Decreased number of circulating progenitor cells in obesity: beneficial effects of weight reduction

Jochen Müller-Ehmsen1*, Daniela Braun1, Thorsten Schneider1, Roman Pfister1, Nicolai Worm1, Klaus Wielckens2, Christof Scheid3, Peter Frommolt4, and Markus Flesch1*

1Department of Internal Medicine III, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany; 2Department of Clinical Chemistry, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany; 3Department of Hematology and Oncology, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany; and 4Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany

Aims Cardiovascular risk factors are associated with decreased levels of circulating progenitor cells (CPC). The aim of this study was to determine whether the number of CPC is an independent correlate of body mass index (BMI) and whether weight loss leads to an increase in CPC.

Methods and results CD34 positive and KDR/CD34, CD133/CD34, and CD117/CD34 double positive cells were measured by fluorescence activated cell sorting (FACS) analysis in peripheral blood of 149 volunteers (52.5 ± 12.0 years, BMI 21.5–52.7 kg/m², mean 31.6 ± 5.1 kg/m²) participating in a weight reduction program offered by German pharmacies. In addition, carotid intima media thickness (IMT) and brachial artery flow-mediated dilatation were determined. After a diet and sports program for 6 months, 86 representing subjects were re-evaluated (mean weight loss 5.8 ± 5.2 kg). There was an inverse correlation between BMI as well as waist circumference and CPC, especially CD34 positive, KDR/CD34 positive, CD133/CD34 positive, and CD117/CD34 positive cells. This decrease in CPC in obesity held true not only for the absolute cell numbers, but also for the relative fractions of KDR, CD133, and CD117 positive cells within the CD34 positive cells, indicating a specific down regulation of these progenitor cell types. Multiple regression analysis revealed that BMI was a more prominent predictor of CPC regulation than blood pressure, LDL cholesterol, triglycerides, fasting glucose, and smoking. IMT increased in dependence on BMI (P < 0.001) and was inversely correlated with the number of CD34 positive cell (P < 0.05). After diet, there was a significant increase of CD34 and CD117/CD34 positive cells, which correlated with the decrease in BMI. Also, weight loss was accompanied by a decrease in IMT (P = 0.015), which also correlated with the increase in CPC (P < 0.001). The increase in the number of CPC was independent from whether weight loss was achieved by increased physical exercise or by reduced calorie intake only.

Conclusion Obesity is associated with decreased numbers of CPC and increased IMT. Diet and weight loss lead to an increase in CPC count, which might contribute to regression of IMT.

Keywords Obesity • Diet • Risk factors • Endothelial function • Endothelial progenitor cells

Introduction In recent years, interest in circulating progenitor cells (CPC) and especially endothelial progenitor cells (EPC) has risen because of their physiological and pathophysiological role in the cardiovascular system as well as due to the advent of cell-based therapies of cardiovascular disease. After acute myocardial infarction, these cells are mobilized into peripheral blood suggesting that they might play a role for endothelial repair, neovascularization or regenerative processes.1–3 In contrast, in patients with stable coronary artery disease, the number of progenitor cells is decreased4 and correlates inversely with the number of coronary risk factors.5 Accordingly, their activity and migratory activity is reduced in patients with coronary heart disease and diabetes.6,7

*Corresponding author. Tel: +49 221 478 32544, Fax: +49 221 478 32397, Email: markus.flesch@uni-koeln.de or muller.ehmsen@uni-koeln.de

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In a recent cohort study, a reduction of CPC number in peripheral blood (PB) was associated with worse outcome in patients with suspected or confirmed coronary artery disease. These findings indicate that the number of CPC may be a marker of cardiovascular risk.

Obesity is an increasingly important and independent risk factor for cardiovascular events. Although obesity itself appears to augment the incidence of cardiovascular events, it is also associated with major risk factors for atherosclerosis including hyperlipidaemia, diabetes mellitus, hypertension, and the metabolic syndrome. However, cardiovascular science is just at beginning to understand the precise mechanisms linking obesity and atherosclerosis. Newly discovered mechanisms include increased systemic oxidative stress, increased inflammation, and release of inflammatory cytokines. In addition to the already known risk factors associated with obesity, such as diabetes, hyperlipoproteinaemia, arterial hypertension, and physical immobility, all leading to decreased CPC count, increased oxidative stress and cytokine release also contribute to a decreased number and disturbed function of CPC. Therefore, one might postulate that CPC count is decreased in obesity. However, so far only very little is known concerning this relationship. Especially, it is unknown whether a decrease in CPC count might be a functional link between obesity and increased cardiovascular risk.

Therefore, in the present study, the number of CPC and endothelial function were studied in overweight volunteers who participated in a diet program initiated by pharmacies throughout the Cologne urban area. Furthermore, the question was addressed whether weight reduction due to diet and increased physical activity might lead to an increase in CPC and an improvement in endothelial function. In the current study, CPC were defined by the expression of the haematopoietic stem-cell marker CD34 or expression of CD34 and additional expression of the VEGF receptor-2 (KDR), additional expression of the receptor for stem-cell factor CD117, or additional expression of the early haematopoietic stem-cell marker CD133.

### Methods

#### Study population, medical history, and physical exam

The voluntary participants of the study were recruited consecutively from a diet program called ‘Leichter Leben in Deutschland’ (living lighter in Germany) between March and May 2006. This program was initiated by German pharmacies in order to provide wide spread support for weight reduction. The aim of this program was to inform about general diet considerations and to assist with diet plans and lifestyle changes. During the first introduction lecture of the program, 297 participants of the weight-loss program were addressed and invited to come for a cardiovascular health check at the University Hospital of Cologne and to participate in this study. Although, the program mainly aimed at overweight and obese people, it was open to anyone interested. Also, participation at the additional health check at the University Hospital was independent from pre-interventional body weight and body mass index (BMI). One hundred and forty nine participants agreed to participate. At the beginning as well as at the end of the study, full medical histories were obtained from these participants as well as physical exams including height, weight, waist circumference, blood pressure, heart rate, electrocardiogram (ECG), and treadmill ECG test. In addition, blood samples were taken to analyse for glucose, total cholesterol, LDL, HDL, and creatinine. In addition, serum samples were frozen and stored at −80°C for further analysis. The demographic data of these patients are listed in Table 1.

#### Diet program

The program consisted of an ad libitum low fat, low glycemic index diet together with recommendation for increased physical activity. The dietary regimen comprised three phases: an initial phase of 2 days on a low carbohydrate diet, the weight-loss phase until reaching the desired weight with an emphasis on a low fat, low glycemic index diet, limiting fat intake to 60 g/day, and a stabilization phase reintroducing a balanced diet. The participants were free in defining their diet goals.

#### Fluorescence activated cell sorting (FACS) analysis

One hundred microlitres of PB collected in EDTA containing tubes were incubated for 20 min with fluorescein isothiocyanate-conjugated anti-CD45 monoclonal antibody and phycoerythrin-conjugated anti-CD34 antibody after erythrocyte lysis. To exclude any bias by the choice of fluorescent dye, another 100 μL sample was incubated with FITC-conjugated anti-CD34 antibody and phycoerythrin (PE)-conjugated anti-CD45 antibody (Becton Dickinson, Heidelberg, Germany). To assess the subpopulations in each case, 100 μL of PB were stained with either PE-conjugated anti-VEGFR-2 (KDR) (eBioscience, San Diego, USA) antibody or anti-CD133 antibody (Miltenyi Biotec, Bergisch-Gladbach, Germany) or anti-CD117 antibody (Bioscience, San Diego, USA) in addition to the FITC-conjugated anti-CD34 antibody (Becton Dickinson). Appropriate isotype controls were used for each staining procedure. After lysis of red cells, the samples were centrifuged and the pellets were resuspended in 450 μL of phosphate buffered saline. Cells were analysed by flow cytometry (FACSCalibur, Becton Dickinson). The analysis of the CD34 positive haematopoietic cells was performed adopting the gating strategy defined by the International Society of Haematotherapy and Graft

### Table 1 Demographic characteristics of the study population

<table>
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<th>n = 149</th>
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<td>Age</td>
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<td>Creatinine</td>
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Engineering (ISHAGE) guidelines and expressed as number per million white blood cells. In order to gain reliable data for the subpopulation analysis, the data of the progenitor population were selectively acquired by only counting CD34 positive cells with a low granularity and the typical forward scatter profile. Then, the subpopulations were defined according to the corresponding isotype control. Cell counts are given as cells per million leucocytes.

**Cell culture**

PB-mononuclear cells (MNCs) were isolated from 15 mL of human EDTA-blood by using Ficoll-density-gradient centrifugation (LSM 1077 PAA Laboratories, Germany). After resuspension in DPBS (Dubecco’s Phosphate Buffered Saline 0.0095 M; CAMBREX Bio Science), 10^6 MNCs were plated on four fibronectin-coated plates and incubated for 4 days with Endothelial Cell Basal Medium MV2 (Promo Cell) containing various growth factors. At day 4, the plate was double-washed with DPBS and the adherent cells were counted.

**Endothelial function and intima media thickness**

Endothelial function was assessed by measuring the flow-mediated dilatation (FMD) of the brachial artery determined by high-resolution ultrasound with a 10 MHz linear array transducer (GE, USA), for which the reported intraobserver variability is up to 50 μm. Variability was minimized by performing five independent measurements in each patient at each examination. The patients were examined in a quiet, dark, air-conditioned room (22–25°C) in the morning. The patients had been instructed to remain fasting for at least 8 h, and to abstain from alcohol, smoking, caffeine, and antioxidant vitamins for at least 12 h prior to the measurements. The diameter of the brachial artery was taken proximal to the antecubital fossa at rest and during the peak of reactive hyperaemia after 5 min of ischaemia, as described before.22 The protocol was in accordance with the published guidelines, yielding a coefficient of variation of less than 1%. FMD was calculated as the peak relative diameter gain after cuff deflation when compared with baseline values. Smooth muscle dilatory function was determined 4 min after sublingual application of 800 μg of glycerol trinitrate (Nitrolingual mite, Pohl, Germany).

The intima media thickness (IMT) was measured using ultrasound of the common carotid artery and the carotid sinus along with their long axis and short axis, as the patient lay supine with the neck in slight extension. B-mode images and the simultaneous ECG recordings were obtained, the end-diastolic far-wall IMT at a site approximately 1–2 cm proximal to the carotid sinus was measured. The mean of three measurements was used as respective values for IMT.

**Statistical analysis**

Continuous variables were summarized as mean ± standard deviation (SD). Statistical analysis was done with SPSS® (SPSS Inc., USA) applying significance tests of Spearman’s rank correlations and Pearson’s correlations against zero, analyses of variance (ANOVA), and multiple linear-regression analysis. A significance level of α = 0.05 was chosen and all statistical tests performed were two-sided. The Bonferroni method was applied to account for the inflation of type I error due to multiple testing in the correlation analysis (Figure 1–5), whereas the P-values in Tables 2 and 3 were computed in an explorative fashion without multiplicity adjustment. For discovery of independent risk factors for metric variables such as decrease in CPC count, a multiple linear-regression model is appropriate if the basic model assumptions are satisfied. Partial regression plots revealed linearity of the respective dependencies for the variables (not shown),

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**Figure 1** Absolute number of circulating progenitor cells per 10^6 leucocytes before diet (n = 149) in relation to the participant’s BMI. Results are based on FACS analysis of peripheral blood samples of all participants, cells were conjugated with specific antibodies against CD34, KDR, CD133, and CD117.
whereas goodness of fit was assessed by showing the regression coefficients to be distinct from zero by ANOVA. Colinearity of covariates was figured out by calculating tolerance scores for the variables involved in the model, where variables with unreasonably small values for these were excluded. The tested variables are given in Table 2.

**Results**

**Circulating progenitor cells before diet**

At baseline, the number of CD34 positive cells was inversely related to the BMI: the higher the BMI, the lower the number of
CD34 cells per million leukocytes. The same relationship was found for the CD117/CD34, CD133/CD34, and KDR/CD34 double positive cells (Figure 1). The relationship held true also when CPC were related to waist circumference (Figure 2). Also, CPC count in cultured MNCs from peripheral blood decreased significantly ($P = 0.022$) with increasing BMI (data not shown). Interestingly, not only the absolute number of CD34 positive cells decreased with increasing BMI, but also the relative counts of KDR, CD133, and CD117 positive subgroups within the group of CD34 positive cells (not shown).

In order to examine whether obesity is an independent risk factor for a decrease in CPC, a collection of known determining factors for CPC counts were analysed and multiple linear-regression analysis was performed. Multiple regression analysis revealed that BMI ($P = 0.012$) and waist circumference ($P = 0.005$) are more powerful predictors of CPC count than systolic and diastolic blood pressure, LDL cholesterol and triglycerides, fasting glucose and smoking (Table 2).

**Intima-media thickness before diet**

Prior to diet, there was a significant positive correlation between BMI and carotid artery IMT ($P < 0.001$, $r = 0.87$), and, as shown in Figure 3, there was a weak, but significant inverse correlation between carotid artery IMT and CD34 ($P = 0.037$) and CD34 cells per million leukocytes. The same relationship was found for the CD117/CD34, CD133/CD34, and KDR/CD34 double positive cells (Figure 1). The relationship held true also when CPC were related to waist circumference (Figure 2). Also, CPC count in cultured MNCs from peripheral blood decreased significantly ($P = 0.022$) with increasing BMI (data not shown). Interestingly, not only the absolute number of CD34 positive cells decreased with increasing BMI, but also the relative counts of KDR, CD133, and CD117 positive subgroups within the group of CD34 positive cells (not shown).

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CD117/CD34 (P = 0.048) positive cells, respectively. There was no significant correlation between CPC count and flow-mediated brachial artery vasodilatation.

**Effect of weight loss on circulating progenitor cells**

At the end of the 6 month diet program, 86 participants represented and were re-evaluated. Change in weight ranged between 2 kg weight gain and 23 kg weight loss (mean 5.2 kg, P = 0.01). Change in BMI ranged between an increase of 0.71 kg/m² and a decrease of 7.77 kg/m² (mean 2.0 ± 1.7 kg/m², P = 0.01).

The correlation for cell counts of CD34 and CD117/CD34 cells with weight loss was significantly larger than zero, which cannot be stated for the KDR/CD34 and CD133/CD34 cells (Figure 4). In patients presenting with a decrease in BMI > 2.5 kg/m², the change in the number of CD34 cells was 30.8 ± 43.7, P = 0.035 and the change in the number CD117/CD34 cells was 27.7 ± 42.6, P = 0.046. Interestingly, this held true for the group of people who combined the diet program with increased physical exercise (20 min, 5 days a week) as well as for those people who reduced calorie intake only without increasing physical activity. However, in this group, the increase was significant only in CD117/CD34 cell count. For CD34 cell count, there was a non-significant trend for an increase in cell count in response to a decrease in BMI (Figure 5).

Weight loss was accompanied by a significant decrease in systolic and diastolic blood pressure, but neither in serum cholesterol and triglyceride values nor in fasting glucose (Table 3). Multiple regression analysis confirmed that also in response to the diet program, changes in BMI are the most important predictive parameter for alterations in CD34 count (P = 0.039 for BMI, all other parameters including blood pressure, LDL cholesterol, triglycerides, fasting glucose, and smoking are non-significant).

**Effect of weight loss on intima-media thickness and endothelial function**

Patients who represented with a weight loss revealed a significant decrease in carotid artery IMT (0.66 ± 0.02 mm prior to diet vs. 0.62 ± 0.01 mm post diet, P = 0.015). Also, there was a significant improvement of brachial artery vasodilatory response in patients representing with a weight loss (13.9 ± 0.6% prior to diet vs. 10.4 ± 0.7% prior to diet, P < 0.01). In a regression analysis, this decrease in IMT showed a significant correlation with the increase in:

<table>
<thead>
<tr>
<th>Table 2 Dependence of CD34 cell number per million leucocytes on waist circumference and other cardiovascular risk factors</th>
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<td>P</td>
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Results were obtained by multiple linear-regression analysis. The regression coefficients were shown to be significantly distinct from zero (P = 0.002 by F-test); collinearity of the covariates was analysed by the tolerance scores displayed in the table. Similar results were obtained for KDR/CD34, CD133/CD34, and CD 117/CD34.

<table>
<thead>
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<th>Table 3 Changes in the demographic characteristics during the diet period</th>
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<td>Age</td>
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<td>BMI (kg/m²)</td>
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<td>Waist circumference</td>
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<td>Weight (kg)</td>
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Statistical evaluation was performed by ANOVA.
Discussion

This study provides first evidence for an inverse correlation between obesity and the number of CPC in peripheral blood. In a cohort of 149 volunteers participating in a weight-loss program, the absolute number of CD34 positive progenitor cells as well as KDR, CD133, and CD117 positive cell subtypes decreased in dependence from increasing BMI and waist circumference. Furthermore, obesity correlated positively and the number of CPC correlated inversely with carotid artery IMT. Weight loss led to an improvement of all parameters, especially a weight-loss-dependent increase in the number of CD 34 and CD117/CD34 cells and a weight-loss-dependent decrease in IMT.

The major finding is that the number of CPC was found to be decreased in people with increased body weight, BMI, and waist circumference. This may not be surprising since people with higher BMI are likely to be less physically active, have a greater incidence of diabetes, and often present with hyperlipidaemia and hypertension. All these factors are known to contribute to a decrease in CPC.14,5,7,22 However, Hill et al.5 reported no correlation between BMI and CPC count. Reasons for this discrepancy might be the larger number of subjects analysed and the choice of other CPC subtypes in our study. Multiple regression analyses underlined that BMI is a more powerful predictor of CPC count than any other risk factor.

In this study, CD34 positive progenitor cells and all studied sub-populations (KDR/CD34, CD133/CD34, and CD117/CD34) were decreased in obesity. Interestingly, also the fractions of KDR/CD34, CD133/CD34, and CD117/CD34 double positive cells within the total number of CD34 cells decreased in overweight probands. Thus, there was a more pronounced decrease in the double positive populations than in the CD34 positive cells. Such kind of specific regulation of subpopulations of CD34 positive cells was also observed in previous studies during myocardial infarction.21–25 The functional relevance has so far not been explained. However, it should be pointed out that, according to some authors, especially KDR/CD34 positive cells should be regarded as EPC rather than CD34 cells, which have the potential to differentiate into fibroblasts and smooth muscle cells.15–19 In our study, the relative decrease in CD34/KDR positive cells was even more pronounced than the decrease in CD34 cells and the decrease in CD34/CD133 and CD34/CD117 cells, suggesting that obesity primarily affects CPC subtypes related to the integrity of the endothelium and to endothelial function.

It has to be noted that an increase in total white blood cell count which is present in obese subjects may have compensatory effects on the decrease in CD34 positive cells per million leucocytes, ultimately leading to an unchanged number of CPC per microlitre blood. However, the decrease in CD34 positive cells observed in the present study in subjects with highest BMI is considerably more pronounced than what could be explained by dilution through approximately 10% increase in leucocytes observed in obesity.26 Even more, the specific downregulation of CD34 subtypes within the group of CD34 cells is independent from total white blood cell and therefore indicates a specific regulation of CPC subtypes.

The potential functional relevance of a decreased CPC count in obesity and its role as a mechanistic links between overweight and atherosclerosis is underlined by the fact that carotid IMT increased inversely to CPC count. To our knowledge, there is only one report, so far, linking a decreased CD34/KDR double positive cell count with increased carotid IMT.7 In this study, Hill et al.5 even demonstrated a correlation between CPC count and flow-mediated brachial artery vasoreactivity which was also found in young UK Asians.27 Although in our study, no correlation between CPC number and flow-mediated vasodilation was found—possibly due to different CPC subtypes analysed—we did find reduced FMD in obese patients, and we did find a correlation between CPC counts and IMT. Why this holds true for CD34 and CD117/CD34 double positive cells, but not for other subtypes is unclear. Nevertheless, several studies point into the same direction that decreased numbers of CPC are associated with early structural and functional changes of atherosclerosis.

A further interesting finding of this study is that the reduction of CPC in overweight probands is reversible upon weight loss. However, this increase in CPC was not observed for all subpopulations studied. While CD34 positive cells and CD117/CD34 double positive cells were increased when compared with the pre-diet status, KDR/CD34 and CD133/CD34 double positive cells remained the same. Interestingly, CD34/CD117 double positive cells, which increased with weight loss, are amongst those which are also mobilized in patients with acute myocardial ischaemia.28,29 These cells are regarded as the earliest differentiation form of CPC and have been reported as being important for neo-vascularization.30,31 Also, this cell type revealed the best inverse correlation with carotid IMT in our hands.

Although the participants of the weight loss program were encouraged to combine a reduction in daily calorie intake with an increase in physical activity, only 57% of those representing for the final check up reported an increase in physical activity. However, also in the subgroup without increased physical activity, weight loss was associated with an increase in CPC, which held true for CD34 cells for trend as well as significantly for CD34/CD117 double positive cells. Thus, the increase in CPC count in response to a decrease in BMI cannot only be attributed to increased physical exercise as reported earlier.32 In contrast, weight loss as such also leads to an improvement in CPC count.

Interestingly, there is only sparse evidence in the literature for diet effects on endothelial function. For a low-carbohydrate diet, which has been favoured in our diet program, a restoration of coronary endothelial function has only been demonstrated in Zucker rats as an animal model of obesity.32 Thus, this study provides also first evidence for an improvement of endothelial function in response to a low-carbohydrate diet induced weight loss in man. Similar to the data obtained in our cohort prior to the diet, there was no correlation between alterations in CPC count and improved endothelial function in response to the diet. However, there was a correlation between weight loss induced changes in CPC count and IMT which might suggest a role of CPC in vascular regeneration.
In conclusion, this study shows that obesity is associated with a decrease in CPC count. Weight loss results in an increase in the number of circulating CPC. The functional importance of this finding is underlined by the fact that decreased CPC count is accompanied by an increase in carotid artery IMT as a sign of early atherosclerosis. Parallel to the increase in CPC count, weight loss leads to a decrease in IMT, leading to the hypothesis that CPC upregulation and improvement of vascular status might be connected.

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References


CLINICAL VIGNETTE

Left ventricular congenital submitial aneurysm

Giovanni Corrado1*, Claudia Borghi2, and Paolo Panisi3

1 Department of Cardiology, Ospedale Valduce, Via Dante 11, Como 22100, Italy; 2 Department of Radiology, Ospedale Valduce, Como, Italy; and 3 Department of Cardiac Surgery, Istituto Clinico S Ambrogio, Milano, Italy

* Corresponding author. Tel: +39 031 324111, Fax: +39 031 308047, Email: gcorr@iol.it

A few days after arrival in Italy from Ghana, a 20-year-old black male presented with a history of fever, headache, nausea, vomiting, and atypical chest pain. Clinical neurological evaluation, brain MNR, and cerebrospinal fluid analysis were negative for CNS disease. ECG showed normal sinus rhythm with non-specific ST-T abnormalities (Panel A). Owing to the presence of chest pain, fever and ECG abnormalities, an echocardiogram was scheduled to rule-out pericardial effusion. Echocardiogram revealed a large submitational aneurysm arising below the posterior mitral leaflet (Panel B). On 64-slice CT scan of the heart (Panel C), normal coronary arteries and a large posterior aneurysm communicating with the main left ventricular cavity were observed. The patient had a successful surgical ventriculoplasty (Panel D); the neck of the aneurysm was sutured and the aneurysmal tissue was utilized to reinforce the contiguous healthy ventricular wall.

Submitrial aneurysm is a peculiar form of left ventricular aneurysm thought to be caused by a congenital defect in the posterior portion of the mitral annulus and occurring almost exclusively in black Africans. Clinical presentation may include symptoms through diastolic overload (by virtue of its volume or by causing mitral annulus distortion and valve incompetence), thromboembolism, arrhythmias, compression of the left circumflex artery, and aneurysm rupture. Immediate surgical treatment should be considered in these patients to prevent major events.

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