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HEART NEWS AND VIEWS

THE NEWS BULLETIN OF THE INTERNATIONAL SOCIETY FOR HEART RESEARCH

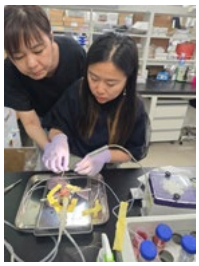
FIRST SEA MEETING SINGAPORE *OCT 2024*

6

ISHR-SEA Council

JMCC PLUS – FIRST IMPACT FACTOR

8

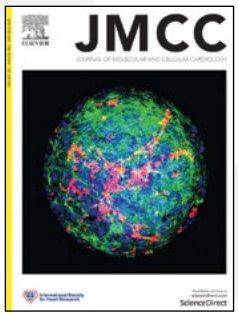


VISITING RESEARCH FELLOW REPORTS *MAY 2025*

10

Liver perfusion procedure

In this Issue:



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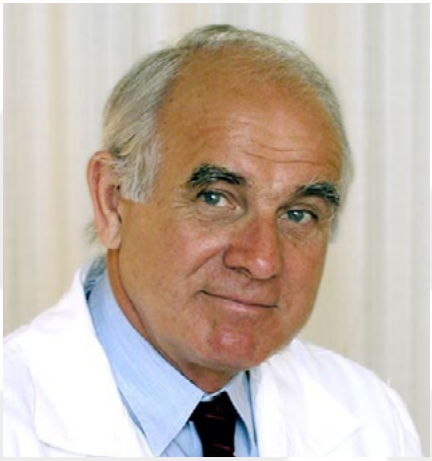
THE HEART OF THE MATTER

MY 60-YEAR CAREER IN CARDIOVASCULAR RESEARCH

The beginning of scientific life, 1963 - 1968



Professor Bohuslav Ošťádal

I was born in Zlin, former Czechoslovakia, January 28, 1940. My university education started in 1957 at the Faculty of Pediatric Medicine of Charles University in Prague where I graduated in 1963. My professional life was fundamentally influenced by outstanding scientific and human personalities. Already during my university studies, Prof. Otakar Poupa, the prominent Czech researcher in experimental cardiology, offered me a volunteer position on his team, and after my graduation as an MD I became a PhD student under his supervision. This exceptional scientist, charismatic teacher, renaissance man in the true sense of this word, founded the cardiology laboratory in the Institute of Physiology of the then Czechoslovak Academy of Sciences. This laboratory worked closely with the Department of Pathological Physiology of the Faculty of Pediatrics (today the Second Faculty of Medicine of Charles University), of which Poupa was also the head. In a short period of time, he managed to create a very unique system of cooperation between the Academy of Sciences and the Faculty of Medicine, both in the field of experimental cardiology and in teaching medical students. He developed broad-based research on the phylogenetic and ontogenetic development of heart muscle, with special attention to the needs of clinical cardiology, particularly pediatric cardiology. Since the very beginning of my scientific career, the main focus of my research has been the development of heart structure and function under normal and pathological conditions. This type of research

(continued on page 2)

My teacher, Prof. Otakar Poupa

would be unthinkable without the advice and help of my second important teacher, advisor and finally very close friend, Dr. Zdenek Rychter, the innovative Czech experimental cardioembryologist. His original studies on experimental morphology of the aortic arches during the heart loop in chick embryos were considered to be at the highest level of world cardiac research. A close cooperation of experimental and clinical cardiologists is essential for developmental cardiology; therefore, I was very fortunate that my third important mentor was the outstanding pediatric cardiologist, founder of the Czech Center of the Pediatric Cardiology, Prof. Milan Samanek. He focused my interest on clinical developmental cardiology, particularly on the comparison of pathophysiology and metabolism of hypoxemic and normoxemic congenital heart defects.

The scientific orientation of Poupa's laboratories attracted many young adepts of science and became the basis of the Prague School of Adaptive and Developmental Cardiology, successfully continuing the Czech tradition of evolutionary medicine. The success of Poupa's Prague School soon crossed the borders of the country. In 1964, during the European Congress of Cardiology, he co-authored the idea (along with the Americans Bing and Bajusz) to create an international scientific society that would bring together experimental cardiologists from all over the world. That idea succeeded a few years later with foundation of the International Study Group for Research in Cardiac Metabolism (now International Society for Heart Research –ISHR), which represents the only international society of its kind. Consequently, Poupa became a founding member of the editorial board of the official journal of this society, the *Journal of Molecular and Cellular Cardiology*, which remains one of the prestigious world-renowned periodicals. The fruitful years of experimental cardiology in Czechoslovakia culminated in the time of Prague Spring when the Poupa received the prestigious State Prize for his research.

1969 - 1989

The Soviet occupation in August 1968, which started the so-called normalization era, adversely affected the development of all areas of Czech science and thus experimental cardiology for many years. Poupa, as one of the authors of the memorable manifesto "Two thousand words", emigrated in September 1968, setting in motion the gradual departure of other Prague School members. In 1969, prof. T.H. Schiebler from the University of Würzburg, Germany, offered me a research fellowship and made me familiar with the possibilities of ultramicroscopic techniques. I thus spent a very fruitful year in his Department of Anatomy.

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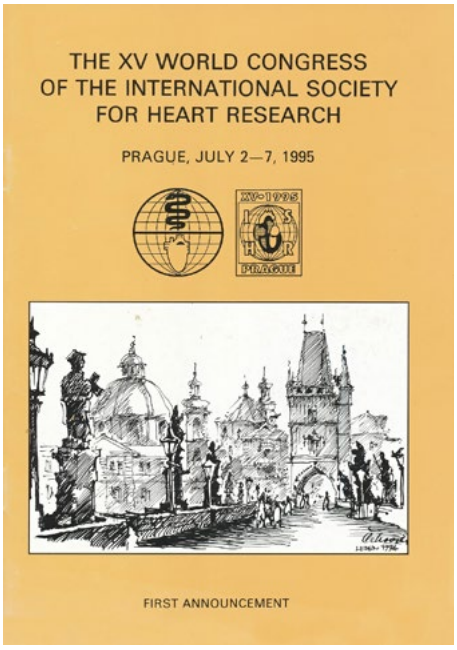

The XV World Congress of ISHR, Prague, 1995 – First announcement

Upon my return to Prague, experimental cardiologists in the Institute of Physiology of the Czech Academy of Sciences followed Poupa's tradition and created a Department of Developmental Cardiology and entrusted me with its management. The main task became the study of the development of structural and metabolic properties of cardiac muscle, which is important for understanding the ontogenetic changes of cardiac resistance to oxygen deprivation. Special attention was paid to the possibilities of protective influence on the myocardium, especially its adaptation to chronic hypoxia. This orientation led to the establishment of very effective cooperation both with other laboratories in the Institute of Physiology as well as with cardiologists dealing with cardiopulmonary diseases (Institute for Clinical and Experimental Medicine, Prague, head Prof. Widimsky) and clinical department of pediatric cardiology (Children's Cardiac Center in Prague, head Prof. Samanek). Unfortunately, the significant limitation of foreign contacts gradually led to professional isolation and lagging behind the accelerating development of world science.

At the moment of greatest depression, my colleague from Brno, Prof. Pavel

The Soviet occupation in August 1968, which started the so-called normalization era, adversely affected the development of all areas of Czech science and thus experimental cardiology for many years.

Braveny, and I came up with the idea to save experimental cardiology by creating a professional forum that would enable its intellectual survival and reduce the negative consequences of the "splendid isolation". We founded the Society for Experimental Cardiology (SEC) at the Physiological Society of the Czechoslovak Medical Society J.E Purkynje, with the main task of introducing theoretical and clinical cardiologists to the advances in world cardiology. The first working conference of the SEC was organized in 1973; the program of the annual meetings was designed monothematically and always "from the molecule up to the patient's bed". It can be stated with pleasure that the character of these meetings has been preserved to the present day. With the passage of years, it is necessary to emphasize that SEC's activities have almost completely fulfilled the goals of its founders. It helped to maintain an acceptable level of awareness, initiated scientific cooperation, educated a number of young cardiologists and, above all, built cardiology as a highly visible science. Last but not least, it created a friendly atmosphere, which in many cases helped to overcome the very complicated relationships of that time.

After 1989

Only the greatest optimist could assume that the possibility of verifying dreams and reality in the open field of world science is not a utopia. The events of November 1989 (so-called velvet revolution) ushered in a transformative era, offering Czech science the invaluable gift of global reintegration. Of course, this also applies to experimental cardiology. Where possible, old contacts were established, long-standing literary acquaintances were personified, and seminal results timidly found their way to scientific meetings and prestigious journals. The explosion of foreign sojourns of young researchers began to bear fruit, and the intellectual and methodological background gradually improved. Very helpful in this respect was Prof. NS Dhalla from the University of Manitoba. In this context it should be stressed that molecular cardiology, without which we can no longer imagine current experimental research, began to be developed without delay. The new grant system established a competitive approach to financial resources and undoubtedly contributed to the improvement of the scientific quality.

My scientific life also changed significantly. In the year 1990, I was elected as the director of the Institute of Physiology of the Czech Academy of Sciences, and I remained in this position for next five years. A great number of concerns arose, related to the unifying of the scientific concept of a large institute (at that time more than 200 employees) and to the constant struggle to secure the necessary financial resources.

The advantage of our experimental cardiology was that it entered the new period organizationally prepared. SEC provided the foundation on which experimental cardiologists from the Institute of Physiology were intrinsically connected, and represented a unique national scientific society, even on a world scale, with its philosophy, organization and scientific activity. This strategic advantage prompted ISHR to entrust SEC with organizing the XV World Congress in Prague. Prof. Pavel Braveny was the President and I had the honor of serving as the secretary general. The entire team of our Department of Developmental Cardiology participated in the organization. We appreciated the help of outstanding scientists and experienced organizers very much, e.g. Professors J. Parratt, NS Dhalla and J. Schaper. With the passage of time, it can be emphasized that the first meeting of ISHR organized east of the Alps, with more than 1200 participants, became a real culmination of the SEC's activities to date. It was also possible to present adequately the traditional issues of our Department, i.e. cardiac development and adaptation.

The scientific research of the Department during this period was concentrated on the question of how to increase cardiac tolerance to oxygen deficiency. Focused investigation probed the molecular and cellular mechanisms involved in the protection of the ischemic myocardium and the analyses of the cardiac resistance during early phases of ontogenetic development. Other studies investigated the effect of increased pressure on neonatal heart growth or right ventricular function in hypoxic pulmonary hypertension. The Department seized opportunities for substantial improvements of methodical equipment as well as for significant expansion of contacts with the top foreign laboratories. The intensive cooperation with groups at the University of Manitoba, Winnipeg, the University of Ottawa, the Max-Planck Institute in Bad Nauheim, Free University Berlin, the University of Strathclyde, Glasgow, INSERM Paris, the Institute for Heart Research, Bratislava, and others was very fruitful. Apart from my scientific work I was active in the committees of several international scientific societies, including ISHR and the International Academy of Cardiovascular Sciences. The international activities of our Department

The events of November 1989 (so-called velvet revolution) ushered in a transformative era, offering Czech science the invaluable gift of global reintegration.

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Heart of the Matter *(continued from page 3)*

continued with the organization of several scientific meetings, such as Czech-French-Slovak symposium on Basic Cardiology (1994, organized together with INSERM Paris), The Developing Heart (2000), Mendel symposium I on Genes and the Heart (2003), Mendel symposium II (2008) and Symposium on Scientific Basis for the Practice of Cardiology (2010). The interest of many pre- and post-graduate students, both from the Faculty of Science and from the Faculty of Medicine, was gratifying. Intensive cooperation has developed with domestic experimental laboratories of the Faculty of Science or the Second Faculty of Medicine and successful collaborations continue with clinical institutions such as Children's Cardiac Centre and IKEM.

In 1999, the first representative research centres were established in Czech Republic as part of a project of the Ministry of Education, Youth and Sports. An informal group of cardiology-oriented, internationally-experienced and freely-cooperating laboratories of the Institute of Physiology of the Czech Academy of Sciences (Department of Developmental Cardiology, Department of Hypertension), of the Second Faculty of Medicine (Departments of Physiology and Pathophysiology) and Centre for Experimental Medicine of IKEM, served as a suitable model. The "Centre for Cardiovascular Research" was acknowledged among the first established; I served as the responsible researcher. The research concept of this Centre aligned with cardiovascular research priorities in the European Union. The aim of the research activity was to clarify some of the molecular and cellular mechanisms involved in the development of ischemic heart disease and main risk factors, such as atherosclerosis and high blood pressure. The focus on a developmental approach in cardiovascular diseases was based on long-standing traditions of Czech cardiac research. At the end of the five-year period the evaluating council stated that the Centre represented a research base that has no parallels in our country, leading to a refunding endorsement for another seven years. New competition rules led to close cooperation with clinical research facilities, including the Children's Cardiac Centre in Prague and the Departments of Cardiology and Cardiac Surgery of IKEM. The Centre gradually ceased to be a formal grouping of individual workplaces and became a virtual institute. New laboratories were created and methodical approaches and technical equipment increased significantly. The main output of the Centre's activities were high-quality original results published in renowned journals. The Centre was very successful in attracting young researchers: several future cardiologists and cardiac surgeons completed their scientific training in experimental and clinical research. The average number of full-time researchers was 109, 30 of them were under 35 years of age. During the existence of the Centre, 25 postgraduate students defended their doctoral thesis. Regrettably, the successful system of scientific centres officially ended in 2012. Although the cessation of the Centre's activities led to the end of joint funding, the scientific cooperation among partners continued and developed further on a bilateral basis.

> We founded the Society for Experimental Cardiology (SEC) at the Physiological Society of the Czechoslovak Medical Society J.E Purkynje, with the main task of introducing theoretical and clinical cardiologists to the advances in world cardiology.

Participants at the Mendel symposium, Prague 2008

Participants at the symposium Scientific Basis for the Practice of Cardiology, Prague 2010

Last years

My position of the head of the Department of Developmental Cardiology officially ended in 2005, when I reached the age of 65. I was very happy that my successor was my best pupil, the excellent experimental cardiologist Prof. Frank Kolar. I greatly appreciate the fact that, as a pensioner, I can continue to work and thus continue to make a small contribution to the scientific output of our group. Recently, the Department (newly Laboratory) has also shown promising developments in advanced molecular biology methods and their use in the study of epigenetic RNA regulatory mechanisms, involved in the ontogenetic development of the heart and in the pathogenesis of heart disease. The large number of young enthusiastic researchers, modern methodologies and attractive scientific programme bode well for a bright future. I cordially wish the third generation of cardiologists (with the new head Dr. Marketa Hlavackova) all the best!

Conclusions

I am convinced that good mentors play a decisive role in the scientific career of each young enthusiast. I am, therefore, very lucky that this condition was completed already at the beginning of my career, thanks to the above-mentioned outstanding scientific personalities. Another important factor in scientific life is a good team of highly educated collaborators, students and technical assistants. It is impossible to present a long list of my colleagues and friends who helped me during the last sixty years and who created an environment of friendly teamwork. Nevertheless, there are two persons that had very special positions in my career and to whom I would like to express my sincere thanks. My former pupil, colleague and later boss, Prof. Frank Kolar, an exceptional experimental cardiologist and very close friend and, last but not least, my wife Ivana. We have been living together for more than 60 years, and she was close to me throughout all happy and sad times. Moreover, she was working with me on the developing heart; many co-authored publications are evidence of that. I am also happy that both of my sons, Petr and Martin, have chosen the medical profession, particularly in disciplines that are very beneficial to elderly parents: cardiology and orthopedics.

Prof. MUDr. B. Ostadal, DrSc.
Institute of Physiology of the Czech Academy of Sciences

I am convinced that good mentors play a decisive role in the scientific career of each young enthusiast.

THE HEART OF THE MATTER

MY 60-YEAR CAREER IN CARDIOVASCULAR RESEARCH – PART 2[1]

My Life with Developmental Cardiology

My close relationship to developmental cardiology started more than 60 years ago, with my university education at the Faculty of Pediatric Medicine of the Charles University in Prague. As mentioned in Part 1[1], since the very beginning of my scientific career my research has focused on the development of heart structure and function under normal and pathological conditions. We have asked the question: What are the roots, main principles, philosophy and advantages of a developmental approach to medicine in general and cardiology specifically?

The origin of developmental biology and medicine as a scientific discipline dates to the discoveries of Darwin and Mendel in the second half of the nineteenth century. When Darwin brought forward the theory of the origin of species by natural selection, there were no other evolutionary theories to compete with it. Its rapid acceptance was due to the fact that evolution was "in the air" at the time. Darwin realized that an understanding of heredity was essential for evolutionary studies but apparently never came across Mendel´s paper, and he stated in the last edition of the *Origin of Species* that the fundamental principles of heredity were still unknown. Only six years after the publication of Darwin´s famous book, Mendel described the laws of heredity. His words were, unfortunately, long forgotten and were only rediscovered 16 years after his death. Today the tenets of Mendel´s principles are the basis of most studies in evolution. It took a long time, however, before both basic theories became an integral part of modern physiology and medicine.

Some of our contributions to developmental cardiology

To evaluate the contribution of scientific work is always tricky; it depends on many points of view. Of primary consideration is the originality of the published results, but it is also necessary to assess who will benefit from the results, what are the prospects for their further use and how the results have been accepted by the world scientific community, *i.e.* how often they were cited. The harshest critic is time, which will test the results and show "evergreen" ones. In a short survey, I would like to summarize some of our results achieved in four closely related areas.

(i) Study of the normal development of the cardiovascular system

In the late 1960s and early 1970s we studied the phylogenetic development of cardiac muscle. Performance of the heart as a pump must be precisely adapted to the oxygen consumption of the total active body mass. As a result, the heart size in different species of vertebrates expressed as the relative heart weight varies considerably, by as much as 20-fold. The relative heart weight is highest in birds, followed by mammals and by poikilotherms. The maximum acceleration of heart weight during phylogeny occurs when the metabolic activity of animal tissues has substantially increased, *i.e.* during the transition from poikilotherms to homeotherms. Significant differences can be observed also in individual classes of vertebrates: relative heart weight in physically active animals is significantly higher in comparison with less active species. Changes in the heart weight are accompanied during phylogeny by transformation of the myocardial structure and blood supply. The myocardium of cold-blooded vertebrates (fish, amphibians, reptiles) is either entirely spongious (supplied by diffusion from the ventricular cavity) or its inner spongy-like layer is covered by the compact myocardium with vascular supply. The thickness of the compact layer depends upon the weight of the animal (law of Laplace). Surprisingly, the activities of the enzymes of energy metabolism are significantly increased in the inner avascular spongious layer as compared with outer compact layer, supplied from coronaries.

Professor Ostadal with his wife, Ivana

(ii) Study of the sensitivity of the developing cardiovascular system to different pathogenetic factors

Cardiotoxic effect of beta-mimetic catecholamines during development

After Rona's discovery of the cardiotoxic properties of isoproterenol in 1956, high doses of isoproterenol were used for the induction of experimental cardiac necrosis. One of the still unresolved questions was the possible participation of coronary arteries in the pathogenesis of these changes. We used our experience with the myocardium of cold-blooded animals and applied high doses of beta-mimetic agent to the turtle. To our surprise, necrotic changes were localized predominantly in the inner non-vascularized layer of the myocardium, suggesting that necrotic changes induced by isoproterenol are not ischemic.

Similarly, we wanted to ascertain the response of the chick embryonic heart to isoproterenol. Information on the toxic effect of β-adrenergic receptors (β-AR) agonists in the immature heart was surprisingly scarce, even though these agents are used in clinical practice both during pregnancy and in early postnatal development. We observed that large doses of β-AR agonists induced malformations of the cardiovascular system; the

(continued on page 8)

Heart of the Matter *(continued from page 7)*

type of change depended upon the time at which the β-AR agonist was administered during embryogenesis. During postnatal ontogeny, the cardiotoxicity of β-AR agonists increased from birth to adulthood. It seems likely that despite interspecies differences, developmental changes in the cardiac sensitivity to β-AR agonists may exist in all mammals depending on the degree of maturation of the system involved in β-adrenergic signaling. All the existing data draw attention to the possible harmful consequences of the clinical use of β-AR agonists as tocolytics (to prevent premature labor) during early phases of cardiac development. Late effects of the early disturbances of the cardiac muscle cannot be excluded.

Developmental and sex differences in cardiac tolerance to oxygen deprivation

Age and sex play essential roles in the cardiac tolerance to ischemia/reperfusion (I/R) injury: cardiac resistance significantly decreases during postnatal maturation and female hearts are more tolerant than the male myocardium. It is widely accepted that mitochondrial dysfunction, and particularly mitochondrial permeability transition pore (MPTP) opening, plays a major role in determining the extent of cardiac I/R injury. The aim of our studies was to analyze (i) whether calcium-induced swelling of cardiac mitochondria is age- and sex-dependent and related to the degree of cardiac tolerance to I/R injury and (ii) whether changes in MPTP components – cyclophilin D (CypD) and ATP synthase – can be involved in this process. We observed that in mitochondria isolated from neonatal and adult myocardium as well as from adult male and female hearts the MPTP has different sensitivity to the calcium load. Neonatal and female mitochondria are more resistant both in the extent and in the rate of mitochondrial swelling at higher calcium concentration. Our data further suggest that age- and sex-dependent specificity of the MPTP is not the result of different amounts of ATP synthase and CypD. Similarly, neonatal and adult hearts contain comparable amount of MPTP and its regulatory protein CypD; parallel immunodetection revealed also the same content of the adenine nucleotide translocator or voltage dependent anion channel. The increased resistance of the neonatal and female heart thus cannot be explained by changes in putative components of MPTP and rather reflects regulation of MPTP function. Our results suggest that mitochondria are deeply involved in the mechanism of the high ischemic tolerance of the immature and female myocardium.

Metabolic adaptation to chronic hypoxia in children with congenital heart disease

The timing of corrective surgery for hypoxemic congenital heart disease is critically important, with early surgery desirable to promote normal development. Many children who undergo cardiac surgery in the first year of life exhibit varying degrees of cyanotic heart disease where the myocardium is chronically perfused with hypoxic blood. We have observed metabolic adaptation to chronic hypoxia (CH) in the myocardium of children with cyanotic congenital cardiac malformations. The capacity of the aerobic energy metabolism was significantly reduced in hypoxic hearts compared to normoxic patients. Understanding the mechanisms by which cyanotic congenital heart disease modifies the myocardium and the modifications impact on cardiac tolerance to ischemia may provide insight into treatments for limiting myocardial damage during cardiac surgery

(iii) Protective strategies for the immature myocardium

Ischemic preconditioning

As mentioned above, cardiac tolerance of the immature heart to oxygen deficiency is significantly higher than the adult myocardium. Thus, the question arises whether we can further increase the already high resistance of the immature heart. I would like to mention our results with two protective phenomena, ischemic preconditioning (IP) and adaptation to CH. Whereas extensive data are available on IP in the adult myocardium, information on whether this protective phenomenon also occurs in immature heart is inadequate. We have shown that classical IP, at least in rats, is not present at birth and that the enhanced postischemic recovery of contractile function can be observed only at the end of the first postnatal week. The decreasing tolerance of the neonatal heart to ischemia is thus counteracted by the development of the inducible endogenous protective mechanism.

Adaptation to chronic hypoxia

The overwhelming majority of studies analyzing the protective effect of adaptation to CH deal exclusively with the adult myocardium. It follows from our results that the protective effect of CH is absent in newborn rats, and it develops – similarly to IP – only during the first postnatal week. These results indicate that we might be dealing with the more general biological phenomenon: the already high resistance of the cardiac muscle cannot be further increased by different protective mechanisms. By analyzing the possible protective mechanisms of CH in the immature heart, we observed that - unlike in IP – both mitochondrial KATP channels and NO may play an important role. Furthermore, we have shown that angiotensin II is also involved in the mechanism of adaptation of the immature heart to CH; the chronic blockade of angiotensin II type I receptors by irbesartan completely abolished the cardiac protection by CH.

(iv) Late effects of early disturbances of cardiovascular system

Human epidemiological studies have shown a clear association between an adverse intrauterine environment and an increased risk of ischemic heart disease in later adult life. One of the most common insults during perinatal development is hypoxemia due to congenital cyanotic

heart defects or pulmonary disease secondary to prematurity. We have found that prenatal CH significantly changed the sensitivity of adult myocardium to I/R injury in a sex-dependent manner: whereas the sensitivity to injury in the adult male myocardium was significantly increased, perinatal exposure to CH in females markedly increased cardiac tolerance to acute ischemic injury. These studies suggest that CH exposure during early development may cause in-utero neonatal programming of several genes that may play an important role in the increased or decreased susceptibility of the adult heart to I/R injury. These results would have important clinical implications since cardiac sensitivity in adult patients may be significantly influenced by perinatal hypoxia in a sex-dependent manner.

Conclusions

The importance of the developmental approach to experimental and clinical cardiology is indisputable. It offers new possibilities in the experimental studies of pathogeny, prevention and therapy of cardiovascular diseases. The structure and function of the developing heart are intrinsically linked, so studying both morphology and physiology provides added value and helps with data interpretation. The differences between individual stages of ontogenetic development are often more profound than differences between species, so translation of data obtained in animal studies to humans needs to be primarily considered in developmental terms (for example, newborn rodents are more like third trimester human fetuses than neonates). Recent advances in our understanding of the reactions of the immature heart could help in devising optimal protection strategies for the immature heart. New methodology, particularly molecular biology and genetics, may substantially help in the laborious search for a better understanding of the underlying mechanisms. Nevertheless, molecular analysis in developmental cardiology is unthinkable without a comprehensive and well-integrated view of the field.

Scientific work is a collective endeavor, and this fully applies to the observations mentioned above, which were developed over a long period of 60 years. I cannot forget my outstanding teachers — Poupa, Rychter, Widimsky, Samanek, Rakusan, Rychterova — nor my closest colleagues from my home institution (Faltová, Pelouch, Prochazka, Bass, later Kolar, Ostadalova, Papousek, Neckar, Drahota, Milerova, and the youngest, Hlavackova, Alanova and Hrdlicka), as well as the successful PhD students Skovranek, Skarka, Szarszoi, Netuka, and Charvatova. It was a joy to learn from distinguished international scientific figures such as Schiebler, Dhalla, and Parratt. Listing all collaborators would go beyond the scope of this account, but all of them deserve my sincere gratitude.

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[1]Read Part 1 of Prof Ostadal's journey in HNV 28:2

JMCC PLUS EDITOR'S UPDATE

JMCC Plus Update

JMCC Plus continues to grow as an open-access home for rigorous and translational cardiovascular science. The journal currently holds a 2.2 Impact Factor, and remains committed to publishing robust mechanistic studies, reviews, resource papers, and reproducibility-focused research.

We are delighted to announce a new **Special Issue led by Dr Vasco Sequeira (University of Würzburg): *"Hypertrophic Cardiomyopathy and its Phenocopies: From Sarcomeres, to Mitochondria to Syndromes."*** This collection will provide a focused platform for new work spanning mechanisms, phenotypes, and emerging translational insights in hypertrophic cardiomyopathy. Researchers interested in this Special Issue, or who may have questions about its scope or suitability, are warmly encouraged to get in touch with Dr Vasco Sequeira (Sequeira_V@ukw.de).

We also invite Early- and Mid-Career Investigators **to propose and lead Special Issues in *JMCC Plus*.** This initiative offers an opportunity to demonstrate academic leadership, gain editorial experience, build international networks, and receive mentorship from the journal's Editorial Board. Prospective Guest Editors are warmly encouraged to get in touch with our Editorial team (d.pavlovic@bham.ac.uk or rebekah.gundry@unmc.edu) to discuss ideas.

In addition, *JMCC Plus* has recently published the abstracts from the **XXV World Congress of the International Society for Heart Research,** held in **Nara, Japan, 11–14 May 2025**, link here, further strengthening the journal's role in showcasing ISHR science.

The journal continues to expand its themed collections, with recent and current topics including electrical and optical mapping technologies, comparative physiology, and omics in heart, vessel and brain diseases.
We thank our authors, reviewers, and readers for their continued support, and we look forward to receiving new submissions, special issue proposals, and contributions from across the ISHR community.

Davor Pavlovic, Editor-in-Chief, JMCC Plus

Rebekah Gundry, Deputy Editor JMCC Plus