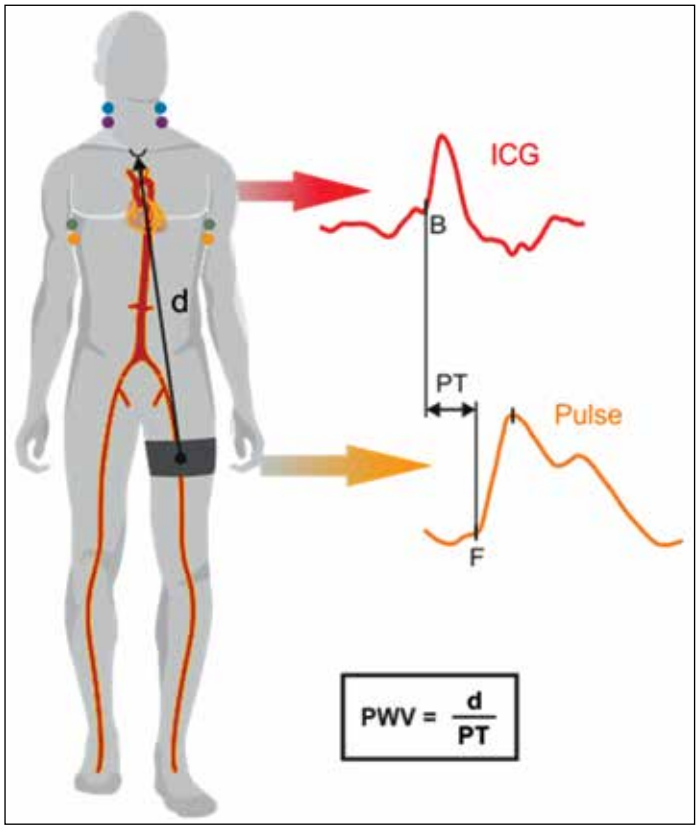

Figure 2: *Principle of measurement of the pulse wave velocity (PWV). For the determination of aortic PWV it is necessary to define when the arterial blood is injected into the aorta what is the starting point of the arterial pulse wave. It corresponds with the opening of the aortic valve what is characterized by the B-point in the ICG (impedance cardiography) wave form. To detect the arrival of the pulse wave in the femoral artery a cuff is placed on the upper leg which has a constant pressure of about 80 mmHg close to the diastolic blood pressure. This cuff allows to measure a pressure pulse wave in which the slope rise onset is defined (F-point). The time delay between the B-point in the ICG (opening of the aortic valve) and the F-point in the pressure pulse wave defines the propagation time (PT) of the arterial pulse wave in the aorta. For the calculation of the aortic pulse wave velocity it is necessary to measure the distance (d) between the middle of the thigh cuff and the jugulum to approximate the length of the aorta.* https://medis.company/cms/index.php?page=pulse-wave-velocity

The speed of propagation of the PWV can be measured on many arterial segments: the aorta (between the common carotid and the common femoral artery), the arterial axis of the forearm (between the humeral and the radial artery), or the arterial axis of the lower limb (between the femoral joint and the posterior tibial artery). In the present times, the speed of propagation of the PWV can be determined automatically, rapidly and non-invasively by many validated devices, available for daily clinical use (7).

Predictive value of parameters reflecting arterial stiffness

Cardiovascular risks and all the parameters of arterial structure or function strongly correlate with age and blood pressure. A large number of epidemiological and clinical studies have shown the significant association between the intima-media thickness of the common carotid artery (measured by ultrasound technique), and various cardiovascular risk factors, such as smoking, dyslipidemia, end-stage renal failure or plasma concentration of homocysteine. In populations at high risk of ischemic heart disease (as in industrial countries) this hypothesis has been confirmed by several prospective studies that evaluated the increased relative risk of myocardial infarction and ischemic stroke in subjects whose intima-media thickness was greater than 1 mm. Assessment of arterial functions by PWV have also shown that the level of this arterial stiffness parameter is correlated not only with age and arterial pressure (particularly at the level of pulse pressure), but also with diabetes, renal insufficiency, dyslipidemia, plasma homocysteine, arterial calcifications or atherosclerosis. Based on epidemiological studies, the increase of pulse pressure (a direct consequence of the increased arterial stiffness) has been validated as a strong independent marker of cardiovascular mortality in both hypertensive and normotensive subjects. At a given age, aortic stiffness is more strongly associated with cardiovascular mortality (calculated by the Anderson equation), than any other cardiovascular risk factor (6; 7)

Therefore, it is necessary to further enhance the development of new diagnostic methods designed for early detection of morbid lethal cardiovascular event, related to a given level of alteration of structural or arterial function parameters for an individual in a given population. This will undoubtedly be the true contribution of these future non-invasive measures to the detection of subjects at high ischemic risk, and the role they can play in the preventive therapeutic interventions for the subjects with cardiovascular risk factors.

Cardio-ankle vascular stiffness index (CAVI)

PWV is traditionally used to predict both cardiovascular disease and overall mortality independently of risk factors; however, its strong dependence on the blood pressure (BP) is a disadvantage for interpreting measured arterial stiffness values. At the beginning of this millennium, a new diagnostic parameter of arterial stiffness called the cardio-ankle vascular index (CAVI) was developed and introduced into clinical practice in Japan (Fig.3).

Figure 3: *CAVI measurement using VaSera 1500 (Fukuda Denshi Co., Tokyo, Japan)*

In brief, CAVI is a stiffness and arteriosclerosis indicator of thoracic, abdominal, common iliac, femoral, and tibial arteries (8). CAVI parameter is based on the concept of stiffness index beta which reflects the change in blood pressure needed to increase the diameter of large arteries. Therefore, CAVI is less influenced by the actual value of arterial pressure (9, 10). CAVI is obtained by recording the distance from the level of the aortic valve (i.e. brachial level) to the measuring point (i.e., the ankle) and the time delay between the closing of the aortic valve to the detected change in arterial pressure wave at the set point. Information for CAVI computation, including PWV, systolic and diastolic blood pressure as well as arterial pulse waveforms, can then be acquired through the electrocardiogram, cardiac phonogram, and the pressure cuffs on the testing subject at the reference points (8; 9). In comparison to baPWV, CAVI has two major distinctive features. First, CAVI changes over a short period of time in response to alterations in circulatory condition. Second, CAVI reflects the state of smooth muscle contraction rather than changes in blood pressure (10). CAVI has also been reported to represent both "functional" and "organic" stiffness (11). The former represents the state of smooth muscle contraction that is subjected to changes in sympathetic tone and pharmacological influence, whereas the latter signifies the physical properties such as sclerotic change of the arterial wall. Up to the present, several studies have shown that CAVI is really independent of BP in both patients with coronary artery disease and also in healthy subjects from population samples (12).

In conclusion, CAVI stiffness parameter has a reliable predictive value for the incidence of cardiovascular diseases in different ethnic groups (13; 14). Moreover, CAVI has sufficient reproducibility

for clinical use and its elevated values correlate well with a number of risk factors and severity of cardiovascular diseases (15).

Cardiovascular risk estimation

The reference for the calculated cardiovascular risk estimate is still Anderson et al. (1991) developed from the Framingham population (16). The advantages of this scale of risk are related to the prospective study that allowed its determination; this study concerned several thousand patients of both sexes, including young and old individuals, the follow-up was particularly rigorous in order to limit the loss of sight, and finally, the follow-up was prolonged. Nevertheless, the calculated estimate of the level of cardiovascular risk that this scale allows has important limitations. First, there is geographical limitation: indeed, for the same level of cardiovascular risk factors, the real risk is lower (approximately half) in France (French paradox) than in the United States. Time limitation is also important to consider - it appears that cardiovascular morbidity and mortality has decreased in recent decades. Finally, and this may be the most important limitation, the parameters that define this risk include only the cardiovascular risk factors that were identified in the early 1980s (17).

In any case, despite these imperfections, the calculated estimate of cardiovascular risk level, combined with the simulation of the effect of different therapeutic interventions, encourages clinicians, taking care of subjects with cardiovascular risk factors, to decide on the most effective preventive therapeutic interventions (18; 19).

Evaluation of the effect of therapeutic interventions on arterial parameters

Various substances used in the acute phase (or for a short period) of the treatment of cardiovascular diseases have shown their effectiveness in improving arterial distensibility (such as nitrates, calcium antagonists or inhibitors of conversion). Nevertheless, it remains to determine the long-term effect of different drugs acting on the arterial wall (statins, different classes of anti-hypertensive drugs, hormones replacing menopause, etc.) and the parameters of arterial structure or function, in combination with their effect on the incidence of cardiovascular events.

Cardio-respiratory fitness and arterial destiffening

Increased fitness is associated with reductions in both arterial stiffness and blood pressure, which not only lower central wave reflection and pulse pressure (in turn) but may also promote each other within their own virtuous sub-cycle. In short – the improved cardio-respiratory fitness and arterial destiffening support each other (20). Reduction in pulse pressure has distinct cardiac and vascular effects, the former including a decrease in myocardial afterload coupled with enhanced coronary blood flow, and the latter facilitating less endothelial damage and curtailing of atherosclerotic burden. These collective cardiovascular adaptations serve to increase myocardial performance, a key determinant of exercise capacity/cardiorespiratory fitness in cardio-metabolic disease populations (21; 22).

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