HEART FAILURE DEVELOPMENT IN AORTIC VALVE INSUFFICIENCY

FAJTL L

VÝVOJ ZLYHANIA SRDCA PRI AORTÁLNEJ INSUFICIENCII

Abstract

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Since left ventricle can cope well with volume overload and patients remain asymptomatic for years, the pharmacological interventions which prolong this period and inhibit heart failure development may be possible. However, understanding the heart failure development in chronic aortic regurgitation is a prerequisite. In this review currently postulated mechanisms of the slow but continuos development of ventricular insufficiency in chronic aortic regurgitation are examined. Based on this analysis the preventive competence of some drugs with remodelling potential is postulated: vasodilators, growth hormone, thyroxin analogues and carnitine-palmitoyltransferase-1 inhibitors. *(Ref. 36.)*
Key words: aortic regurgitation, heart failure, heart hypertrophy.

Abstrakt

Fajtl L.:
Vývoj zlyhania srdca pri aortálnej insuficiencii
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Keďže ľavá srdcová komora dokáže dobre zvládnuť objemové preťaženie a pacienti ostávajú asymptomatickí niekoľko rokov, možno toto obdobie predĺžiť a zastaviť vývoj zlyhania srdca pomocou vhodných farmakologických zásahov. To však predpokladá porozumenie vývoja zlyhania srdca pri aortálnej insuficiencii. Tento prehľadový článok sa zaoberá v súčasnosti navrhovanými možnými mechanizmami pomalého, ale trvalého vývoja komorovej insuficiencie pri chronickej aortálnej insuficiencii. Na základe tejto analýzy sa uvádzajú niektoré lieky s predpokladaným preventívnym účinkom: vazodilatačné látky, rastový hormón, tyroxínové analógy a inhibítory karnitín-palmitoyl-1-transferázy. *(Lit. 36.)*
Kľúčové slová: aortálna insuficiencia, zlyhanie srdca, hypertrofia srdca.

Implantation of artificial aortic valves is still associated with various complications resulting in notable morbidity and mortality. The decision on surgical correction of aortic regurgitation remains a very complicated task, especially in asymptomatic or low symptomatic patient with severe aortic valve insufficiency. Premature timing of the surgical correction may unnecessarily shorten the patients life span. However, too late operation, despite the successful correction of the hemodynamic abnormality, may not halt the progression of the left ventricular insufficiency (Treasure, 1993).

Currently, detection of decreased myocardial contractility, apart from a low life quality, is considered as decisive ground for surgical intervention. It is namely believed that once myocardial contractility has decreased, it will remain impaired also after valve replacement and will produce congestive heart failure in these patients (Cheitlin, 1998). Nevertheless, two main problems are responsible for the high degree of uncertainty in the use of this criterion. Firstly, the assessment of myocardial contractility is susceptible to serious errors. Secondly, the sequence of events in the transition from compensatory hypertrophy to heart failure in aortic valve insufficiency is fully unclear and various different scenarios are postulated. Thus, theoretical framework is absent, within which the moment may be defined, when the vicious circle of heart failure development in aortic regurgitation becomes irreversible.

Clinical data on heart failure pathogenesis in aortic valve insufficiency are very limited and also experimentally, volume overload as a cause of heart failure is significantly less explored as the pressure overload. In contrast to the pressure overload, which is associated with decreased myocardial contractility also in the compensatory stage, ventricular adaptation to the volume overload is initially either not changed or even increased (Turcani and Jacob, 1998). Yet, some functional alterations of organelles involved in the transport of activator calcium are detectable very early (Fizel et al., 1981; Fizel et al., 1986a). However, decreased specific sarcoreticular calcium transport activity is, at first, compensated by

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the increased quantity of the sarcoplasmic reticulum (Turcani et al., 1983). Amount of mitochondria is elevated (Turcani et al., 1991) without alteration in their respiratory function (Fizel et al., 1986b). Hypertrophied cardiomyocytes contain enlarged contractile apparatus with preserved actomyosin activity (Fizel et al., 1984). Thus, no apparent alterations were revealed at the subcellular level in developed excentric hypertrophy which may be responsible for the later transition to heart failure (Turcani et al., 1988).

Despite this experimentally and clinically proved good adaptation of the left ventricle to often very severe aortic regurgitation, progressive dilatation of the overload ventricle emerges at last. This process is principally different from the excentric hypertrophy and leads to heart failure (Turcani et al., 1987). Experimentally, before the process of terminal dilatation begins, the relative decrease in cardiac dimensions was identified (Fizel et al., 1984). This may cause the afterload mismatch and start the process of progressive dilatation of the left ventricle. Unfortunately, the causes of the "spontaneous regression" are not known. Identification of such period of relative hypertrophy regression in the human pathology would be of great importance for the timely prediction of heart failure development (Šimko, 1994).

Continuing left ventricular deterioration in aortic regurgitation is attributable to the progressively increased hemodynamic overload and/or to the advancing deterioration of the myocardial inotropic and lusitropic properties. Regurgitant volume in aortic valve insufficiency depends on the aortic regurgitant orifice area the duration of diastole, and the transvalvular pressure gradient throughout the diastole (Gorlin and Gorlin, 1951). Thus bradycardia and enlargement in the aortic regurgitant orifice area or diastolic transvalvular pressure gradient enhance the volume overload of the left ventricle.

The underlying cause of aortic valve insufficiency is either a defect of the aortic cusps, mostly of rheumatic, infectious and congenital origin or the aortic root pathology (age-related dilation, Marfan's syndrome, syphilis, Reiter's disease, ankylosing spondylitis, giant cell arteriitis) (Mangion and Tighe, 1995). It is usually assumed that in primary aortic valve diseases the lesion is fixed. However, in aortic root diseases, the reguritant orifice area may be liable to progressive enlargement. This is not surprising in Marfan's syndrome but the Framingham heart study reported that also in overall population aortic root diameter increases by 0.008 cm/year in man and 0.009 cm/year in women (Vasan et al., 1995). In patients with aortic valve insufficiency aortic root enlarges even more rapidly. The rate of increase in aortic root dimensions depends not on the etiology of aortic valve lesion but on the severity of aortic regurgitation. More severe regurgitation shows faster dilatation of the aortic root and faster progression in the degree of regurgitation (Padial et al., 1997). Particularly patients with chronic aortic regurgitation who have dilation of the aortic root involving the supraaortic ridge and proximal portion of ascending aorta also have a markedly hypertrophied and dilated ventricle (Guiney et al., 1987). Supraaortic ridge supports the valve cusps at their commisures. Dilatation at the level of this annulus causes a central defect in the aortic orifice that cannot be closed by the cusps. A vicious cycle of progressive aortic regurgitation ensues. Greater aortic root dilatation causes greater regurgitation. The resultant increases in stroke volume imposes more stress on the aortic root which increases its dilation further (Guiney et al., 1987). Thus, volume overload of the left ventricle caused by aortic valve insufficiency may be progressively increased independently of the primary valve lesion stability.

Left ventricle adapts to the aortic regurgitation by excentric hypertrophy. Left ventricular cavity enlarges and ventricular wall thickens in such a way that the wall stresses are normalized despite large blood volumes handled by the ventricle. This adaptation is very effective and aortic regurgitation may be tolerated for years without symptoms. However, experimental data show that additional pressure load on volume overloaded ventricle dramatically accelerates heart failure development. (Noma et al., 1988; Gilson et al., 1990) Also in patients with aortic regurgitation double loading the left ventricle may significantly impair pump performance. To maintain mechanical efficiency of the blood pumping during adaptation to aortic regurgitation, the arterial system may also adapt with a reduction in total arterial elastance. However in some patients total arterial elastance may increase, providing an additional afterload on the left ventricle and reducing the left ventricular-arterial coupling ratio (Devlin et al., 1999). This leads to a reduction in left ventricular performance and pump efficiency. Increased arterial elastance may represent one mechanism for the heart failure development in aortic regurgitation and theoretical framework for the vasodilator therapy in this disease. The long-term benefit observed with vasodilator therapy in asymptomatic patients with moderate-to-severe aortic regurgitation may be related to optimization of the total arterial elastance through a reduction in peripheral vascular resistance (Scognamiglio et al., 1994; Alehan and Ozkutlu, 1998).

Aortic distensibility is another important determinant of the total arterial elastance. Increasing age and a long-term impact of large stroke volume on proximal aorta are associated with reduced aortic distensibility. Aortic valve insufficiency itself increases systolic arterial pressure and decreases diastolic arterial pressure. Diminution of aortic distensibility amplified these pressure changes and imposed a higher afterload on the left ventricle (O'Rourke, 1990). Further reduction in diastolic pressure may compromise the high requirements for myocardial blood flow of hypertrophied left ventricle, particularly if coronary vessels are affected by atherosclerotic process. Thus, reduced aortic distensibility may contribute to the left ventricular hemodynamic overload in aortic regurgitation and may be partially responsible for the progressive nature of this disease (Wilson et al., 1992).

Maladaptation of the arterial system in the form of decreased arterial distensibility or increased peripheral vascular resistance may contribute to afterload excess and the impairment of left ventricular performance most prominently in heart with impaired contractility. Ventricular contractility depends on the number of viable cardiomyocytes and on their contractility. Ventricular contractility decreases after a loss of cardiomyocytes, e.g. during ischemic heart disease. Second possibility is the decrease in cardiomyocyte contractility. Hypertrophied cardiomyocytes are characterized by progressive contractility diminution (Houser and Lakatta, 1999). The rate of this diminution may by very different but leads to an afterload mismatch compensated only by the incremental ventricular dilation at last. The causal sequence of events in this progressive lost of contractility is not yet elucidated. Quantitative and qualitative changes in cardiomyocytes gene expressions during hypertrophic growth have many adaptive fe-

atures. However, contractile properties of the hypertrophied cardiomyocytes are not stable and progressively deteriorate. Fetal transformation of the hypertrophied myocardium, insufficient expression of the sarcoreticular calcium pump, disassembly of the contractile apparatus, insufficient energy production or the alteration in myocardial proteosynthesis and/or degradation are most often postulated as a causative factors (Houser and Lakatta, 1999). To alleviate the cardiomyopathy of overload, hypertrophy regression or reversed remodeling of the failing ventricle is suggested (Katz, 1990; Katz, 1998). This seems to be reasonable if the hypertrophy regression is associated with an overload reduction. If not, survival prolongation may be limited (Linz et al., 1997; Sutton et al., 1997). Thus, in compensated aortic valve insufficiency, where the surgical correction is not unambiguous indicated or in the double loaded ventricles with aortic regurgitation and ischemic heart disease, principally different pharmacological intervention may be useful, namely the induction of hypertrophy with increased contractility. Growth hormone (Yang et al., 1995; Tajima et al., 1999), insulin-like growth factor-1 (Ambler et al., 1993), thyroid hormone analogues (Penncock et al., 1993; Mahaffey et al., 1995) and carnitine-palmitoyltransferase-1 inhibitors (Litwin et al., 1991; Turcani and Rupp, 1997; Turcani and Rupp, 1999) are currently experimentally tested as drugs with the ability to induce cardiomyocytes hypertrophy with increased contractility. Extra hypertrophy with parallel addition of new sarcomeres, normal or even increased contractility may normalize diastolic and systolic wall stresses, improve pump performance and efficiency and prevent the development of terminal ventricular dilation.*

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PREDSTAVUJEME NOVÉ KNIHY

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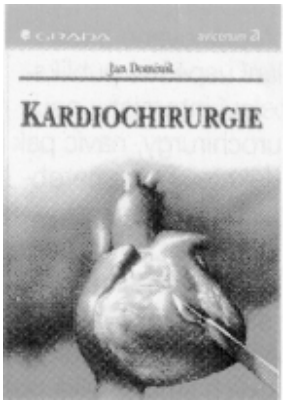

Z recenzného posudku prof. MUDr. J. Černého, DrSc.: „Doc. MUDr. J. Dominik, CSc., pripravil vynikajúci prehľad súčasnej kardiochirurgie. Jeho kniha čerpá najmä z rozsiahlych skúseností autora, ktorý počas svojej chirurgickej praxe zvládol kardiochirurgiu v celom jej rozsahu — od chirurgie vrodených srdcových chýb u malých detí až po získané chlopňové chyby v dospelosti. Kniha je napísaná veľmi zrozumiteľne a je doplnená vynikajúcou obrazovou dokumentáciou a názornými schémami, ktoré dokresľujú opis operačných metód. Dominikova „Kardiochirurgia“ znamená významný prínos do mašej modernej medicínskej literatúry“. Dovolil som si použiť pohľad odborného recenzenta, ktorý stál pri zrode tohto diela a ktorý vystihol najpodstatnejšie črty tejto monografie.

V knihe autor na malom priestore podáva najdôležitejšie informácie z týchto okruhov: operácie na zatvorenom a otvorenom srdci (princíp mimotelového obehu, postperfúzny sy, hypotermia, ochrana myokardu pred ischémiou), operačné prístupy v kardiochirurgii, ICHS, chlopňové chyby, anuloaortálne ektázie, disekcia hrudnej aorty, choroby perikardu, nádory srdca, transplantácia srdca, podporné systémy srdca, vrodené chyby srdca, reoperácie v kardiochirurgii a pooperačná starostlivosť. Záver knihy tvoria najdôležitejšie hemodynamické hodnoty a dáta z dejín kardiochirurgie. Pre lepšiu orientáciu a aj vzhľadom na charakter publikácie chýba vecný index.

Kniha nie je určená len kardiochirurgom a kardiológom, ale aj širokej lekárskej verejnosti. Najnovšie informácie z oblasti možností kardiochirurgie usmerňujú pediatrov, internistov a ďalších odborníkov pri manažmente mnohých závažných kardiovaskulárnych ochorení.

M. Bernadič