Atherosclerosis 227 (2013) 153–158

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

# Association of variance in anatomical elements of myocardial bridge with coronary atherosclerosis

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ARTICLE INFO

*Article history:*
Received 2 July 2012
Received in revised form
6 November 2012
Accepted 29 November 2012
Available online 28 December 2012

*Keywords:*
Myocardial bridge
Atherosclerosis
Coronary artery
Adipose tissue
Anatomy

ABSTRACT

*Objectives:* The myocardial bridge (MB) is an anatomical structure consisting of myocardium covering a part of the left anterior descending coronary artery (LAD). The extent and spatial distribution of atherosclerosis in the LAD with an MB is influenced by the anatomical properties of the MB. In this study, the relationship between the overall anatomical framework of the MB including the periarterial adipose tissue as well as fibrosis of the MB itself and coronary atherosclerosis was histomorphometrically examined.

*Methods:* Full-length LADs with an MB from 180 autopsied hearts were cross-sectioned at 5-mm intervals. Together with measurements of MB – length, thickness, and location, proportional decrease of the atherosclerosis ratio of LAD segments beneath MB for that of LAD segments proximal to MB was defined as the atherosclerosis suppression ratio. The area ratio of adipose tissue in the periarterial area beneath MB and area ratio of fibrosis in the MB muscle were also measured.

*Results:* The atherosclerosis suppression ratio was significantly proportional to MB length and thickness. Periarterial adipose tissue beneath MB was detected in all cases (100%), and fibrosis within MB muscle for 136 cases (75.6%). The amount of adipose tissue beneath MB and MB fibrosis did not statistically affect the atherosclerosis suppression ratio. Multivariate analysis revealed MB length and thickness were the independent factors affecting the atherosclerosis suppression ratio.

*Conclusions:* The anatomical properties of an MB, especially of its length and thickness, play decisive roles as regulators of atherosclerosis in the LAD regardless of the amount of adipose tissue around LAD and MB fibrosis.



## 1. Introduction

A myocardial bridge (MB) is an anatomical structure consisting of myocardial tissue that covers a part of the coronary artery in the epicardial adipose tissue [1]. It presents almost exclusively in the left anterior descending coronary artery (LAD) and is detected angiographically by a finding of coronary stenosis during cardiac systole, which is caused by contraction of the bridging myocardium [2]. Its frequency in the LAD varies from 0.5% to 60% as assessed by coronary angiography, multidetector computed tomography, or autopsy [3]. As for clinical significance, MBs have been considered benign anomalies of the coronary arteries [4–7], but are sometimes associated with various coronary heart diseases [2,8]. Histopathological studies have determined that the LAD segment beneath MB is always free from atherosclerosis, but the LAD segment proximal to MB is susceptible to it. The extent of atherosclerosis suppression in the LAD segment beneath MB is dependent on the anatomical properties of MB, such as its length and thickness [9]. This implies that compressive force from the MB to the LAD segment beneath the MB is closely related to atherosclerosis suppression in this LAD segment.

It has recently been suggested that perivascular tissue beneath MB is histopathologically notable in the longitudinal sections of the LAD [10]. This perivascular space contains adipose tissue which may practically function as a “coronary cushion” against compression by the MB during systole [10]. Furthermore, a perivascular adipose tissue surrounding the coronary artery may be involved in local stimulation of atherosclerotic evolution through active functions of proinflammatory cytokines and adipokines secreted from the periarterial adipose tissue [11–13]. The significance of the presence of periarterial adipose tissue on atherosclerosis suppression in the LAD segment beneath MB has not yet been examined. In addition, when examining the MB histopathologically, fibrotic changes in the bridging myocardium are sometimes apparent. Fibrotic change of varying degrees may reduce the compressive force of the MB influencing on atherosclerosis progression.

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http://dx.doi.org/10.1016/j.atherosclerosis.2012.11.036

In this study, using a histomorphometric approach, we attempted to clarify the significance of the anatomical framework of the MB – including its thickness, length, and location, the perivascular adipose tissue, and the extent of fibrosis in the MB muscle itself – to the development of atherosclerosis in the LAD.

## 2. Materials and methods

### 2.1. Materials

A total of 180 autopsied hearts having an MB over the LAD were collected at Ohmori Hospital, Toho University Medical Center from 2006 to 2010 (Table 1). None of the patients had a history of cardiovascular disease and none of the autopsied hearts had histopathological evidence of significant lesions. The study protocol was approved by the Ethics Committee of Toho University (No. 22001).

### 2.2. Tissue preparation

The LAD from the left coronary ostium to the cardiac apex was removed from the heart together with the surrounding adipose and myocardial tissue at autopsy. They were fixed in 10% neutral buffered formalin, and the full-length LAD was cross-sectioned at 5-mm intervals. Each tissue section was embedded in paraffin, which was then thin-sectioned at 4–5 μm. Thin-sectioned specimens were stained with hematoxylin and eosin and elastic van Gieson (EVG). After microscopic observation, the sections showing the LAD covered by the MB were then stained with Azan-Mallory [14] for an estimation of myocardial fibrosis comprising the MB. In addition, on the purpose of discriminating adipocytes and identifying collagen fibers, immunohistochemistry using antibodies against S-100 protein (rabbit polyclonal; Dako, Japan, Tokyo), collagen type I (mouse monoclonal; Abcam, Tokyo, Japan), collagen type III (rabbit polyclonal; Abcam, Tokyo, Japan), collagen type IV (rabbit polyclonal; Abcam, Tokyo, Japan) was performed by the labeled streptavidin–biotin complex method (Dako, Carpinteria, CA, USA). The immunostaining was visualized by treating the slides with 3,3′-diaminobenzidine tetrahydrochloride and then counterstained with hematoxylin.

In cases having multiple MBs in one LAD, only the most proximal MB was assessed in this study. In each anatomical element, the cases were divided into three groups by almost trisection of the largest value in each categorical element.

**Table 1**
Patient background.

| | |
|---|---|
| Number of cases | 180 cases |
| Sex (male/female) | 131/49 |
| Mean age (mean ± SD) | 67.9 ± 11.9 years (range 19–92) |
| Main disease | |
| Malignant tumor | 106 cases (58.9%) |
| Pneumonia | 38 cases (21.1%) |
| Liver failure | 19 cases (10.6%) |
| Renal failure | 6 cases (3.3%) |
| Others | 11 cases (6.1%) |

SD, standard deviation; MB, myocardial bridge.

### 2.3. Atherosclerosis ratio and atherosclerosis suppression ratio

To evaluate the extent of atherosclerosis, we measured the area of intima and media in each LAD section with EVG staining using automated image analysis system of Visual Measure 32 (Rise System, Sendai, Japan). The ratio of the cross-sectional area of the intima to media was defined as atherosclerosis ratio as follows:

$$\text{Atherosclerosis ratio} = \frac{\text{Cross-sectional area of the intima}}{\text{Cross-sectional area of the media}}$$

In addition, atherosclerosis suppression ratio was defined as the percentage as follows:

$$\text{Atherosclerosis suppression ratio} = 100 \times \left(100 - \frac{\text{Mean atherosclerosis ratio of the bridged segment}}{\text{Mean atherosclerosis ratio of the three sections proximal to MB}}\right)$$

As mean MB length was 1.5 cm which corresponded to the length of three paraffin blocks, we used mean atherosclerosis ratio of three sections proximal to MB.

### 2.4. MB location

Distance from the left coronary ostium to the first segment of the LAD covered by the MB was defined as MB location. Cases were classified into three categories according to MB location: proximal (≤3.5 cm from the left coronary ostium), common (4.0–5.0 cm), and distal (≥5.5 cm).

### 2.5. MB length

The number of sections covered by the MB multiplied by 5 mm was defined as MB length. Cases were classified into three categories according to MB length: short (≤1.0 cm), common (1.5–2.0 cm), and long (≥2.5 cm).

### 2.6. MB thickness

The thickness of myocardial tissue covering the LAD was measured microscopically, and the largest value was defined as MB thickness. Cases were classified into three categories according to MB thickness: thin (<500 μm), common (500–1000 μm), and thick (>1000 μm).

### 2.7. Adipose tissue density beneath MB

The area except myocardial tissue beneath MB was measured in the LAD section with the thickest MB by the same method as for the atherosclerosis ratio, using a section stained with Azan-Mallory. The periarterial space area beneath MB was also measured. The periarterial space mostly consists of adipose tissue, including nerve fibers and small veins, but in this study all of the periarterial area was treated adipose tissue area. The ratio of adipose tissue area to all tissue area beneath MB was defined as adipose tissue density (%). All cases were classified into three groups according to adipose tissue density; small (<30%), common (30–60%), and large (>60%).