Percutaneous Femoral Arteriovenous Shunt Creation for Advanced Chronic Obstructive Pulmonary Disease
A Single-Center Safety and Efficacy Study

Stefan C. Bertog, MD; Christina Kolmer, MD; Swetlana Kleschnew, MD; Jennifer Franke, MD; Nina Wunderlich, MD; Peter Kardos, MD; Horst Sievert, MD

Background—Advanced chronic obstructive pulmonary disease causes a significant reduction in functional capacity because of dyspnea and fatigue, partially related to hypoxemia and compromised oxygen delivery. Percutaneous creation of an arteriovenous shunt may increase oxygen delivery and, hence, improve patients’ functional capacity.

Methods and Results—This is a prospective, single-center, proof-of-concept pilot study. Patients with advanced chronic obstructive pulmonary disease underwent percutaneous arteriovenous shunt creation. End points were the change in 6-minute walking distance; quality of life, measured by St George’s Respiratory Questionnaire; and physiological parameters at 12-week follow-up. Fifteen patients underwent percutaneous arteriovenous shunt creation. Cardiac output and oxygen delivery increased significantly from 4.1 L/min at baseline to 5.9 L/min at 12 weeks (P < 0.01) and from 751 mL/min at baseline to 972 mL/min at 12 weeks (P < 0.01), respectively; however, there was a trend toward a significant decrease in the 6-minute walking distance between baseline (338 m) and 12-week follow-up (294 m) (P = 0.07). There was no significant difference in the St George’s Respiratory Questionnaire score, oxygen saturation, or lung function tests. Lower extremity edema, venous stenosis, right heart failure, and deep venous thrombosis occurred in 10, 7, 4, and 4 patients, respectively.

Conclusions—Though it causes a significant increase in cardiac output and oxygen delivery, the creation of an arteriovenous shunt in the setting of severe chronic obstructive pulmonary disease did not improve functional capacity or quality of life. A significant number of adverse events occurred. This concept cannot be recommended for routine clinical use in unselected patients with advanced chronic obstructive pulmonary disease. (Circ Cardiovasc Interv. 2012;5:118-126.)

Key Words: COPD arteriovenous fistula

Chronic obstructive pulmonary disease (COPD) is a common clinical problem. Some individuals have advanced disease, causing lifestyle limitations despite optimal medical management and are not candidates for lung transplantation or lung volume reduction. Therefore, alternative treatment options are needed.

In COPD, the functional limitation is thought to be related at least partially to limited oxygen delivery (DO₂) caused by poor blood oxygenation. Not infrequently, improvements in oxygenation by conventional therapy are not attainable, and supplemental oxygen has a limited effect on blood oxygenation. This is the consequence of severe ventilation-perfusion mismatch and exhaustion of the respiratory muscle pump. An increase in mixed venous oxygen saturation (MVO₂) may improve the systemic arterial oxygen content. Moreover, an increase in cardiac output (CO) may further improve DO₂. The creation of an extracardiac arteriovenous shunt (AVS) has been demonstrated to increase MVO₂, CO, and total DO₂. It is therefore conceivable that creation of an AVS may improve functional capacity in patients with COPD. Indeed, an improvement in 6-minute walking distance (6MWd) and increase in CO in patients with endstage COPD who underwent predominantly surgical creation of an arteriovenous fistula has been reported.

Percutaneous, rather than surgical, establishment of an AVS avoids a substantial surgical risk in patients with endstage lung disease. The purpose of our study was the evaluation of safety and efficacy of percutaneous AVS creation in humans with advanced COPD.

Methods

This is a prospective open-label, uncontrolled, single-center safety and efficacy study. The protocol and consent forms were approved by the institutional review board and independent ethics committee (Freiburger Ethik Kommission International, code 07/1378), and written consent was obtained by all patients prior to study participation.

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From the Cardiovascular Center Frankfurt, Frankfurt, Germany (S.B., C.K., S.K., J.F., N.W., H.S.); Klinik Maingau, Frankfurt, Germany (P.K.).
Correspondence to Dr Horst Sievert, CardioVascular Center Frankfurt, Seckbacher Landstrasse 65, 60389 Frankfurt, Germany. E-mail info@CVCFrankfurt.de
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WHAT IS KNOWN

- Creation of an arteriovenous fistula increases oxygen delivery in animal models and patients with advanced chronic obstructive pulmonary disease (COPD).
- Limited data suggest a clinical benefit of predominantly surgical creation of an arteriovenous fistula in patients with advanced COPD.

WHAT THE STUDY ADDS

- We demonstrate that percutaneous creation of an arteriovenous fistula in patients with advanced COPD causes an increase in cardiac output and oxygen delivery; however, this is not accompanied by clinical benefits but rather by a number of adverse events.
- Our findings raise concerns regarding the physiological basis and safety of the concept of arteriovenous fistula creation for the treatment of COPD.

Patients
Inclusion and exclusion criteria are outlined in Tables 1 and 2, respectively.

Device and Procedure
The device is a single self-expanding nitinol clip (Rox Medical). Femoral arterial and venous access is obtained using standard interventional techniques. The ROX crossing needle is then placed over a guide wire into the vein and tracked up to the femoral/iliac region, where the artery and vein are adjacent to one another. With fluoroscopic assistance, the crossing needle is pushed through the venous wall into the adjacent artery. The guide wire is then advanced through the needle into the vein. The needle is removed and the delivery system placed over the guide wire. Using the thumb tab on the delivery system, the ROX nitinol clip is tracked up the vein and deployed in the puncture site, connecting the femoral or iliac artery and vein, thereby creating an AVS. The expanded arms of the clip attach to the inner walls of each vessel, and smaller retention arms maintain the clip in the proper position. The delivery system is then removed, and a 5-mm balloon catheter is inserted into the center of the clip lumen. The balloon is inflated to expand the clip to a 5-mm fistula. Subsequently, the balloon is deflated and removed with the delivery system. Manual compression is applied to achieve hemostasis.

Protocol
At baseline, the 6MWD, St George Respiratory Questionnaire, New York Heart Association class, Modified Medical Research Council Dyspnea Scale, Borg scale, Bode Index, and left and right ventricular systolic function (visual assessment by transthoracic echocardiography) were assessed. In addition, right heart catheterization and lung function tests were performed. A minimum of 75 mg orally daily of acetylsalicylic acid for at least 12 months and clopidogrel 75 mg orally daily for 12 weeks was recommended. Parameters obtained at 12 weeks are outlined in Table 3. Some patients underwent 6-month (n=11), 9-month (n=8), and 12-month (n=6) follow-up with evaluation of 6MWD.

End Points
The predefined primary end point was a change in exercise capacity on room air, assessed by measurement of 6MWD at 12-week follow-up. The secondary end point was the change in quality of life, assessed via the St George Respiratory Questionnaire at 12-week follow-up.

Statistical Analysis
Continuous variables were summarized with descriptive statistics, including the mean and standard error. A 2-sided paired Student t test was used to compare baseline parameters with follow-up parameters. A probability value of <0.05 was considered statistically significant. Subjects who were missing an evaluation were excluded from the analyses of that particular parameter/visit. Based on interim results provided by Rox Medical (San Clemente, CA), of 12 patients who...
underwent surgical fistula creation in a feasibility study demonstrating a mean improvement in 6MWD of 37+/−76 m on room air, enrollment of 30 patients was initially planned; however, though there were no predefined criteria for study discontinuation, given the significant number of adverse events, we decided to discontinue further enrollment.

### Results

#### Procedure

Fifteen patients were enrolled between July 19, 2007, and September 18, 2008. During this time period, 1 to 3 procedures were performed per month, with the exception of 6 months when no procedures were performed. The procedure was performed with technical success in all patients. Follow-up was complete in all but 1 patient who refused to return for evaluation. The mean fistula diameter determined by ultrasound post-procedure was 3.8+/−0.36 mm, with no significant change at 12 weeks.

#### Baseline Characteristics

Baseline characteristics are outlined in Table 3.

#### Primary End Point

There was a trend toward a decrease in 6MWD (by 44+/−21 m) at 12-week follow-up (Table 3 and Figure 1). Of note, 6MWD in oxygen nonresponders and oxygen responders (defined as improvement in 6MWD of at least 55 m at baseline) is shown in Table 4.

#### Secondary End Point

There was no significant difference in the St George Respiratory Questionnaire score between baseline and 12-week follow-up (Table 3).

#### Additional Parameters

At 12-week follow-up, CO, DO₂, MVO₂, pulmonary artery pressure, right atrial pressure, and pulmonary capillary wedge pressure increased significantly (Table 3, Figure 2, 3 and 4), although pulmonary vascular resistance remained unchanged (Figure 4). There was a minor reduction in the hemoglobin concentration.

There was no significant difference in lung function tests, including total lung volumes or arterial oxygen or carbon dioxide.
dioxide saturations. Likewise, there was no difference in the Modified Medical Research Council Dyspnea Scale or BODE index; however, the New York Heart Association class improved slightly (Table 3). In those patients (n = 6) who underwent 12-month follow-up, there was no significant difference in 6MWD.

Of note, left ventricular systolic function, visually assessed by transthoracic echocardiography, was normal in all patients. Likewise, right ventricular systolic function was normal in all patients; however, right ventricular hypertrophy and mild right ventricular dilatation were noted in 3 patients and 1 patient, respectively.

Oxygen saturations measured by pulse oximetry at baseline prior to and after the 6-minute walk test (6MWT) off oxygen were 91% and 81% respectively (Figure 5).

6MWD indicates 6-min walking distance; SEM, standard error of the mean. *Oxygen responders were defined as subjects who at baseline increased the 6-min walking distance by at least 55 meters with supplemental oxygen.

Deaths and Adverse Events Thought to Be Definitely, Probably, or Possibly Procedure- or Device-Related

One death occurred after more than 6-month follow-up. This patient was diagnosed with right heart failure likely related to the AVS. He was treated successfully with diuresis. In addition, he was diagnosed with a deep venous thrombosis ipsilateral to the AVS and treated with 6 months of oral anticoagulation. His wife reported that he collapsed and died while walking to the bathroom. The death occurred 9 months after AVS creation. No autopsy was performed.

Adverse events thought to be definitely, probably, or possibly procedure- or device-related after AVS creation; most commonly, lower extremity edema. With the exception of 4 minor hematomas and 1 pseudoaneurysm discovered between the day of the procedure and 15 days after the procedure, the average time interval between the procedure and the first adverse event was 110 days (range: 2 to 337 days). The average time interval between the procedure and the most common adverse event (edema) was 112 days (range: 2 to 337 days). In 8 patients, adverse events were considered severe enough to warrant fistula closure (average time interval between procedure and fistula closure: 398 days, range: 109 to 1020 days).

In the remainder, adverse events were mild and/or managed satisfactorily medically (with compression stockings and/or diuretics for lower extremity edema and anticoagulation in all cases of venous thrombosis).

Fistula Closure

A total of 8 patients underwent percutaneous fistula closure with a covered stent graft. The indications for closure were an ipsilateral external iliac vein stenosis and/or ipsilateral lower extremity edema in 7 patients and right heart failure in 1 patient.
Discussion
The concept that AVS creation might improve functional capacity in patients with COPD has significant support. An increase in MVO$_2$, by improving oxygen saturation in shunted blood, may increase the arterial oxygen content. An increased CO, in conjunction with higher arterial blood oxygen content, could improve total DO$_2$. Indeed, it has been well-documented that arteriovenous fistulae increase CO$^{3,4}$ and arterial oxygen saturation$^5$ and that an increase in CO is accompanied by an increase in MVO$_2$. Likewise, exercise-induced arterial desaturation has been shown to be less pronounced after creation of an AVS.$^9$ Provided the functional limitation seen in patients with severe COPD is at least partially related to DO$_2$, the conclusion that creation of an AVS may enhance functional capacity appears reasonable. In fact, initial experience with AVS in patients with endstage COPD has been encouraging. Faul and colleagues reported that surgical creation of an AVS in patients with endstage COPD is accompanied by a significant improvement in functional capacity.$^8$ In our study, as expected, the creation of an AVS was associated with a significant increase in CO and total DO$_2$ and an increase in MVO$_2$; however, the hemodynamic effects were accompanied by an undesirable trend toward a decrease in functional capacity (6MWD). In an uncontrolled study, the significant improvement in New York Heart Association class should be viewed with caution, given the potential for observer bias and placebo effect.

In light of these discrepant clinical results, review of the hypothesized physiological benefits of AVS formation is in order. Two main questions are to be addressed. First, is our

![Figure 2. Cardiac output (L/min) at baseline and 12-week follow-up in oxygen responders (dashed lines) and nonresponders (solid lines).](http://circinterventions.ahajournals.org/)

![Figure 3. Oxygen delivery at baseline and 12-week follow-up in oxygen responders (dashed lines) and nonresponders (solid lines).](http://circinterventions.ahajournals.org/)
current understanding of how an AVS may favorably affect functional capacity sound? Second, what are the potential adverse consequences of an AVS in patients with COPD?

First, it is important to determine precisely what limits the functional capacity in patients with COPD. Though it is plausible that hypoxemia may be to blame, other factors such as dyspnea related to increased work of breathing, caused by expiratory flow limitation because of decreased elastic recoil and bronchial constriction; increase in mean pulmonary artery pressure; and compromised right ventricular function may also be important. Let us assume that compromised tissue oxygenation is a significant source of functional limitation. It is dependent on 2 parameters, tissue perfusion (defined as the difference between CO and fistula flow) and arterial oxygen content. Thus, it can only be enhanced in 1 of 3 ways: The arterial oxygen content increases while at least maintaining or increasing tissue perfusion, the oxygen content remains unchanged but tissue perfusion increases, or the

Figure 4. Hemodynamic parameters (mean values) at baseline and 12-week follow-up. CO indicates cardiac output; PAP, pulmonary artery pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; WU, Woods units.

Figure 5. Oxygen saturation before (solid black bars) and after (gray bars) 6-minute walk test off oxygen at baseline and follow-up (mean±SEM). 6MWT, indicates 6-minute walk test; 12W, 12 weeks; 6M, 6-months; 9M, 9-months; 12M, 12 months; SEM, standard error of the mean.
increase in oxygen content exceeds a reduction in tissue perfusion. It is evident that CO and total DO₂ (defined as the product of arterial oxygen content and CO) alone are inaccurate measures of tissue perfusion and oxygenation in patients with an AVS. For example, the AVS may increase CO and, thus, calculated total DO₂, but if the shunt flow exceeds the increment in CO, the remaining tissue perfusion and oxygenation may actually decrease. Indeed Frank and colleagues demonstrated a reduction in tissue flow in an animal model immediately after the creation of an AVS. It is not clear, however, how tissue flow changes with chronic arteriovenous shunting. It is possible that the initial decrement in body flow and blood pressure may, in the long-term, be offset by sodium retention and higher blood volume, allowing maintenance of, or increase in, tissue perfusion. For example, after AVS placement in dogs, saline infusion caused an increment in CO that exceeded the increment in fistula flow, thus indicating an increase in tissue perfusion; however, maintenance of, or increase in, tissue perfusion with chronic arteriovenous shunting has not yet been shown, and it is, therefore, not clear whether the increase in CO and total oxygen delivery seen in our study translate into better tissue perfusion or oxygenation. In addition to CO, shunt volume assessment is required for the calculation of tissue perfusion and oxygenation. This parameter cannot be assessed accurately noninvasively and therefore was not determined in our study. Hence, a conclusion regarding tissue perfusion or oxygenation cannot be made. The second component determining tissue oxygenation is arterial oxygen content. Though an increase in this parameter has been seen in 1 animal model, no significant improvement occurred in our patient population after AVS creation and, in fact, this parameter significantly decreased in the previously mentioned study by Faul and colleagues.

It is also important to evaluate potential adverse effects of an AVS. Naturally, in patients who are prone to the development of pulmonary hypertension and cor pulmonale, concerns may be raised that a supraphysiologic increase in CO may exacerbate pulmonary hypertension and accelerate pulmonary vascular disease. In the current study, patients with more than mild pulmonary hypertension at baseline (mean pulmonary artery pressure >35 mm Hg) were excluded. Even so, a significant increase in mean pulmonary arterial pressure (9 mm Hg) was observed in our patient population related to flow, although pulmonary vascular resistance remained unchanged. Faul and colleagues found no change in mean pulmonary artery pressure and a trend toward a significant decrease in pulmonary vascular resistance after AVS creation in patients with endstage COPD. Left-to-right shunts in patients with congenital heart disease do not usually cause pulmonary vascular disease or hypertension unless they are large. Moreover, it has been proposed that an increase in mixed venous oxygen content may have a favorable effect on the pulmonary vasculature by vasodilatation. Nonetheless, a beneficial effect of increased MVO₂ on the pulmonary vasculature has not been conclusively demonstrated, and it has been shown that it is predominantly alveolar partial oxygen pressure, rather than MVO₂, that determines pulmonary vascular tone. Importantly, the long-term effects of an AVS on the pulmonary circulation in patients with COPD and abnormal baseline pulmonary hemodynamics remain to be determined.

A further concern in patients with AVS is the development of heart failure. Experience with arteriovenous dialysis fistulae does not suggest a high incidence of heart failure, despite significant shunt volumes. Indeed, a reduction in left ventricular size and volume, along with impaired left ventricular diastolic filling, in patients with COPD has been reported, perhaps the result of diminished right heart function and left ventricular underfilling because of static hyperinflation. Thus, in theory, AVS creation may improve left ventricular filling and performance; however, heart failure because of arteriovenous fistula formation has been reported, and despite the reduction in systemic vascular resistance, an increase in left ventricular stroke work after AVS creation has been shown. Four patients in our study developed right heart failure. In addition, in our patient population, albeit mild, an increase in right atrial pressure and pulmonary capillary wedge pressure was seen. Thus compromise in cardiac performance may have contributed to the lack of clinical benefit.

It has been proposed that an increase in MVO₂ may result in blood flow redistribution into poorly ventilated lung segments, thereby exacerbating ventilation-perfusion abnormalities; however, while large changes in ventilation-perfusion inequality can be seen with increased CO during conditions of hyperoxia, these changes are minor during normoxia or hypoxia, reflecting the dominant role of alveolar rather than mixed venous oxygen tension in determining pulmonary vascular tone.

It could be argued that the lack of clinical benefit in our study, compared with the previously published favorable results, may have been related to a different study population. Indeed, our population was characterized by less-pronounced impairment of lung function (higher baseline peripheral arterial oxygen saturation, forced expiratory volume in 1 second, and 6MWD) and functional capacity (mean baseline, 6MWD off oxygen 322 m in oxygen responders and 358 m in nonresponders in our study versus 99 m and 217 m in the prior study). A potentially more-favorable effect in patients with poorer baseline functional capacity cannot be excluded. In the previous study, the improvement in functional capacity was limited to patients who, at baseline, responded to

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<th>Table 5. Adverse Events Definitely, Probably, or Possibly Related to the Procedure or Device</th>
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<td>Right heart failure</td>
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<td>Gingival/nose bleeding</td>
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<td>Miscellaneous</td>
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Miscellaneous: melena (1 patient), mild hemoptysis (1 patient), contrast reaction (rash) at 12 month follow-up (1 patient).
supplemental oxygen with an increase in 6MWD of at least 54 m (oxygen responders). It might be thought that there were predominantly nonresponders in our cohort; however, our population included both oxygen responders and nonresponders, in neither of which, an improvement in 6MWD was seen. One could also hypothesize that patients in our study were limited mainly by ventilatory impairment rather than by limited oxygen delivery. Neither in our study nor in the previous was cardiopulmonary exercise testing or assessment of forced expiratory volume in 1 second before and after the 6MWT performed. Therefore, it is not possible to exclude an important ventilatory or pulmonary impairment that would be unaffected by AVS creation but may be the more important limitation to the functional capacity than oxygen delivery. Though patients with a current diagnosis of cardiac disease requiring medical intervention were excluded in this study, given the higher prevalence of coronary disease in patients with COPD, it is conceivable that an increase in cardiac workload may have limited any potentially beneficial effects of the AVS. Further, left ventricular diastolic dysfunction was not systematically assessed in our study and may have contributed to peripheral edema or heart failure. Thus, more careful patient selection, for example, with exclusion of those who have significant coronary disease or increased left- or right-sided filling pressures, may result in more favorable results after AVS creation. An argument can be made that a long-term decline in 6MWD can be expected in patients with COPD and that the absence of a decline would be a clinical success; however, the follow-up time is too short in this study to allow any conclusions regarding the potential prevention of such a decline. The significant but mild reduction in hemoglobin level could be interpreted as the consequence of an improvement in oxygen delivery to the kidneys; however, it may also be related to renal salt and water retention for the maintenance of blood pressure after a reduction in vascular resistance caused by the fistula.

Finally, one needs to critically review device or procedural complications. No complications during the procedure were seen; however, in the current study, 1 death occurred more than 9 months after the procedure. In the absence of an autopsy, a relation to the AVS cannot be clarified; however, it is possible that, given a high incidence of venous thrombosis after AVS creation in our study and the presence of a deep venous thrombosis in this patient, it may have been related to pulmonary embolism. In addition, the incidence of right heart failure (4 patients), venous stenosis (7 patients), deep venous thrombosis (4 patients), and lower extremity edema (10 patients) is concerning. The reason for the high incidence of venous stenoses and deep venous thromboses is not clear; however, the change in flow dynamics and/or venous dilatation and shear stress because of the supraphysiological venous flow may be related to these events. The need to place an arterial stent graft in 8 patients to close the shunt is particularly concerning.

It is important to note that most of the potentially serious complications (particularly venous stenosis, thrombosis, and right heart failure) did not occur during the procedure or in the immediate postprocedural period but at follow-up. Therefore, prevention of these events cannot be expected by modification of the procedural technique.

Limitations
The number of patients was limited, and, though not apparent in our study, a clinical benefit cannot be ruled out with certainty. It is possible that any potential benefit may be limited to selected patients. Further, the nonrandomized nature of our study and the absence of a control group do not allow us to rule out the possibility that patients treated conventionally may experience more rapid symptom progression than those with an AVS. Finally, due to the open label design, results are subject to significant observer bias and placebo effect.

Conclusion
In summary, percutaneous creation of an AVS appears to be technically feasible. Although clinical benefits have previously been reported, we have not been able to reproduce them and there are significant limitations in the currently available data examining the effect of AVS creation on the physiological and clinical status of patients with COPD. Most importantly, it has not been elucidated what effect the creation of a shunt has on tissue oxygenation. In addition, the intermediate and long-term effect of increased pulmonary flow on pulmonary vascular resistance is unclear. Given the present lack of evidence pointing to a clear benefit and the number of concerning adverse events, careful further investigations of the chronic effect of arteriovenous fistula creation on tissue oxygenation in an animal model are warranted before further pursuit of the concept of AVS creation in patients with COPD. Even if a physiological benefit can be demonstrated, to prevent potentially serious adverse events, AVS creation outside a strictly controlled trial cannot be justified.

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