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Percutaneous approach to a stent-based ventricle to coronary vein bypass (venous VPASSTM): comparison to catheter-based selective pressure-regulated retro-infusion of the coronary vein

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Aims Percutaneous stent-based ventricle-to-coronary vein bypass (venous VPASSTM) is a new approach to chronic venous arterialization as a treatment modality in an otherwise no option patient with coronary artery disease. In this study, the efficacy of venous VPASSTM was compared with catheter-based selective pressure-regulated retro-infusion of arterial blood during acute ischaemia.

Methods and results In seven pigs, venous VPASSTM was established using a percutaneous ultrasound-guided puncture from the anterior cardiac vein to the left ventricle, with subsequent implantation of an ePTFE-covered stent graft. During left anterior descending artery (LAD) occlusion, coronary venous pressure in the distal anterior cardiac vein increased to 55 ± 4 mmHg under conditions of venous VPASSTM compared with 78 ± 5 mmHg during selective pressure-regulated retro-infusion. Significant preservation of regional myocardial function was observed during venous VPASSTM ($67 \pm 6\%$ baseline) and during selective retro-infusion ($83 \pm 4\%$) compared with control LAD occlusion ($0.4 \pm 2\%$).

Conclusion Percutaneous implantation of a PTFE covered stent (venous VPASSTM) was feasible and associated with significant preservation of regional myocardial function during acute ischaemia in pigs at reasonable levels of mean coronary venous pressure to avoid tissue damage during chronic application.

Introduction

Selective retrograde perfusion of the coronary veins has gained renewed interest as an option for patients who are otherwise not candidates for conventional revascularization procedures.¹ Arterialization of a coronary vein for retrograde perfusion of ischaemic myocardium has been performed previously by cardiac surgeons,²⁻⁴

but never reached widespread clinical application due to limited efficacy and severe complications such as haemorrhagic infarction in some of the patients.³ More recently, percutaneous *in situ* arterialization of a cardiac vein (PICVA) has been developed to provide arterial blood flow from the native coronary artery to the coronary vein, of which the outflow towards the coronary sinus is blocked at the same time. Although initial clinical experience appeared to be promising,¹ major drawbacks of PICVA are the complexity of the procedure as well as safety concerns with regard to the chronic

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increase in coronary venous pressure, which may promote the occurrence of complications.⁵

Ventricle to coronary artery or vein bypass are new revascularization procedures providing predominantly systolic blood flow directly from the left ventricle to a coronary artery^{6,7} or a coronary vein. Surgical implantation of an ePTFE-covered stent (VSTENTTM) connecting the coronary artery to the left ventricle has been shown to be feasible and efficient in pre-clinical studies⁶ and is currently under investigation in a European multi-centre clinical study.⁷

In this study, we developed a percutaneous stent-based approach for ventricle to coronary vein bypass (venous VPASSTM) with the aim to provide efficient systolic arterialization of the vein in conjunction with diastolic drainage into the left ventricle through the valveless VSTENTTM.

The efficacy of venous VPASSTM was compared directly with selective pressure-regulated retro-infusion which has been previously shown to be the most efficient catheter-based device for short-term retrograde delivery of arterial blood to ischaemic myocardium.^{8,9} Any kind of short-term or long-term retroperfusion has to consider the heterogeneity of the venous anatomy, in particular, with regard to venous-venous shunts and Thebesian's veins¹⁰ influencing individual coronary venous pressure dynamics during retroperfusion. Coronary venous occlusion pressure (CVOP) reflects these differences in capacity and anatomy of the cardiac veins¹¹ and is very easy to determine before treatment. Therefore, individual CVOP measurements were analysed with regard to the efficacy of subsequent retrograde perfusion using either selective pressure-regulated retro-infusion of arterial blood or venous VPASSTM in a pig model of acute myocardial ischaemia.

Methods

The present investigation was carried out according to the 'Guide for the Care and Use of Laboratory Animals' published by the US National Institutes of Health and was approved by the Bavarian Animal Care and Use Committee.

Seven German farm pigs (39 ± 6 kg) were anaesthetized and monitored as described previously.⁶ A catheter introducer sheath was placed into the right and left carotid artery (9F) and right jugular vein (11F). Heparin 20 000 IE i.v. was injected prior to catheterization followed by continuous 5000 IU/h i.v. infusion. A 6F Millar microtip catheter (SPG-572, Millar, Houston, TX, USA) was placed into the left ventricle to measure left ventricular pressure and its first derivative (dp/dt).

In an intra-individual randomized protocol selective pressure-regulated retro-infusion was compared with the effects of percutaneous venous VPASSTM (Figure 1).

Selective pressure-regulated retro-infusion

An 8F retro-infusion catheter was placed into the anterior cardiac vein and the systolic coronary venous occlusion pressure (SCVOP) was determined by a 30 s balloon occlusion of the vein.^{9,12} Coronary venous pressure was determined by a pressure wire (RADI, Germany) placed distal to the tip of the retro-infusion catheter. Selective pressure-regulated retro-infusion of arterial blood was performed as described previously in detail.^{8,9} During

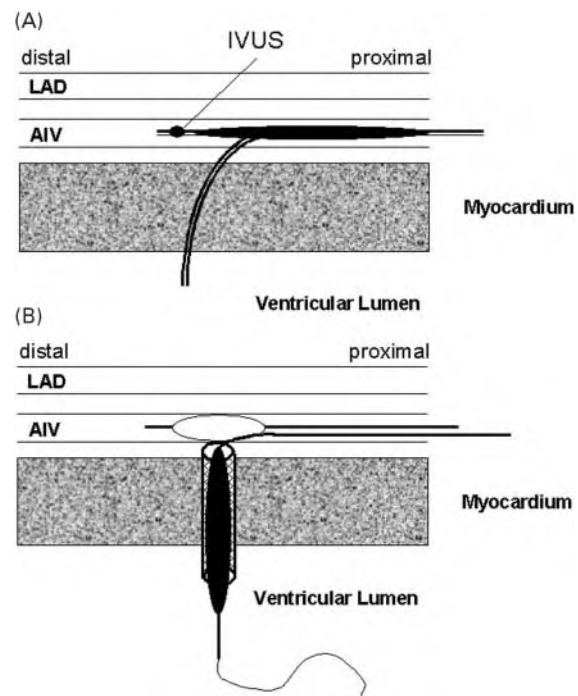


Figure 1 Diagram of the implantation procedure: (A) intravalvular ultrasound (IVUS)-guided puncture from the coronary vein to the left ventricle with the transaccess-catheter; (B) implantation of the venous VSTENTTM with the double balloon technique, ensuring proper deployment of the venous VSTENTTM at the floor of the coronary artery.

ischaemia and treatment by selective retro-infusion, the preset coronary venous pressure was chosen 20 mmHg higher than the individual SCVOP determined before ischaemia.¹²

Percutaneous ventricle-to-coronary vein bypass (venous VPASSTM)

In all pigs, venous VPASSTM was established by using a percutaneous approach before opening of the chest. After wiring the anterior cardiac vein, the ultrasound-guided puncture from the anterior cardiac vein into the left ventricle (Figure 1) was done using a TransAccess catheter with a 24-gauge nitinol needle (TransVascular Inc., Menlo Park, CA, USA) under fluoroscopic control. A second wire (0.014 roadrunner, William Cook Europe, Bjaeverskov, Denmark) was placed through the needle access into the left ventricle and was advanced retrogradely through the left atrium into a pulmonary vein (Figure 1A). The puncture catheter was removed and the channel from the anterior cardiac vein to the left ventricle was pre-dilated using a PTCA balloon (3.0 mm in diameter). Thereafter, a pre-mounted ePTFE membrane covered stent (Percardia Inc., Merrimack, NH, USA) was advanced so that the distal end reached the left ventricle, whereas the proximal end was placed at the site of the anterior cardiac vein. Using a double balloon technique (with two separate balloon catheters, one loaded with the VSTENT) with inflation of a short balloon (11 mm length, 3.5 mm in diameter) in the anterior cardiac vein first, followed by the inflation of the VSTENT balloon, correct placement and deployment of the VSTENT at the floor of the cardiac vein was assured (Figure 1B). After removal of the two balloon catheters, successful implantation of the VSTENT and non-compromised flow through the VSTENT into the distal anterior cardiac vein were confirmed by angiography

(Figure 2). The two wires were left in the distal anterior cardiac vein and the pulmonary vein to facilitate catheter placement throughout the subsequent study protocol (Figure 3). The tip of the retro-infusion catheter was placed 2 cm proximal to the VSTENT.

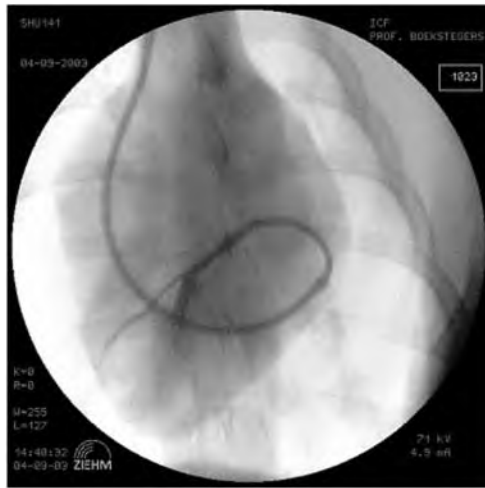


Figure 2 Angiogram of the anterior inferior cardiac vein after percutaneous ultrasound-guided venous VPASS™. Contrast agent is filling the distal AIV as well as the VSTENT™ which drains into the left ventricular cavity during diastole.

Measurements

Baseline measurements under the conditions of patent left anterior descending artery (LAD) and patent anterior interventricular coronary vein (AIV) were taken 15 min after placement of the ultrasonic crystals. After percutaneous implantation of the venous VSTENT (Figure 1), access to the heart was through sternotomy in all pigs, after the percutaneous procedures were completed. Ultrasonic crystals were placed in the LAD and LCx region to determine subendocardial segment shortening as described earlier.^{6,13}

Subsequently, the randomized study protocol was started. All measurements were taken at the end of brief complete LAD occlusions (90 s) (Figure 3). The study design was an intra-individual comparison of the performance of the venous VSTENT and the retro-infusion. In a randomized sequence, the following three conditions were analysed in each pig: (i) acute ischaemia (LAD occlusion), (ii) the venous VSTENT, and (iii) the retro-infusion (Figures 3 and 4). For control LAD occlusion, the LAD was blocked by a PTCA balloon (3.0 mm diameter) and the VSTENT was blocked as well. For assessment of the performance of the venous VSTENT, the LAD was occluded and the AIV was blocked proximal to the venous VSTENT by the retro-infusion catheter, to block outflow of the anterior cardiac vein (Figure 4A). During selective pressure-regulated retro-infusion, the LAD was occluded, the AIV was blocked by the retro-infusion catheter and the venous VSTENT was occluded by a PTCA balloon (Figure 4B). After the completion of the randomized protocol, VSTENT performance was determined during a 2 h complete LAD occlusion in four pigs (Figure 3).

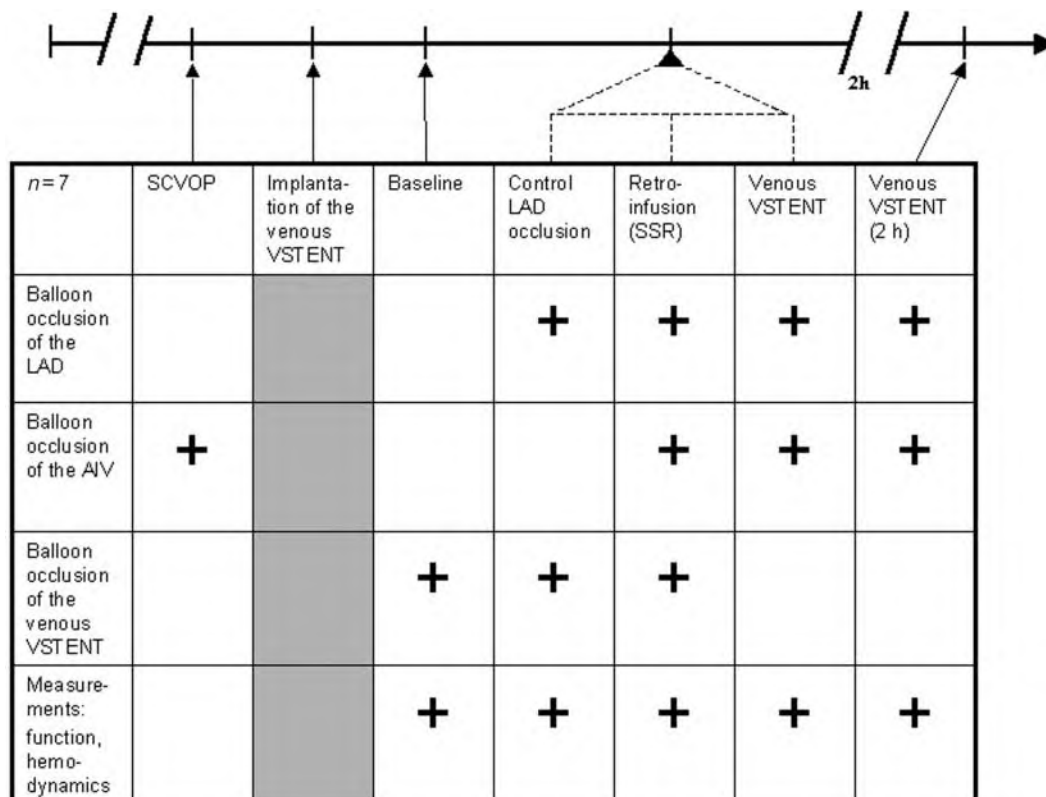


Figure 3 Diagram of the experimental protocols: SSR, selective suction and pressure-regulated retro-infusion; '+' indicates the presence of the condition (mentioned in the left column) at each timepoint (mentioned in the first line); dashed arrows indicate that these conditions were studied in a randomized sequence.

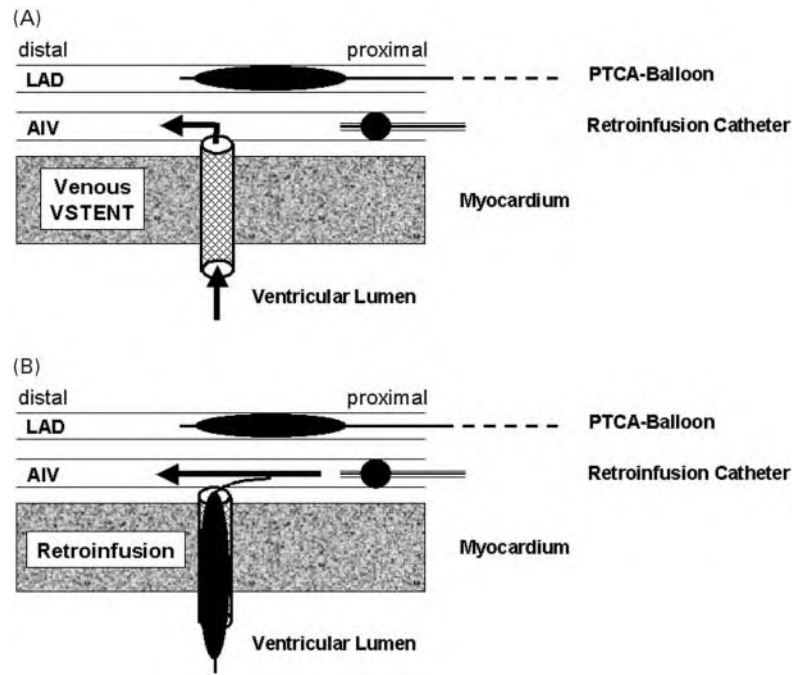


Figure 4 (A) Diagram of the venous VSTENT™ and (B) the retro-infusion.

Statistics

All data were analysed using SPSS™ (USA). The results are given as mean \pm SEM. Statistical analysis was performed using repeated measurements analysis of variance (ANOVA). Whenever a significant effect was obtained with ANOVA, we performed comparison tests between the conditions using a paired Wilcoxon-test. The relationship between SCVOP and subendocardial segment shortening was analysed by linear regression using the Pearson's correlation coefficient (r). A P -value less than 0.05 was considered statistically significant.

Results

In all pigs, baseline values of systolic arterial blood pressure, heart rate, and regional myocardial function were similar before each period of brief ischaemia (Table 1). All control occlusions of the left anterior descending coronary artery for 90 s resulted in a decrease in mean systolic segment shortening to $<5\%$ of baseline values. SCVOP of the anterior cardiac vein, determined before ischaemia, ranged between 49 and 105 mmHg (mean 71 ± 4.1 mmHg).

Percutaneous ventricle-to-coronary vein bypass (venous VPASS™)

Percutaneous ventricle-to-coronary vein bypass (venous VPASS™) was successfully established in all pigs. A single up to four ultrasound-guided punctures (mean 1.6 ± 0.4) were needed to reach and wire the left ventricle. Subsequent VSTENT™ implantation was successful after pre-dilatation of the intra-myocardial channel in all pigs. No pericardial effusion or tamponade occurred

during the procedures. However, we observed some limited myocardial haemorrhage at the puncture and VSTENT™ implantation site close to the anterior cardiac vein in five of seven pigs after excision of the heart at the end of the experiment. Angiographically, blood flow into the distal anterior cardiac vein was not compromised immediately ($n = 7$) or 2 h ($n = 4$) after VSTENT™ implantation (Figure 2).

Comparison of venous VPASS™ and selective retro-infusion during ischaemia

During a brief occlusion (90 s) of the left anterior descending coronary artery, without treatment the mean regional myocardial function in the ischaemic zone decreased to $0.4 \pm 2\%$ of baseline subendocardial segment shortening (Figure 5). In contrast, a significant preservation of regional myocardial function was observed during pressure-regulated retro-infusion ($83.1 \pm 3.0\%$, $P = 0.0005$) and venous VPASS™ ($67.5 \pm 6.2\%$, $P = 0.0006$) (Figure 5) during complete LAD occlusion compared with complete LAD occlusion (Figure 5). Under conditions of venous VPASS™, this preservation of regional myocardial function was sustained over a 2 h period.

As expected, pressure-regulated retro-infusion resulted in an increase of mean (63.4 ± 5.0 mmHg, $P = 0.002$) and systolic (78.4 ± 9.5 mmHg, $P = 0.004$) coronary venous pressure during treatment compared with complete LAD occlusion. Under conditions of venous VPASS™, mean (38.9 ± 3.7 mmHg) and systolic (55.0 ± 4.2 mmHg) coronary venous pressures were increased compared with baseline (mean $P = 0.016$, systolic $P = 0.009$) but were significantly lower than during

Table 1 Haemodynamics and regional myocardial function

	Control occlusion		Retro-infusion (90 s)		Venous VPASS (90 s)		Control occlusion		Venous VPASS (2 h, n = 4)	
	Before	During	Before	During	Before	During	Before	During	Before	During
MAP (mmHg)	80 ± 3.7	68 ± 2.7	81 ± 5.9	74 ± 4.7	83 ± 3.7	79 ± 4.4	79 ± 4.3	70 ± 3.3	80 ± 2.9	74 ± 3.2
Heart rate (beats/min)	84 ± 3.6	86 ± 2.2	82 ± 3.5	79 ± 4.2	80 ± 2.9	83 ± 4.0	85 ± 3.7	84 ± 3.6	86 ± 3.1	85 ± 2.8
LVEDP (mmHg)	9.7 ± 1.8	14.7 ± 2.9	10.5 ± 1.4	12.5 ± 1.7	9.5 ± 2.1	11.5 ± 1.9	10.7 ± 1.8	14.9 ± 2.1	9.9 ± 2.1	11.8 ± 2.0
SS (%)	23.3 ± 1.3	0.9 ± 0.9	22.9 ± 1.3	19.1 ± 2.1	23.0 ± 1.5	15.5 ± 1.4	23.9 ± 1.4	1.2 ± 1.0	22.7 ± 1.5	13.8 ± 1.7

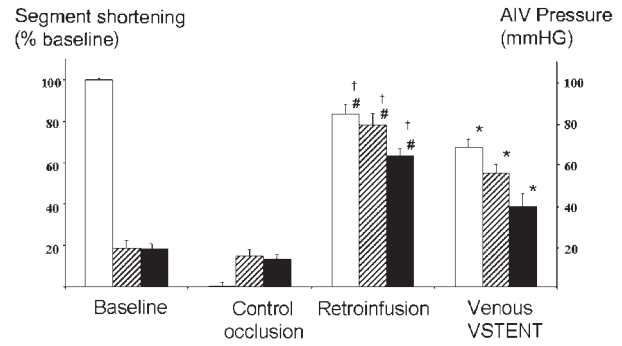


Figure 5 Comparison of selective pressure-regulated retro-infusion to the effects of percutaneous stent-based ventricle-to-coronary vein bypass (venous VPASS™) in seven pigs. Regional myocardial function (sub-endocardial segment shortening, per cent baseline) (white columns) and systolic (hatched columns) and mean (black columns) coronary venous pressure (mmHg) during acute ischaemia. **P* < 0.05 condition venous VPASS™ vs. control occlusion; #*P* < 0.05 condition retro-infusion vs. control occlusion; †*P* < 0.05 condition retro-infusion vs. venous VPASS™.

retro-infusion (mean *P* = 0.023, systolic *P* = 0.032) (Figure 5). Systolic blood flow provided by the venous VPASS™ resulted in a sharp increase of coronary venous pressure at the onset of systole followed by a decrease of coronary venous pressure below 0 mmHg during diastole (Figure 6; see Supplementary material online). The ventricle-to-coronary vein pressure gradient was similar in all pigs at the beginning of systole (range 90–96 mmHg). However, the resulting coronary venous peak pressure during systole ranged between 48 and 93 mmHg and was related closely to the individual SCVOP determined before ischaemia (*r* = 0.91). There was a linear relationship between individual SCVOP and preservation of regional myocardial function during ischaemia supported by pressure-regulated retro-infusion (Figure 7; see Supplementary material online). The same linear relationship was observed for venous VPASS™. However, venous VPASS™ resulted in a moderately, but significantly, lower preservation of regional myocardial function than selective pressure-regulated retro-infusion (*P* = 0.047) (Figures 5 and 7).

Discussion

In this study, in a pig model of acute ischaemia, we demonstrated for the first time that percutaneous stent-based ventricle to coronary vein bypass (venous VPASS™) was technically feasible and able to significantly preserve regional myocardial function in case of a complete coronary artery occlusion. Direct comparison of venous VPASS™ to catheter-based selective pressure-regulated retro-infusion revealed a similar linear relationship between the individual coronary venous systolic occlusion pressure and the efficacy of venous VPASS™ to preserve regional myocardial function (Figure 7). This important finding implies the ability to predict the efficacy of venous VPASS™ for an individual coronary venous system and suggests a self-adjusting mechanism which determines and limits coronary venous peak pressure under the conditions of venous VPASS™.

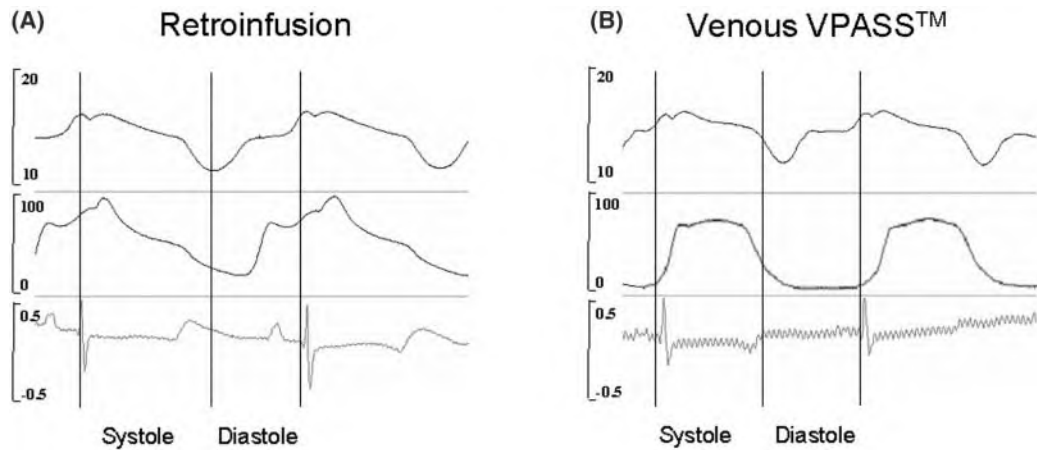


Figure 6 Original recordings of subendocardial segment shortening (top line) (distance in mm of ultrasonic crystals), AIV pressure (middle line) (mmHg), and ECG (bottom line) (mV): (A) during retro-infusion and (B) during venous VPASS™.

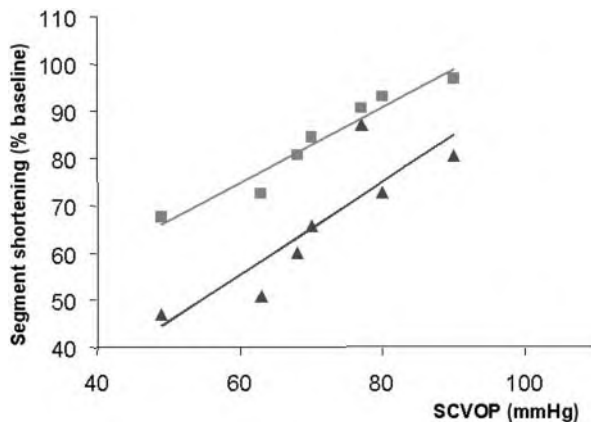


Figure 7 Relationship between SCVOP (mmHg) and preservation of regional myocardial function (SS, subendocardial segment shortening). Triangles, under conditions of venous VPASS™. Squares, under conditions of selective pressure-regulated retro-infusion. Each dot represents one animal.

Comparison of venous VPASS™ with selective pressure-regulated retro-infusion

According to the concept derived from previous studies,^{9,12,13} selective pressure-regulated retro-infusion was performed at a preset coronary venous pressure ~20 mmHg higher than the individual SCVOP, thereby adapting retrograde blood flow to the individual venous system. Under these conditions there was a linear relationship between SCVOP and maximal efficacy of selective retro-infusion during ischaemia (Figure 7), suggesting a more efficient nutritive perfusion at the capillary level in pigs with higher SCVOP.

The lower the peak plateau of systolic venous occlusion pressure, the more blood is probably shunted away from nutritive capillaries or the venovenous networks within the microcirculation¹⁴ through venovenous and veno-arterial collaterals or 'thebesian channels'.^{10,11}

Interestingly, the same linear relationship was observed under conditions of venous VPASS™ though

regional myocardial function was preserved at a level ~20% lower than during selective retro-infusion (Figure 7).

Under conditions of venous VPASS™, the driving force for systolic retrograde flow into the coronary vein is the pressure gradient between the left ventricle and the coronary vein. Although this pressure gradient was similar in all pigs at the beginning of systole, the resulting coronary venous peak pressure during systole ranged between 48 and 93 mmHg and was related closely to the individual SCVOP determined before ischaemia ($r = 0.91$). From these observations we infer that the individual coronary venous system was able to handle non-regulated systolic retrograde flow under venous VPASS™ conditions in a self-adjusting manner which determined and limited peak coronary venous pressures to levels similar to the individual SCVOP.

The small but significant difference in preservation of regional myocardial function between venous VPASS™ and selective retro-infusion (Figures 5 and 7) can be explained by the significantly lower level of systolic and mean coronary venous peak pressure under the conditions of venous VPASS™ retrograde perfusion (Figure 5). Furthermore, retrograde venous VPASS™ perfusion leads to a predominantly systolic increase of coronary venous pressure in contrast to selective retro-infusion, with an increase of coronary venous pressure starting during diastole and extending into systole (Figure 6). Thus, the lack of a valve within the VSTENT™ resulted in diastolic backflow thereby rapidly decreasing coronary venous pressure. As a consequence, distal retrograde filling of the coronary venules and capillaries might have been less complete and limited to a shorter time period during the cardiac cycle suggesting a less effective nutritive perfusion, which would also explain the somewhat lower preservation of regional myocardial function under conditions of venous VPASS™. Notably, the preservation of regional myocardial function under conditions of venous VPASS™ was sustained during a 2 h complete occlusion of left anterior descending artery. Though this study was not designed to determine

the chronic effects of retrograde venous VPASS™ perfusion, it supports the assumption that systolic retrograde flow with diastolic drainage might provide sustained preservation of regional nutritive perfusion at reasonable levels of coronary venous pressure to avoid tissue damage.

Limitations

Limitations of the application of a percutaneous ventricle to coronary vein bypass for chronic arterialization of the coronary vein in patients can be assumed, because of the necessity of selective catheterization of the veins draining the ischaemic territory. Implantation of a venous VSTENT™ should be possible in most patients with stenosis or occlusion of the left anterior descending coronary artery. In case of implantation of the VSTENT™ into the vein draining the circumflex territory, arterial retroperfusion might be less effective if more than one draining coronary vein is present. This is the case in ~25% of humans.^{8,9}

Pressure overload and subsequent myocardial haemorrhage might be a major limitation of chronic coronary artery-to-venous bypass procedure (e.g. PICVA) in patients; the outflow to the coronary sinus is blocked completely after the PICVA procedure.¹ From our data in these acute experiments we assume that chronic pressure overload will be released in case of the ventricle to coronary vein bypass (venous VSTENT™), as diastolic backflow into the left ventricle allows pressure relief of the coronary venous system. The limited myocardial haemorrhage at the puncture site of VSTENT™ implantation site was not related to pressure overload but to the implantation procedure. However, chronic experiments are mandatory to definitively exclude pressure overload and haemorrhagic infarction, also in the case of chronic ventricle-to-coronary vein bypass (venous VSTENT™).

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