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Original Investigation

Hemodialysis-Induced Regional Left Ventricular Systolic Dysfunction and Inflammation: A Cross-sectional Study

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Background: Hemodialysis may acutely induce regional left ventricular (LV) systolic dysfunction, which is associated with increased mortality and progressive heart failure. We tested the hypothesis that hemodialysis-induced regional LV systolic dysfunction is associated with inflammation and endothelial injury. Additionally, we studied whether hemodialysis-induced LV systolic dysfunction is associated with an exaggerated bioincompatibility reaction to hemodialysis.

Study Design: Cross-sectional study.

Setting & Participants: 105 hemodialysis patients on a thrice-weekly dialysis schedule were studied between March 2009 and March 2010.

Predictors: Plasma indexes of inflammation (high-sensitivity C-reactive protein, pentraxin 3 [PTX3], interleukin 6 [IL-6], and IL-6:IL-10 ratio), bioincompatibility (leukocytes, neutrophils, complement C3, and myeloperoxidase), and endothelial function (soluble intercellular adhesion molecule 1 [ICAM-1], von Willebrand factor, proendothelin, and endothelin) were measured just before dialysis and at 60, 180, and 240 minutes intradialysis.

Outcomes: Hemodialysis-induced regional LV systolic function. Wall motion score was measured by echocardiography at 30 minutes predialysis, 60 and 180 minutes intradialysis, and 30 minutes postdialysis. We defined hemodialysis-induced regional LV systolic dysfunction as an increase in wall motion score in 2 or more segments.

Results: Patients with hemodialysis-induced regional LV systolic dysfunction (n = 29 [27%]) had significantly higher predialysis high-sensitivity C-reactive protein, PTX3, IL-6, and IL-6:IL-10 ratio values. Predialysis levels of bioincompatibility and endothelial markers did not differ between groups. Intradialysis courses of markers of inflammation, bioincompatibility, and endothelial function did not differ in patients with versus without hemodialysis-induced regional LV systolic dysfunction.

Limitations: Coronary angiography or computed tomography for quantification of coronary calcifications in our patients was not performed; therefore, we could not relate markers of inflammation to the extent of atherosclerosis.

Conclusions: Patients with hemodialysis-induced regional LV systolic dysfunction have a proinflammatory cytokine profile. There was no indication of an association with an exaggerated bioincompatibility reaction to hemodialysis.

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INDEX WORDS: Cardiac stunning; hemodialysis; left ventricular systolic dysfunction; proinflammatory cytokine; biomarker; high-sensitivity C-reactive protein (hs-CRP); interleukin 6 (IL-6); pentraxin 3 (PTX3); progressive heart failure; hemodynamic instability; echocardiography.

Hemodialysis is life-saving in patients requiring replacement of kidney function, but the adverse effects of the hemodialysis procedure may contribute to the high cardiovascular risk observed in these patients. The hemodialysis procedure clearly is stressful for the cardiovascular system because it often is accompanied by hemodynamic instability.[1] We and other investigators have shown that regular hemodialysis sessions can induce reversible reductions in myocardial blood flow, with such severity as to lead to transient left ventricular (LV) systolic dysfunction.[2,3] Subsequent studies have shown that

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hemodialysis-induced LV systolic dysfunction is relatively frequent and is associated with an increased incidence of all-cause mortality and progressive heart failure.[4,5]

The pathogenesis of hemodialysis-induced LV systolic dysfunction currently is unknown. In the general population, acute and chronic cardiac ischemia and heart failure are all associated with a proinflammatory cytokine pattern, and inflammation is thought to play a pivotal role in the progression of these conditions.[6] Hemodialysis patients have markedly elevated levels of various proinflammatory cytokines, and higher levels of these inflammatory markers are associated with increased risk of cardiovascular events and mortality.[7] We hypothesized that systemic inflammation also has a role in the pathophysiology of hemodialysis-induced regional LV systolic dysfunction, for example, by its negative effects on endothelial function of the myocardial microcirculation and/or by cardiodepressive effects of proinflammatory cytokines.[8,9] The first objective of this study therefore was to evaluate whether patients with hemodialysis-induced regional LV systolic dysfunction have elevated predialysis plasma levels of markers of inflammation and endothelial injury. The second objective was to investigate whether patients with hemodialysis-induced regional LV systolic dysfunction have an exaggerated bioincompatibility response to hemodialysis as a potential source of systemic inflammation.

METHODS

Patients and Study Design

Hemodialysis patients from the Dialysis Center Groningen and University Medical Center Groningen were eligible for this study if they were treated with hemodialysis for more than 3 months and were on a thrice-weekly hemodialysis schedule. Patients with severe heart failure (New York Heart Association class IV) and patients who did not have an adequate window for transthoracic echocardiography imaging were excluded. The recruitment process of participants is outlined in Fig 1. Of the 235 in-center patients during the study period, 76 patients were not eligible for the study. Of these, 41 patients did not fulfill inclusion criteria, 27 patients were excluded due to severe heart failure, and 8 patients were excluded due to lack of a proper window for echocardiographic imaging.

Patients were studied at the dialysis session following the longest interdialytic interval (3 days). Dialysis session length was 4 hours. Patients' characteristics were assessed at study entry. Diabetes was defined as fasting blood glucose level $\geq$ 7 mmol/L or use of antidiabetic drugs. Hypertension was defined as predialysis systolic blood pressure $>$ 140 mm Hg and/or diastolic blood pressure $>$ 90 mm Hg or use of antihypertensive drugs. Cardiovascular history was defined as a history of ischemic heart disease, congestive heart failure, coronary artery bypass grafting, percutaneous coronary intervention, stroke, or peripheral vascular disease. These data were obtained from patients' medical records.

Blood pressure and heart rate were measured before and after dialysis. Ultrafiltration rate was expressed in milliliters per hour per kilogram by dividing ultrafiltration volume by dialysis session length and target weight.[10] Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentrations according to the second-generation logarithmic Daugirdas equation.[11] Nutritional status was assessed with the 7-point subjective global assessment.[12] Patients with subjective global assessment score of 5 or lower were defined as malnourished. The study was performed according to the Declaration of Helsinki and was approved by the Medical Ethical Committee of the University Medical Center Groningen. All patients gave written informed consent. The study was performed between March 2009 and March 2010.

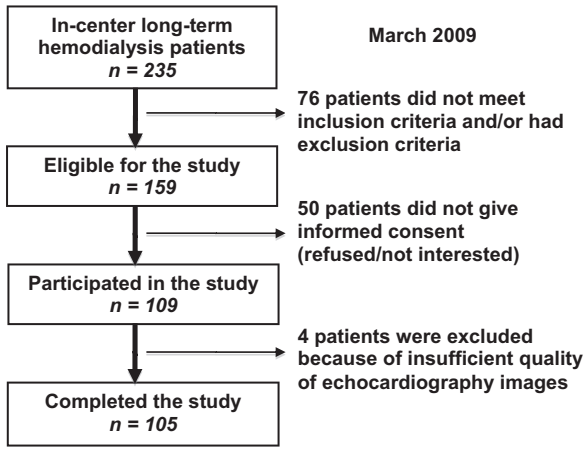

Figure 1. Recruitment process of study participants.

Dialysis Settings

All patients were on bicarbonate dialysis with a low-flux polysulfone hollow-fiber dialyzer (F8; Fresenius Medical Care). Blood flow and dialysate flow rates were 250-350 and 500 mL/min, respectively. Dialysate temperature was 36.0°C in all patients. Dialysate composition was as follows: sodium, 139 mmol/L; calcium, 1.5 mmol/L; magnesium, 0.5 mmol/L; chloride, 108 mmol/L; bicarbonate, 34 mmol/L; acetate, 3.0 mmol/L; and glucose, 1.0 g/L. Potassium concentration was 1.0 or 2.0 mmol/L, depending on prevailing plasma potassium concentrations. We used constant ultrafiltration rate and dialysate conductivity. The water for hemodialysis complied with the requirements of the European Pharmacopoeia ($<$100 colony-forming units/mL; $<$0.25 endotoxin units/mL). Patients received a light meal after the echocardiography at 60 minutes intradialysis. Patients received dialysis in a supine position, which was convenient for echocardiography and excluded the effect of posture changes on blood volume.

Echocardiography Examination

A team of 3 experienced technicians performed 2-dimensional echocardiography using a General Electric VIVID 7 system with a 2.5-mHz probe. Echocardiography was performed 4 times: before hemodialysis, at 60 and 180 minutes intradialysis, and 30 minutes postdialysis. Global and regional systolic function was evaluated by LV ejection fraction (LVEF) and wall motion score index (WMSI), respectively. LVEF was calculated using the biplane Simpson method. WMSI was evaluated according to the 16-segment model as recommended by the European Society of Echocardiography[13] by a single technician (Y.M.H.) who was blinded to the order of echocardiography studies. For each patient, the number of LV regions that developed new regional wall motion abnormalities during hemodialysis was calculated. Regional wall motion abnormality was defined as an increase in wall motion score in that specific LV segment occurring at either 60 or 180 minutes intradialysis or 30 minutes posthemodialysis in