

REVIEW

Sixty Years of Heart Research in the Institute of Physiology of the Czech Academy of Sciences

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Summary

In 2023 six decades have elapsed since the first experimental work on the heart muscle was published, in which a member of the Institute of Physiology of the Czech Academy of Sciences participated as an author; Professor Otakar Poupa was the founder and protagonist of this research domain. Sixty years – more than half of the century – is certainly significant enough anniversary that is worth looking back and reflecting on what was achieved during sometimes very complicated periods of life. It represents the history of an entire generation of experimental cardiologists; it is possible to learn from its successes and mistakes. The objective of this review is to succinctly illuminate

the scientific trajectory of an experimental cardiological department over a 60-year span, from its inaugural publication to the present. The old truth – *historia magistra vitae* – is still valid.

Key words

Heart • Adaptation • Development • Hypoxia • Protection

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Fig. 1. Participants of the Symposium on Scientific Basis for the Practice of Cardiology", organized by Department of Developmental Cardiology in Prague, 2010.

Introduction

Cardiovascular diseases represent the most serious health disorders in the contemporary era, accounting for over 50 % of total mortality in the developed countries. A singular illness, ischemic heart disease, is responsible for half of this grim statistic. It is, therefore, understandable that the interest of both experimental and clinical cardiologists is driven by the effort to positively influence this unfavourable situation. Moreover, clinical-epidemiological studies have clearly shown that the risk factors of serious cardiovascular diseases manifest already during the early phases of ontogenetic development. Hence, ischemic heart disease and atherosclerosis are thus no longer diseases of the fifth and higher decades of life, necessitating a shift in experimental studies on the pathogenetic mechanisms of these disturbances to the early phases of ontogenetic development. Moreover, sex differences in the sensitivity to ischemia-reperfusion injury are so obvious that they should be taken into consideration in both experimental and clinical cardiology. The importance of the developmental and sex approach for experimental and clinical cardiology is thus indisputable. And, finally, cardiology is the scientific discipline where the close cooperation between the theoretical and clinical cardiologists has the longstanding tradition, spanning from the molecular level to the patient's bed.

The aim of the present survey is to demonstrate briefly the real scientific life of one experimental cardiological department over the 60-year period, from its inaugural experimental work to the present time. It is necessary to emphasize that the program of the cardiovascular research in the Institute of Physiology of the Czech Academy of Sciences was based on all the above presumptions.

Establishment of the Prague school of experimental cardiology

In 2023, six decades have elapsed since the first experimental work on the heart muscle was published, in which a member of the Institute of Physiology participated as an author; he was the founder and protagonist of this research domain, professor Otakar Poupa [1]. This luminary scientist, possessing charisma and renaissance qualities, came with his "Laboratory for Physiology and Pathophysiology of Metabolism" to the Institute of Physiology from the then Institute for

Nutrition Research. In a short time, within the newly established department, he founded a cardiological laboratory, which worked closely with the Institute of Pathological Physiology of the Faculty of Pediatrics (today the 2nd Faculty of Medicine of the Charles University), of which he concurrently assumed external leadership. Shortly, he managed to create very unique example of cooperation between the Academy of Sciences and the Faculty of Medicine, both in the field of experimental research and in teaching the medical students. He developed broad-based research on the phylogenetic and ontogenetic development of the heart muscle, with special attention to the needs of clinical cardiology, particularly pediatric cardiology. This orientation attracted a large number of young adepts of science and became the basis of the Prague School of Adaptive and Developmental Cardiology, successfully continuing the Czech tradition in evolutionary medicine, pioneered by Eduard Babák. There were published numerous still cited original results about the development of cardiac muscle during phylogeny and ontogeny [2-8], the cardioprotective effect of adaptation to chronic hypoxia [9,10] and factors influencing the extent of experimental cardiac necrosis, induced by high doses of isoproterenol [11-13]. Studies on increasing cardiac tolerance to oxygen deprivation in animals adapted to chronic hypoxia were the first published experimental results in this field. Poupa's group closely cooperated with the excellent cardioembryologist Zdeněk Rychter, author of the first work on experimental heart defects [14], one of the founders of Czech experimental embryology. In this connection it is necessary to mention, that even a modern cardioprotective phenomenon – preconditioning – has its roots in Poupa's department. Already in 1966, twenty years before the originally recognized discovery of this phenomenon, Poupa and his colleagues published a paper in which they showed that repeated administration of small doses of isoprenaline significantly reduced the extent of heart muscle damage, induced by subsequent high dose of this catecholamine [15]. Unfortunately, this work was published in the local journal, and the described effect was not given a commercially successful name. However, persisting interest of world cardiologists in this originally forgotten publication remains a source of pride for Czech cardiologists. The successes of Poupa's Prague school soon crossed the borders of the country. By the late 1960s, Poupa in collaboration with US scientists Bing and Bajusz conceived the idea to create an international

scientific society that would bring together experimental cardiologists from all over the world. This was indeed successful, and the International Society for Heart Research (ISHR), as it is now called, represents the only world society of its kind. Naturally, Poupá became a member of the editorial board of the official journal of this society, the *Journal of Molecular and Cellular Cardiology*, which is still one of the prestigious world-renowned periodicals. The fruitful years culminated in the time of the Prague Spring during which Poupá's merits were recognized with a state prize.

Development after 1968

The Soviet occupation in August 1968, which started the so-called normalization era, adversely affected the development of the entire Czech science including experimental cardiology for many years. Poupá, as one of the authors of the memorable manifesto "Two Thousand Words", chose emigration in September 1968, setting in motion the gradual departure of other Prague school members. The significant limitation of foreign contacts gradually led to the interruption of promising development, to professional isolation and a substantial lag behind global scientific advancements.

Experimental cardiologists in the Institute of Physiology (Faltova, Ostadal, Pelouch, Prochazka, later Kolar, Ostadalova, Papousek and Rychter) perpetuated Poupá's legacy, establishing the Department of Developmental Cardiology (further Department). Their main task became the study of the structural, functional and metabolic properties of the developing cardiac muscle, crucial for understanding the ontogenetic changes of cardiac resistance to oxygen deprivation [16-19]. Interestingly, it was observed that fetal spongy musculature persists in children with congenital heart disease [20]. Special attention was paid to the possibilities of protective influence on the myocardium, especially by the adaptation to chronic hypoxia [21-25]. Moreover, for the first time sex difference in cardiac sensitivity to hypoxia was described [26]. This orientation led to the establishment of very effective cooperation both with other laboratories in the Institute of Physiology as well as with cardiologists addressing cardiopulmonary diseases (Institute for Clinical and Experimental Medicine - IKEM Prague, led by Jiří Widimský) [27-32] and clinical department of pediatric cardiology (Children's Cardiac Center Prague-Motol, under the leadership of Milan Samanek) [33-39].

Simultaneously, at the Institute of Physiology, Krecek's department continued the research activities in the field of ontogenesis: developmental aspects of the pathogenesis of hypertension were very successfully addressed by Jelinek, Kunes and Zicha [40,41]. However, the history of this research would deserve a separate treatise.

Period after November 1989

Only a 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 ushered in a transformative era, offering Czech science the invaluable gift of global reintegration. First came the altruistic invitations from foreign colleagues but at the same time become clear that excuses for past unhappy years would not be enough. Of course, all of 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. In this context, it should be stressed that molecular cardiology, without which we can no longer imagine current experimental research, began to be developed with great delay. The grant system established a competitive approach to financial resources and undoubtedly contributed to the improvement of the scientific quality.

The advantage of our experimental cardiology was that it entered the last 30 years organizationally prepared. The Committee of Experimental Cardiology (KEK), with the foundation of which (1973 by Braveny and Ostadal) the cardiologists from the Institute of Physiology are intrinsically connected, 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 KEK with organizing the 1995 World Congress in Prague. The president was Pavel Braveny from Brno, the secretary general Ostadal and the entire team of the Department participated in the organization. With the passage of time, it can be emphasized that the first meeting of ISHR organized east of Alps, with more than 1200 participants, became a real culmination of the KEK's activities to date. It was also possible to present

adequately the traditional issues of the Institute of Physiology, i.e. cardiac development and adaptation.

The scientific research of the Department during this period was concentrated on the question, how to increase cardiac tolerance to oxygen deficiency. Focused investigation probed the molecular and cellular mechanisms involved in the protection of the ischemic myocardium [42-56] and the analyses of the cardiac resistance during early phases of ontogenetic development [57-62]. Other studies have investigated e.g. the effect of increased pressure on neonatal heart growth [63-65] or right ventricular function in hypoxic pulmonary hypertension [43, 66-68]. The Department seized opportunities offered both for substantial improvements of methodical equipment as well as for significant expansion of contacts with the top foreign laboratories. Very fruitful was the intensive cooperation with the groups at University of Manitoba, Winnipeg [69-71], University of Ottawa [72-78], Max-Planck Institute in Bad Nauheim [79], Free University Berlin [80-82], Catholic University of Louvain in Brussels [83-85], University of Strathclyde, Glasgow [86], INSERM Paris [87,88], Institute for Heart Research, Bratislava [89,90], and others. The representatives of the Department became members of the committees of the international scientific societies, such as ISHR and the International Academy of Cardiovascular Sciences. International activities of the Department continued in the organization of several scientific meetings, such as *Czech-French-Slovak Symposium on Basic Cardiology* (1994), *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 2nd Faculty of Medicine and continued successful collaboration with the clinical institutions such as Children's Cardiac Center and IKEM.

Research Center for Cardiovascular Diseases

In 1999, the first representative research centers were established 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 2nd Faculty of Medicine (Departments of Physiology and Pathophysiology) and Center for Experimental Medicine of IKEM, seemed to be a suitable model for this purpose. "Center for Cardiovascular Research" was acknowledged among the first, with Ostadal as the responsible researcher. The research concept of this Center 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 orientation on 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 Center represents a research base that has no parallels in our country, leading to a resounding endorsement for another seven years. New competition rules included the close cooperation with clinical research facilities, Children's Cardiac Center in Prague-Motol and Departments of Cardiology and Cardiac Surgery of IKEM. The theoretical part was further significantly strengthened by a group from the Faculty of Science and two further departments of the Institute of Physiology, the newly established Department of Cardiac Morphogenesis and the Department of Biomaterials and Tissue Engineering. The Center gradually ceased to be a formal grouping of individual workplaces but became a virtual institute. New laboratories were created and methodical approaches and technical equipment increased significantly. The main output of the Center's activities were high-quality original results published in renowned journals. The Center was very successful in attracting young researchers: a number of future cardiologists and cardiac surgeons completed their scientific training in the experimental and clinical research. The number of full-time researchers was in average 109, 30 of them were under 35 years of age. During existence of the Center, 25 postgraduate students defended their PhD thesis. Regrettably, the dissolution of this long-established team of experimental and clinical researchers interrupted the well-started and effective cooperation; the successful system of scientific centers officially terminated in 2012.

Cardiovascular research in the last decade

Although the cessation of the Centre's activities led to the end of joint funding, the scientific cooperation

of the Department with several partners, in particular the Faculty of Science, continued and developed further on a bilateral basis. In the framework of this collaboration, a number of studies have recently been published that have further characterized the differences in cardioprotective mechanisms induced by various regimens of continuous and intermittent chronic hypoxia [91-97]. Together with the Center for Experimental Medicine of IKEM, we have also addressed questions concerning the influence of comorbidities, especially various forms of systemic hypertension, on myocardial ischemic tolerance and new possibilities of therapeutic pharmacological interventions [98-102]. The merger with the Department of Cardiac Morphogenesis has led to the expansion of the studied topics to include the development of the structure and function of the cardiac conduction system and to the enrichment of the methodological tools [103-106]. Special attention was paid to the developmental and sex differences in cardiac tolerance to ischemia/reperfusion injury and the possible role of mitochondria in this process [107-116]. A newly established international collaboration with the Medical College of Wisconsin, Milwaukee, has yielded new findings with translational potential on the beneficial effects of eicosanoids on cardiac injury by ischemia and on the development of post-ischemic heart failure [117-120]. The traditional focus of the Department's research programme on the cardiovascular effects of chronic hypoxia has prompted joint projects with the Laboratory of Molecular Pathogenetics, Institute of Biotechnology, investigating the role of the transcription factor HIF-1 α in the mechanism of ischemic tolerance and in the pathogenesis of diabetic cardiomyopathy and heart failure [121-124]. Last but not least, we are involved with colleagues from Comenius University in Bratislava in research on mechanisms of new forms of cell death in myocardial infarction and heart failure [125-127]. 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 [128-131]. Number of young enthusiastic researchers, modern methodologies and attractive scientific programme represent promising perspectives for future.

The scientific contribution of experimental cardiologists from the Institute of Physiology

To evaluate the contribution of scientific work is always tricky; it depends on many points of view. On the first place is of course the originality of the published results, but it is also necessary to assess to whom the results will help, what are the perspectives of their further use and how they 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. For the sake of completeness, we would like to summarize at least some of them.

- studies on the normal phylogenetic and ontogenetic development of the cardiac muscle, myocardial blood supply and conduction system;
- persistence of the fetal avascular spongy myocardium, supplied by diffusion from the ventricular cavity in patients with pulmonary stenosis;
- cardiac adaptation to pressure overload during early postnatal development;
- the first observation in experimental cardiology, demonstrating that the female heart is more tolerant to hypoxia than the male heart;
- developmental and sex differences in cardiac tolerance to oxygen deprivation; the role of mitochondria, and protective strategies for the immature myocardium;
- metabolic adaptation to chronic hypoxia in children with congenital heart disease;
- intermittent chronic hypoxia-induced right ventricular hypertrophy and pulmonary hypertension; possibilities of pharmacological interventions;
- studies on the effect of perinatal hypoxia on the sex-dependent hypoxic tolerance of the adult myocardium;
- molecular mechanisms of the long-lasting cardioprotective effect of adaptation to chronic hypoxia, regular exercise and other adaptive interventions;
- altered cardiac ischemic tolerance associated with various forms of systemic hypertension; possibilities of genetic and pharmacological interventions;
- pathogenetic mechanisms of diabetic cardiomyopathy; ischemic tolerance of diabetic heart;

- progression of post-ischemic heart failure in hypertensive animals; novel experimental therapy;
- role of epitranscriptomic regulatory mechanisms in heart physiology and pathophysiology.

Conclusion

60 years – more than half of the century – is certainly significant enough anniversary that it is worth looking back and reflecting on what has been achieved. It represents the history of an entire generation of experimental cardiologists; it is possible to learn from its

successes and mistakes; and that was the main purpose of this historical reflection. Indeed, the old truth – *historia magister vitae* – is still valid.

Conflict of Interest

There is no conflict of interest.

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Fig. 2. Participants of the "Mendel symposium II: Genes and the Heart", organized by Department of Developmental Cardiology in Liblice, 2008.

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