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EDITORIAL

The Coronary Artery – From Geometry to RNA Turnover.

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Summary

This review compares the geometry of conduit coronary arteries in man and animals, namely the wall/diameter ratio (1:7.4 and 1:15 respectively). The left and right ventricle volume determines the geometry (segment length and diameter) of both branches of the left coronary artery: ramus interventricularis anterior and ramus circumflexus; the range of deformation of the latter was substantially smaller. The heterogeneity of deformation was also found along the ramus interventricularis anterior, the deformation decreasing towards the apex. The above relations have consequences (i) on the haemodynamics (passive changes in conduit segment resistance), (ii) the deformation of coronary arteries triggers metabolic processes in the coronary wall. Four hours' lasting cardiac volume or pressure overload brought about an increase in the RNA content not only in the myocardium, but also in the coronary artery. The process is reversible. Moreover, the range of the RNA increase is in full concert with the heterogeneous deformability of the respective segment of the coronary tree.

Key words

Coronary artery – Geometry – Cardiac-overload – RNA – Deformation heterogeneity

In an extremely attractive book "Men and Ideas" (Fishman and Richards 1964) one can learn that already the ancient Egyptians, about 5 thousand years ago, had in their mind the significance of the heart. This fact was revealed by E. Smith who decoded the "Surgical Papyrus". The anatomy of "Coronales Arterie" was drawn by Leonardo da Vinci (1452-1519) and later by Vessalius (1514-1564), a great enthusiast for medicine, and his illustrator Kalkar who came from Tizian's School (Fishman and Richards 1964). The real function of coronary circulation was not described until 1628 by Harvey in his *"Exercitatio anatomica de motu cordis et sanguinis in animalibus"* (English translation by Leake 1970).

From the phylogenetic aspect, the compact layer of the myocardium was shown to play a key role in the development of distinct coronary arteries. The compact layer of the myocardium with a distinct coronary tree, beside remnants of the spongious layer endowed with lacunae, was found first in fishes, larger amphibians and reptiles (Juhász-Nagy *et al.* 1963, Ošťádal *et al.* 1970). In birds and mammals the only compact layer of the heart is nourished exclusively by a distinct coronary tree (Benninghoff 1930).

Footnotes

This paper is dedicated to the memory of Ján Gero and Ervin Bárta who died in 1991.

The data of this Editorial were partly presented in the "Purkyně Lecture" delivered at the Meeting of the Czechoslovak Physiological Society in Prague, February 1992.

From the aspect of ontogenesis, the coronary arteries develop in the earliest ontogenetic period in the human foetus at 7-8 weeks (Bogers *et al.* 1988), in comparison to the chick at 7-9 days, or the rat foetus at 16-19 days (Rychter *et al.* 1968, Ošťádal *et al.* 1968). Two opposite views have been discussed dealing with the growth direction of the conduit coronary artery. According to Bogers *et al.* (1988) the coronary artery grows into the aorta. In contrast to this, Dbalý *et al.* (1968) suppose that a bud is protruding from the aorta and joins the coronary artery which had already developed in the myocardium.

Considering the geometry of the human coronary artery, and namely the key parameter the wall/diameter ratio, the growth of the individual layers of the wall during ontogenetic development is important. The tunica media increases from the first month to adulthood from 45 μm to about 200 μm, i.e. about 4-5 times, and does not change further. Whereas the tunica intima increases from 6 μm in the first month to 300 μm in adulthood, i.e. 50 times and the increase in thickness continues (Rabe 1973). Consequently, the parameter crucial for closing the artery in adults, calculated according to the data by Rabe (1973) and Purinja (1984), is 1:7.4.

On the other hand, the geometry of coronary artery in animals is surprisingly auspicious. Levický and Gerová (1981) found the wall/diameter ratio in adult dogs as 1:15, a value remarkably lower in comparing to the human coronaries. Sims confirmed the thin wall of the coronary artery in other 10 animal species (1989).

The above data on the geometry of coronary arteries are basic, albeit static. About 200 hundred years after Harvey published *"De motu cordis"*, Purkyně wrote and lectured in Breslau (1843) on the suction and pumping function of the heart: "Die Muskelsubstanz der Ventrikel nach allen Dimensionen zusammenziehen müsse und das Herz sich ... sowohl verkürzt als auch verengt". Purkyně's observation had an inevitable consequence for the biomechanics of the coronary tree, including the conduit portion. Being, in principle, an elastic tube and firmly tethered to the myocardium, the conduit portion of the coronary tree has to be subjected to any change in the geometry of the heart, so that deformation in length and diameter are to be expected. The dynamics of deformation in relation to ventricular volume was studied in an isolated, non-beating heart, placed in a bath. Increasing the left ventricular volume stepwise from zero to a value of normal diastolic filling and higher (by about 100-150 %), the segment length of the ramus interventricularis anterior increases in a stepwise manner and the diameter decreases accordingly, both in the range of about 12 % and 10 % respectively – Fig. 1. (Gerová *et al.* 1989).

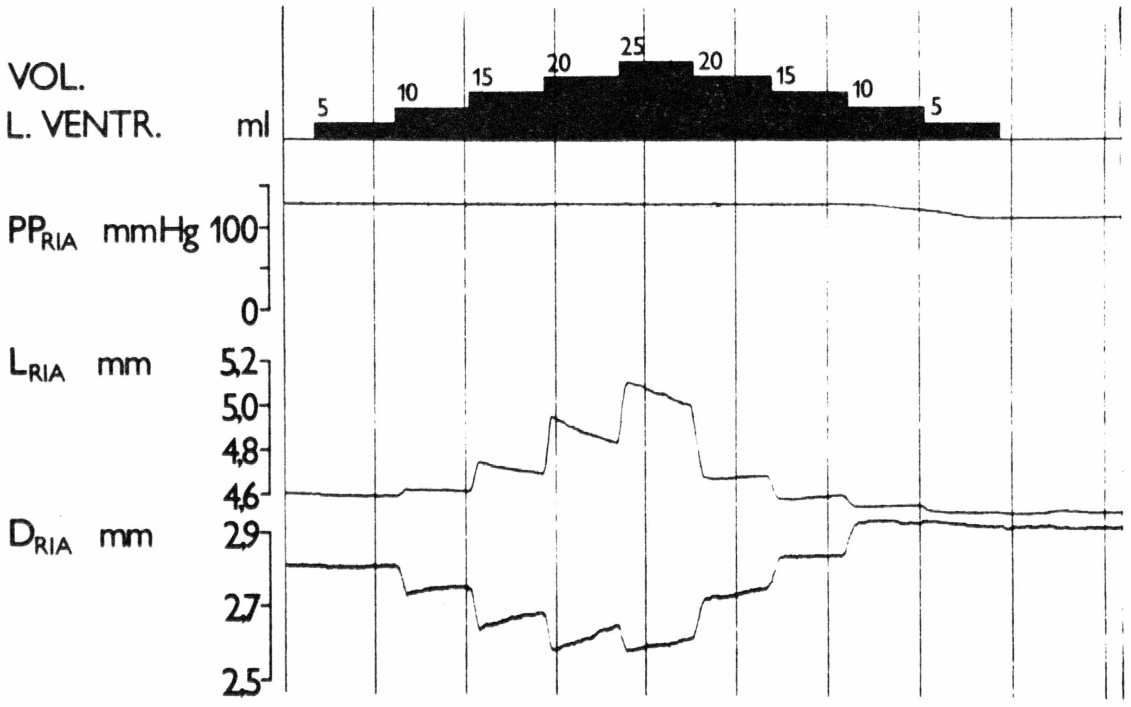

Fig. 1
Original record of the perfusion pressure (PP_{RIA}), segment length (L_{RIA}) and diameter of RIA (D_{RIA}) during stepwise changes of left ventricle volume. From Gerová *et al.* 1989, with permission.

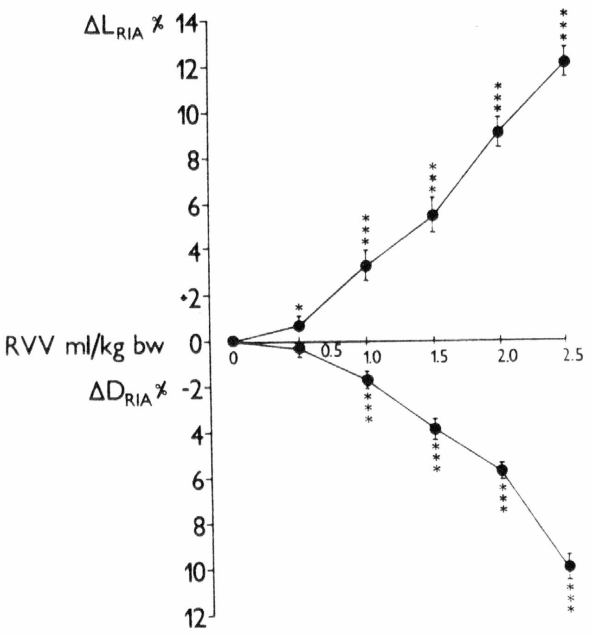

Fig. 2
Mean values ± S.E.M. of ΔL_{RIA} in percentage of resting value (top of ordinate) and ΔD_{RIA} in percentage of resting diameter (bottom of ordinate) of ramus interventricularis anterior during a stepwise increase of RVV. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. From Gerová *et al.* 1992, with permission.

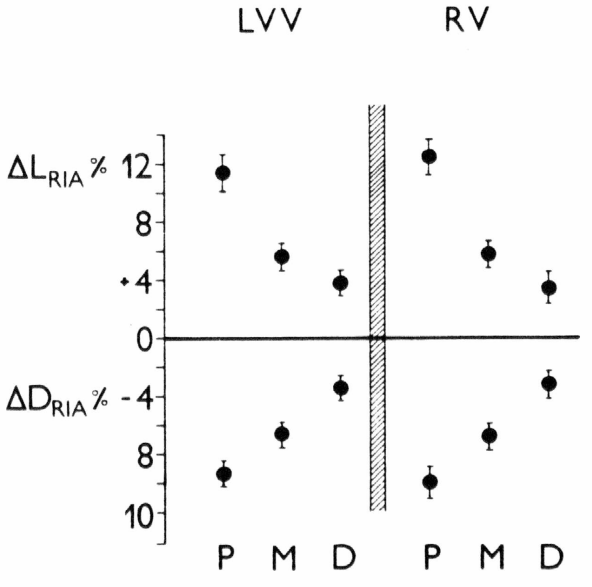

Fig. 3
ΔL_{RIA} and ΔD_{RIA} after left ventricular volume (LVV, left part), and right ventricular volume (RVV, right part) was increased by 150 % of its normal value. Values are registered in the proximal (P), middle (M), and distal (D) part of ramus interventricularis anterior. From Gerová *et al.* 1992, with permission.

Surprising enough, the right ventricle filling from zero up to a 100-150 % increase of diastolic filling brought about the same range of segment length and diameter deformation, inspite of the fact that ramus interventricularis anterior runs exclusively over the left ventricle – Fig. 2. Studies on the biomechanical interdependence of the left and right ventricle mediated particularly by the interventricular septum (Puff 1960, Santamore *et al.* 1986, Slinker *et al.* 1986), makes this phenomenon conceivable.

However, the alterations in geometry along the ramus interventricularis anterior are not uniform at the same filling of the left, or right ventricle: the length segment increase and the diameter decrease are the largest in the proximal third and decrease distally towards the apex – Fig. 3. (Gerová *et al.* 1989).

Heterogeneous deformation was also found in the two main branches of the left coronary artery. The increase of segment length and decrease of diameter of the ramus interventricularis anterior at the same filling of the left or right ventricle as above, are significantly larger, than the respective values of ramus circumflexus (maximum segment length increases by 2 % and diameter decreases by 4 %). The smaller deformation of ramus circumflexus is supposed to be a consequence of the fact, that the vessel is running loosely in the fat tissue in the atrio-ventricular groove. Moreover, it runs above an almost non-deformable anullus fibrosus. In conclusion, the alterations in geometry of the individual segments of the conduit coronary arteries follow the geometry of the respective underlying myocardial area most closely (Gerová *et al.* 1992).

By projecting the above findings into coronary hemodynamics, it is possible to draw the following conclusions. The passive deformation of the coronary artery in segment length and diameter due to changes in left or right ventricle volume implies a change in resistance to the flow in this particular conduit portion (Gerová *et al.* 1989) Such a situation may occur, for example, during stimulation of the vagus nerve, when during vagal bradycardia with a prolongation of the diastole, the ventricle filling increases markedly, the coronary segment length increases and its diameter decreases (Gerová *et al.* 1987, Gerová 1992). Thus the resistance to flow increases in the particular conduit segment.

A reverse situation might be expected during increased cardiac sympathetic activity, when ventricle filling decreases during tachycardia and shortening of the diastole. The coronary segment length also decreases and the diameter increases passively. The passive biomechanical process counteracts and the small sympathetic coronary constriction becomes even smaller (Gerová *et al.* 1979, Gerová 1982).

Besides the geometry of the coronary artery affects the coronary haemodynamics, the dynamics of coronary deformation, transferred to individual cells of the coronary wall, might well serve as a signal for altering cell metabolism. Both vascular smooth muscle

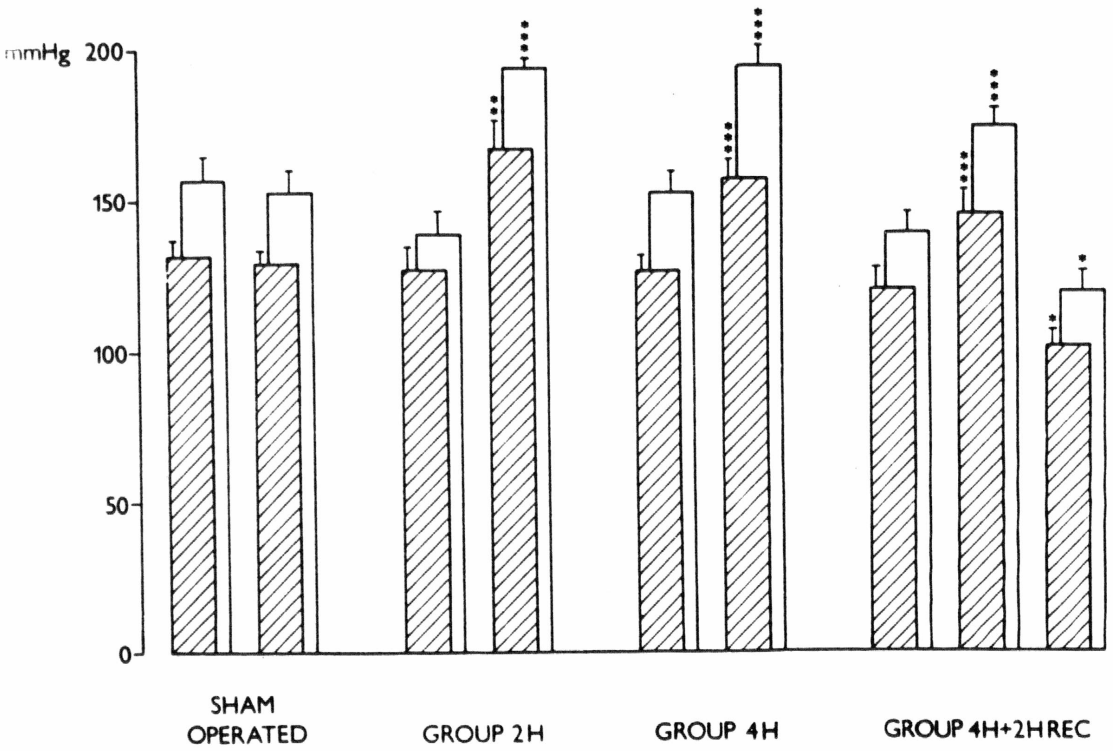

Fig. 4
Diastolic and systolic blood pressure in individual groups of experiments: in the group of sham operated, in the group of BP increase lasting 2 hours, in the group of BP increase lasting 4 hours and in the last group in which the four hours' BP increase after aortic constriction was released with consequent BP decrease.

cells and endothelial cells, as well as cardiac myocytes, cultured on an elastic plate which was continuously deformed, were shown to initiate alterations in metabolism in comparison to the cells cultured on a static plate (Leung *et al.* 1976, Sumpio *et al.* 1988, Mann *et al.* 1989, Kent *et al.* 1989). Even bearing in mind that the collagen-elastic scaffold might buffer the deformation of the individual cell components in the coronary artery of a living animal (Glagov *et al.* 1992) certain cell deformation might be expected as follows from basic functional studies of individual segments of the vascular tree (Gerová and Gero 1967, Davis and Dow 1972).

In a series of experiments on anaesthetized dogs, the volume overload of the heart was brought about by shunting blood flow from the left carotid artery into the left auricula, at a rate representing 25 % of the estimated cardiac output (Altman and Dittmer 1974). The pulse pressure amplitude increased significantly by 9 %, however, no change occured in the mean blood pressure. A significant increase in RNA content in the myocardium was found after four hours lasting volume overloading of the heart proving the experimental model as adequate. And from the point of view of this study the most important finding was the increased RNA content in the wall of the left coronary artery, both branches being analyzed together (Pecháňová *et al.* 1990). No changes were found either in the DNA content, or in prolin content both in the myocardium and the coronary artery.

The pressure overload of the heart and coronary artery in relation to protein metabolism was also studied. In this study two more aims were followed, namely: (i) the time course and/or the reversibility of changes in RNA content of the coronary wall; (ii) the other question was whether the heterogeneity of deformation, proved in two main branches of the left coronary artery, would be reflected in protein metabolism. A pressure overload of the heart and coronary arteries was induced by constriction of the abdominal aorta above the renal arteries. The experimental animals were exposed to high blood pressure (Fig. 4) in the first series for 2 hours, in the second series for 4 hours, and in the third series after 4 hours of the pressure overload the aortic constriction was released and the blood pressure decreased. Sham operated animals were used as controls for RNA analysis. Fig. 5 demonstrates that there is a tendency to increase the RNA content in the myocardium and the coronary arteries after 2 hours' pressure overload which, however, is not yet significant. After 4 hours' pressure overload, a clearcut increase was found in the RNA content in the myocardium and in the ramus interventricularis anterior. It was remarkable that no significant increase in the RNA content was found in the ramus circumflexus.

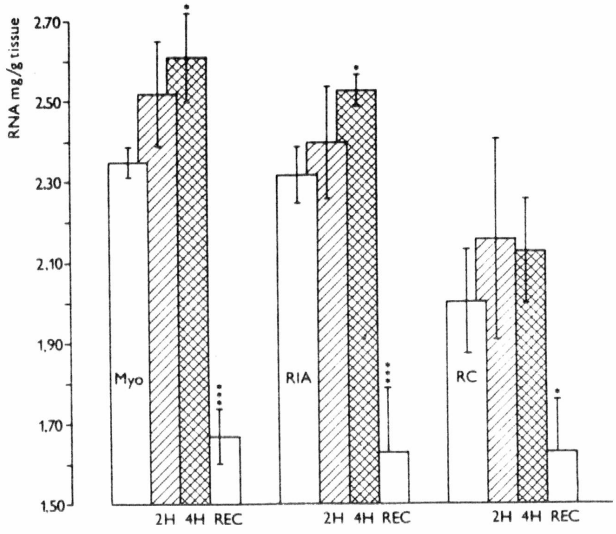

Fig. 5
RNA content in the myocardium, ramus interventricularis anterior and ramus circumflexus in sham operated animals (white columns), after 2 hours' lasting BP increase (hatched columns), after 4 hours' lasting BP increase (cross-hatched columns) and 2 hours after release the 4 hours' lasting aortic constriction (white columns - REC).

The results proved that changes in cardiac volume-overload, or pressure-overload, lasting 4 hours induce changes in the RNA content not only in the myocardium, but in the coronary arteries as well. They proved further the reversibility of the process. Two hours' lasting decrease in blood pressure after 4 hours pressure overloading, is accompanied by decrease in RNA content in the myocardium and in the coronary artery (Fig. 5). Moreover, the results of heterogeneous alterations of the RNA content in two main branches of the left coronary artery during pressure-overload, closely reflect the heterogeneous deformability of the two branches (Gerová *et al.* 1992). These findings prove that, *in vivo,* relatively shortlasting waving in blood pressure, are accompanied by waving in metabolism of RNA in the coronary wall. They support the idea that deformation of cells in the coronary wall triggers the metabolic processes.

The DNA content did not change in the above experiments. The alterations in RNA content concerned mainly the smooth muscle cells forming 17-20 layers in the coronary wall. It is not clear how the endothelial cells reflect the volume- or pressure-overload. According to Sumpio *et al.* (1988), the endothelial cells in culture respond to dynamic deformation in a different way from smooth muscle cells.

The processes described are the early links in the metabolic cascade in the coronary wall during volume or pressure overload and they are reversible. Extending the loading for months, remarkable remodelling of the coronary wall was found, characterized by a relative increase in noncellular substance and by alterations in the ultrastructure of smooth muscle cells (Kristek *et al.* 1989). The morphological alterations are accompanied by functional failure of the coronary smooth muscle, namely by a decrease in its contraction efficiency (Holécyová *et al.* 1987).

The process of transduction of haemodynamics to the metabolic changes of the coronary smooth muscle and/or the endothelial cell obviously includes many, more subtle links, as one can suppose from single cell studies, e.g. stretch activated ionic channels of the vascular smooth muscle cell (Somlyo and Somlyo 1992) and also of those of endothelial cell (Lansman *et al.* 1987), autacoids produced by endothelial cells, which besides the vasomotor effect (Furchgott and Zawadski 1980, Yanagisawa *et al.* 1988) were proven to have a distinct trophic effect and, moreover, the trophic effect may be amplified by linking to growth factors (Chien *et al.* 1991) etc. The above cascade always remains reductionistic, and is mentioned just to show how poor our knowledge about the coronary artery still is.

References

ALTMAN P.L., DITTMER D.S.: *Biology Data Book.* FASEB, Bethesda MD, 1974.

BENNINGHOFF A.: Blutgefäss – und Lymphgefäss apparat. In: *Handbuch der Mikroskopischen Anatomie des Menschen.* W. VON MÖLLENDORFF (ed), Springer Verlag, Berlin, 1930, pp. 217–223.

BOGERS A.J.J.C., GITTENBERGER-DE GROOT A.C., DUBBELDAM J.A., HUYSMANS H.A.: The inadequacy of existing theories on development of the proximal coronary arteries and their connections with the arterial trunks. *Int. J. Cardiol.* **20**: 117–123, 1988.

CHIEN K.R., KNOWLTON K.U., ZHU H., CHIEN S.: Regulation of cardiac gene expression during myocardial growth and hypertrophy: molecular studies of an adaptive physiologic response. *FASEB J.* **5**: 3037–3046, 1991.

DAVIS D.L., DOW P.: Intraluminal pressure and rate and magnitude of arterial constrictor responses. *Am. J. Physiol.* **222**: 415–420, 1972.

DBALÝ J., OŠŤÁDAL B., RYCHTER Z.: Development of the coronary arteries in rat embryos. *Acta Anat.* **71**: 209–222, 1968.

FISHMAN A.P., RICHARDS D.W.: *Circulation of the Blood: Men and Ideas.* Oxford University Press, New York, 1964.

FURCHGOTT R.F., ZAWADSKI J.V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acelylcholine. *Nature* **288:** 373–376, 1980.

GEROVÁ M., GERO J.: Effector mechanisms induced by baroreceptor stimulation. In: *Baroreceptors and Hypertension.* P. KEZDI (ed.), Pergamon Press, Oxford and New York, 1967, pp. 225–233.

GEROVÁ M., BÁRTA E., GERO J.: Sympathetic control of major coronary artery diameter in the dog. *Circ. Res.* **44:** 459–467, 1979.

GEROVÁ M.: Autonomic innervation of coronary vasculature. In: *The Coronary Artery.* S. KALSNER (ed.), Croom and Helm Ltd, London, 1982, pp. 189–215.

GEROVÁ M., BÁRTA E., KOŽÍK J., GERO J.: Does the vagus share in the control of diameter of conduit coronary artery? *Physiol. Bohemoslov.* **36:** 573, 1987.

GEROVÁ M., BÁRTA E., STOLÁRIK M., GERO J.: Geometry of the conduit coronary artery in diastole is determined by the volume of the left and right ventricles. *Basic Res. Cardiol.* **84:** 583–590, 1989.

GEROVÁ M., BÁRTA E., STOLÁRIK M., GERO J.: Heterogeneity in geometrical alterations of two main branches of left coronary artery induced by increase in left and right ventricle volume. *Am. J. Physiol.* **262:** H1049–H1053, 1992.

GEROVÁ M.: Conduit coronary artery. Structure and function. In: *Heart. Function in Health and Disease.* B. OŠŤÁDAL, N.S. DHALLA (eds), Kluwer Academic Publ., Boston, Dordrecht, London, 1993, pp. 273–286.

GLAGOV S., VITO R., GIDDEUS D.P., ZARIUS C.K.: Microarchitecture and composition of artery walls: relationship to location, diameter and the distribution of mechanical stress. *J. Hypertension* **10**(Suppl.6): S101–S104, 1992.

HARVEY W.: Exercitatio anatomica de motu cordis et sanguinis in animalibus. English translation by C.D. LEAKE, CH.C. THOMAS, Springfield, 1970.

HOLÉCYOVÁ A., GEROVÁ M., FÍZEĽ A., FÍZEĽOVÁ A.: Constriction ability of coronary artery in volume overload cardiac hypertrophy. *Physiol. Bohemoslov.* **36:** 105–111, 1987.

JUHÁSZ-NAGY A., SZENTIVÁNYI M., SZABÓ M., VÁMOSI B.: Coronary circulation of the tortoise heart. *Acta Physiol. Hung.* **23:** 33–48, 1963.

KENT R.L., HOOBER J.K., COOPER G.: Load responsiveness of protein synthesis in adult mammalian myocardium: role of cardiac deformation linked to sodium influx. *Circ. Res.* **64:** 74–85, 1989.

KRISTEK F., GEROVÁ M., FÍZEĽ A., FÍZEĽOVÁ A.: Morphometry of conduit coronary artery in volume-overload cardiac hypertrophy. *Physiol. Bohemoslov.* **38:** 514, 1989.

LANSMAN J.B., HALLAM T.J., RINK T.J.: Single stretch activated ion channels in vascular endothelial cells as mechanotransducers? *Nature* **325:** 811–813, 1987.

LEUNG D.Y.M., GLAGOV S., MATHEWS M.B.: Cyclic stretching stimulates synthesis of matrix components by arterial smooth muscle cells in vitro. *Science* **191:** 475–477, 1976.

LEVICKÝ V., GEROVÁ M.: Relative volumes of structural components in ventral interventricular branch (VIB) in the left coronary artery in dogs – functional interpretation. In: *Cardiovascular Physiology. Heart, Peripheral Circulation and Methodology.* A.G.B. KOVÁCH, E. MONOS, G. RUBANYI (eds), Pergamon Press, Akadémiai Kiadó, Budapest, 1981, pp. 253–262.

MANN D.L., KENT A.L., COOPER G.: Load regulation of the properties of adult feline cardiocytes: growth induction by cellular deformation. *Circ. Res.* **64:** 1079–1090, 1989.

OŠŤÁDAL B., RYCHTER Z., POUPA O.: Qualitative development of the terminal coronary bed in the perinatal period of the rat. *Folia Morphol.* **16:** 116–125, 1968.

OŠŤÁDAL B., RYCHTER Z., POUPA O.: Comparative aspects of the development of the terminal vascular bed in the myocardium. *Physiol. Bohemoslov.* **19:** 1–10, 1970.

PECHÁŇOVÁ O., GEROVÁ M., BÁRTA E., KOŽÍK J.: Turnover of nucleic acid in coronary artery and myocardium during short lasting volume overload. *Physiol. Bohemoslov.* **39:** 557, 1990.

PUFF A.: *Der functionelle Bau der Herzkammern.* Thieme, Stuttgart, 1960.

PURINJA B., KASJANOV B.A.: *Biomechanics of Large Conduit Arteries in Man* (in Russian). Zinatne, Riga, 1984.

PURKYNĚ J.E.: Die Saugkraft des Herzens. In: Jahresbericht d. schles. Ges. f. vaterl. Cultur, Breslau, 1843, pp. 157–164.

RABE D.: Kalibermessung an den Herzkranzarterien und dem Sinus Coronarius. *Basic Res. Cardiol.* **68:** 356–379, 1973.

RYCHTER Z., OŠŤÁDAL B.: Periodisation of the blood supply development of the myocardium in chick embryos. *Physiol. Bohemoslov.* **17:** 485, 1968.

SANTAMORE W.P., SHAFFER T., HUGHES D.: A theoretical and experimental model of ventricular interdependence. *Basic Res. Cardiol.* **81:** 529–537, 1986.

SIMS F.H.: A comparison of structural features of the walls of coronary arteries from 10 different species. *Pathology* **21**: 115–124, 1989.

SLINKER B.K., GLANTZ S.A.: End-systolic and end-diastolic ventricular interaction. *Am. J. Physiol.* **251**: H1062–H1075, 1986.

SOMLYO A.P., SOMLYO A.V.: Smooth muscle structure and function. In: *The Heart and Cardiovascular System.* H.A. FOZZARD, E. HABER, R.B. JENNINGS, A.M. KATZ, H.E. MORGAN (eds), Raven Press, New York, 1992, pp. 1295–1324.

SUMPIO B.E., BANES A.J., BUCKLEY M., JOHNSON G.: Alterations in aortic endothelial cell morphology and cytoskeletal protein synthesis during cyclic tensional deformation. *J. Vasc. Surgery* **7**: 130–138, 1988.

YANAGISAWA M., KURIHARA H., KIMURA S., TOMOBE Y., KOBAYASHI M., MITSUI Y., YAZAKI Y., GOTO K., KASAKI T.: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* **332**: 411–415, 1988..

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