Identification of a specific pattern of downregulation in expression of isoforms of vascular endothelial growth factor in dilated cardiomyopathy


Recent work suggests that myocardial hypoxia or ischaemia are also pathophysiologic factors in idiopathic dilated cardiomyopathy (IDC). Besides several other factors (increased wall stress, endothelial dysfunction, decreased coronary reserve), the observed decreased capillarisation in IDC, disproportionate to the rate of hypertrophy, may further contribute to this oxygen demand–supply mismatch. The reason for this seemingly decreased angiogenic capacity remains unclear, however a role for microvascular abnormalities in heart failure is now recognised. Hypoxia is the key factor in the induction of vascular endothelial growth factor (VEGF). Increased expression of VEGF causes angiogenesis, and expression level of VEGF could therefore mediate the capillarisation in IDC. Recently, data have been reported on this issue, and the authors found a downregulation of VEGF121, VEGF165, and VEGF189 isoforms. The VEGF121 however was not investigated, although it has been suggested that this isoform in particular has powerful angiogenic capacities. Additionally, it is unclear whether VEGF expression is related to the severity of the disease.

SUBJECTS AND METHODS
We analysed 28 patients with IDC. Patients had enlarged left ventricular end diastolic and systolic diameters (LVEDD 69 (2.1) mm, LVEDD 61 (2.6) mm), and decreased left ventricular ejection fraction (LVEF) (0.27 (0.03)), and elevated wedge (15 (2.1) mm, LVESD 61 (2.6) mm), and decreased left ventricular end diastolic and systolic diameters (LVEDD 69 (2.1) mm, LVEDD 61 (2.6) mm), and decreased left ventricular ejection fraction (LVEF) (0.27 (0.03)), and elevated wedge (15 (2.1) mm, LVESD 61 (2.6) mm). Echocardiography did not reveal cardiac failure. We analysed 28 patients with IDC. Patients had enlarged left ventricular end diastolic and systolic diameters (LVEDD 69 (2.1) mm, LVEDD 61 (2.6) mm), and decreased left ventricular ejection fraction (LVEF) (0.27 (0.03)), and elevated wedge (15 (2.1) mm, LVESD 61 (2.6) mm), and decreased left ventricular end diastolic and systolic diameters (LVEDD 69 (2.1) mm, LVEDD 61 (2.6) mm), and decreased left ventricular ejection fraction (LVEF) (0.27 (0.03)), and elevated wedge (15 (2.1) mm, LVESD 61 (2.6) mm). Echocardiography did not reveal cardiac failure.

Animal studies have supported the possible involvement of VEGF in the pathophysiology and progression of heart failure. Additionally, it is well established that in IDC capillary density is decreased, and capillary morphology is altered (luminal swelling, lumen narrowing), and these microvascular abnormalities are thought to play an important role in the perpetuation of heart failure. VEGF is a key determinant in capillary growth. Therefore, we propose a concept in which the level of VEGF expression mediates, at least in part, the capillary abnormalities and hence the myocardial contractility in...
cardiomyopathies, also in the absence of overt coronary artery occlusions. Since we found an equally lowered level of VEGF mRNA expression in mild and severe IDC, the decreased VEGF expression level may represent a mechanism in the progression of IDC.

Thus far, only one report (Abraham and colleagues) is available on the expression of VEGF in IDC; the present findings are in line with this report with respect to the down-regulation of VEGF_{121} and VEGF_{165}. Abraham and colleagues, however, did not investigate the presence of VEGF_{189}; the isoform that we found decreased the most. All three isoforms have angiogenic properties, however the shorter isoforms have been shown to be more potent than VEGF_{189}. The longer VEGF isoforms, especially VEGF_{165} and to a lesser extent VEGF_{189}, are more tightly bound to the cellular surface and matrix than VEGF_{121}. Given the abundant apposition of matrix-heparin sulfates in IDC, it may be possible that VEGF_{121} and VEGF_{165} are accumulated in the matrix, and are less available. VEGF_{121} that is not bound to the matrix can diffuse more readily in the tissue and may therefore be the most potently mitogenic VEGF isoform in the failing heart.

In conclusion, the results of this study show that the condition of IDC per se leads to decreased expression of VEGF, especially the potent pro-angiogenic isoform VEGF_{121}. VEGF expression is probably not regulated by common cardiac stress pathways, since its decline was not correlated with left ventricular functional parameters. We speculate that interventions that induce angiogenesis, like therapeutic angiogenesis with VEGF_{121} protein or gene transfer, could be beneficial for patients with IDC.

ACKNOWLEDGEMENTS

Dr Van Veldhuisen and Dr Tio are supported by the Netherlands Heart Foundation (grants D97-017 and D95-019, respectively).

Authors’ affiliations

R A De Boer, R A Tio, Y M Pinto, D J Van Veldhuisen, Thoraxcenter, Department of Cardiology, University Hospital Groningen, The Netherlands
R H Henning, W H Van Gilst, Department of Clinical Pharmacology, University of Groningen, The Netherlands
R M H J Brouwer, Institute for Cardiothoracic Surgery, University Hospital Nijmegen, The Netherlands
R J Ploeg, Department of Surgery, University Hospital, Groningen, The Netherlands
M Böhm, Universitäts und Poliklinik für Innere Medizin III, Homburg/Saar, Germany

Correspondence to: Rudolf A de Boer MD, Thoraxcenter, Department of Cardiology, University Hospital Groningen; PO Box 30.001, Groningen 9700 RB, The Netherlands; r.a.de.boer@thorax.azg.nl

Accepted 12 June 2002

REFERENCES

2 Liu PP, Mak S, Stewart DJ. Potential role of the microvasculature in progression of heart failure. Am J Cardiol 1999;84:231–26L
A 60 year old man presented with increasing breathlessness one month following an uncomplicated mitral valve repair. An echocardiogram showed a moderately sized pericardial effusion of 2 cm. Subxiphoid drainage of the pericardial effusion yielded 200 ml of blood stained fluid. Ten hours later the patient complained of palpitations, and telemetry showed a "broad complex tachycardia" (see 12 lead ECG below). The patient was haemodynamically stable.

The patient was initially treated with 100 ml of intravenous lignocaine and subsequently converted to sinus rhythm (right upper panel) after synchronised cardioversion with a 200 J shock. Looking back at his ECG, he was in atrial flutter with 2:1 block (right lower panel) before drainage of his pericardial effusion.

Close inspection of the 12 lead ECG (below) showed several features to suggest that this may not be ventricular tachycardia. Firstly, not all the QRS complexes in all 12 leads are broad (that is, > 120 ms), particularly in limb lead III. Secondly, the QRS complexes in the anterior leads give a false impression of being broad because the up sloping portion of the ST segment can easily be mistaken as part of the QRS complexes. There is no evidence of atrioventricular dissociation.

After DC cardioversion, the patient remained in sinus rhythm without the need for any antiarrhythmics. There were no further recurrence of his pericardial effusion or tachycardia.