Medial tunica degeneration of the ascending aortic wall is associated with specific microRNA changes in bicuspid aortic valve disease

CALOGERA PISANO[1*], ANTONELLA MARINO GAMMAZZA[2*], FRANCESCA RAPPA[2*], ROSARIO BARONE[2], ROSALINDA ALLEGRO[3], ALESSANDRO PITRUZZELLA[2], ALESSANDRA TAGLIAVIA[4], VIRGINIA AGOSTARA[4], GIOVANNI RUVOLO[1], FRANCESCO CAPPELLO[1] and VINCENZO ARGANO[4]

[1]Cardiac Surgery Unit, Tor Vergata University Hospital, I-00133 Rome; Departments of [2]Biomedicine, Neurosciences and Advanced Diagnostics, [3]Statistics and [4]Cardiac Surgery, University of Palermo, I-90100 Palermo, Italy

Received October 11, 2020; Accepted July 6, 2021

DOI: 10.3892/mmr.2021.12516

Abstract. Ascending aortic diameter is not an accurate parameter for surgical indication in patients with bicuspid aortic valve (BAV). Thus, the present study aimed to identify specific microRNAs (miRNAs/miRs) and their expression levels in aortic wall aneurysm associated with BAV according to severity of medial degeneration and to elucidate the association between the tissue expression levels of the miRNAs with their expression in plasma. Aortic wall and blood specimens were obtained from 38 patients: 12 controls and 26 patients with BAV with ascending aortic aneurysm. Of the patients with BAV, 19 had cusp fusions of right and left, 5 of right and non-coronary, and 2 of left and non-coronary. Two groups of patients were identified according to the grade of medial degeneration (MD): Low-grade D group (LGMD) and high-grade MD group (HGMD). Expression level of miR-122, miR-130, miR-718 and miR-486 were validated by reverse transcription-quantitative PCR in plasma and tissue samples. MD grade was found to be independent from the BAV phenotype. The HGD group showed increased expression levels of MMP-9 and MMP-2, and an increase in the number of apoptotic cells. Tissue expression levels of miR-718 and miR-122 were lower in the LGMD and HGD groups compared with expression in the control group; the HGD group showed increased levels of miR-486. Plasma expression levels of miR-122 were decreased in the LGMD and HGD groups, and miR-718 was only reduced in the HGD group. On the contrary, expression of miR-486 was increased in the LGMD and HGD groups. The data suggested that miR-486 may be considered as a non-invasive biomarker of aortic wall degeneration. Dysregulation of this putative biomarker may be associated with high risk of dissection and rupture in patients with BAV.

Correspondence to: Professor Calogera Pisano, Cardiac Surgery Unit, Tor Vergata University Hospital, 81 Viale Oxford, I-00133 Rome, Italy
E-mail: lindapisano82@gmail.com

*Contributed equally

Key words: bicuspid aortic valve disease, microRNAs, ascending aorta, biomarkers

Introduction

Bicuspid aortic valve disease (BAV) represents the most common congenital heart defect. BAV is generally considered to affect 0.5 to 1.4% of the population, with a male prevalence based on autopsy studies and small echocardiographic studies (1-3). BAV is a complex and heterogeneous disease accounting for more premature deaths than all other congenital heart diseases combined (4). The mechanism of the disease process is still unclear, and a number of questions remain unanswered. BAV can occur as a component of genetic syndromes. For example, 30% of women with Turner syndrome also have BAV (5). On the other hand, evidence of familial clustering of BAV suggests that familial inherited BAV aligns with autosomal dominant transmission with reduced penetrance (6). Analysis of particular pedigrees, positional cloning approach, and genetic analysis have proven to be crucial to the discovery of multiple genetic loci associated with familial BAV, including the involvement of the Notch1 and GATA binding protein 5 (7,8) Different phenotypes of BAV have been identified according to cusp fusion (9): i) Phenotype I, right-left (R-L) coronary cusp fusion, which is associated with coarctation of the aorta, aortic stenosis and increased aortic wall shear stress; ii) phenotype II, right-non-coronary (R-NC) cusp fusion, associated with cusp pathology, aortic stenosis and regurgitation, aortic aneurysm, larger aortic arch dimensions and myxomatous mitral valve disease; and iii) phenotype III, left-non-coronary (L-NC) cusp fusion, which is rare.

The most common abnormality in adults with BAV is enlargement of the thoracic aorta (10) and this varies according to the pattern of cusp fusion, with faster rates of aortic sinus and ascending aortic dilatation associated with the L-R compared with the R-NC morphology.