Congestive heart failure (CHF) is the inability of the heart to deliver a sufficient oxygen supply to meet the metabolic demands of the tissues at normal filling pressures, both at rest and during exercise. CHF may arise from reduced inotropy, volume overload, pressure overload, or reduced diastolic dilatation. Long-standing hypertension causes CHF by increased pressure overload. With time’s passage, pressure overload induces expression of proto-oncogenes (such as c-fos, c-myc, c-jun, and others) that foster myocardial hypertrophy. Hypertrophy entails an increase in the size of individual muscle cells and the overall muscle mass. However, the heart developing hypertrophy under these conditions is limited because the heart operates at a lower inotropic state. Furthermore, structural and biochemical changes occur that have long-term deleterious effects, notably dilatation. Chronic pressure overload is thus accompanied by progressive growth abnormalities and apoptotic cell death. The condition has been termed the “cardiomyopathy of overload.” The heart’s adaptation to overload is wide, perhaps because hypertension itself is heterogeneous. For instance, hypertension is strongly associated with obesity that has its own blood pressure-independent effects on the heart. In young obese persons, subclinical left ventricular diastolic dysfunction is present in all grades of isolated obesity, whereas systolic function is actually increased. How such persons present clinically 40 years later is unclear, but because large segments of society now qualify as obese, the topic is of major concern.

Presentation of the Case
A 65-year-old woman was transferred to our intensive care unit because of heart and renal failure. Three months before admission, she had become progressively dyspneic. Attempts had been made to treat her with an angiotensin-converting enzyme inhibitor, β-blocker, and furosemide to no avail. She had increasing abdominal girth and edema. Her painful brawny lower extremity skin changes were interpreted as cellulitis, for which she was administered antibiotics on numerous occasions. The origin of her heart failure was unclear. Numerous echocardiograms indicated “good ventricular function.” She had been overweight all her life. Thirty years ago, she was found to be hypertensive and had been treated with various regimens “off-and-on.” Three years before admission, atrial fibrillation developed and, because her heart rate was slow, a transvenous ventricular demand pacemaker was implanted. At that time, she had a blood pressure of 180/100 mm Hg despite diuretic and β-blocker therapy. She had no diabetes mellitus or other known chronic diseases.

Her height was 165 cm. Her weight was 108 kg. Body mass index (BMI) (weight [kg]/height [m²]) was >35. The blood pressure was 110/70 mm Hg. The heart was paced at a 75-bpm rate. The respiratory rate was 24/min. She appeared cachectic despite her obesity. Her neck veins were distended and the central venous pressure was estimated at 16 cm H₂O. She had rales bilaterally and left-side posterior percussion dullness. Her heart sounds were distant. A systolic murmur was present but no gallop rhythm was heard. Her liver was enlarged; the spleen was not palpable. Ascites and generalized anasarca were present. The lower extremities showed an erythematous brawny painful edema shown in Figure 1.

The hemoglobin was 10 g/dL, the hematocrit was 33 vol%. The white blood cell count was 11 000 μL. The electrolytes were Na 126 mmol/L, Cl 88 mmol/L, K 3.6 mmol/L, and HCO₃ 29 mmol/L. The pH was 7.46, and on room air the PaO₂ was 63, and the PaCO₂ was 42 mm Hg. The troponin I and CKMB were not elevated. The brain natriuretic peptide concentration was 8-fold above the normal limit. The urinalysis showed no glucose, +1 protein, and many granular casts. A 24-hour protein excretion was 372 mg in a urine volume of 430 mL. The creatinine was 257 μmol/L (2.8 mg/dL), and the urea was 19 mmol/L (BUN 52 mg/dL). The fractional excretion of sodium was 1.7%; however, the patient had received furosemide that day. The fractional excretion of urea was 25%. The patient was intermittently febrile during her stay and her CRP was above the normal range.

The chest roentgenogram showed a markedly widened cardiac silhouette and a large left-side pleural effusion, as shown in Figure 2. An echocardiogram revealed a sizable pericardial effusion, but nevertheless a left ventricular ejec-
tion fraction (EF) >60%. We drained the pleural and pericardial effusions and performed cardiac catheterization. End-diastolic pressure in the right and left ventricle was $\approx 20$ mm Hg, not dissimilar from the end-diastolic pressures in the pulmonary artery and the right atrium. The pressure curves before pericardial drainage are shown in Figure 3. Left and right ventricular curves and left ventricular with pulmonary capillary wedge pressure (PcWP) curves are shown. The end-diastolic pressures were similar and little different from the right atrial pressure as shown in the Table. After pericardiocentesis, the pressures curves were essentially unchanged. Echocardiography was performed several times. Representative views are shown in Figure 4. Remarkable was the relatively bland hypertrophy and the preserved EF at $\approx 60%$. Doppler studies of transmitral valve flow showed a short deceleration time consistent with limited rapid ventricular filling and barely any variability with respiration consistent with restriction, as shown in Figure 4.

We found no amyloid, idiopathic myocardial fibrosis, Fabry disease, hemochromatosis, sarcoid heart disease, or Löeffler endocardial fibrosis. Management with a $\beta$-blocker (up to 100 mg/d metoprolol), angiotensin-converting enzyme inhibitor (ramipril 5 mg/d), spironolactone (25 mg/d), loop (furosemide up to 250 mg/dL), and thiazide diuretics (indapamide 2.5 mg/d) aggravated hypotension but was not successful in alleviating the dyspnea. We placed a peritoneal dialysis catheter. Her weight was reduced from 107 to 89 kg, and her symptoms improved. Erythropoietin was administered. We repeated the hemodynamic studies as shown in Table. The values were significantly improved and her cardiac output was 5 L/min. Two months after initiation of peritoneal dialysis, the patient died suddenly.

**Differential Diagnosis**

**Pericardial and Restrictive Cardiac Disease**

We agreed that CHF was present. We had excluded other causes of inadequate oxygen delivery. For instance, the patient clearly did not have circulatory collapse from hemorrhage or other causes of severe volume loss. We found no evidence for thyrotoxicosis, arteriovenous fistulae, Paget disease, or profound anemia. We were not able to ascribe the severe pulmonary congestion solely to volume overload. Conceivably, the patient could have had a primary renal disease. Her renal function was markedly compromised. However, her urinary sediment did not suggest a chronic renal disease, and her renal size was normal by ultrasound examination. Her fractional excretion of sodium exceeded 1% with chronic diuretic therapy. However, her fractional urea excretion was $<30%$. A recent study has documented the usefulness of fractional urea excretion in determining prerenal azotemia in the face of diuretic therapy.5

The patient’s filling pressures were clinically increased. The brain natriuretic peptide values were markedly elevated. Nevertheless, we were surprised by the echocardiographic findings indicating a normal EF. The sizable pericardial effusion was not accompanied by echocardiographic findings of pericardial tamponade, nor was the pericardium remarkable on echocardiographic examination. There was no right atrial or right ventricular wall collapse. We had no evidence for the more common chronic pericardial effusion causes, such as neoplasia, uremia, postmyocardial infarction, viral infection, collagen vascular disease, or tuberculosis.6 Large pericardial effusions are commonly chronic and idiopathic. We speculated that the effusion was secondary to CHF rather than the cause of volume retention. There was no clear-cut indication for pericardial drainage in this patient, because she had no evidence for tamponade or an inflammatory/infectious cause.7 Nevertheless, we reasoned that we might obtain some diagnostic information or perhaps a therapeutic response. However, the pericardial fluid was not diagnostically helpful, and from the pressure curves, we saw little improvement in her functional status. The right and left ventricular end-diastolic pressures were similar before and after complete pericardial drainage.
Diastolic Heart Failure

Because the EF was unimpaired, we concluded that our patient had diastolic heart failure. Our initial considerations were an epicardial or pericardial cause of diastolic heart failure. We obtained pulse Doppler measurements to observe passive mitral filling (E). Active mitral filling (A) was obviously not present in our patient. The deceleration slope and isovolumetric relaxation time strongly suggested compromised diastolic filling. The failure of the Doppler signal to be influenced by the patient’s respiration reinforced the notion that a restrictive cardiomyopathy was present. Moreover, we had elevated brain natriuretic peptide levels with a normal EF. This finding at rest or during exercise may serve as a diagnostic technique to identify patients with diastolic heart failure.8,9

The differential diagnosis of increased diastolic filling resistance is extensive.8 We ruled out epicardial/pericardial causes in our patient. The coronary circulation in our patient was normal on cardiac catheterization, although we were unable to assess possible microcirculatory malfunction. We had no evidence for endocardial disease in our patient. The mitral valve appeared normal and the tricuspid valve was relatively functionally incompetent. Endocardial fibroelastosis appeared unlikely in our patient. Thus, we postulated a myocardial cause for diastolic heart failure in our patient. Although difficult to rule out without a myocardial biopsy, we had no evidence for an infiltrative cause such as amyloidosis, hemochromatosis, sarcoidosis, or Fabry disease. However, postinfarct scarring, diffuse fibrosis, and cardiomyocyte hypertrophy can also compromise the ventricular passive stiffness. Microvascular ischemia, myocyte hypertrophy, aging, and hypothyroidism are causes that compromise active ventricular relaxation. We had ruled out hypothyroidism but could only speculate about the remaining possibilities.
Hypertension and Heart Failure With Preserved EF

Recently, patients entering an emergency room with acute pulmonary edema were examined echocardiographically before and after medical treatment. The EF of these patients showed a mean value of 50% before treatment. This value was largely unchanged by treatment, although the pulmonary edema was markedly improved and the roentgenograms showed clearing of the pulmonary edema. The study underscored the existence of diastolic heart failure and implicated hypertension as a common cause. Currently, half of patients with heart failure are said to have diastolic heart failure. Heart failure with preserved EF is not benign. Recently, 413 heart failure patients were evaluated prospectively and were divided into those with EF ≥ 40% (mean 60% ± 8%) or those with less than that value (mean 28% ± 10%). Hypertension was present in 80% of those with preserved EF, although the diagnosis also occurred in 60% of those with diminished EF, underscoring the role of hypertension as a cause of heart failure irrespective of EF. Patients with preserved EF were also more commonly older, more commonly female, and less commonly had coronary disease than were patients with diminished EF. After 6 months, 13% of the preserved EF patients had died, whereas 21% of the depressed EF patients had died. Although the mortality was higher in the heart failure patients with diminished EF, the functional capacity of the 2 groups declined similarly. Thus, although heart failure patients with preserved EF may have a bit lower mortality, their morbidity seems slightly different and their number of hospitalizations is likely to be the same.

In an accompanying editorial, the author pointed out some major difficulties with the notion of diastolic heart failure that have resulted in the term “heart failure with preserved EF.” The measurement of diastolic function is indirect, difficult, or both. There are no clear-cut diagnostic criteria for diastolic heart failure. EF measurements indicate little about the pathophysiology. Patients with diastolic heart failure may have concomitant systolic disturbances despite preserved EF. Some patients labeled as having diastolic heart failure may not have heart failure. Some diastolic heart failures do not have discernible diastolic abnormalities. The current consensus, as derived from the Group for the European Society of Cardiology, is that diastolic heart failure can be diagnosed in the presence of 2 criteria: (1) symptoms and signs of heart failure and (2) a normal (>50%) EF.

When spontaneously hypertensive rats (SHR) with established hypertension were challenged with abrupt volume expansion (preload), they were able to increase their cardiac outputs per gram of left ventricle reasonably well at 11 and 24 weeks of age, compared with normotensive Wistar-Kyoto (WKY) controls. However, at 83 weeks, a biological age corresponding to our patient, there was a considerable reduction in left ventricular pumping ability when the ventricle was challenged. The normal relationship between ventricular mass and pumping ability was markedly deranged. An extension of these observations showed that concentric hypertrophy developed in these aging SHR that subsequently also included the right ventricle, although the septum was largely spared. The failure to accommodate preload with an
increase in cardiac output suggests that ventricular function curves were depressed and that the ventricular compliance in these SHR was markedly impaired. Admittedly, the increased afterload with ever-increasing blood pressure may also have contributed. The authors did not use the term diastolic dysfunction. However, at the time of their investigations, they were not able to measure diastolic dysfunction directly.

We did not measure diastolic function in our patient directly. We relied on echocardiography. We also performed cardiac catheterization, which demonstrated increased ventricular diastolic pressure with preserved systolic function and normal ventricular volumes. The pressures in the cardiac chambers proximal to the affected ventricle were also elevated, namely the left atrial pressure and the pulmonary capillary wedge pressure. However, a micromanometric catheter, which we routinely use in studies on mice, would have been ideal to measure peak negative dP/dt and the time constant of left ventricular dilatation, tau (τ). Others have performed micromanometric studies in small animals with highly relevant results. For instance, the gene for parvalbumin was expressed in the hearts of Sprague-Dawley rats. The protein’s presence was verified by immunofluorescence. The investigators demonstrated a substantial increase in diastolic relaxation. Parvalbumin is a calcium-binding protein that facilitates ultrafast specialized muscle relaxation, such as muscles that control eye movements. Perhaps by expressing parvalbumin in the human heart failing from diastolic heart failure, an improvement could be realized.

Micromanometric measurements are also possible in patients. Left ventricular pressure-volume relationships were measured in 10 heart failure (NYHA II/III) patients with preserved EF, 9 asymptomatic age-matched controls, 14 young normotensive controls, and 25 age- and blood pressure-matched controls. A conductance micromanometric catheter was used in all but the latter 25 patients. Preload was reduced during the measurements with pressure on the inferior vena cava. Sustained hand-grip studies and bicycle ergometry were also used in some subjects. EF in the heart chambers proximal to the affected ventricle were also elevated, namely the left atrial pressure and the pulmonary capillary wedge pressure. However, a micromanometric catheter, which we routinely use in studies on mice, would have been ideal to measure peak negative dP/dt and the time constant of left ventricular dilatation, tau (τ). Others have performed micromanometric studies in small animals with highly relevant results. For instance, the gene for parvalbumin was expressed in the hearts of Sprague-Dawley rats. The protein’s presence was verified by immunofluorescence. The investigators demonstrated a substantial increase in diastolic relaxation. Parvalbumin is a calcium-binding protein that facilitates ultrafast specialized muscle relaxation, such as muscles that control eye movements. Perhaps by expressing parvalbumin in the human heart failing from diastolic heart failure, an improvement could be realized.

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Obesity
Obese persons already show echocardiographic evidence of diastolic dysfunction even when hypertension is not present.4 The 2 conditions are clearly associated.21 Recently, a study using microneurography in CHF patients showed that those who had obesity combined with hypertension exhibited considerably more sympathetic activation than CHF patients who had either condition alone.22 The authors implicated impaired baroreflex regulation in their obese, hypertensive CHF patients. Another concomitant feature of obesity and hypertension is sleep apnea, which we did not exclude with precision in our patient but should have.23 Once they have heart failure, obese patients may do better than lean or emaciated patients. This finding comes as no surprise, because cachexia is a sequel to heart failure and, although overweight does not exclude cachexia, obesity may provide a cushion for some patients (starvation in a sea of plenty).24 Obesity is associated with generalized inflammation, particularly around blood vessels.25 In an earlier study, we examined the relationship between adiponectin, an anti-inflammatory factor produced by adipocytes, and inflammatory mediators in obese but otherwise healthy women.26 While CRP and interleukin (IL)-6 concentrations were directly correlated with BMI in these women, adiponectin and adipose tissue adiponectin gene expression were inversely correlated with BMI.

Adipocytes are not solely responsible for the production of inflammatory cytokines in obesity. Recently, macrophage recruitment and infiltration into white adipose tissue was shown in obese animal models.27,28 Adipose tissue macrophages were responsible for almost all adipose tissue tumor necrosis factor (TNF)-α, IL-6, and inducible nitric oxide synthase expression in the models. Moreover, the macrophage migration from bone marrow into adipose tissue preceded an increase in the animals’ circulating insulin levels. The insulin-sensitizing drug rosiglitazone downregulated the inflammatory genes in the macrophages. Human obesity can feature profound inflammation in so-called Weber-Christian disease.29 This condition features signs of systemic inflammation and an intense panniculitis. Clinicians have argued whether Weber-Christian disease exists as a distinct entity.29 However, the inflammatory spectrum in obesity is surely a continuum and possibly Weber-Christian disease represents the extreme of a distribution curve. The deleterious role of TNF-α on systolic and diastolic function was documented earlier, although heart failure intervention studies with a soluble TNF-α receptor were disappointing.30

Dialysis as a Treatment Option
Heart failure refractory to all drug therapy warrants an assist device for patients eligible for transplantation or hemofiltration for symptomatic relief. We selected peritoneal dialysis. This therapy is experimental and only anecdotal reports are available.31 We used an intermittent, automated, cycler-driven approach. Ultrafiltration effectively treated our patient’s refractory edema and improved her symptoms. We are not certain that we
prolonged her life. However, we lowered her filling pressures, consistent with the clinical improvement.

**The Clinical Diagnosis (Dr Pilz and Dr Luft)**
The clinical diagnosis was obesity-related, hypertension-induced, “overload” cardiomyopathy with diastolic heart failure and prerenal azotemia.

**Final Pathological Diagnosis (Dr Bräsen and Dr Schneider)**
The heart weighed 720 g (twice normal) and showed evidence of marked eccentric cardiac hypertrophy. The coronary arteries showed minimal evidence of atherosclerosis and no evidence for recent or earlier myocardial infarction was found. The atria were both enlarged. However, there were no adherent thrombi. The pericardium was thickened but not adherent. The valve leaflets were soft without evidence of disease. There was no patent foramen ovale. Histologically, the ventricular cardiomyocytes showed evidence of hypertrophy (Figure 5A), and the connective tissue matrix was increased, consistent with interstitial fibrosis. Each kidney weighed 250 g. They were imbedded in a hardened layer of adherent perirenal fat. The capsule could not be stripped. The cortex was not diminished and the renal papillae showed no evidence of necrosis. Histologically, the glomeruli were unremarkable. The tubules showed evidence of postmortem changes. However, there was little interstitial fibrosis and the vessels showed only moderate evidence of arteriolosclerosis.

In obese hypertensive rabbits, the renal medullary interstitium was found to be expanded and stained intensely with periodic acid Schiff and Alcian blue, and tissue hyaluronic content was elevated in the renal inner medulla. We found no evidence of such changes in the kidneys.

A surprising finding was evidence for a widespread panniculitis with extensive macrophage infiltration. Skin lesions on the lower extremities showed a lobular panniculitis. The small vessels within the subcutis (Figure 5B) showed evidence of calciphylaxis involving small arteries, arterioles, and even capillaries. However, the parathyroid glands were normal. The small vessels of the myocardium showed no such changes. The epicardial and the mediastinal fat showed evidence of inflammatory changes; namely, panniculitis was present. The pathological picture is consistent with Pfeifer-Weber-Christian disease. The condition has been associated with cardiac dilatation and congestive heart failure. Endomyocardial biopsy demonstrated myocyte degeneration and interstitial fibrosis in the patient described, but no typical features of acute inflammation. Clinical symptoms of congestive heart failure also were recognized in 7 of the 11 reported autopsy cases of Pfeifer-Weber-Christian disease having cardiac involvement. The primary feature in these patients was acute and chronic inflammatory cell infiltration in the myocardium consistent with myocarditis. The patients had severe left ventricular systolic function impairment as the cause of their heart failure. They also had epicardial and pericardial changes that compromised their function further. Our patient had fibrosis but not myocarditis.

Weber and Christian separately described a relapsing, nonsuppurative nodular panniculitis commonly presenting as a generalized inflammatory disorder. Pfeifer described the condition in the German language. Whether the nodular panniculitis exists as a discrete entity is a matter of debate. We cannot state for certain that this patient’s cardiac failure was related to her panniculitis, although the generalized systemic inflammation may have very well contributed. Certainly her long-standing poorly treated hypertension can explain the eccentric cardiac hypertrophy and diastolic dysfunction. Numerous complimentary mechanisms have been implicated in obesity-associated hypertension. We can only speculate what role the panniculitis in the perirenal fat might have played in causing renal dysfunction or possibly sodium retention. The panniculitis may explain a role in her intermittent fever episodes and signs of inflammation. The skin changes were probably erroneously ascribed to cellulitis.

**Pathological Diagnoses (Drs Bräsen and Schneider)**
The pathological diagnoses were biventricular eccentric cardiac hypertrophy and Pfeifer-Weber-Christian panniculitis.
involving skin with calciphylaxis, in the mediastinum, epicardium, and perirenal fat.

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Obesity and Hypertension-Induced Restrictive Cardiomyopathy: A Harbinger of Things to Come
Bernhard Pilz, Jan-Hinrich Bräsen, Wolfgang Schneider and Friedrich C. Luft

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