Assessment of Arterial Stiffness in Stable Heart Transplant Recipients

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ABSTRACT

Introduction. Arterial stiffness depends on both genetic and environmental factors. The aim of this study was to assess arterial stiffness in patients after heart transplant.

Methods. The study was conducted between May and June 2017. Fifty patients from the Transplantology Clinic of the Institute of Cardiology in Anin, Warsaw, Poland, were enrolled in the study. Pulse wave velocity (PWV), central systolic blood pressure (CSBP), and central diastolic blood pressure (CDBP) were measured and patients' medical records were also analyzed.

Results. In the study, 50 patients aged 57.9 years on average were evaluated, of whom 88% were male patients, with average PWV of 8.94 m/s and an average time after transplant of 9.7 years. The study has shown that age ($R = 0.77$), total cholesterol concentration ($R = 0.22$, $P = .017$) and creatinine concentration ($R = 0.34$; $P = .15$) show positive correlation with PWV.

Conclusions. Our data indicates that age has significant impact on arterial stiffness and the type of immunosuppressive drugs and transplant rejection episodes do not impact an increase in arterial stiffness.

THE assessment of arterial stiffness is increasingly considered to be a surrogate measure of cardiovascular disease. In addition to invasive methods, arterial stiffness can be measured by non-invasive methods that are easily replicable and relatively inexpensive techniques. Thus, the arterial stiffness examination is suitable for studies on a much larger scale. Arterial stiffness is related to the presence of cardiovascular disease (CVD) risk factors [1,2]. The properties of arterial elasticity are increasingly used when diagnosing many diseases, and the recent recommendations of the European Society of Hypertension and European Society of Cardiology regarding the treatment of hypertension suggested pulse wave velocity (PWV) measurement, which is considered to be the gold standard method of assessing aortic stiffness [3,4]. In order to characterize the properties of large arteries, the following measures should be used: susceptibility, expansion, and stiffness. Susceptibility is described as elasticity and is defined as a relative change in the blood vessel diameter compared to the change in arterial blood pressure. Expansion is the ratio of susceptibility and initial vessel volume. The mutual relation of both measures is shown by the following formula: $C = D \times V$, where C is susceptibility, D is expansion, and V is vessel volume. Considering the above formula, arterial stiffness is negatively correlated with susceptibility and expansion. Arterial stiffness changes the properties of large arteries, causing mostly reduction of their cushioning ability. In the structural sense, changes in arterial stiffness are rather long term. Ratios used to describe them, especially indirect ones, show large short-term correlation with arterial blood pressure, left ventricular ejection fraction (LVEF), or heart rate [5]. Artertial stiffness can be indirectly related to short-term changes in arterial blood pressure. Special attention is paid to pulse pressure (PP). Large increases in PP over time indicates developing arterial stiffness. A link between increasing PP and long-term cardiovascular death risk has been shown [6]. Increased uric acid levels are better correlated with arterial stiffness as measured by PWV rather

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than C-reactive protein (CRP) [7]. Orthotopic heart transplant (OHT) is a validated method of treating patients with end-stage heart failure. In recent decades, post-OHT survival rate improved with the development of immunosuppressive treatment [8,9]. In clinical transplantology, free radical reactions are responsible both for the damage to the transplant and cardiovascular complications. Most tests in post–kidney transplant (KTx) patients show intensification of free radical processes, especially lipid peroxidation. The answer to whether tacrolimus (TAC) and other calcineurin inhibitors inhibit or intensify oxidative stress in post-KTx patients is key. Tacrolimus (FK-506) is widely used in immunosuppressive therapy and has a better heart profile than cyclosporine A (CsA). "The beneficial impact of TAC on oxidative stress levels has been widely reported. In vitro and in vivo tests on animals have shown the antioxidative properties of TAC; a decrease in oxidative stress parameters has been observed, including malondialehyde levels, myeloperoxidase activity, and the presence of neutrophil infiltration, in response to TAC use" [10]. Endothelial dysfunction is an early marker of post-OHT atherosclerotic lesions; therefore, it is important to know how drugs administered after transplantation impact the endothelial free radical processes. In vitro cultivation of human endothelial cells from microvessels has shown that CsA, rapamycin, and mycophenolate mofetil (MMF) induced oxidative stress more strongly compared to methylloprednisolone and TAC. Oxidative stress induction by immunosuppressive drugs was linked to metabolic activity and apoptosis. Except for TAC, all the drugs tested increased the production of the free radical nitrogen oxide (NO). It should be emphasized that methylprednisolone and MMF caused smaller changes in the functioning of endothelial cells compared to CsA, rapamycin, and TAC [11]. Short-term post-OHT results improved significantly, yet long-term ones remain poor due to cardiac allograft vasculopathy (CAV) [9]. Assessment of arterial elasticity may provide important information about early functional changes which precede initial arterial wall thickening and later development of CAV. Studies in the general population have demonstrated that small artery elasticity (SAE) and large artery elasticity (LAE) measured through radial artery is a prognostic factor for CVD, CHD, stroke, and heart failure events. LAE, a marker of arterial stiffness, which entails structural damage to peripheral arteries, is linked to cardiovascular risk [12]. The purpose of this study was to assess arterial stiffness and the underlying factors among post-OHT patients.

METHODS

This single-center, case-control observational study was conducted between May and June 2017. Fifty patients of the Institute of Cardiology in Anin, Warsaw, Poland, were enrolled in the study. Subjects enrolled in the study were informed orally and in writing about the rules, purposes, and benefits of the study. They consented to participate in the study in writing. The inclusion criterion was age over 18 years, post-OHT time between 3 months to 20 years, and provision of a signed informed consent form to participate in the study. The study was carried out in accordance with the principles of ethics (Declaration of Helsinki) and has been approved by the Regional Bioethics Committee of the Institute of Cardiology (approval no. 1620). PWV measurements were taken during the patient's routine visit to the Transplantology Clinic. All PWV measurements were taken by 1 trained investigator. The following laboratory tests were used in the study: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, sodium, potassium, uric acid, creatinine, urea, glucose, bilirubin, creatine kinase (CK), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), CRP, hemoglobin, hematocrit, and platelets, which were taken from the patients' medical records. The purpose of the study was to provide information about the general clinical condition of the study group, characteristics of the laboratory tests, and to present the impact of diabetes, immunosuppressive treatment, and OHT rejection on arterial stiffness. Wide inclusion criteria were used to determine what factors determine the increase in arterial stiffness in post-OHT patients. PWV measurements were taken using BR-102 plus PWV (Schiller, Baar, Switzerland) recommended by the European Society of Hypertension. Patients were examined between 8:00 am and noon after a 15-minute rest in a sitting position. The device measured PWV, CSBP), and CDBP. Compared with the transplant recipients, the control group consisted of 20 healthy volunteers, mean age was 38 years ($P < .001$), 20% male ($P < .001$), mean PWV of 6.4 m/s ($P < .001$), mean SBP of 121 mm Hg ($P < .001$), mean CSBP of 115 mm Hg ($P < .001$), and mean waist circumstance of 80 cm ($P < .001$). , Continuous variables were presented in the form of mean ± standard deviation (SD), and the qualitative features were presented as a percentage distribution. Variables of normal distribution and the homogeneous variances were verified by Student t test. Pearson's linear correlation coefficient was used to study the relationship between variables. Variables that did not have a normal distribution were subjected to non-parametric tests for unrelated variables Kruskal-Wallis test or χ^2. Statistical analysis was performed using Statistica 13.1 software (StatSoft Inc., Tulsa, Okla, United States), assuming a threshold of significance at $P < .05$.

RESULTS

In the study, 50 post-OHT patients aged 57.9 years on average were evaluated, of whom 88% were male patients, with average PWV of 8.94 m/s and average time after transplant of 9.7 years. Age showed positive correlation with PWV ($r = 0.77$). CSBP showed positive correlation with PWV ($r = 0.47$). PWV also showed positive correlation with CDBP ($r = 0.38$). There was a positive correlation between post-OHT time and PWV ($R = 0.43$). The results have not demonstrated any impact of transplant rejection on PWV. Average PWV of patients without rejection history was 9.08 m/s. On the other hand, patients with rejection history had an average PWV of 8.46 m/s ($P = .31$). CSBP in patients with rejection history was higher compared to patients without rejection history (134 vs 127 mm Hg, $P = .374$). The results do not demonstrate any impact of diabetes on PWV in post-OHT patients. PWV was slightly higher in patients with diabetes, who had an average PWV of 9.11 m/s compared to non-diabetics with an average PWV of 8.78 m/s ($P = .525$). Post-OHT patients treated with CsA demonstrated higher