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Original Article

# Predictive value of circulating osteonectin in patients with ischemic symptomatic chronic heart failure


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ABSTRACT

*Background:* Osteonectin (OSN) plays a pivotal role in cardiac remodeling, but predictive value for OSN in ischemic chronic heart failure (CHF) has not been defined. The aim of the study was to evaluate the prognostic value of OSN for cumulative survival and hospitalization among patients with ischemic-induced CHF.
*Methods:* A total of 154 patients with ischemic symptomatic moderate-to-severe CHF were enrolled in the study at discharge from the hospital. Observation period was up to 3 years (156 weeks). Blood samples for biomarkers measurements were collected at baseline prior to study entry. ELISA methods for measurements of circulating level of OSN were used.
*Results:* During a median follow-up of 2.18 years, 21 participants died and 106 subjects were re-admitted. Medians of circulating levels of OSN in survival and died patient cohorts were 670.96 ng/mL (95% confidence interval [CI] = 636.53–705.35 ng/mL) and 907.84 ng/mL (95% CI = 878.02–937.60 ng/mL). Receiver operation characteristic curve analysis has shown that cut off point of OSN concentration for cumulative survival function was 845.15 ng/mL. It has been found a significant divergence of Kaplan–Meier survival curves in patients with high (>845.15 ng/mL) and low (<845.15 ng/mL) concentrations of OSN. Circulating OSN independently predicted all-cause mortality (odds ratio [OR] = 1.23; 95% CI = 1.10–1.36; $p < 0.001$), CHF-related death (OR = 1.46; 95% CI = 1.22–1.80; $p < 0.001$), and also CHF-related re-admission (OR = 1.92; 95% CI = 1.77–2.45; $p < 0.001$) within 3 years of observation period.
*Conclusion:* Increased circulating secreted protein acidic and rich in cysteine family member OSN associates with increased 3-year CHF-related death, all-cause mortality, and risk for recurrent hospitalization due to CHF.

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## At a glance commentary

### *Scientific background on the subject*

Osteonectin plays a pivotal role in extracellular matrix remodeling in various diseases, including chronic heart failure. Elevation of osteonectin associates with cardiac hypertrophy and impaired heart function. However, the independent prediction of elevated serum osteonectin in heart failure patients is still not completely clear.

### *What this study adds to the field*

This study adds new information regarding the predictive role of elevated serum osteonectin in patients with chronic heart failure. Osteonectin is posed as an inflammatory biomarker with possible predictive value. Results of the study reported being of an independent association of elevated osteonectin with poor 3-year prognosis in chronic heart failure patients.

Matrix cellular proteins, that is, secreted protein acidic and rich in cysteine (SPARC), play a key role in postsynthetic procollagen processing in heart failure myocardium and regulate cell adhesion, growth factor activity, and cell cycle [1]. It has been found that SPARC family member osteonectin (OSN) causes myocardial hypertrophy, increased fibrillar collagen content, stimulates cell signaling, adhesion, survival, proliferation, and migration in several cell types, mediates calcification of the vascular wall, coagulation, and endothelial dysfunction [2]. Moreover, OSN increases collagen deposition in response to myocardial infarction (MI) or in some types of cardiac hypertrophy can impair heart function [3]. Recent animal studies have been revealed that increased circulating OSN level strongly associates with a higher incidence of mortality following MI. Therefore, clinical studies have shown that serum OSN level relates to increased rates of cardiac wall rupture and newly, heart failure in MI subjects [4,5]. However, the role of OSN in ischemic-induced chronic heart failure (CHF) development and progression has not been defined. The aim of the study was to evaluate the prognostic value of OSN for cumulative survival and hospitalization among patients with ischemic-induced CHF.

## Methods

The study prospectively evolved 154 patients (86 male, 68 females) aged 48–62 years with ischemic symptomatic CHF with II–IV New York Heart Association (NYHA) class. CHF was diagnosed according to current European Society of Cardiology clinical guidelines [6]. The exclusion criteria are: Q-wave and non-Q-wave MI within 3 months before study entry; severe kidney and liver diseases that may affect clinical outcomes; malignancy; creatinine plasma level above 440 μmol/L; estimated glomerular filtration rate (GFR) < 35 mL/min/$m^2$; brain injury within 3 months before the enrollment; body mass index (BMI) above 30 kg/$m^2$; pulmonary edema; tachyarrhythmia; valvular heart disease; thyrotoxicosis; ischemic stroke; intracranial hemorrhage; acute infections; surgery; trauma; all the ischemic events within three previous months; inflammations within a previous month; neoplasm; pregnancy; implanted pacemaker, any disorder that may discontinue patient's participation in the study according to investigators; and patient's refusal to participate in the study or to give his consent for it. Observation period was up to 3 years (156 weeks). We analyzed cumulative survival related to CHF, and additionally all-cause mortality was examined.

### *Methods for visualization of coronary arteries*

Multi-spiral computed contrast enhanced tomography angiography and/or angiographic study have been carried out to verify the ischemic nature of the disease prior to the study entry. Angiographic procedure was used when ischemic signs were presented at baseline, and no MI was found previously. Multi-spiral computed contrast enhanced tomography angiography was performed when no current ischemic signs/previously documented old MI at baseline were detected, but signs and symptoms of CHF were presented. Multi-spiral computed tomography angiography has been carried out for all the patients prior to their inclusion in the study. When atherosclerotic lesions of the coronary arteries were verified, patients were subjected to the conventional angiographic examination provided indications for re-vascularization were available. Coronary artery disease (CAD) was considered to be diagnosed upon availability of previous angiographic examinations carried out not later than 6 months ago provided no new cardiovascular events occurred for this period, and the procedure is available for assay. The coronary artery wall structure was measured by means of contrast spiral computed tomography angiography on Somatom Volume Zoom Scanner (Siemens, Erlangen, Germany) with two detector rows when holding patients breathe at the end of breathing in [7]. After preliminary native scanning, nonionic contrast Omnipaque (Amersham Health, Ireland) was administered for the optimal image of the coronary arteries. To reconstruct the image, 0.6-mm width axial tomographic slices were used. When >50% of the diameter of three and more coronary arteries were found, the multi-vessel disease was determined.

### *Transthoracic echocardiography*

Transthoracic echocardiography was performed according to a conventional procedure on ACUSON apparatus, Siemens, Germany, in B-mode regimen and tissue Doppler echocardiography regimen from parasternal, subcostal, and apical positions over the short and long axis with phased transducer of 5 MHz. Left ventricular end-diastolic and end-systolic volumes were measured by modified Simpson's method. Left ventricular ejection fraction (LVEF) was assessed in compliance with the requirements of American Society of Echocardiography [8]. Tissue Doppler echocardiography was carried out in 4-, 3- and 2-chamber projections in each of 16 segments of the left ventricle and in 4 spots of the mitral annulus: At the base of posterior septal, lateral, inferior, and anterior left ventricular

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