High Prevalence of Cardiac Parvovirus B19 Infection in Patients With Isolated Left Ventricular Diastolic Dysfunction

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Background—The etiology of left ventricular (LV) isolated diastolic dysfunction often remains unclear. In the present study, we report a strong association between parvovirus B19 (PVB19) genomes and isolated LV diastolic dysfunction.

Methods and Results—In 70 patients (mean±SD age, 43±11 years) admitted with exertional dyspnea and/or reduced exercise tolerance despite preserved LV systolic contractility (ejection fraction=68%), isolated diastolic dysfunction was clinically suspected. Patients with classic risk factors for diastolic dysfunction such as hypertension, coronary heart disease, diabetes mellitus, or pulmonary disease had been excluded. Diastolic function was assessed by echocardiography and LV and RV catheterization. Endomyocardial biopsies (EMBs) were analyzed for the presence of storage or infiltrative diseases or myocarditis, including molecular screening for cardiotropic virus genomes. In a substudy of 24 patients who reported atypical angina, coronary endothelial function was additionally investigated with a coronary Doppler flow-wire technique. In 37 of 70 patients (53%), isolated diastolic dysfunction was confirmed as the cause of their clinical symptoms. No evidence for cardiac storage or infiltrative diseases was found in these cases, but in 35 of 37 of these patients (95%), cardiotropic virus genomes were detected in EMBs (P<0.001). PVB19 was the most frequent pathogen in 31 of 37 patients (84%). In a subgroup of 10 patients with diastolic dysfunction and coexisting endothelial dysfunction, all 10 (100%) were PVB19 positive.

Conclusions—PVB19 genomes were predominant in patients with unexplained, isolated diastolic dysfunction. A strong association with the incidence of endothelial dysfunction was obvious, consistent with the hypothesis that PVB19-induced endothelial dysfunction may be a possible pathomechanism underlying diastolic dysfunction. (Circulation. 2005;111:879-886.)

Key Words: diastole ■ endothelium ■ myocarditis ■ viruses ■ biopsy

The clinical syndrome of congestive heart failure (CHF) occurs in the presence of both preserved and depressed left ventricular (LV) function. Thirty percent to 50% of patients with clinically suspected CHF but normal LV systolic function have isolated diastolic dysfunction or failure. The clinical manifestations of diastolic and systolic heart failure are similar, although the primary hemodynamic mechanisms are different. Decreased ventricular compliance and abnormal diastolic filling are the key functional anomalies in patients with diastolic dysfunction, causing symptoms of pulmonary congestion during exercise (diastolic dysfunction) or at rest (diastolic heart failure).1,2 The prevalence of diastolic dysfunction increases with age and may reach 50% in the elderly, in whom age-related causes of LV diastolic dysfunction such as hypertension, coronary artery disease, diabetes mellitus, and obesity are common. Isolated diastolic dysfunction is less common in younger patients and has many causes, eg, hypertrophic, infiltrative, or restrictive cardiomyopathies and pericardial or valvular diseases. However, the pathophysiological basis for this syndrome very often remains unclear, especially in younger patients in whom comorbidity is rather low compared with the elderly.3 To further investigate the possible etiology of isolated diastolic dysfunction, we analyzed endomyocardial biopsies (EMBs) for the presence of storage or infiltrative diseases or myocarditis, including a molecular screening for cardiotropic virus genomes in a series of middle-aged patients with clinically suspected CHF despite preserved LV systolic contractility and dimensions.

Methods

Patient Population

We investigated consecutive patients admitted to our unit between March 2001 and December 2003 who had exertional...
dyspnea and/or reduced exercise tolerance as their chief complaints despite preserved LV contractility and dimensions, as determined by echocardiography. Exclusion criteria were age >70 years, hypertension, LV hypertrophy (LV wall thickness >11 mm), coronary heart disease, diabetes mellitus, obesity, valvular disease, arrhythmias, lung disease, renal dysfunction, or other severe concomitant diseases. We identified 70 patients who met these criteria and gave informed, written consent for invasive diagnostic procedures, including echocardiography, right and left cardiac catheterization, and right ventricular (RV) biopsies, which were performed by using standard techniques. All patients had normal lipid profiles.

Definition and Assessment of Diastolic Dysfunction
According to the guidelines from the European Study Group on Diastolic Heart Failure, a diagnosis of diastolic dysfunction was defined after evidence of abnormal LV relaxation, filling, and/or diastolic distensibility in the presence of clinical signs of CHF with demonstrable normal or only mildly impaired systolic function (ejection fraction [EF] >50%). During LV angiography, slow, isovolumic LV relaxation was indicated by an increase in dp/dtmax (greater than -1100 mm Hg/s) and/or prolongation of the time constant of LV pressure decay (r >48 ms), as derived from LV pressure recordings, and/or during echocardiography (ViNGMED system FiVc) by a prolongation of isovolumic relaxation time as derived from LV outflow tract Doppler signals. Slow, early LV filling was indicated by a reduction of the ratio of E-wave to A-wave peak velocities and/or an increase of the E-wave deceleration time, as derived from LV Doppler signals. Because the specificity and sensitivity of any one of these 3 echocardiographic parameters per se is low, diastolic dysfunction was considered when at least 2 of these parameters were abnormal after adjustment for age and heart rate. Reduced LV diastolic distensibility was indicated by an increase in LV end-diastolic pressure (>16 mm Hg) as derived from LV pressure recordings and/or by pulmonary capillary wedge pressure measured by right heart catheterization (Swan-Ganz catheter) at rest (>12 mm Hg) or during exercise (>20 mm Hg by bicycle ergometry). In addition, N-terminal (NT) pro-B-type natriuretic peptide (NT-pro-BNP) plasma levels (Elecsys 2010, Roche Diagnostics) were determined.

Coronary Angiography and Endothelial Function Test
To exclude abnormal systolic LV function and/or coronary heart disease, LV angiography and standard coronary angiography were performed in all patients. We also sought to clarify whether diastolic dysfunction coexisted with coronary endothelial dysfunction in a subgroup of 24 of our patients reporting atypical angina. After analyzing the hemodynamic indices of LV diastolic function, coronary endothelial function was assessed in an additional protocol after analyzing the hemodynamic indices of LV diastolic function, coronary endothelial function was assessed in an additional protocol after intracoronary injection of acetylcholine (ACh). In brief, via a 6F guiding catheter, a 3.6F infusion catheter (Medtronic) was advanced over a 0.014-in. Doppler flow-velocity guidewire equipped with a 20-MHz pulse Doppler ultrasound crystal at its tip (FlowMAP, Cardiometrics) and was carefully positioned in a straight proximal segment of the left descending coronary artery to achieve a laminar flow profile. Coronary blood flow (CBF) at baseline and after ACh injection in 3 incremental doses (0.072 μg/min, 0.72 μg/min, and 7.2 μg/min, each over 2.5 minutes) was estimated as previously described. The increase of CBF after intracoronary injection of ACh (7.2 μg/min) was used to quantify endothelial function. Maximal increase in CBF being lower than twice that evoked by ACh injection was considered a sign of coronary endothelial dysfunction.

Endomyocardial Biopsies
Six EMBs were obtained from the RV septum of each patient with a flexible biopsome (Westmed) via the femoral vein approach as described elsewhere. Two biopsy samples were used for histological and immunohistological evaluation, and the remaining 4 were subjected to DNA and RNA extraction for amplification of viral genomes.

Histological and Immunohistological Assessment of EMBs
Histological evaluations were performed on paraffin sections according to the Dallas classification. Immunohistological assessment of EMBs was carried out as described elsewhere.

Detection of Viral Genomes in EMBs by nPCR and qPCR
DNA and RNA were extracted simultaneously from snap-frozen EMB probes as described elsewhere. Detection of parvovirus B19 (PVB19) DNA by nested PCR (nPCR) was performed as described previously with primers specific for the VP1/VP2 coding sequence. PVB19-specific primers used for PCR resulted in a PCR amplicon of 290 bp and, in the second round of PCR, in a 173-bp amplicon. Specificity of PCR products was confirmed by automated DNA sequencing. Detected sequences were matched with the NCBI GenBank and compared with a recently described PVB19 genome (GenBank accession No. U38509). In addition, PCR/quantitative, real-time PCR (qPCR) was performed for the detection of enteroviruses (EVs), including coxsackieviruses and echoviruses; adenoviruses; human cytomegalovirus; Epstein-Barr virus; human herpesvirus 6 (HHV6); and Borrelia burgdorferi. As a control for successful extraction of nucleic acids, primer sequences were chosen from the sequence of the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene.

Primers and probe for PVB19 qPCR (Taqlman 7000, Applied Biosystems) were designed from the PVB19 VP1/2 open reading frame as described previously. Reactions and cycling were performed as recommended by the manufacturer’s instructions. PVB19 plasmid DNA in different dilutions (3.5 to 3.5 x 10^6 genomes per qPCR) was included to standardize the system. PVB19-infected bone marrow tissue served as a positive control (8 x 10^6 PVB19 genome equivalents per microgram nucleic acid).

All samples were analyzed at a minimum in duplicate. As a control for successful extraction of nucleic acids and the addition of equivalent amounts of human DNA used in the qPCRs, a qPCR of the ATP synthase-6 gene was performed as previously described.

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BMI indicates body mass index; MAP, mean arterial pressure. Other abbreviations are as defined in text.
Statistical Analysis

SPSS for Windows standard version 11.0.1 was used for statistical analysis. Results are expressed as mean±SD (range), unless stated otherwise. Quantitative, normally distributed data were compared by 1-way ANOVA and Student t test. The nonparametric Wilcoxon/Kruskal-Wallis test was used for nonnormally distributed variables. To compare qualitative data, χ² and 2-tailed Fisher exact test were performed. P<0.05 was considered statistically significant.

Figure 1. Relation between isolated diastolic dysfunction and detection of cardiotropic virus genomes. Prevalence of cardiac viral genomes was 95% in patients with isolated diastolic dysfunction of unknown cause. In contrast, in patients with concomitant clinical symptoms of CHF but undetectable diastolic dysfunction, prevalence of cardiac viral genomes was only 24%.
Figure 2. Qualitative and quantitative presentation of PVB19 genomes in EMBs of patients with endothelial and diastolic dysfunction. A, PVB19 DNA loads in EMBs of 14 representative patients (depicted at right) are demonstrated by qPCR amplification plot. Fluorescence reporter signal (Rn) emitted by Taqman probe was measured and plotted against cycle number. Insert demonstrates reference curve obtained by correlation of crossing-point values determined from amplification plot and PVB19 DNA copy number per PCR reaction. B, qPCR amplification plot of housekeeping gene ATP synthase-6 of same biopsy specimens shown in A. Additional amplification curves obtained from PVB19-negative biopsy samples (a–h) were also included. C, Graph of PVB19 DNA copy number per μg isolated nucleic acid of 12 PVB19-positive and 2 PVB19-negative patients calculated from respective amplification plot. D, Graph of ATP synthase-6 amplification plot shown in B, demonstrating that equivalent amount of human DNA were included in each qPCR. E, Qualitative detection of PVB19 DNA was performed by nPCR with PVB19-VP1/2–specific primers, generating 173-bp PVB19 VP2 fragment. PVB19–specific DNA fragments are shown for 12 PVB19-positive and 2 PVB19-negative patients (lanes 4 through 18; see also A). Note that no PVB19 DNA was amplified from patients 55 and 59 (lanes 6 and 10). In these lanes and in negative control (lane 3), only primers are
Results

Study Participants
All 70 patients had clinical signs of CHF with preserved normal LV systolic function and dimension. Mean age (±SD) was 43±11 years; 38 (54%) were men; 32 (46%) were women; and mean LVEF was 68±9% (Table 1).

Diastolic Dysfunction
Among these 70 consecutive admissions with suspected CHF despite preserved systolic LV function, in 37 cases (53%), abnormal diastolic function was confirmed as the cause of their symptoms. Thirty-three of these had isolated diastolic dysfunction, and 4 had diastolic heart failure. Diastolic dysfunction was confirmed by abnormal values of LV end-diastolic pressure, pulmonary capillary wedge pressure at rest or exercise, , isovolumic relaxation time, deceleration time, and/or the E-wave to A-wave ratio. , which probably reflects more systolic relaxation than diastolic function, did not differ between groups (Table 2). Plasma pro-NT-BNP levels were increased 3-fold in patients with diastolic abnormalities compared with patients considered to have normal LV diastolic function (17.9±18.6 versus 6.9±5.3 pmol/L, \(P=0.003\)).

Histology and PCR Analysis
None of the analyzed EMBs showed evidence of infiltrative cardiomyopathies or storage disorders like hemochromatosis, amyloidosis, or mucopolysaccharidosis; also, no active or borderline myocarditis according to the Dallas criteria was present. Thirty-five of 37 patients (95%) with diastolic dysfunction were virus positive in the PCR analysis, but only 8 of 33 patients (24%) without evidence of diastolic dysfunction were virus positive (Figure 1). Among the 37 patients with diastolic dysfunction, 31 (84%) had PVB19 genomes. Of these PVB19-positive patients, 24 of 37 (65%) had a PVB19 monoinfection, 6 of 37 (16%) had a coinfection with HHV6, and 1 of 37 (3%) had a coinfection with HHV6 and Epstein-Barr virus. The EV and HHV6 genomes as monoinfections occurred in 2 of 37. In patients without evidence of LV diastolic dysfunction, PVB19 genomes were detected in only 7 of 33 (21%) (monoinfection, 6/33 [18%]; coinfection with HHV6, 1/33 [3%]) and monoinfection with EV and HHV6 in 1 of 33 (3%) and 0 of 33 (0%), respectively. The prevalence of virus genome was significantly increased in patients with diastolic dysfunction compared with patients without evidence of LV diastolic dysfunction (35/37 versus 8/33, \(P<0.001\)) as summarized in Figure 1.

To determine the phenotype of PVB19 in patients with proven diastolic dysfunction, we determined the qualitative and quantitative presentation of PVB19 genomes in cardiac tissue specimens (Figure 2). Additionally, the sequences of the amplified PVB19 VP2 regions were analyzed and compared with each other as one additional measure to exclude cross-contamination, which may occur during the highly sensitive nPCR processes (Figure 2G). Representative qPCR and gel electrophoresis results of amplified PVB19 genomes are given in Figure 2A through 2F. The amplification plot of the qPCR (Figure 2A) and the calculation of viral load (Figure 2C) demonstrated low viral titers of myocardial PVB19 genomes of approximately \(10^2\) to \(10^3\) PVB19 genome visible. PCR products were separated on 1.8% agarose gels and visualized by ethidium bromide staining. F, PCR amplification of housekeeping gene GAPDH demonstrating that equivalent quantities of human DNA were included in each PCR. Panels E and F represents composite of individual routine agarose gels. PhiX174 BsuRI DNA marker is seen in lane 1. G, PVB19 sequences of virus-positive patients were aligned with reference PVB19 sequences (accession No. U38509). Sequence homologies are denoted as dots; point mutations are shown in letters. Ruler on top was numbered according to VP1 sequences (VP1 ATG=1, minus strand). NTC indicates negative control.
equivalents per microgram of nucleic acid, which is consistent with a persistent type of infection. The corresponding gel electrophoresis results of the PVB19 VP2 fragments amplified by nPCR in the respective patients are shown in Figure 2E. Note that for the negative control (lane 3), no PVB19-specific, 173-bp fragment was visible (Figure 2E). In this case, only the primer pairs could be recognized as faint bands. The intensities of the PVB19-specific bands shown by gel electrophoresis (Figure 2E) were well correlated with the PVB19 viral load as determined by the qPCR experiments (Figure 2C). To demonstrate that equivalent amounts of DNA were used in the PCRs and qPCRs, the housekeeping genes ATP synthase-6 and GAPDH were amplified in parallel from the same patient samples (Figure 2B, 2D, and 2F).

All PCR amplicons were sequenced and confirmed the positive PVB19 PCR results (Figure 2G). Sequence analyses of PVB19 revealed randomly distributed point mutations in the VP1/2 region of the PVB19 isolates. With respect to quality control of the PCR assays, it is noteworthy that the PVB19 isolates showed sequence differences when compared with each other. Therefore, cross-contamination of the patient’s samples with PVB19, as may occur during nPCR procedures, can be excluded. Interestingly, sequence variations at positions 817, 861, 864, and 902 of the VP2 region might reflect different PVB19 genotypes (Figure 2G). However, the possible presence of different genotypes still has to be elucidated in more detail.

**Coronary Endothelial Dysfunction**

The results for those patients who had atypical angina symptoms and consented to the endothelial function substudy (n=24) are summarized in Figure 3. We diagnosed endothelial dysfunction in 13 of 24 patients (54%), as indicated by a lower increase in CBF (230±12% versus 153±13%, \( P=0.028 \)) during the ACh test. Ten of 13 (77%) of these patients also had diastolic dysfunction, and these 10 patients were all positive for PVB19 genomes (73% monoinfection, 27% coinfection with HHV6). In comparison with virus-negative patients with normal diastolic and endothelial function who had atypical angina, however, the increase in CBF of these 10 patients was significantly reduced (Figure 4). Only 3 patients with normal endothelial function showed diastolic dysfunction, from which group just one was also virus positive. In contrast, 7 of 8 patients (88%) without endothelial or diastolic dysfunction were virus negative.

**Discussion**

**High Prevalence of PVB19 in Patients With Isolated Diastolic Dysfunction**

Our study showed a high prevalence of cardiotropic viral genomes in patients with diastolic dysfunction of unknown origin. This association was revealed by the use of a novel molecular genetic screening procedure to detect a broad panel of cardiotropic viruses.

More than one third of patients presenting with symptoms and signs of CHF have isolated diastolic dysfunction. Clinical examination cannot distinguish between systolic and diastolic dysfunction or failure. The clinical management of diastolic heart failure includes the elimination or reduction of factors known to cause diastolic dysfunction, eg, myocardial hypertrophy, fibrosis, or ischemia. However, the involved factor(s) often remains unknown, and clinical management is restricted to the treatment of the consequences of diastolic dysfunction, such as venous congestion. Because diastolic dysfunction is associated with increased mortality and morbidity, clarification of involved pathomechanisms is important and may lead to novel treatment options.

The pathomechanisms that cause anomalies of diastolic function may be classified as extramyocardial and intramyocardial. The latter include disturbances within the cardiomyocytes, including changes in calcium homeostasis, changes within the extracellular matrix, and those that stimulate neurohumoral activation or inhibit cardiac endothelial systems. A broad range of cardiomyopathies, including storage and infiltrative diseases and myocarditis, all which can be definitely diagnosed only after analysis of EMBs, may affect any of these cardiac compartments and are possible candidates for the induction of isolated diastolic dysfunction. We report here isolated diastolic dysfunction to be strongly associated with the presence of cardiotropic virus genomes in the myocardium.

**Cardiotropic Viral Infection and Their Clinical Manifestations**

Cardiac viral infections have no typical clinical presentation. The symptoms of myocarditis patients are highly variable and range from severely impaired cardiac dysfunction or failure to unexplained arrhythmias to atypical chest discomfort. Patients may also be asymptomatic. This complex and highly variable clinical phenotype, in combination with mostly negative or inconsistent results of the histological evaluation of EMBs according to the Dallas criteria, has contributed to the frequent failure to confirm the clinical
suspicion of myocarditis. Cardiotropic viruses may also influence diastolic function via cytokine-dependent pathomechanisms, leading to an impairment of the intracellular calcium cycle by inducing changes in the extracellular matrix composition or by impairment of the nitric oxide synthase pathway, resulting in endothelial dysfunction.

**PVB19 as a Cardiac Pathogenic Agent**

In our study, the most common infectious pathogen found by PCR in the EMBs of patients with diastolic dysfunction was PVB19. Although PVB19 is the only known human pathogenic virus with a serological rate of infection of >70% in human controls, there are several indicators attributing cardiotropic properties to PVB19. PVB19 DNA has been found in fetal myocardial cells, in patients with suspected myocarditis, and in patients with cardiac allograft rejection after heart transplantation. The significance of PVB19 genomes in EMBs of patients with “idiopathic” dilated cardiomyopathy has not yet been clarified, but it appears to play a role in the induction of endothelial dysfunction and coronary vasospasms in patients with acute myocarditis mimicking acute myocardial infarction. Endothelial cells have been recognized as targets for PVB19 infection in small cardiac vessels, whereas cardiomyocytes have so far not been described as targets for this virus type. The most likely cardiac location of PVB19 in our patient is the endothelium, based on all currently available studies in humans. Alternatively, PVB19 could also reside in other cardiac cell types or in blood-borne cells, which previously might have migrated into the heart. However, at the time of investigation, no circulating cells carrying PVB19 were detected in any patient. However, depending on the specific cardiac cellular location of PVB19 in our patients, its association with endothelial dysfunction may be direct (endothelial location) or indirect (other cell types).

The icosahedral capsid of PVB19 consists of 2 structural proteins, VP1 and VP2. Both proteins also have a variety of other functions that are important for the viral life cycle, including the induction of cytokines and/or of phospholipase A2, which is an intermediate during the synthesis of the eicosanoids, prostaglandins, and leukotrienes that play an important role in inflammatory reactions and that may also lead to host cell dysfunction. Therefore, PVB19 infection of the endothelium may cause endothelial dysfunction in infected patients without coronary artery disease. This dysfunction appears to reach a very high level during acute infections, mimicking the clinical phenotype of myocardial infarction. Coinfection with PVB19 and HHV6, as seen in 7 of 37 (19%) of our patients, has been previously reported in fulminant myocarditis, and it has been suggested that HHV6-induced immunosuppression can lead to enhanced dissemination of PVB19. However, HHV6, as seen in 9 of 37 (24%) of our patients, is thought to exhibit a unique spectrum of biological properties that make it an immunosuppressive agent of its own. In this context, it should be noted that vasculotropism of HHV6 has also recently been demonstrated in human cardiac microvessels. HHV6 can modulate the de novo synthesis of regulated upon activation of normal T cell expressed and secreted chemokine, also indicating a major role for HHV6 in endothelial cell biology and the development of inflammatory processes. Although EVs can infect endothelial cells, EV infections appears to be less frequent in patients with isolated diastolic heart failure than PVB19 or HHV6.

**Possible Association Between Endothelial and Diastolic Dysfunction in Viral Cardiomyopathy**

Transient myocardial ischemia induced by endothelial dysfunction is associated with a rapid reduction in ATP concentration, depletion of glycogen storage, and a transition from aerobic to anaerobic metabolism. Thus, a reduction in energy and the nitric oxide supply belongs to the involved mechanisms that also cause impairment of LV relaxation. Therefore, ischemic changes, eg, by coronary vasospasms, whether silent or symptomatic, can cause reduced wall motion and/or isolated cardiac contractile dysfunction, including diastolic dysfunction and progression of cardiomyopathy. Myocardial inflammation is associated with endothelial dysfunction. In particular, the high prevalence of PVB19 infection in acute myocarditis patients with the clinical presentation of acute myocardial infarction in the absence of relevant coronary artery stenoses suggests that this infection mode may contribute to coronary dysfunction and/or vasospasm.

In summary, our data suggest a possible pathogenic role for PVB19 in a considerable fraction of patients with isolated diastolic dysfunction of unknown origin. In about half of our study group, diastolic dysfunction could not be verified as a cause for clinical symptoms, and the prevalence of cardiac viral genomes was low in this group. Even EMBs taken in a search for infiltrative, storage, or other morphologically detectable cardiac diseases could not identify a possible reason for their symptoms, which remained cryptogenic.

In conclusion, PVB19 was the most frequent viral genome in the myocardium of patients with isolated diastolic dysfunction in whom classic causes like LV hypertrophy, coronary heart disease, or diabetes had been excluded. A strong association of PVB19 with the incidence of endothelial dysfunction was obvious, suggesting PVB19-induced impairment of the coronary microcirculation as a possible trigger of diastolic dysfunction. PVB19 should therefore be considered a potential cardiotropic pathogenic factor in patients with isolated diastolic dysfunction.

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**References**


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