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Infection Diseases Section *Review Article*

Cytomegalovirus Infection and Atherosclerosis: A Systematic Review

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Abstract

Cytomegalovirus (CMV) infection is one of the most common infections that affects humans' cardiovascular system. Although the literature includes controversial evidence for any correlation between CMV infection and arterial atherosclerosis, the majority of studies, especially those with larger patient population and stronger data stand for such a relationship. However, the number of prospective studies was very limited. So, we believe that future studies should be directed towards prospective studies investigating either the impact of CMV infection or antiviral treatment on atherosclerosis formation and advancement in different patient populations including patients undergoing CABG and/or patients with moderate atherosclerosis.

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Introduction

The first evidence as to existence of a potential correlation between infectious agents and atherosclerosis was found on the bacterial infections in the late 19th century when Huchard suggested an association between childhood infections and the development of atherosclerosis and shortly after him, three other authors namely Weisel (1906), Klotz (1906) and Osler (1908) reported relationships between atherosclerosis and some other infections mostly bacterial except for measles virus [1]. Then after in the 1940s, Paterson and Cottral [2], proposed that Marek disease virus (MDV), a herpes-type DNA virus, a well demonstrated cause of T-cell type lymphomas, has potential connections with the development of atherosclerosis, and subsequent experimental studies confirmed existence of such an association [3,4].

The human cytomegalovirus (CMV), another member of the herpes virus family whose genome consisted of double-stranded DNA, has one of the largest infection rates among all infectious agents affecting human populations [5]. Besides during its acute phase, CMV can establish a latent infectious course in the hosts' endothelial and peripheral blood mononuclear cells which persists for a lifetime [6]. Although in most cases, CMV induces the initial CMV infection with a self limiting and benign course, it can induce a life threatening disseminated disease [7,8]. CMV infection has also been accused of accelerating atherosclerosis course. Because of the inconsistencies in our knowledge on the CMV atherosclerosis inducing activities, several studies have been conducted to

investigate the potential latency and replication sites of CMV, to determine whether and how CMV infection can lead to atherosclerosis. In a previous study, we examined the prevalence of CMV institution within atherosclerotic plaques of coronary artery disease patients undergoing coronary artery bypass grafting (CABG) identified by PCR test, and found that it was significantly higher than normal artery specimens. In the current study, we aim to review the existing literature to reach to a comprehensive conclusion, based on the existing evidence in the current literature.

Methods

To conduct our systematic review, the primary search was done using the terms "CMV" and “atherosclerosis” as the keywords within the time-span of 1990-2013. The literature search was performed using the Pubmed database, which we believe provides relatively the largest published data of the most relevant studies in the fields of microbiology and angiology. The search was repeated in Google Scholar to find citations of the found articles to achieve potential major published reports which either have not been indexed in Pubmed or have not been retrieved through Pubmed search.

In our search, overall, 242 studies were found upon a search of the literature by Pubmed using the mentioned keywords. Then abstracts of the found reports were screened to find appropriate studies associated with our systematic review. A majority of the studies, despite the keywords used to find them were not associated with our review. Finally, 49 studies have been remained, and reviewed according to the following categorization of the research: Serological evidence for associations between CMV infection and atherosclerosis, carotid artery, CMV antibody and atherosclerosis in Aorta and peripheral arteries, and atherosclerosis and histopathological evidence for CMV replication.

Serological Evidence for Associations between CMV Infection and Atherosclerosis

Despite strong evidence suggesting a significant role for CMV infection on the development of atherosclerosis, the nature of the relationship has not yet been well elucidated. Several epidemiological studies have shown significant correlation between CMV serology and cardiovascular diseases, and in addition to them there are controversial data defying such a relationship. Moreover, it seems that CMV has differential impact on various arteries. So, we believe that any investigation regarding effects of CMV infection on atherosclerosis formation should be specific to each artery.

Coronary Artery Disease

Coronary artery is the most frequently investigated artery for the examination of the relation between atherosclerosis and different infectious agents, especially CMV. This correlation has been demonstrated in different ways, including relation to clinical events (myocardial infarction, acute coronary syndrome, developing ischemic heart disease) or to the extent of atherosclerosis progression. The approaches used by the studies are also inconsistent. Some have investigated the seropositivity of CMV in patients with and without coronary artery disease, while in some others the end-point and the initial data was vice versa. In some studies recurrent coronary events have been investigated and in some mortality was the end-point. Some others also investigated that whether the titre of the anti-CMV IgG can predict clinical outcome. One study also investigated the relevance of active CMV infection defined by CMV IgM and clinical disease. The findings reported by different studies are also quite controversial. Gredmark et al. [9] in a study on 140 patients including forty patients with acute coronary syndrome (ACS), 50 patients with stable angina (SA) with angiographically verified CAD and 50 clinically healthy controls. The prevalence of active CMV infection defined by IgM positivity was significantly higher in patients with ACS (15%) and in patients with stable angina (10%) compared with controls (2%) [9]. In a prospective cohort study of 433 coronary artery disease patients and equal number of controls followed for 4 years, Mundkur et al. [10] found that among 4 infectious types, only anti-CMV

antibody levels were a significant risk factor for coronary artery disease occurrence (OR 2.23 [95% CI 1.20 to 4.15]; P=0.011) and recurrent cardiac events (OR 1.94 [95% CI 0.85 to 4.45]; P=0.015) [10]. Rajasekhar et al. in a case-control study of 117 patients [unstable angina (UA) n=101 and chronic stable angina (CSA) n = 16] found no significant association between CMV seropositivity and coronary syndromes [11]. Al-Ghamdi [12] in another case-control study on 75 cardiovascular disease patients and 15 healthy controls reported that CMV IgG positive rate was significantly higher in the case group, and individuals with CMV-specific IgG were more liable to have vascular disease compared to those without (OR=4.10, CI= 1.07-15.75). They also found that the CMV-IgG titer was significantly correlated with having atherosclerotic vascular disease [12]. In another case-control study on 50 patients with coronary artery disease and 15 healthy controls, a slightly higher rate of CMV IgG was found among the patients, but no significance level was observed [13]. Safaie et al. [14] in a study on 157 patients undergoing coronary angiography, reported that the prevalence of CMV positivity was significantly higher in coronary artery diseases patients than in those without coronary artery diseases (83.2% versus 63.6%) [14]. In a very large Indian study on over 6 thousand people, Shanker et al. [15] reported that coronary artery disease patients were significantly more likely to be CMV seropositive. Jha et al. [16] in a case-control study of 192 CAD patients and 192 healthy controls reported that CMV IgG was significantly more prevalently positive among CAD cases than healthy controls (62/192 vs 38/192) (P = 0.01). Another study involving 192 CAD patients and 140 CAD-patients' close relatives revealed no significant difference regarding CMV IgG positive rate (62 vs 44) [17]. Rothenbacher et al, in a prospective cohort of a median follow up time of 38.2 months of 300 consecutive patients with angiographically defined CAD reported no significant association between seropositivity to CMV and an increased risk for cardiovascular events during follow-up [18]. Heltai et al. [19] in a case control study of 40 cases of acute myocardial infarction, 43 case of stable angina and 46 healthy controls reported no significant difference in CMV antibody titers among the three groups. In a prospective cohort study of 60 ACS patients and 31 CAD controls who were admitted for elective angiography, Timóteo et al. [20] studied the difference between serum CMV antibodies (IgG/IgM) at admission and at 30 days afterwards, and then compared their survival at the 30th day and 6th month after admission. On admission, ACS cases significantly had higher rate of CMV positivity than controls (95% vs. 81%). Patients whose CMV antibody titer doubled or more (<3 times) during the 30 days were significantly more likely to die (17% vs. 11%), and the same observation has been reported at the 6th month of follow up (50% vs. 15%). No one in the control group died. Grahame-Clarke et al. [21] in an interesting study on 400 subjects found that CMV positive patients had impaired vascular function defined by independent significant reductions in responses to bradykinin and glyceryl trinitrate; but the association between CMV seropositivity and coronary artery calcification did not reach the significance level (P=0.09) [21]. In a group of 140 patients with unstable angina pectoris (UA) and in a matched control group, Altannavch et al. [22] reported that patients with UA had a significantly increased titers of IgG antibodies against CMV [22]. Khairy et al. [23] in a cross sectional study on 65 male subjects without CAD reported 34.9% positivity rate for CMV serology, but no dose-response trends between serum titers and endothelial function was reported [23]. Witherell *et al.* [24] compared 121 cases of first MI with 204 controls without MIand found no association between cytomegalovirus and MI [24]. Gattone et al. [25] investigated 120 post-MI patients and compared them with 120 age-matched controls and found that anti-CMV IgG was more frequently observed in the MI cases than in the control subjects. After adjustment for coronary risk factors and socioeconomic status, the OR (95% CI) for premature MI was 2.9 (1.5-5.8) for CMV seropositivity [25]. Another case-control study investigated 152 CAD cases (61 unstable angina

patients, 43 acute myocardial infarction, 26 stable angina, and 22 peripheral arteriopathy) and 30 healthy controls; and found that mean IgG titers were significantly higher in patients from all groups compared to healthy subjects [26]. In a group of 112 patients with or without type 2 diabetes mellitus (NIDDM) and/or coronary artery disease (CAD), CMV IgG titres, was not different among any of the 4 subgroups: 29 (54%) in DM (-) MI (-) group, 9 (60%) in MI (+), DM (-) group, 12 (55%) in DM (+) MI (-) group, and 10 (48%) in MI (+) DM (+) group [27]. In a case control study of 233 patients undergoing coronary angiography and 68% of them representing evidence of CAD, multivariate analyses revealed no significant difference regarding CMV seropositivity for patients with and without CAD [28].

In a population-based prospective cohort study of 726 individuals, after adjusting for demographic data, those with the highest CMV antibody levels (the upper 20%) showed an increased relative risk (RR) of 1.76 (95% CI, 1.00-3.11) for the coronary heart disease. 81 patients were categorized as having single-, double-, triple-, or no coronary vessel involvement. Anti-CMV antibodies could significantly predict the extent of atherosclerosis [29]. The association between CAD and CMV infection has also been reported to be dependent to other factors. A cross-sectional study by Zhu et al. [30] blood samples were taken from 238 individuals being evaluated for CAD by coronary angiography and tested for CMV seropositivity and CRP levels. Multivariate analysis showed that CMV seropositivity was significantly associated with coronary artery disease only when it was simultaneous with elevated CRP. Neither CRP nor CMV seropositivity were alone not significant predictors of CAD [30]. In a prospective cohort study by Blum et al. [31] 65 patients (50 men and 15 women) with coronary artery disease were followed for 12 months with a thallium perfusion scan, after undergoing balloon coronary angioplasty. Patients with high antibody titer (> or = 1:800) had a higher restenosis rate than patients with a low antibody titer (< or = 1:400) [31]. However, another study bu Adler et al. [32] on non-transplant patients undergoing coronary angiography showed no significant relationship between CMV and development of CAD [32]. Finally a meta-analysis involving 9,000 cases and 8,608 controls reported that people with CMV infection had a significant risk for CAD [OR 1.67 (95% CI 1.56-1.79)] relative to those not exposed. CMV infection was a risk factor for coronary disease in both prospective studies [OR, 1.31; 95% CI, 1.132-1.517] and retrospective studies [OR, 1.79; 95% CI, 1.659-1.939], and in both Asian group [OR, 2.69; 95% CI, 2.304-3.144] and non-Asian group [OR, 1.48; 95% CI, 1.371-1.600] [33]. Gabrylewicz et al. [34] investigated 158 subjects (70 patients with acute MI, 40 patients with stable angina, and 48 healthy controls) and found that anti-CMV IgG positivity was significantly more likely to be found in the 110 CAD patients than that in the healthy controls, but the difference between the first two groups was not significant [34].]. Table 1. summarizes data of studies investigating serological evidence of associations between CMV infection and atherosclerosis

Carotid Artery

Carotid artery atherosclerosis and its correlation with CMV seropositivity has also been investigated in several articles. Espinola-Klein et al. [35] in a study on 504 patients (75% men) measured the intima-media thickness (IMT) of the common carotid artery and the prevalence of a internal or external carotid artery stenosis; and after adjustments for common risk factors, they reported that CMV independently increased the risk for the internal or external carotid artery stenosis (OR 1.7, 95% CI 1.1 to 2.8) for IgG titers and for IgA titers (OR 2.3, 95% CI 1.1 to 4. 9)[35].

In another study, authors studied the association between CMV antibody titers of 300 adult residents. The association between CMV antibodies and carotid atherosclerosis was restricted to those with high lipoprotein(a) and fibrinogen values [36]. In a Canadian study on 76 patients with carotid artery stenosis, endarterectomy specimens were studied for atherosclerotic plaques and correlated with CMV seropositivity.

Table 1. Associations between CMV seropositivity and coronary artery disease

Study	Reff	Population	CMV determinant	End-point	Relation	Study methodology
Gredmark et al.	9	140: 40 ACS; 50 SA; 50 HC	CMV IgM	ACS, SA	Exists	Case-control
Mundkur et al.	10	866: 433 CAD & 433 HC	Seropositivity	CAD; recurrent cardiac events	Exists	Prospective cohort
Rajasekhar et al.	11	117: 101 UA; 16 SA	Seropositivity	UA, SA	Not exists	Case-control
Al-Ghamdi et al.	12	90: 20 ACS; 15 Cerebral Stroke; 15 PAD; 15 HC	CMV IgG	ACS, SA, SS, PAD	Exists	Case-control
Al-Ghamdi et al.	13	65: 20 ACS, 30 SA, 15 HC	CMV IgG	ACS, SA	Not exists	Case-control
Safaie et al.	14	157; coronary angiography	CMV IgG	CAD confirmed by angiography	Exists	Case-control
Shanker et al.	15	6053: 2131 CAD; 3901 HC	CMV IgG	Antibody titers in CAD	Exists	Case-control
Jha et al.	16	384: 192 CAD; 192 HC	CMV IgG	CAD	Exists	Case-control
Jha et al.	17	332; 192 CAD; 140 first degree relatives	CMV IgG	CAD	Not exists	Case-control
Rothenbacher et al.	18	300 CAD confirmed by angiography	CMV-serology	Cardiovascular events	Not exists	Prospective cohort
Heltai et al.	19	129; 40AMI; 43 SA; 40 HC	CMV-serology	Antibody titers	Not exists	Case-control
Timóteo et al.	20	91; 60 AMI; 31 CAD on elective angiography	CMV serology	Death	Exists	Prospective cohort
Grahame-Clarke et al.	21	400: 157 underwent venous occlusion plethysmography	CMV IgG	1. Response to bradykinin/ glyceryl trinitrate; 2. Coronary artery calcification	1. exists 2. not exists	Case-control
Altannavch et al.	22	280: 140 UA; 140 HC	CMV IgG	Antibody titer	Exists	Case-control
Khairy et al.	23	65 male without CAD	CMV IgG/IgM (positivity & titer)	Endothelial dysfunction	1. Exists 2. Not exists	Case-control
Witherell et al.	24	325: 121 MI; 204 no MI	CMV IgG	MI	Not exists	Case-control
Gattone et al.	25	240: 120 MI; 120 no MI	CMV IgG	MI	Exists	Case-control
Borgia et al.	26	182: 61 UA; 43 MI; 26 SA; 22 PAD; 30 HC	Mean IgG titers	CAD	Exists	Case-control
Weber et al.	27	112	IgG positivity	CAD and/or T2DM	Not exists	Case-control
Zhu et al.	28	233: 68% CAD	IgG seropositivity	CAD confirmed by angiography	Not exists	Case-control
George et al.	29	81 patients under coronary angiography	CMV antibodies	Extent of coronary disease	Exists	Case-control
Zhu et al.	30	238 patients under coronary angiography	CMV antibodies	CAD	Exists (conditional]	Case-control
Blum et al.	31	65 CAD undergoing balloon angioplasty	CMV titer	Restenosis	Exists	Prospective cohort
Adler et al.	32	900 patients under coronary angiography	CMV antibody	CAD	Not exists	Case-control
Gabrylewicz et al.	34	158: 70 acute MI; 40 SA; 48 HC	CMV IgG	CAD	Exists	Case-control
Sorlie	42	726: 221 CAD; 505 HC	Highest CMV titer (upper 20%)	CAD	Exists	Prospective cohort

CMV antibody was detected in 27 (35.5%) subjects (CI, 24.9% to 47.3%; p<0.001); moreover, CMV (57.8%) was more prevalently found in the atherosclerotic plaques with thrombosis than those without (58% vs. 17%, respectively) [37]. In a cross-sectional study of 163 patients receiving virologically suppressive cART, no difference in anti-CMV IgG was detected respecting IMT pathological status [38]. Anti-CMV antibody titers of 109 high-grade internal carotid artery stenosis patients (asymptomatic n = 40, symptomatic n = 69) undergoing surgery were found seropositive in 72,5% of the cases, but there was no significant relationship between CMV serology and symptomatic atherosclerosis [39]. In a cross-sectional survey including 237 adults, in univariate linear analysis, increased IMT was associated with CMV IgG titer but in multivariate analysis, there was no independent significant relationship [40]. In another case-control study by Nieto et al. [41] 150 individuals with increased carotid IMT were controlled by 150 age- and sex-matched individuals with low IMT. Case subjects had higher mean CMV antibody titers in their sera than control subjects, although after adjustments for other cardiovascular risk factors, the difference was not statistically significant. However, when the data have been graded, they found a significant relation between the odds of IMT and the levels of CMV antibodies that remained significant after adjustment for the main cardiovascular risk factors [41]. CMV antibody was measured in 340 matched case-control pairs from the Atherosclerosis Risk in Communities (ARIC) Study, and there was a modest but not significant association between CMV and asymptomatic carotid wall thickening consistent with early atherosclerosis [42]. The levels of CMV antibody have been determined in 157 caucasian male patients undergoing vascular surgery for atherosclerosis and their data has been compared to a matched control group of patients with high cholesterol levels; and the prevalence of CMV positivity and high antibodies titers were both higher was higher in the surgical group than in the control group [43].

CMV Antibody and Atherosclerosis in Aorta and Peripheral Arteries

The significance of positivity of CMV antibody in the arteries other than coronary and/or carotid has not been vastly investigated. However, we tried our best to find any study that have issued this topic. Grub et al. [44] in a case-control study of 149 subjects (including 119 patients and 30 healthy controls), but found no significant associations between CMV antibody and the occurrence of aortic adventitial mononuclear cell infiltrates [44]. In another study of 155 individuals (119 patients with abdominal aortic aneurysm and 36 matched controls) were investigated prospectively by CMV serology. The study findings suggests that patients with ruptured abdominal aortic aneurysm have similar levels of IgG antibodies against CMV as patients with nonruptured abdominal aortic aneurysm, small abdominal aortic aneurysm, and controls without abdominal aortic aneurysm [45]. In another case-control study, 31 patients suffering from lower limb ischemia and 11 healthy controls were investigated about their anti-CMV IgG titers, and the study showed that CMV-IgG titers were significantly more frequently positive for either patients with peripheral arterial disease or patients with diabetic macroangiopathy, compared to healthy controls [46]. In a large population-based study of 1931 individuals, increased CMV antibody titres were significantly associated systolic and diastolic blood pressure elevation, and associated inversely with brachial artery flow-mediated dilation in males, but in females, no significant association was found. Multivariate regression models confirmed independent association with all of the 3 mentioned factors in men [47]. Another population-based study by Bloemenkamp et al. [48] using serum samples of 228 young women with PAD and 643 control women, CMV IgG antibody titres were determined. There was a significant relation between serological evidence for infection with CMV and PAD [OR 1.6 (95%

CI; 1.1-2.3] [48]. 96 angiographic evaluations on 100 patients with of clinical signs or symptoms suggesting renovascular hypertension have been reported by van der Ven et al. [49] from which atherosclerotic lesions were documented in 67 patients (70%), and in 49 patients (51%) such lesions were present at the level of the renal artery. However authors reported no significant relation between CMV seropositivity and atherosclerosis [49].

Atherosclerosis and Histopathological Evidence for CMV Replication

Although the first and largest evidence regarding potential associations between CMV and atherosclerosis came from seroepidemiological studies, more recent histopathological studies confirming replication of the virus within the atherosclerotic artery walls have strongly confirmed such a relationship. On the other hand, there are controversial reports that either have detected no CMV DNA within atherosclerotic plaques or the difference to the healthy arterial walls was not significant. We start reviewing this section with our own study, which we believe that it provides one of the best evidence on such a relationship to the literature, due to its large sample size and strong methodology. This study included 105 patients undergoing coronary artery bypass grafting (CABG) at our institution, and atherosclerotic plaques as well as 53 specimens from the mamillary artery of these same patients were analyzed by PCR. The CMV PCR test result was positive for 28 (26.7%) of patients with coronary artery atherosclerosis. After adjusting for other risk factors, patients with a history of acute coronary syndrome were more likely to be positive for CMV PCR test (P=0.027; odds ratio: 4.2; 95% CI: 1.18-15.0) and they were also more likely to have a positive family history for cardiovascular diseases [50]. In another cross sectional study, percent positivity scores for CMV in different vascular locations were as follows: aorta (11.7%); carotid (9%); coronary artery (16.6%). Aorta and coronary artery were more susceptible to these pathogens as compared with carotid artery. [34]. In a cross sectional study on large cerebral vessels, autopsy specimens from ten men and nine women were included in the study but authors failed to detect CMV in any of the investigated specimens [52]. In a Japanese study, overall 50 carotid atherosclerotic plaques resected during carotid endarterectomy and analyzed by PCR, but no positive case for CMV DNA has been deteced [53].Samples from 3 different vascular wall specimens (coronary, carotid and abdominal aortas) of 30 patients (23 male, 7 female) were obtained for pathologic and microbiologic investigations during autopsy. CMV DNA was found in 37.9% atherosclerotic and 32.7% non-atherosclerotic vascular wall specimens (3(50%) atherosclerotic vs. 4(16.7%) non atherosclerotic coronary; 5(41.7%) atherosclerotic vs. 7 (38.9%) non-atherosclerotic carotid; 3(27.3%) atherosclerotic vs. 9 (47.4%) non-atherosclerotic abdominal aortic arteries.). No statistically significant differences were found between the atherosclerotic and non-atherosclerotic groups in any of the 3 investigated arteries [54]. Fifteen atherosclerotic coronary artery specimens and 15 samples from internal mammary arteries without atherosclerotic degeneration were investigated. CMV was detected in 67% samples from cases and in 47%) samples of the internal mamillary artery; no comparison has been performed, although there seems not to be a significant difference between the two groups [55]. In a population based study, individuals with echolucent (n=29) or echogenic (n=28) carotid artery plaques, and controls without carotid plaques (n=38) were investigated for CMV DNA in thier peripheral blood mononuclear cells sample; but no positive case has been detected [56]. In a case-control study, authors divided 38 coronary plaque specimens obtained from 38 patients who underwent coronary atherectomy or thrombectomy into an ACS group (n = 21) and a non-ACS group (n = 17). The detection rate for CMV-positive cells in ACS patients was slightly

higher than non-ACS controls [57]. In a cross-sectional study by Westphal et al. [58], aortic biopsy as well as blood samples of 68 CABG patients was investigated for CMV-DNA detection and CMV-DNA was detected in the aortic tissue of 76% of patients [58]. Müller et al. [39], investigated 53 carotid plaques (asymptomatic n = 17, symptomatic n = 36) for CMV DNA by PCR test, but found no CMV in any of the plaques [39]. Latsios et al. [59] investigated 83 carotid atherosclerotic specimens but found no individual positive case of CMV DNA in any of the examined samples (0%) [59]. In a Syrian study, Ibrahim et al. [60] investigated 48 biopsies from atherosclerotic plaques extracted by endarterectomy (46 coronary arteries, 2 carotid arteries), and in tissue from non-atherosclerosis vessels from the same patient as controls (23 internal mammary arteries, 43 saphenous veins). CMV DNA was exclusively detected in the atherosclerotic plaques (10%) but in no controls [60]. Gabrylewicz et al. [34] in a case control study, investigated 158 subjects (divided into 3 groups: 70 with acute MI, 40 with stable angina, and 48 healthy controls), and found that patients with acute MI had a significantly higher prevalence of serum DNA CMV than in the remaining groups [34]. Shi et al. [61] studied aortic tissues from 33 autopsies, atherosclerotic tissues were positive for CMV in 40%. CMV DNA was detected more extensively in atherosclerotic lesions than in non-atherosclerotic samples [61]. We collected coronary arterial walls from thirty patients as research material at autopsy. Leukocytes were obt ained from 210 patients with atherosclerostic cerebral infarction and were used to detect CMV. 86.7% and 83.3% of the samples obtained from atherosclerotic carotid and coronary arterial walls, respectively, were positive for contain viral nucleic acids (CMV), CMV could be found among 6.7% of patients' arterial wall without atherosclerosis, significant difference can be found between them ($P < 0.01$). In blood CMV could be found in 42.4% of patients with atherosclerosis, in the control group, only 3% of samples had CMV, $P < 0.01$ [62]. Rassu et al. [63] cross-sectionally investigated 18 patients with atherosclerosis of 5 major arteries, and CMV found only in 17% of them [63]. Saetta et al. [64] investigated carotid endarterectomy specimens from 40 patients suffering from atherosclerosis and showed the absence of CMV particles or CMV DNA sequences analyzed using immunohistochemistry and PCR in all the specimens [64]. Horváth et al. studied 244 ischemic heart disease patients and compared their data with 87 coronarographically negative controls. The CMV DNA was found significantly more frequently in the ischemic group than in controls (76% and 59%, respectively) [65]. Bartels et al. [66] studied 38occluded coronary artery vein grafts and 20 native saphenous veins, but found no positive case of CMV DNA test in any of the specimens [66]. Melnick et al. [67] obtained arterial specimens from 135 patients with symptomatic atherosclerotic disease and analyzed the samples by PCR for the presence of CMV DNA. CMV DNA was detected in over $3/4^{th}$ of atherosclerotic plaque tissues as well as in uninvolved aortic tissue of surgical patients [67]. Tissue samples were obtained from 44 patients undergoing reconstructive vascular surgery for obstructive atherosclerotic disease in (femoral artery (22 cases), abdominal aorta (22cases); and their data was compared to the autopsy-control series containing 34 patients whose samples were taken from the abdominal aorta. By PCR 90% of the samples obtained from atherosclerotic patients were positive for CMV DNA compared to 53% of patients with maximally grade I atherosclerosis, which showed statistically significant difference [68]. Gredmark-Russ et al. [69] surveyed the prevalence of CMV in abdominal aortic aneurism specimens from 22 patients undergoing surgery and found that 21(95%) of the specimens

Table 2. Associations between CMV Histopathological evidence and atherosclerotic disease

Study	Reff	Population	End-point	Relation	Study methodology
Gabrylewicz et al.	34	158; 70 MI; 40 SA; 48 HC	CMV DNA in serum	Exists	Case-control
Müller et al.	39	53 carotid specimen; 17 asympt; 36 sympt.	CMV DNA prevalence	0%	Cross-sectional
Izadi et al.	50	105 CABG	ACS; family history	Exists	Cross-sectional
Voorend et al.	52	19 autopsy specimen	CMV DNA within large cerebral vessels	Not exists	Cross-sectional
Hagiwara et al.	53	50 carotid endarterectomy	CMV DNA	Not exists	Cross-sectional
Kilic et al.	54	30 autopsy specimens	CMV DNA	No significance	Cross-sectional
Pucar et al.	55	15 CABG	CMV DNA	No significance	Cross-sectional
Halvorsen et al.	56	95; 29 echolucent; 28 echogenic carotid A.; 38 HC	CMV DNA in peripheral blood	Not exists	Cross-sectional
Liu et al.	57	38; 21 ACS; 17 no ACS	CMV antigen	Exists	Case-control
Westphal et al.	58	68 CABG	CMV DNA prevalence	76%	Cross-sectional
Latsios et al.	59	83 carotid specimens	CMV DNA prevalence	0%	Cross-sectional
Ibrahim et al.	60	48 endarterectomy	CMV DNA	Exists	Cross-sectional
Shi et al.	61	33 autopsies; 10 atherosclerotic aortic sample; 23 non atherotic	CMV DNA	Exists	Case-control
Hu et al.	62	90; 60 atherosclerotic (30coronary/30carotid) and 30 no atherotic	CMV DNA	Exists	Case-control
Rassu et al.	63	18 patients with atherosclerosis	CMV DNA prevalence	17%	Cross-sectional
Saetta et al.	64	40 carotid endarterectomy	CMV DNA & particles; prevalence	0%	Cross-sectional
Horváth et al.	65	244 ischemic heart disease; 87 non-ischemic samples	CMV DNA	Exists	Case-control
Bartels et al.	66	58; 38 coronary artery vein grafts; 20 naives	CMV DNA	Not exists	Case-control
Melnick et al.	67	135 patients with symptomatic atherosclerosis	CMV DNA prevalence	3/4th of the tested specimens	Case-control
Hendrix et al.	68	78; 44 atherosclerotic; 34 controls	CMV DNA	Exists	Case-control
Gredmark-Russ et al.	69	22 cases of abdominal aortic aneurism	CMV DNA prevalence	95%	Cross-sectional
Reszka et al.	70	60; 40 atherosclerotic patients; 20 controls	CMV DNA	Not exists	Case-control
Radke et al.	71	53 coronary endarterectomy	Restenosis	Exists	Case-control

were CMV positive [69]. Reszka et al. [70] evaluated he specimens obtained from 40 patients with atherosclerotic three-vessel stable coronary artery disease and compared them with specimens obtained from 20 healthy controls undergoing aortic valve replacement. CMV DNA was found in 22 (55%) cases, and authors concluded that there was no significant difference in the frequency of finding CMV DNA between cases and controls [70]. Radke et al. [71] investigated 53 cases of coronary endatherectomy and found CMV DNA in 30% and restenosis were more likely to be found in specimens in which CMV was detected (five of 16 versus two of 37) [71]. Table 2 summarizes data of studies investigating histopathological evidence of associations between CMV infection and atherosclerosis.

Conclusion

Although the literature includes controversial evidence for any association between CMV infection and arterial atherosclerosis, the majority of studies, especially those with larger patient population and stronger data are in favor of existence of such a relationship. However, there was no study investigating the impact of antiviral therapy on this risk evaluation. Moreover, the number of prospective studies was very limited. So, we believe that future studies should be directed towards prospective studies investigating either the impact of CMV infection or antiviral treatment on atherosclerosis

formation and advancement in different patient populations including patients undergoing CABG and/or patients with moderate atherosclerosis.

References

1. Kälvegren H. The Role of Chlamydia pneumoniae-induced Platelet Activation in Cardiovascular Disease. LTAB Linköpings Tryckeri AB, Sweden, 2007; p.18.
2. Paterson JC, Cottral GE. Experimental coronary sclerosis: lymphomatosis as a cause of coronary sclerosis in chickens. Arch Pathol 1950;49:699-709.
3. Fabricant CG, Fabricant J, Litrenta M, Minick C. Virus-induced atherosclerosis. J Exp Med 1978;148:335-40.
4. Minick CR, Fabricant CG, Fabricant J, Litrent M. Atherosclerosis induced by infection with a herpesvirus. Am J Pathol 1979; 96:673.
5. Crumpacker CS. Invited commentary: human cytomegalovirus, inflammation, cardiovascular disease, and mortality. Am J Epidemiol. 2010;172(4):372-4.
6. Nichols WG, Boeckh M. Recent advances in the therapy and prevention of CMV infections. J Clin Virol. 2000;16(1):25-40. Review.
7. Cascio A, Iaria C, Fries W. Cytomegalovirus pneumonia: a possible cause of death in patients with Crohn's disease. Am J Gastroenterol. 2013;108(3):454.
8. Boivin G, Chou S, Quirk MR, Erice A, Jordan MC. Detection of ganciclovir resistance mutations quantitation of cytomegalovirus (CMV) DNA in leukocytes of patients with fatal disseminated CMV disease. J Infect Dis. 1996;173(3):523-8.
9. Gredmark S, Jonasson L, Van Gosliga D, Ernerudh J, Söderberg-Nauclér C. Active cytomegalovirus replication in patients with coronary disease. Scand Cardiovasc J. 2007;41(4):230-4.
10. Mundkur LA, Rao VS, Hebbagudi S, Shanker J, Shivanandan H, Nagaraj RK, Kakkar VV. Pathogen burden, cytomegalovirus infection and inflammatory markers in the risk of premature coronary artery disease in individuals of Indian origin. Exp Clin Cardiol. 2012 Summer;17(2):63-8.
11. Rajasekhar D, Subramanyam G, Latheef SA, Vanajakshamma V, Srilatha A, Chaudhury A. Infectious aetiology in acute coronary syndromes. Indian J Med Microbiol. 2002;20(2):83-7.
12. Al-Ghamdi A. Role of herpes simplex virus-1, cytomegalovirus and Epstein-Barr virus in atherosclerosis. Pak J Pharm Sci. 2012;25(1):89-97.
13. Al-Ghamdi A, Jiman-Fatani AA, El-Banna H. Role of Chlamydia pneumoniae, helicobacter pylori and cytomegalovirus in coronary artery disease. Pak J Pharm Sci. 2011;24(2):95-101.
14. Safaie N, Ghotaslou R, Montazer Ghaem H. Seroprevalence of cytomegalovirus in patients with and without coronary artery diseases at Madani Heart Center, Iran. Acta Med Iran. 2010;48(6):403-6.
15. Shanker J, Maitra A, Rao VS, Mundkur L, Dhanalakshmi B, Hebbagodi S, Kakkar VV. Rationale, design & preliminary findings of the Indian Atherosclerosis Research Study. Indian Heart J. 2010 Jul-Aug;62(4):286-95.
16. Jha HC, Prasad J, Mittal A. High immunoglobulin A seropositivity for combined Chlamydia pneumoniae, Helicobacter pylori infection, and high-sensitivity C-reactive protein in coronary artery disease patients in India can serve as atherosclerotic marker. Heart Vessels. 2008 Nov;23(6):390-6.
17. Jha HC, Mittal A. Coronary artery disease patient's first degree relatives may be at higher risk for atherosclerosis. Int J Cardiol. 2009;135(3):408-9; author reply 410. doi: 10.1016/j.ijcard.2008.03.031.
18. Rothenbacher D, Brenner H, Mertens T, Hoffmann MM, Hoffmeister A, Koenig W. Prognostic value of interleukin-1 receptor antagonist gene polymorphism and cytomegalovirus seroprevalence in patients with coronary artery disease. BMC Cardiovasc Disord. 2005:5(1):10.
19. Heltai K, Kis Z, Burian K, Endresz V, Veres A, Ludwig E, Gönczöl E, Valyi-Nagy I. Elevated antibody levels against Chlamydia pneumoniae, human HSP60 and mycobacterial HSP65 are independent risk factors in myocardial infarction and ischaemic heart disease. Atherosclerosis. 2004;173(2):339-46.
20. Timóteo A, Ferreira J, Paixão P, Aguiar C, Teles R, Cardoso E, Silva JA, Marques T, Seabra-Gomes R. Serologic markers for cytomegalovirus in acute coronary syndromes. Rev Port Cardiol. 2003;22(5):619-31.
21. Grahame-Clarke C, Chan NN, Andrew D, Ridgway GL, Betteridge DJ, Emery V, Colhoun HM, Vallance P. Human cytomegalovirus seropositivity is associated with impaired vascular function. Circulation. 2003 Aug 12;108(6):678-83.
22. Altannavch Ts, Roubalová K, Broz J, Hrubá D, Anděl M. Serological markers of Chlamydia pneumoniae, cytomegalovirus and Helicobacter pylori infection in diabetic and non-diabetic patients with unstable angina pectoris. Cent Eur J Public Health. 2003;11(2):102-6.
23. Khairy P, Rinfret S, Tardif JC, Marchand R, Shapiro S, Brophy J, Dupuis J. Absence of association between infectious agents and endothelial function in healthy young men. Circulation. 2003;107(15):1966-71. Epub 2003 Apr 7.
24. Witherell HL, Smith KL, Friedman GD, Ley C, Thom DH, Orentreich N, Vogelman JH, Parsonnet J. C-reactive protein, Helicobacter pylori, Chlamydia pneumoniae, cytomegalovirus and risk for myocardial infarction. Ann Epidemiol. 2003;13(3):170-7.
25. Gattone M, Iacoviello L, Colombo M, Castelnuovo AD, Soffiantino F, Gramoni A, Picco D, Benedetta M, Giannuzzi P. Chlamydia pneumoniae and cytomegalovirus seropositivity, inflammatory markers, and the risk of myocardial infarction at a young age. Am Heart J. 2001;142(4):633-40.
26. Borgia MC, Mandolini C, Barresi C, Battisti G, Carletti F, Capobianchi MR. Further evidence against the implication of active cytomegalovirus infection in vascular atherosclerotic diseases. Atherosclerosis. 2001;157(2):457-62.
27. Weber C, von Stülpnagel C, Weber KS, Hengel H, Weber PC. Association of myocardial infarction with

mononuclear cell expression of the cytomegalovirus chemokine receptor US28 in patients with NIDDM. Exp Clin Cardiol. 2001;6(2):105-8.
28. Zhu J, Quyyumi AA, Norman JE, Csako G, Waclawiw MA, Shearer GM, Epstein SE. Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. Am J Cardiol. 2000 Jan 15;85(2):140-6.
29. George J, Ahmed A, Patnaik M, Adler Y, Levy Y, Harats D, Gilburd B, Terrybery J, Shen GQ, Sagie A, Herz I, Snow P, Brandt J, Peter J, Shoenfeld Y. The prediction of coronary atherosclerosis employing artificial neural networks. Clin Cardiol. 2000;23(6):453-6.
30. Zhu J, Quyyumi AA, Norman JE, Csako G, Epstein SE. Cytomegalovirus in the pathogenesis of atherosclerosis: the role of inflammation as reflected by elevated C-reactive protein levels. J Am Coll Cardiol. 1999 .15;34(6):1738-43.
31. Blum A, Giladi M, Weinberg M, Kaplan G, Pasternack H, Laniado S, Miller H. High anti-cytomegalovirus (CMV) IgG antibody titer is associated with coronary artery disease and may predict post-coronary balloon angioplasty restenosis. Am J Cardiol. 1998:1;81(7):866-8. Reff197
32. Adler SP, Hur JK, Wang JB, Vetrovec GW. Prior infection with cytomegalovirus is not a major risk factor for angiographically demonstrated coronary artery atherosclerosis. J Infect Dis. 1998 Jan;177(1):209-12.
33. Ji YN, An L, Zhan P, Chen XH. Cytomegalovirus infection and coronary heart disease risk: a meta-analysis. Mol Biol Rep. 2012;39(6):6537-46. doi: 10.1007/s11033-012-1482-6.
34. Gabrylewicz B, Mazurek U, Ochała A, Sliupkas-Dyrda E, Garbocz P, Pyrlik A, Mróz I, Wilczok T, Tendera M. Cytomegalovirus infection in acute myocardial infarction. Is there a causative relationship? Kardiol Pol. 2003;59(10):283-92.
35. Espinola-Klein C, Rupprecht HJ, Blankenberg S, Bickel C, Kopp H, Rippin G, Hafner G, Pfeifer U, Meyer J. Are morphological or functional changes in the carotid artery wall associated with Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, or herpes simplex virus infection? Stroke. 2000;31(9):2127-33.
36. Nieto FJ, Sorlie P, Comstock GW, Wu K, Adam E, Melnick JL, Szklo M. Cytomegalovirus infection, lipoprotein(a), and hypercoagulability: an atherogenic link? Arterioscler Thromb Vasc Biol. 1997;17(9):1780-5.
37. Chiu B, Viira E, Tucker W, Fong IW. Chlamydia pneumoniae, cytomegalovirus, and herpes simplex virus in atherosclerosis of the carotid artery. Circulation. 1997 7;96(7):2144-8.
38. Merlini E, Luzi K, Suardi E, Barassi A, Cerrone M, Martínez JS, Bai F, D'Eril GV, Monforte AD, Marchetti G. T-cell phenotypes, apoptosis and inflammation in HIV+ patients on virologically effective cART with early atherosclerosis.PLoS One. 2012;7(9):e46073.
39. Müller BT, Huber R, Henrich B, Adams O, Berns G, Siebler M, Jander S, Müller W, Loncar R, Godehardt E, Sandmann W. Chlamydia pneumoniae, herpes simplex virus and cytomegalovirus in symptomatic and asymptomatic high-grade internal carotid artery stenosis. Does infection influence plaque stability? Vasa. 2005;34(3):163-9.
40. McDonald SP, Maguire GP, Duarte N, Wang XL, Hoy WE. Carotid intima-media thickness, cardiovascular risk factors and albuminuria in a remote Australian Aboriginal community. Atherosclerosis. 2004;177(2):423-31.
41. Nieto FJ, Adam E, Sorlie P, Farzadegan H, Melnick JL, Comstock GW, Szklo M. Cohort study of cytomegalovirus infection as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis. Circulation. 1996.1;94(5):922-7.
42. Sorlie PD, Adam E, Melnick SL, Folsom A, Skelton T, Chambless LE, Barnes R, Melnick JL. Cytomegalovirus/herpesvirus and carotid atherosclerosis: the ARIC Study. J Med Virol. 1994;42(1):33-7.
43. Adam E, Melnick JL, Probtsfield JL, Petrie BL, Burek J, Bailey KR, McCollum CH, DeBakey ME. High levels of cytomegalovirus antibody in patients requiring vascular surgery for atherosclerosis. Lancet. 1987 8;2(8554):291-3.
44. Grub C, Brunborg C, Hasseltvedt V, Aukrust P, Førre O, Almdahl SM, Hollan I. Antibodies to common infectious agents in coronary artery disease patients with and without rheumatic conditions. Rheumatology (Oxford). 2012;51(4):679-85.
45. Nyberg A, Skagius E, Nilsson I, Ljungh A, Henriksson AE. Abdominal aortic aneurysm and cytomegalovirus infection. J Med Virol. 2008;80(4):667-9.
46. Rabczyński M, Adamiec R. Role of chronic infection and heat shock proteins in peripheral arterial disease. Przegl Lek. 2007;64(6):419-22.
47. Haarala A, Kähönen M, Lehtimäki T, Aittoniemi J, Jylhävä J, Hutri-Kähönen N, Taittonen L, Laitinen T, Juonala M, Viikari J, Raitakari OT, Hurme M. Relation of high cytomegalovirus antibody titres to blood pressure and brachial artery flow-mediated dilation in young men: the Cardiovascular Risk in Young Finns Study. Clin Exp Immunol. 2012;167(2):309-16.
48. Bloemenkamp DG, Mali WP, Tanis BC, Rosendaal FR, van den Bosch MA, Kemmeren JM, Algra A, Ossewaarde JM, Visseren FL, van Loon AM, van der Graaf Y. Chlamydia pneumoniae, Helicobacter pylori and cytomegalovirus infections and the risk of peripheral arterial disease in young women. Atherosclerosis. 2002 Jul;163(1):149-56.
49. van der Ven AJ, Hommels MJ, Kroon AA, Kessels A, Flobbe K, van Engelshoven J, Bruggeman CA, de Leeuw PW. Chlamydia pneumoniae seropositivity and systemic and renovascular atherosclerotic disease. Arch Intern Med. 2002 Apr 8;162(7):786-90.
50. Izadi M, Fazel M, Saadat SH, Nasseri MH, Ghasemi M, Dabiri H, Aryan RS, Esfahani AA, Ahmadi A, Kazemi-Saleh D, Kalantar-Motamed MH, Taheri S. Cytomegalovirus localization in atherosclerotic plaques is associated with acute coronary syndromes: report of 105 patients. Methodist Debakey Cardiovasc J. 2012;8(2):42-6.
51. Jha HC, Srivastava P, Divya A, Prasad J, Mittal A. Prevalence of Chlamydophila pneumoniae is higher in aorta and coronary artery than in carotid artery of coronary artery disease patients. APMIS. 2009 Dec;117(12):905-11.

52. Voorend M, van der Ven AJ, Kubat B, Lodder J, Bruggeman CA. Limited role for C. pneumoniae, CMV and HSV-1 in cerebral large and small vessel atherosclerosis. Open Neurol J. 2008;2:39-44.
53. Hagiwara N, Toyoda K, Inoue T, Shimada H, Ibayashi S, Iida M, Okada Y. Lack of association between infectious burden and carotid atherosclerosis in Japanese patients. J Stroke Cerebrovasc Dis. 2007;16(4):145-52.
54. Kilic A, Onguru O, Tugcu H, Kilic S, Guney C, Bilge Y. Detection of cytomegalovirus and Helicobacter pylori DNA in arterial walls with grade III atherosclerosis by PCR. Pol J Microbiol. 2006;55(4):333-7.
55. Pucar A, Milasin J, Lekovic V, Vukadinovic M, Ristic M, Putnik S, Kenney EB. Correlation between atherosclerosis and periodontal putative pathogenic bacterial infections in coronary and internal mammary arteries. J Periodontol. 2007;78(4):677-82.
56. Halvorsen DS, Karlsen J, Notø AT, Mathiesen EB, Njølstad I, Gutteberg TJ, Vorland LH, Hansen JB. No detectable Chlamydia pneumoniae and cytomegalovirus DNA in leukocytes in subjects with echolucent and echogenic carotid artery plaques. Int J Cardiol. 2007 May 2;117(3):388-94.
57. Liu R, Moroi M, Yamamoto M, Kubota T, Ono T, Funatsu A, Komatsu H, Tsuji T, Hara H, Hara H, Nakamura M, Hirai H, Yamaguchi T. Presence and severity of Chlamydia pneumoniae and Cytomegalovirus infection in coronary plaques are associated with acute coronary syndromes. Int Heart J. 2006 Jul;47(4):511-9.
58. Westphal M, Lautenschlager I, Backhaus C, Loginov R, Kundt G, Oberender H, Stamm C, Steinhoff G. Cytomegalovirus and proliferative signals in the vascular wall of CABG patients. Thorac Cardiovasc Surg. 2006 Jun;54(4):219-26.
59. Latsios G, Saetta A, Michalopoulos NV, Agapitos E, Patsouris E. Detection of cytomegalovirus, Helicobacter pylori and Chlamydia pneumoniae DNA in carotid atherosclerotic plaques by the polymerase chain reaction. Acta Cardiol. 2004 Dec;59(6):652-7.
60. Ibrahim AI, Obeid MT, Jouma MJ, Moasis GA, Al-Richane WL, Kindermann I, Boehm M, Roemer K, Mueller-Lantzsch N, Gärtner BC. Detection of herpes simplex virus, cytomegalovirus and Epstein-Barr virus DNA in atherosclerotic plaques and in unaffected bypass grafts. J Clin Virol. 2005 Jan;32(1):29-32.
61. Shi Y, Tokunaga O. Herpesvirus (HSV-1, EBV and CMV) infections in atherosclerotic compared with non-atherosclerotic aortic tissue. Pathol Int. 2002 Jan;52(1):31-9.
62. Hu W, Liu J, Niu S, Liu M, Shi H, Wei L. Prevalence of CMV in arterial walls and leukocytes in patients with atherosclerosis. Chin Med J (Engl). 2001 Nov;114(11):1208-10.
63. Rassu M, Cazzavillan S, Scagnelli M, Peron A, Bevilacqua PA, Facco M, Bertoloni G, Lauro FM, Zambello R, Bonoldi E. Demonstration of Chlamydia pneumoniae in atherosclerotic arteries from various vascular regions. Atherosclerosis. 2001 Sep;158(1):73-9.
64. Saetta A, Fanourakis G, Agapitos E, Davaris PS. Atherosclerosis of the carotid artery: absence of evidence for CMV involvement in atheroma formation. Cardiovasc Pathol. 2000 May-Jun;9(3):181-3.
65. Horváth R, Cerný J, Benedík J Jr, Hökl J, Jelínková I, Benedík J. The possible role of human cytomegalovirus (HCMV) in the origin of atherosclerosis. J Clin Virol. 2000 Feb;16(1):17-24.
66. Bartels C, Maass M, Bein G, Malisius R, Brill N, Bechtel JF, Sayk F, Feller AC, Sievers HH. Detection of Chlamydia pneumoniae but not cytomegalovirus in occluded saphenous vein coronary artery bypass grafts. Circulation. 1999 23;99(7):879-82.
67. Melnick JL, Hu C, Burek J, Adam E, DeBakey ME. Cytomegalovirus DNA in arterial walls of patients with atherosclerosis. J Med Virol. 1994;42(2):170-4. Reff216
68. Hendrix MG, Salimans MM, van Boven CP, Bruggeman CA. High prevalence of latently present cytomegalovirus in arterial walls of patients suffering from grade III atherosclerosis. Am J Pathol. 1990;136(1):23-8.
69. Gredmark-Russ S, Dzabic M, Rahbar A, Wanhainen A, Björck M, Larsson E, Michel JB, Söderberg-Nauclér C. Active cytomegalovirus infection in aortic smooth muscle cells from patients with abdominal aortic aneurysm. J Mol Med (Berl). 2009;87(4):347-56. doi: 10.1007/s00109-008-0413-4.
70. Reszka E, Jegier B, Wasowicz W, Lelonek M, Banach M, Jaszewski R. Detection of infectious agents by polymerase chain reaction in human aortic wall. Cardiovasc Pathol. 2008;17(5):297-302. doi: 10.1016/j.carpath.2007.11.002.
71. Radke PW, Merkelbach-Bruse S, Messmer BJ, vom Dahl J, Dörge H, Naami A, Vogel G, Handt S, Hanrath P. Infectious agents in coronary lesions obtained by endatherectomy: pattern of distribution, coinfection, and clinical findings. Coron Artery Dis. 2001;12(1):1-6.