Catheter-based management of aortic valve regurgitation in experimental cardiology

Jan Sochman[1),2)], Jan H. Peregrin[2),3)]

[1)] Clinic of Cardiology, Institute for Clinical and Experimental Medicine, Prague,

[2)] Center for Cardiovascular Research, Prague, Czech Republic,

[3)] Department for Radiodiagnostic and Interventional Radiology, Prague, Czech Republic

Correspondence to: Jan Sochman, Clinic of Cardiology, IKEM, Videnska 1958/9, 146 22 Prague 4, Czech Republic.

E-mail: jan.sochman@medicon.cz

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Summary

Non-surgical management of aortic valve disease has been given considerable attention. There have been several initial publications recently reporting its use in clinical practice. The main issue is to get an understanding of the pathophysiological processes and, most importantly, extensive experimental activity. In addition to testing of various animal models, technical and material aspects are also being intensively investigated. It is not clear yet whether the durability and applicability of this promising development will be comparable with the standard of current cardiac surgery. Nonetheless, even the use of some of the models as a temporary approach helping to improve the circulatory status, not allowing safe surgery, is certainly justified. At any rate, a new stage of research and clinical application has set off. Still, experimental background continues to be simply indispensable. The paper is a short review of the issue.

Key words: **Aortic valve regurgitation, experimental research, catheterization**

Elementary physiology and pathophysiology of the aortic valve

The left ventricle generates a pressure under which a certain amount of blood is transported behind the aortic valve. Ideally, none of the expelled volume returns behind the valve. Trace regurgitation, demonstrable solely using auxiliary imaging techniques (e.g., by echocardiography) need not necessarily, in the presence of an otherwise normal finding, a deviation from the physiological range. However, the transport of blood from the ventricle to the circulation does not occur completely unopposed. It is opposed by hydrostatic pressure from area situated at a level higher than the left ventricle and, most importantly, by resistance of the large vessels (whose elastic properties allow the shift of the pulse wave) and resistance of the vascular capacitance bed, which may additionally alter its own vasomotor characteristics thus significantly affecting the resistance. The resistance created in such a way generates a pressure shock, which passively closes the aortic orifice and provides rough information dealing with diastolic pressure. Under physiological conditions at rest, the systolic/diastolic difference is not in excess of 100 mmHg. Aortic valve disease may be due either to orifice narrowing or loss of functional valve closure. In the former case, pressure-type of heart failure with respect to the prolonged period of time sets in with a component of relatively long-lasting compensatory mechanisms. In the latter case, the compensatory process is made shorter by the component of left ventricular hypertrophy, with the volume type of heart failure possibly developing in the future. There are situations whereby both impairments combine. Likewise, there are conditions whereby aortic valve disease develops quickly or, more often, whereby all factors of physiological compensation are suddenly exhausted. It is in these cases that radical management is considered. While the current therapeutic standard is cardiac surgery, catheterization-based approaches have been proposed. However, these approaches continue to be essentially derived from

experimental techniques. This text is a brief overview of the development of experimental methods modulating aortic valve disease, and aortic regurgitation in particular. At the same time, it is critical to balance neatly between views perceiving catheter-based approaches as definitive therapy and approaches, which are only transient. Definitive catheter-based management of aortic insufficiency has not been completely defined. One simply cannot copy the situation seen during pulmonary artery valve disease. Current catheter-based techniques are only applicable in cases whereby surgical management is not safe given the situation. Once hemodynamic status has improved as a result of the catheter-based approach, it is possible to consider a definitive surgical solution proven by current therapy.

Historical overview

Efforts over the past 40 years at creating a catheter-based cardiac valve replacement have evolved from experimental work to initial clinical application. Initially, these efforts were aimed at managing valve diseases in tubular structures such as the pulmonary artery or the aorta. The idea was to provide temporary support to the failing myocardium and reduce the impact of heart failure on organs so eventual improvement could be followed by a definitive surgical treatment. Clearly, there has been a paralled effort to manage the valve problem not temporarily, but permantly using a direct catheter-based approach. In regards to valve regurgitation, the issue is not homogenous. One option of management is focused on techniques modifying the orifice per se and the second one is represented by valve-replacing techniques. Very often, the procedures require the close cooperation of an interventionalist with the surgeon. The text below examines some techniques employed in the presence of valve regurgitation as related to their basic shape structure and experimental data as well as technical valve designs and

overall philosophy governing their use. We are no doubt at the start of new techniques where only the future will show how much these steps have been successful. Use of a catheter-based techniques is logically justified only in cases where it is necessary to bridge the period to safe surgery (provisional catheter-based treatment) or in cases where current techniques have been shown to be effective and durable for a period comparable with that of surgery (i.e., roughly more than five years). Experimental background has been essential.

Aortic valve parameters

Aortic valve fits into the tubular structures problems. The valve apparatus consists of three well defined leaflets with definitive passive motion during systole and diastole. Due to relatively high systolic and diastolic pressure the aortic valve is confronted with a relatively high mechanical stress and, in terms of morphology, consideration is to be made of the relation to origin of the coronary arteries. The movement of the tube during systole and diastole in all directions is very limited. Most of all useful parameters is derived from echocardiography followed by MR imaging or contrast aortography. Here again, the key considerations are the diameters of the aortic valve orifice and of the adjoining segment of the ascending aorta.

Aortic valve regurgitation

Experimental efforts and proposed designs seeking reduction or complete elimination of aortic regurgitation date back more than four decades ago. Initial studies were based on the fact verified surgically that the valve can also be placed in a supra-coronary position (Hufnagel and Harvey 1953, Hufnagel *et al.* 1954, Harken *et al.* 1960). Optional positions of the aortic prosthesis placed using a catheter-based procedure could be

described in relation to virtual line of leaflet coaptation. The choice is as follows: supracoronary and infracoronary, orthotopic or heterotopic.

Experimental models

All initial designs made use of the mechanical components. The pioneering work apparently dates back to 1965 (Davies 1965) providing for a temporary solution to aortic regurgitation. This was followed by a number of proposed techniques, all essentially a modification of the original idea whereby a catheter is temporarily advanced to the aortic region and its modification should reduce or, ideally, completely stop the regurgitating blood flow (Moulopoulos *et al*. 1971, Moulopoulos 1972, Philips *et al*. 1976, Boretos and Poirier 1977, Matsubara *et al*. 1992). The specific idea was to use the intraaortic balloon pump with a timing different from that used conventionally (Moulopoulos *et al*. 1980). A completely revolutionizing approach was published in 1992, fully eliminating the previously advanced cathether as an anchoring mechanism. The new design remotely resembled a stent at one end and the cage of a surgically used ball mechanical prosthesis at the other (Pavcnik *et al*. 1992). The whole prosthesis was implanted in two steps: first, the actual cage carrier and, second, a detachable balloon filled with a fluid with an admixture of a contrast medium (Fig.1).

This was followed by a series of investigations, which already divided the next approaches to a purely mechanical prostheses implanted using a catheter, bioprostheses implanted using the same technique, and hybrid approaches. In our department, we tested the purely mechanical prostheses in a two-stage experiment, with the stent carrier inserted first to be followed by valve disc placement (Sochman *et al*. 2000)(Fig.2).

This was already an imitation of the model of disc prosthesis proven by surgical practice. From a family of catheter-implantable biprostheses as well as from a historical

overview, some approaches affecting clinical practice could be quoted (Andersen *et al*. 1992, Moazami *et al*. 1996, Boudjemline *et al*. 2002, Boudjemline and Bonhoeffer 2002, Lutter *et al*. 2002, Boudjemline and Bonhoeffer 2002, Boudjemline and Bonhoeffer 2003, Huber *et al*. 2004). While the advantage of this model was prosthesis implantation at the time, its drawback was the relatively bigger caliber of the instrumentarium. The above techniques made use of a stent carrier, which had to be dilated during deployment by a balloon catheter. However, there are designs using a self-expandable carrier with an anchored biological valve (Ferrari *et al*. 2004). Besides, hybrids have been developed which, while seeking to resemble, in their design, the shape of the native valve, made use of plastic membranes of most varied properties (Hilbert *et al*. 1987, Lo *et al*. 1988). Currently, a new option is being tested experimently whereby the membrane component of the valve is not made of plastic or conventional biological material (pericardium, homogenized animal valve, etc.). Instead, the material used is small intestinal submucosa (Pavcnik *et al*. 2001). Because of material duration and biodegradability characteristics, research has again focused on an area showing less demands on mechanical stress (Ruiz *et al*. 2005). Presently, the bioprosthetic models clearly predominate. Their advantages includes the orthotopic position (i.e., infracoronary and valvular with respect to the annular position). However, mechanical prostheses, which are used less often, have improved in being capable of being estabishled at the time, as is the case of bioprotheses (Sochman *et al*. 2006). However, their position is supracoronary (i.e., supravalvular in relation to the annulus) (Fig.3).

We are currently testing a completely different – infracoronary and infravalvular - mechanical prosthesis position. First experiments were encouraging (Fig. 4).

Purely catheter-based options in clinic application

There are at present initial papers reporting catheter-based therapy also in man. Quite surprisingly, the problem was not aortic regurgitation but aortic stenosis in the group of so–called "no-option treatment" patients. They were patients not indicated for surgical therapy because it was considered too risky; moreover, they were patients at an advanced age. In addition, aortic balloon valvuloplasty, as previously considered, was no longer concerned. In this particular case, a stent carrier with a biological valve was introduced into the aortic orifice, with the stent carrier pushed into the aortic wall using the balloon in orthotopic position. Initial results are said to be most encouraging (Cribier *et al*. 2002, Cribier *et al*. 2004, Bauer *et al*. 2004, Hanzel *et al*. 2005, Grube *et al*. 2005). Still, nothing is known about the durability of the above measure.

Potential role for catheter-based managements

There is no doubt that the key method for managing any valve disease is surgery. This is supported by time-proven clinical practice, declared outcomes and undisputed durability. Still, the era of catheter-based therapy has begun: in some centers, it is most successful option, in other centers, it has not moved past the experimental stage In still other centers, it is the object of skepticism, critique or concern. However, if it does handle a temporary problem making safe surgery unfeasible, it should be accepted. This applies in particular to acute and life-threatening states. Logically, one should conclude that a biological prosthesis is not the only solution. In non-acute cases, other logical requirements are to be met in addition to the clear-cut requirement ruling out "major surgery". These requirments include reliability and feasibility in an acceptable form and, most importantly, outcome durability. However, only the future will tell. At any rate, there will be no progress without experimental work.

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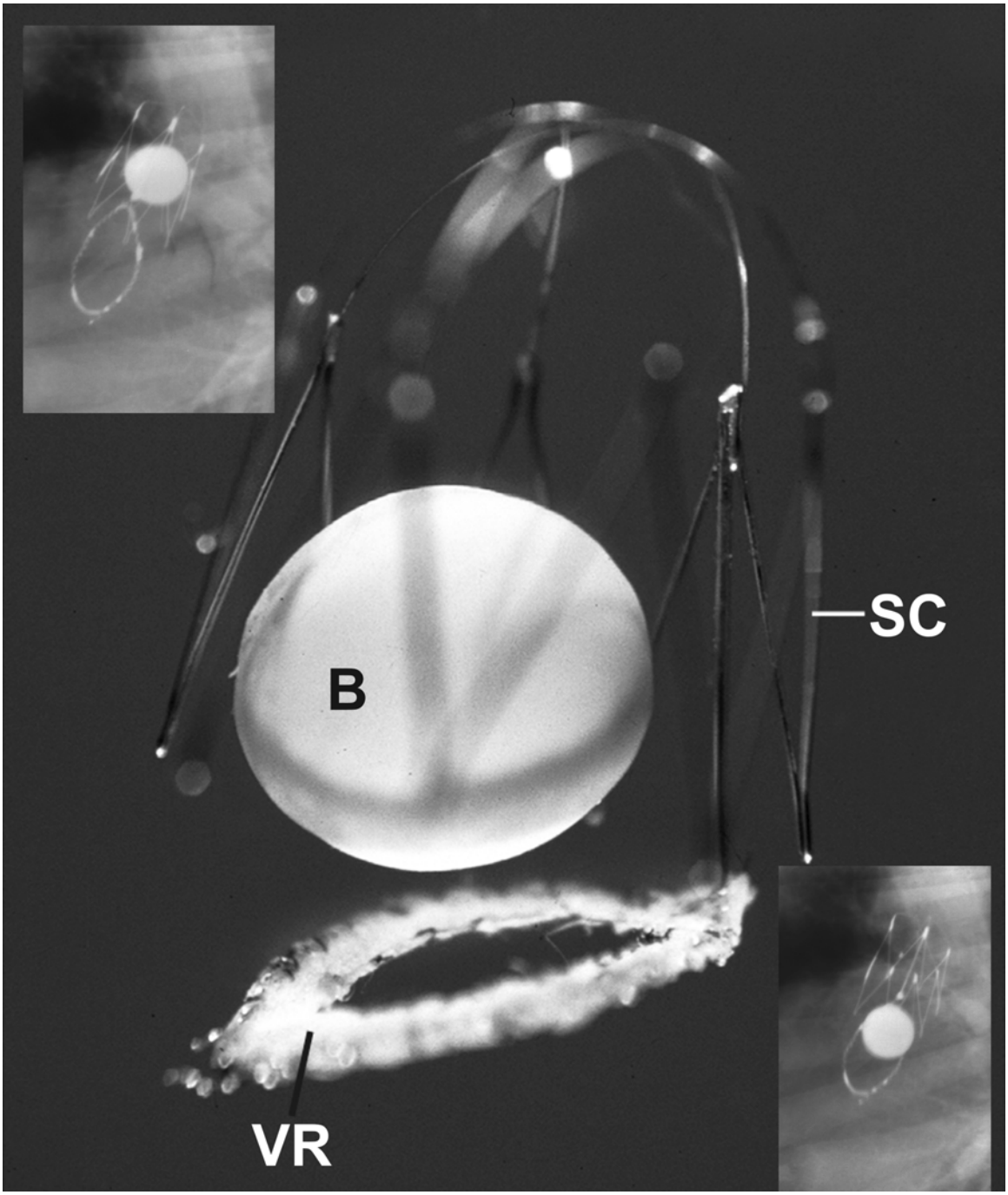
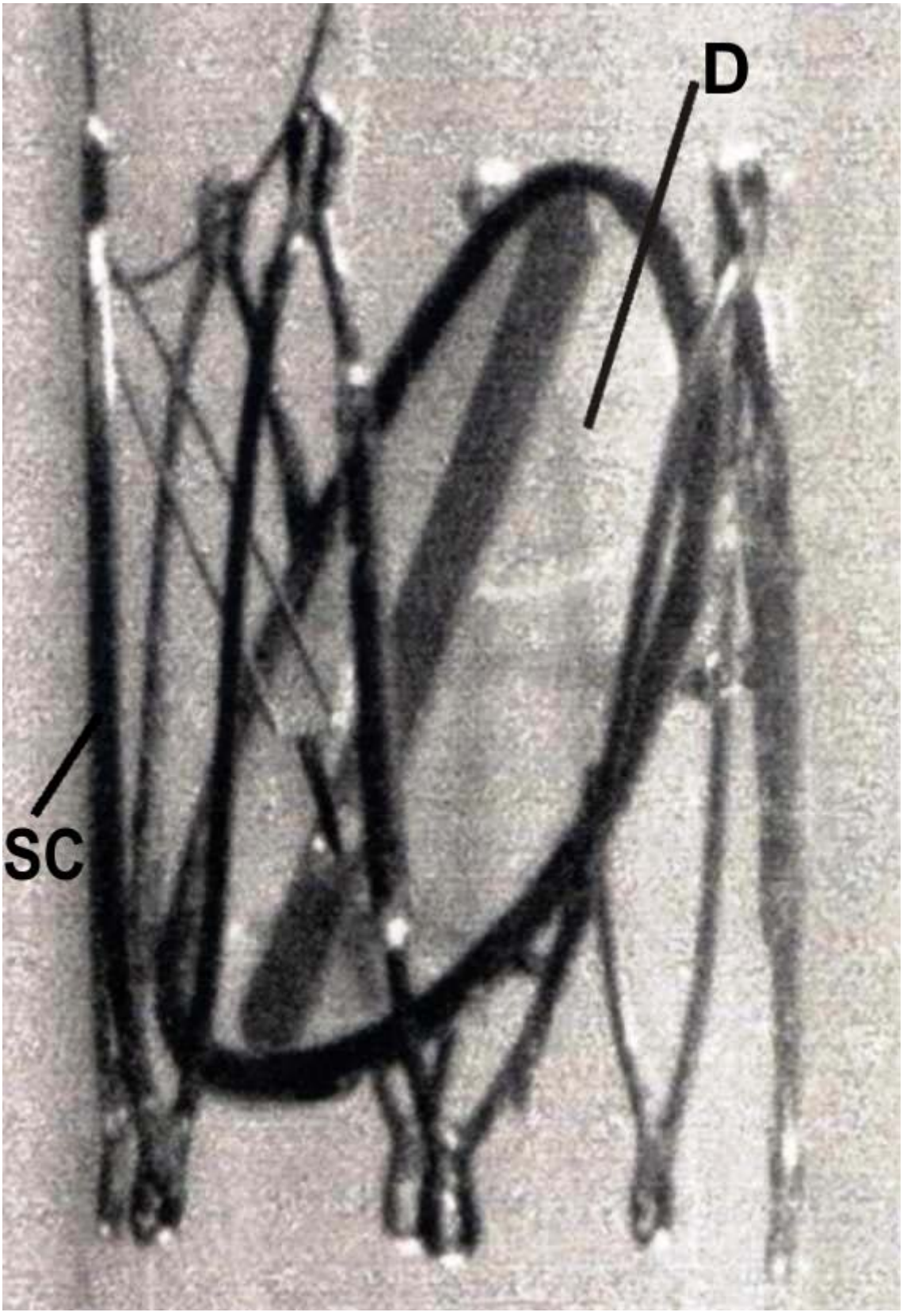
Figure legends

Fig. 1 Ball and cage design for catheter-based aortic valve prosthesis deployment



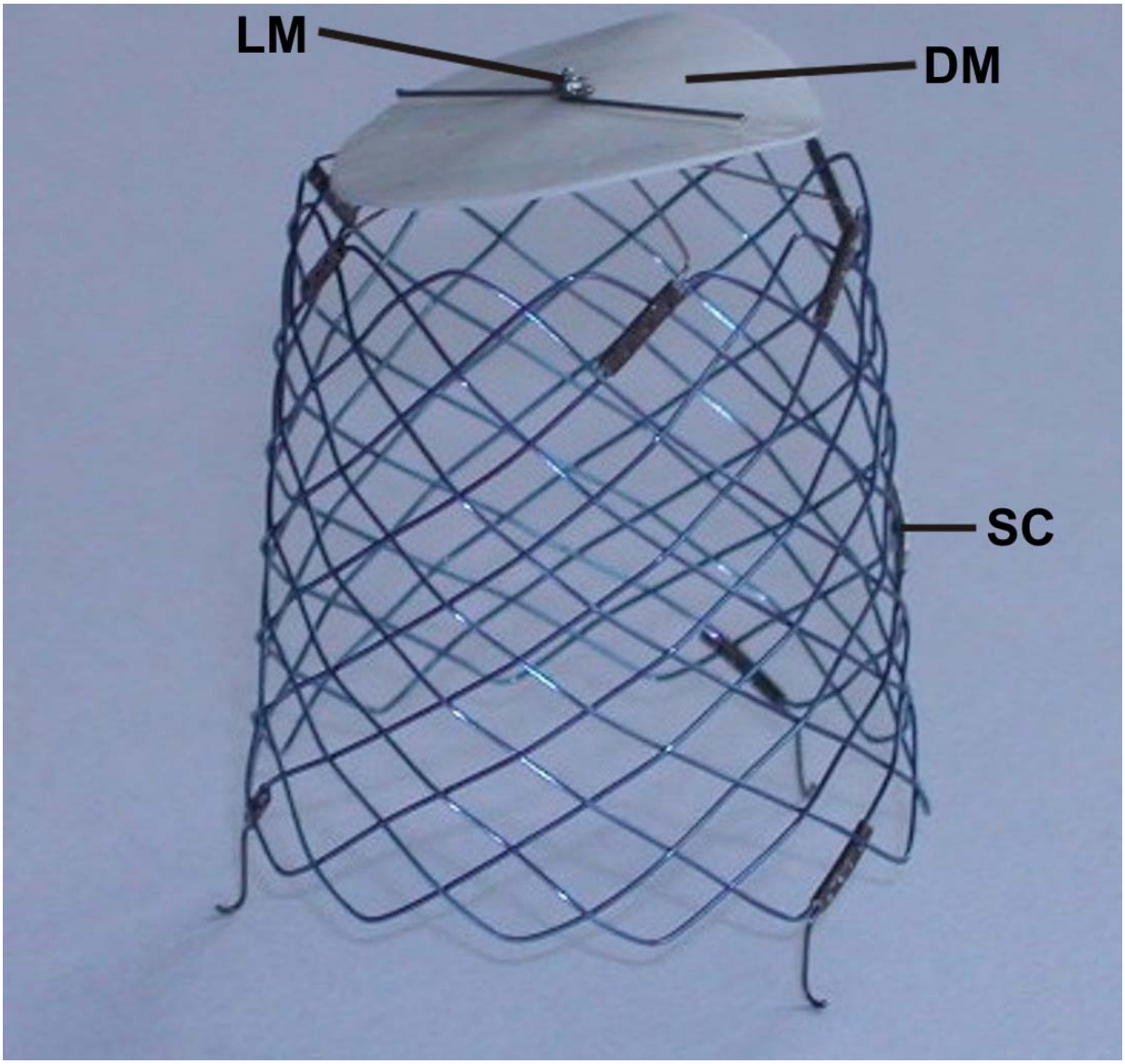
Abbreviations: SC – Gianturco-Rösch Z stent carrier, B – ball, VR – valve ring for the new orifice. In the left upper corner: scene from cinefluorography in systole, in the right lower corner: in diastole. Pictures were supplied with a courtesy by D. Pavcnik

Fig.2 Mechanical disc valve design for two-step deployment



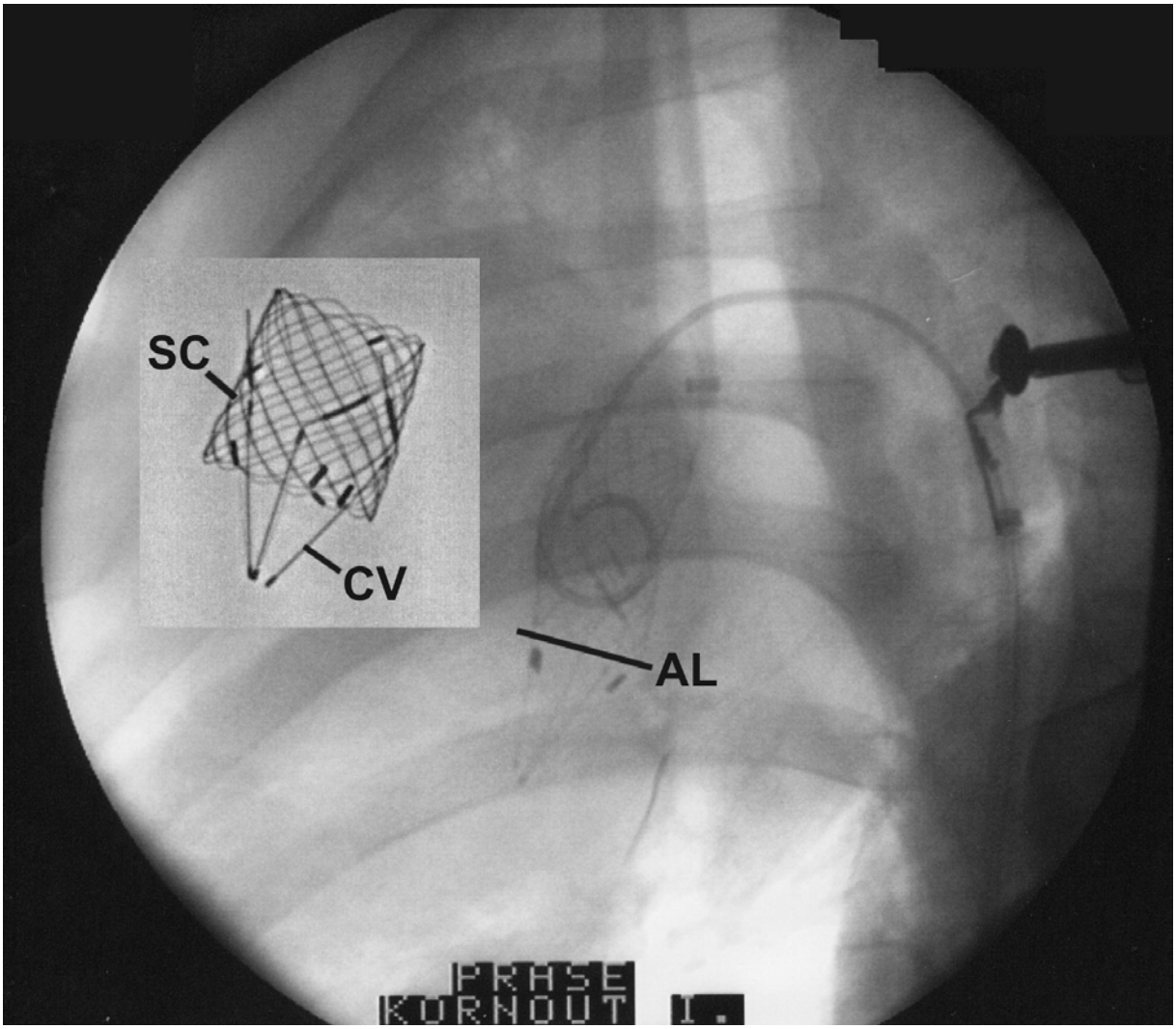
Abbreviations: SC – stent carrier (deployed in the first step), D – disc (deployed and locked in the second step)

Fig.3 Mechanical disc valve design for one-step deployment



Abbreviations: SC – SX braided stent carrier, DM – flexible disc membrane, LM – locking mechanism

Fig.4 Mechanical cone valve design for infracoronary positioning



Abbreviations: in the plain X-ray picture: SC – stent carrier, CV – cone valve struts. In the pig model: AL – annular level (left ventricular outflow tract is below the line !)