Hypertension Research (2017) 40, 324–328
© 2017 The Japanese Society of Hypertension All rights reserved 0916-9636/17
www.nature.com/hr

REVIEW

Periodontitis and myocardial hypertrophy

Jun-ichi Suzuki[1], Hiroki Sato[2], Makoto Kaneko[2], Asuka Yoshida[2], Norio Aoyama[2], Shouta Akimoto[1], Kouji Wakayama[1], Hidetoshi Kumagai[1], Yuichi Ikeda[3], Hiroshi Akazawa[3], Yuichi Izumi[2], Mitsuaki Isobe[4] and Issei Komuro[3]

There is a deep relationship between cardiovascular disease and periodontitis. It has been reported that myocardial hypertrophy may be affected by periodontitis in clinical settings. Although these clinical observations had some study limitations, they strongly suggest a direct association between severity of periodontitis and left ventricular hypertrophy. However, the detailed mechanisms between myocardial hypertrophy and periodontitis have not yet been elucidated. Recently, we demonstrated that periodontal bacteria infection is closely related to myocardial hypertrophy. In murine transverse aortic constriction models, a periodontal pathogen, *Aggregatibacter actinomycetemcomitans* markedly enhanced cardiac hypertrophy with matrix metalloproteinase-2 activation, while another pathogen *Porphyromonas gingivalis* (*P.g.*) did not accelerate these pathological changes. In the isoproterenol-induced myocardial hypertrophy model, *P.g.* induced myocardial hypertrophy through Toll-like receptor-2 signaling. From our results and other reports, regulation of chronic inflammation induced by periodontitis may have a key role in the treatment of myocardial hypertrophy. In this article, we review the pathophysiological mechanism between myocardial hypertrophy and periodontitis.
Hypertension Research (2017) **40,** 324–328; doi:10.1038/hr.2016.146; published online 10 November 2016

Keywords: clinical observation; experimental models; myocardial hypertrophy; periodontitis

INTRODUCTION

There is a deep relationship between cardiovascular disease and periodontitis; however, the detailed mechanisms between myocardial hypertrophy and periodontitis have not yet been elucidated.[1] Recently, we demonstrated that periodontal bacteria infection accelerated myocardial hypertrophy.[2–4] Chronic inflammation induced by periodontitis may have a key role in the development of myocardial hypertrophy. In this article, we review the pathophysiological mechanism between myocardial hypertrophy and periodontitis.

MYOCARDIAL HYPERTROPHY AND CHRONIC INFLAMMATION

Among the various cardiovascular diseases, myocardial hypertrophy is the most common manifestation because hypertension and other systemic diseases induce the condition.[5] It is recognized that chronic inflammation induced by infection could be a cause of myocardial hypertrophy. HIV infection is the most well-known pathogenesis of myocardial hypertrophy. Kearney *et al.*[6] revealed that more than half of the children with HIV infection had myocardial hypertrophy. This was proved by echocardiogram and postmortem cardiac pathology. Similarly, Georgescu *et al.*[7] showed that 25.6% of child patients with HIV infection had left ventricular (LV) myocardial hypertrophy judged by echocardiogram. Breuckmann *et al.*[8] also revealed that a quarter of patients with HIV infection had myocardial hypertrophy. This evaluation was performed by MRI. At this moment, there is no clinical report to show the direct relationship between myocardial hypertrophy and chronic inflammation induced by bacterial infection. However, Kita *et al.*[9] showed that *Escherichia coli* endotoxin enhanced myocardial hypertrophy in rats with chronic alcohol consumption. Thus, chronic inflammation induced by bacterial infection may be a cause of myocardial hypertrophy. Persistent inflammation has a pathogenic role in chronic heart failure by influencing heart contractility, inducing hypertrophy and promoting apoptosis, which contributes to myocardial remodeling.[10,11] It was also reported that the heart failure with preserved ejection fraction paradigm shifted from LV afterload excess to coronary microvascular inflammation. The new paradigm consists of a systemic proinflammatory state that causes coronary microvascular endothelial inflammation that reduces nitric oxide bioavailability, cyclic guanosine monophosphate content and protein kinase G (PKG). Low PKG activity enhances myocardial hypertrophy development because of hypophosphorylation of titin.[12] Biwer *et al.*[13] showed the temporal response to nitric oxide synthase (NOS) and renin-angiotensin system inhibition with respect to cardiac hypertrophy in rats. They demonstrated that L-NAME with enalapril accelerated a significant increase in cardiac mass in the spontaneously hypertensive rat (SHR). Thus, NOS and renin-angiotensin system also has critical roles in cardiac hypertrophy. Nakashima *et al.*[14] showed

[1]Department of Advanced Clinical Science and Therapeutics, The University of Tokyo, Tokyo, Japan; [2]Department of Periodontology, Tokyo Medical and Dental University, Tokyo, Japan; [3]Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan and [4]Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan
Correspondence: Dr J Suzuki, Department of Advanced Clinical Science and Therapeutics, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan.
E-mail: junichisuzuki-circ@umin.ac.jp
Received 25 July 2016; revised 15 September 2016; accepted 3 October 2016; published online 10 November 2016

that reactive oxygen species are critical in angiotensin II-induced vascular remodeling. Taken together, several factors are involved in pressure overload-induced cardiovascular remodeling.

PERIODONTITIS IS A MAJOR CAUSE OF CHRONIC INFLAMMATION

Many researchers have studied the relationship between periodontitis and systemic diseases, because periodontitis is a major cause of systemic and chronic inflammation.[15,16] Because a relationship between periodontal disease and cardiovascular disease has been broadly recognized,[17] we investigated the pathophysiological relationship between periodontitis and cardiovascular disease.[18,19] Periodontitis is an infectious disease induced by many species of periodontal bacteria, such as *Porphyromonas gingivalis* (*P.g.*), *Aggregatibacter actinomycetemcomitans (A.a.)* and *Prevotella intermedia*.[20] It was reported that each periodontal pathogen influenced the progression of abdominal aortic aneurysm.[21–23] We also reported that *P.g.* accelerated the progression of abdominal aortic aneurysm through Toll-like receptors (TLRs) and matrix metalloproteinases (MMPs) using experimental murine models.[24–26] On the other hand, there are limited clinical and experimental reports revealing the relationship between periodontitis and myocardial hypertrophy at this point. Moreover, the clinical influence of specific periodontal bacterium on myocardial hypertrophy has not been clarified epidemiologically.

MYOCARDIAL HYPERTROPHY MAY BE AFFECTED BY PERIODONTITIS IN CLINICAL SETTINGS

Clinical observations revealed a relationship between myocardial hypertrophy and periodontitis. The Hisayama study showed that mean probing depth, mean attachment loss, number of teeth and plaque index were associated with LV hypertrophy. In multivariate analysis, the subjects with deep pocket depth had an increased risk of LV hypertrophy compared with the subjects without deep pocket depth. Subjects with severe attachment loss also had significant risk of LV hypertrophy. Although this observation clearly showed the relationship between LV hypertrophy and periodontitis, it has a study limitation because they only judged LV hypertrophy using electrocardiogram (ECG).[27] Angeli *et al.*[28] showed a clinical association between periodontitis and LV mass in subjects with essential hypertension. LV mass progression was dependent on the severity of periodontitis. Body surface area, systolic and diastolic blood pressure, and LV mass were determinants of a composite of severe periodontitis. In a multivariate logistic analysis, LV mass was the only determinant of severe periodontitis. Their findings suggested a direct association between the severity of periodontitis and increased LV mass in subjects with essential hypertension. Although they measured LV mass using echocardiogram, this paper has a study limitation in the diagnosis of periodontitis. They evaluated periodontitis using only the community periodontal index of treatment needs (CPITN). CPITN is a convenient methodology to diagnose the severity of periodontits, for example, CPITN 0 (periodontal health), CPITN 1 (gingival bleeding), CPITN 2 (calculus), CPITN 3 (pockets 4–5 mm) and CPITN 4 (pockets $\geqslant$6 mm), it lacks other periodontal information such as attachment loss, number of teeth, and plaque index.[28] Franek *et al.*[29] also demonstrated an association between chronic periodontitis and increased LV mass in subjects with Type 2 diabetes mellitus. They clarified that subjects with periodontitis had larger LV mass compared with non-periodontitis subjects. They concluded that periodontitis was associated with increased LV mass and elevated central and systemic blood pressure in subjects with Type 2 diabetes. This study clearly demonstrated the relationship between precisely measured LV mass and periodontitis. However, periodontitis was judged as three biofilm-gingival interface groups; healthy, gingivitis and periodontitis using semi-quantitative methods. Thus, lacking enough information of periodontitis and patients enrollment only from Type 2 diabetes are the study limitation of this paper.[29] Although these clinical observations had some study limitations, they strongly suggest a direct association between severity of periodontitis and LV hypertrophy. (Table 1)

SPECIFIC PERIODONTAL PATHOGENS DETERIORATE LOAD-INDUCED MYOCARDIAL HYPERTROPHY

We demonstrated that some specific periodontal pathogens accelerated myocardial hypertrophy. First, we showed that a major periodontal pathogen deteriorated pressure overload-induced myocardial hypertrophy in mice. To establish myocardial hypertrophy in an animal model, transverse aortic constriction (TAC) was performed in mice. We injected a periodontal pathogen, *A.a.* in the infected group and phosphate buffered saline (PBS) in the control group. We showed that heart per body weight ratio increased in the *A.a.* infected group compared with the control group. Histopathologically, *A.a.*-infected mice showed markedly enhanced cardiac hypertrophy, fibrosis and arteriosclerosis 4 weeks after TAC operation. Immunohistochemistry revealed that expression of MMP-2 in the interstitial tissue was enhanced in the *A.a.*-infected group.[2] Pressure overload-induced myocardial hypertrophy is known to be caused by changes in cardiac myocytes and abnormalities in the extracellular matrix network.

Table 1 Clinical observations which revealed a relationship between myocardial hypertrophy and periodontitis

Authors	*Patients number*	*Periodontal diagnosis*	*Myocardial hypertrophy diagnosis*	*Major findings*	*Study limitation*	*Published journal and year*	*Reference*
Shimazaki *et al.*	957	Number of teeth, plaque index, PD and CAL	LV hypertrophy (Minnesota code 3-1) and ST depression (4-1, 2, 3) using ECG	Mean PD, mean attachment loss, number of teeth and plaque index were significantly associated with ECG abnormalities.	LV hypertrophy was not evaluated by echocardiogram.	*J Periodontol* 2004	27
Angeli *et al.*	104	CPITN: 0–4	LV mass using echocardiogram	There was a progressive increase in LV mass with increasing severity of periodontitis.	It lacked detailed periodontal information.	*Hypertension* 2003	28
Franek *et al.*	155	BGI: H, G and P	LV mass using echocardiogram	BGI-P and BGI-G subjects had higher LV mass compared with BGI-H.	There was limited Type 2 DM patients. It lacked detailed periodontal information.	*J Clin Periodontol* 2010	29

Abbreviations: BGI, biofilm-gingival interface; CAL, clinical attachment level; CPITN, community periodontal index of treatment needs; DM, diabetes mellitus; ECG, electrocardiogram; G, gingivitis; H, healthy; LV, left ventricular; P, periodontitis; PD, probing depth.

Progressive LV remodeling and extracellular matrix degradation is associated with increased MMP activity. It is also well recognized that periodontal pathogens increase the activity of MMPs. The activation of MMP-2 was also induced by the lipopolysaccharides of *A.a.*[30] MMP-2 is involved in physiological tissue remodeling and pathological extracellular matrix degradation in the pathogenesis of periodontal diseases.[31] Thus, our results suggest that a periodontal pathogen causes a deterioration of pressure overload-induced myocardial hypertrophy through MMP-2 activation. We also evaluated the effect of another periodontal pathogen, *P.g.* on TAC-induced myocardial hypertrophy. Interestingly, *P.g.* worsened area of myocardial fibrosis, while the degree of hypertrophy was comparable between the *P.g.*-infected group and the control group.[3] At this moment, the reason why the different pathogens showed different results is to be clarified. It is known that *A.a.* secretes leukotoxin, which affects polymorphonuclear leukocytes, lymphocytes and macrophages via TLR2 and TLR4. If these cells are activated, proinflammatory cytokines are produced, and it results in enhanced inflammation. On the other hand, *P.g.* secretes gingipine which works to degrade cytokines, thereby downregulating the host response in the form of reduced inflammation through TLR2 signaling.[32–35] Therefore, the effect of periodontal pathogens is varied on the progression of myocardial hypertrophy induced by pressure overload.

A PERIODONTAL PATHOGEN ACCELERATES ISOPROTERENOL-INDUCED MYOCARDIAL HYPERTROPHY

Next, we observed the effect of a periodontal pathogen on catecholamine induced myocardial hypertrophy. To make the model, we subcutaneously implanted a coil-shaped chamber into the back of a mouse and *P.g.* was injected into the chamber. Following this, an osmotic pump was implanted to infuse isoproterenol systemically. Four weeks after the isoproterenol infusion, we performed an echocardiography and harvested the hearts and blood. Microscopically, we found stronger cardiomyocyte hypertrophy in *P.g.*-infected mice compared with the control mice. We also detected a higher level of mRNA expression in TLR2 and NADPH oxidase 4 (Nox4) in *P.g.*-infected mice compared with the control mice.[4] It is well known that *P.g.* enhanced the expression of TLR2 in various kinds of cells. Because we detected a higher expression of TLR2 in *P.g.*-injected mice, it implied that *P.g.* enhanced the expression of TLR2 in the hearts. Regarding cardiac hypertrophy, a study using the TAC model reported that the hypertrophy was suppressed in TLR2-deficient mice.[36] These results and our observation suggest that TLR2 may have a critical role in cardiomyocyte hypertrophy induced by periodontal pathogens. It was also reported that *P.g.* enhanced the expression of Nox4 in some cells. Nox4 is known to have an important role in cardiomyocyte hypertrophy. Upregulation of Nox4 in the myocardium causes cardiac remodeling through the activation of Akt-mTOR and NF-κB signaling pathways.[37] Therefore, *P.g.* infection enhances Nox4, resulting in cardiomyocyte hypertrophy. These results suggest that a periodontal pathogen effects isoproterenol-induced cardiac hypertrophy via oxidative stress.

POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS BETWEEN PERIODONTITIS AND MYOCARDIAL HYPERTROPHY

The systemic inflammatory state induced by periodontal pathogens affects the human coronary endothelium.[38,39] Proinflammatory cytokines (for example, interleukin-6, tumor necrosis factor-alpha) induce vascular cell adhesion molecule-1 and E-selectin expression on the endothelium.[40] Their expression leads to activation and subendothelial migration of circulating leukocytes.[41] These cytokines also induce endothelial production of reactive oxygen species through activation of nicotinamide adenine dinucleotide phosphate oxidases.[42] Production of reactive oxygen species leads to formation of peroxynitrite (ONOO-) and reduced nitric oxide (NO) bioavailability, both suppress soluble guanylate cyclase activity in adjacent cardiomyocytes. NO is also known to contribute to pathological effects of periodontitis in the heart.[43] Lower soluble guanylate cyclase activity decreases cyclic guanosine monophosphate concentration and PKG activity. Low PKG activity increases resting tension of cardiomyocytes because of hypophosphorylation of titin and removes the brake on prohypertrophic stimuli, inducing cardiomyocyte hypertrophy.[12] The PKG function as a brake on myocardial hypertrophy has been observed in a wide variety of experimental and clinical settings. In cardiomyocytes cultured from neonatal rat hearts, NO or a cyclic guanosine monophosphate analog attenuated the norepinephrine-induced hypertrophic response.[44] Ruiz-Hurtado *et al.*[45] showed that LA-419, which protected NO from degradation, has been found to restore the complete NO signaling cascade and reduce LV remodeling in a model of aortic stenosis-induced pressure overload. Because LA-419 did not restore the original pressure gradient, the increasing NO bioavailability has a possible direct anti-proliferative effect on cardiac myocytes. In mice subjected to TAC, sildenafil, which increases myocardial PKG activity through inhibited

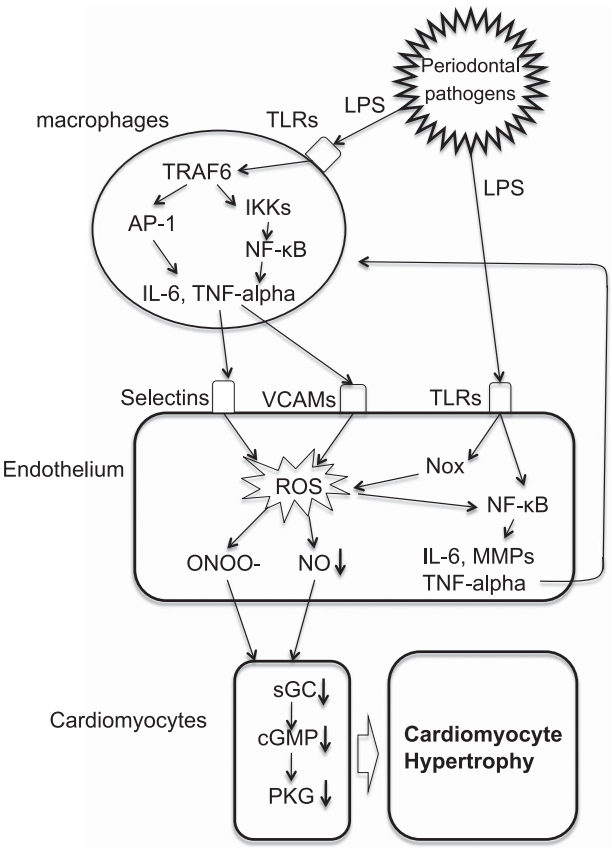

Figure 1 Possible mechanisms between periodontitis and myocardial hypertrophy. cGMP, cyclic guanosine monophosphate; IL, interleukin; MMPs, matrix metalloproteinases; NF-κB, nuclear factor-kappa B; NO, nitric oxide; Nox, nicotinamide adenine dinucleotide phosphate oxidase; ONOO, peroxynitrite; PKG, protein kinase G; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; TNF, tumor necrosis factor; TLRs, Toll-like receptors; VCAMs, vascular cell adhesion molecules.

breakdown of cyclic guanosine monophosphate by phosphodiesterase 5 (PDE5), prevented or reversed cardiomyocyte hypertrophy by deactivating multiple prohypertrophic pathways.[46] In patients with diabetic cardiomyopathy and concentric LV remodeling, sildenafil treatment reduced the LV mass/volume ratio.[47] In line with these experimental and clinical findings, lower myocardial PKG activity was shown to correlate with a larger cardiomyocyte diameter. A similar relationship between myocardial PKG activity and cardiomyocyte hypertrophy was also present in aortic stenosis patients who had less myocardial PKG activity and more cardiomyocyte hypertrophy.[48] We demonstrated the hypothetical idea with representative factors which have a relationship between periodontal pathogen-induced chronic inflammation and cardiomyocyte hypertrophy (Figure 1).

In conclusion, periodontitis contributes to a systemic inflammatory state, which induces oxidative stress in the coronary microvascular endothelium. This reduces myocardial NO bioavailability and leads to reduced PKG activity in cardiomyocytes, which enhances myocardial hypertrophy. The new paradigm between periodontitis and myocardial hypertrophy has important diagnostic and therapeutic implications.

CONFLICT OF INTEREST

JS received research funding of 2 000 000 yen or more in 1 year. The remaining authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Ms Noriko Tamura for excellent contributions. This work was supported by grants from Mitsui Life Insurance Research Foundation, Mitsui Sumitomo Marine Welfare Research Foundation, Geriatric Dental Research Foundation, Human Health Future Research Foundation, St Luke's Hospital Research Foundation, Health Management Foundation, Taiyo Life Insurance Research Foundation, The 8020 Promotion Foundation, Terumo Science Foundation, Pfizer Health Research Foundation, General Health Promotion Foundation, Suzuken Memorial Foundation, Health Science Center Foundation, Kobayashi International Scholarship Foundation, Hakujikai Institute of Gerontology Foundation and the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 15K20616 and 16H05824.

1 Suzuki J, Aoyama N, Ogawa M, Hirata Y, Izumi Y, Nagai R, Isobe M. Periodontitis and cardiovascular diseases. *Expert Opin Ther Targets* 2010; **14**: 1023–1027.
2 Sekinishi A, Suzuki J, Aoyama N, Ogawa M, Watanabe R, Kobayashi N, Hanatani T, Ashigaki N, Hirata Y, Nagai R, Izumi Y, Isobe M. A periodontal pathogen *Aggregatibacter actinomycetemcomitans* deteriorates pressure overload-induced myocardial hypertrophy in mice. *Int Heart J* 2012; **53**: 324–330.
3 Kaneko M, Suzuki J, Aoyamay N, Watanabe R, Yoshida A, Shiheido Y, Izumi Y, Isobe M. Toll-like receptor-2 in periodontal pathogen-induced myocardial fibrosis in pressure overloaded murine hearts. *Hypertens Res* 2017; **40**: 110–116.
4 Sato H, Suzuki J, Aoyama N, Watanabe R, Kaneko M, Shiheido Y, Yoshida A, Wakayama K, Kumagai H, Ikeda Y, Akazawa H, Komuro I, Isobe M, Izumi Y. A Periodontal pathogen *Porphyromonas gingivalis* deteriorates Isoproterenol-Induced myocardial remodeling in mice. *Hypertens Res* 2017; **40**: 35–40.
5 Oka T, Akazawa H, Naito AT, Komuro I. Angiogenesis and cardiac hypertrophy: maintenance of cardiac function and causative roles in heart failure. *Circ Res* 2014; **114**: 565–571.
6 Kearney DL, Perez-Atayde AR, Easley KA, Bowles NE, Bricker JT, Colan SD, Kaplan S, Lai WW, Lipshultz SE, Moodie DS, Sopko G, Starc TJ, Towbin JA. Postmortem cardiomegaly and echocardiographic measurements of left ventricular size and function in children infected with the human immunodeficiency virus. The Prospective P2C2 HIV Multicenter Study. *Cardiovasc Pathol* 2003; **12**: 140–148.
7 Georgescu AM, Moldovan C, Azamfirei L, Georgescu D. Ultrasound and histopathological features of myocardial involvement in HIV infection in children. *Rom J Morphol Embryol* 2014; **55**: 773–779.
8 Breuckmann F, Nassenstein K, Kondratieva J, Esser S, Erbel R, Potthoff A, Brockmeyer NH, Neumann T, Barkhausen J. MR characterization of cardiac abnormalities in HIV+ individuals with increased BNP levels. *Eur J Med Res* 2007; **12**: 185–190.
9 Kita T, Nagano T, Kasai K, Tanaka N. *E. coli* endotoxin enhances cardiomyopathy in rats with chronic alcohol consumption. *Int J Legal Med* 1996; **109**: 37–41.
10 Aukrust P, Yndestad A, Damås JK, Gullestad L. Inflammation and chronic heart failure-potential therapeutic role of intravenous immunoglobulin. *Autoimmun Rev* 2004; **3**: 221–227.
11 Aukrust P, Gullestad L, Ueland T, Damås JK, Yndestad A. Inflammatory and anti-inflammatory cytokines in chronic heart failure: potential therapeutic implications. *Ann Med* 2005; **37**: 74–85.
12 Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2013; **62**: 263–271.
13 Biwer LA, D'souza KM, Abidali A, Tu D, Siniard AL, DeBoth M, Huentelman M, Hale TM. Time course of cardiac inflammation during nitric oxide synthase inhibition in SHR: impact of prior transient ACE inhibition. *Hypertens Res* 2016; **39**: 8–18.
14 Nakashima T, Umemoto S, Yoshimura K, Matsuda S, Itoh S, Murata T, Fukai T, Matsuzaki M. TLR4 is a critical regulator of angiotensin II-induced vascular remodeling: the roles of extracellular SOD and NADPH oxidase. *Hypertens Res* 2015; **38**: 649–655.
15 Offenbacher S. Periodontal diseases: pathogenesis. *Ann Periodontol* 1996; **1**: 821–878.
16 Offenbacher S, Barros SP, Beck JD. Rethinking periodontal inflammation. *J Periodontol* 2008; **79**: 1577–1584.
17 Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, Wilson WR, Smith SC Jr, Baddour LM, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association? A scientific statement from the American Heart Association. *Circulation* 2012; **125**: 2520–2544.
18 Suzuki J, Aoyama N, Aoki M, Tada Y, Wakayama K, Akazawa H, Shigematsu K, Hoshina K, Izumi Y, Komuro I, Miyata T, Hirata Y, Isobe M. Incidence of periodontitis in Japanese patients with cardiovascular diseases -a comparison between abdominal aortic aneurysm and arrhythmia. *Heart Vessels* 2015; **30**: 498–502.
19 Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. *J Periodontol* 2013; **84**: S51–S69.
20 Socransky SS, Haffajee AD. Dental biofilms: difficult therapeutic targets. *Periodontol 2000* 2002; **28**: 12–55.
21 Kurihara N, Inoue Y, Iwai T, Umeda M, Huang Y, Ishikawa I. Detection and localization of periodontopathic bacteria in abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2004; **28**: 553–558.
22 Paraskevas KI, Mikhailidis DP, Giannoukas AD. Periodontitis and abdominal aortic aneurysms: a random association or a pathogenetic link? *Int Angiol* 2009; **28**: 431–433.
23 Delbosc S, Alsac JM, Journe C, Louedec L, Castier Y, Bonnaure-Mallet M, Ruimy R, Rossignol P, Bouchard P, Michel JB, Meilhac O. Porphyromonas gingivalis participates in pathogenesis of human abdominal aortic aneurysm by neutrophil activation. Proof of concept in rats. *PLoS ONE* 2011; **6**: e18679.
24 Aoyama N, Suzuki J, Wang D, Ogawa M, Kobayashi N, Hanatani T, Takeuchi Y, Izumi Y, Isobe M. Porphyromonas gingivalis promotes murine abdominal aortic aneurysms via matrix metalloproteinase-2 induction. *J Periodontal Res* 2011; **46**: 176–183.
25 Aoyama N, Suzuki J, Ogawa M, Watanabe R, Kobayashi N, Hanatani T, Yoshida A, Ashigaki N, Izumi Y, Isobe M. Clarithromycin suppresses the periodontal bacteria-accelerated abdominal aortic aneurysms in mice. *J Periodontal Res* 2012; **47**: 463–469.
26 Aoyama N, Suzuki J, Ogawa M, Watanabe R, Kobayashi N, Hanatani T, Ashigaki N, Sekinishi A, Izumi Y, Isobe M. Toll-like receptor-2 plays a fundamental role in periodontal bacteria-accelerated abdominal aortic aneurysms. *Circ J* 2013; **77**: 1565–1573.
27 Shimazaki Y, Saito T, Kiyohara Y, Kato I, Kubo M, Iida M, Koga T. Relationship between electrocardiographic abnormalities and periodontal disease: the Hisayama Study. *J Periodontol* 2004; **75**: 791–797.
28 Angeli F, Verdecchia P, Pellegrino C, Pellegrino RG, Pellegrino G, Prosciutti L, Giannoni C, Cianetti S, Bentivoglio M. Association between periodontal disease and left ventricle mass in essential hypertension. *Hypertension* 2003; **41**: 488–492.
29 Franek E, Napora M, Blach A, Budlewski T, Gozdowski D, Jedynasty K, Krajewski J, Gorska R. Blood pressure and left ventricular mass in subjects with type 2 diabetes and gingivitis or chronic periodontitis. *J Clin Periodontol* 2010; **37**: 875–880.
30 Tiranathanagul S, Yongchaitrakul T, Pattamapun K, Pavasant P. Actinobacillus actinomycetemcomitans lipopolysaccharide activates matrix metalloproteinase-2 and increases receptor activator of nuclear factor-kappaB ligand expression in human periodontal ligament cells. *J Periodontol* 2004; **75**: 1647–1654.
31 Sorsa T, Tjäderhane L, Konttinen YT, Lauhio A, Salo T, Lee HM, Golub LM, Brown DL, Mäntylä P. Matrix metalloproteinases: contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. *Ann Med* 2006; **38**: 306–321.
32 Sun Y, Shu R, Li CL, Zhang MZ. Gram-negative periodontal bacteria induce the activation of Toll-like receptors 2 and 4, and cytokine production in human periodontal ligament cells. *J Periodontol* 2010; **81**: 1488–1496.
33 Burns E, Eliyahu T, Uematsu S, Akira S, Nussbaum G. TLR2-dependent inflammatory response to *Porphyromonas gingivalis* is MyD88 independent, whereas MyD88 is required to clear infection. *J Immunol* 2010; **184**: 1455–1462.
34 Stathopoulou PG. Epithelial cell pro-inflammatory cytokine response differs across dental plaque bacterial species. *J Clin Periodontol* 2010; **37**: 24–29.
35 Olsen I, Shah HN, Gharbia SE. Taxonomy and biochemical characteristics of *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. *Periodontol 2000* 1999; **20**: 14–52.

36 Higashikuni Y, Tanaka K, Kato M, Nureki O, Hirata Y, Nagai R, Komuro I, Sata M. Toll-like receptor-2 mediates adaptive cardiac hypertrophy in response to pressure overload through interleukin-1b upregulation via nuclear factor κB activation. *J Am Heart Assoc* 2013; **2**: e000267.
37 Zhao QD, Viswanadhapalli S, Williams P, Shi Q, Tan C, Yi X, Bhandari B, Abboud HE. NADPH oxidase 4 induces cardiac fibrosis and hypertrophy through activating Akt/mTOR and NF-κB signaling pathways. *Circulation* 2015; **131**: 643–655.
38 Honda T, Oda T, Yoshie H, Yamazaki K. Effects of *Porphyromonas gingivalis* antigens and proinflammatory cytokines on human coronary artery endothelial cells. *Oral Microbiol Immunol* 2005; **20**: 82–88.
39 Yun PL, Decarlo AA, Hunter N. Gingipains of *Porphyromonas gingivalis* modulate leukocyte adhesion molecule expression induced in human endothelial cells by ligation of CD99. *Infect Immun* 2006; **74**: 1661–1672.
40 Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, von Schlippenbach J, Skurk C, Steendijk P, Riad A, Poller W, Schultheiss HP, Tschöpe C. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. *Circ Heart Fail* 2011; **4**: 44–52.
41 Van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbély A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, Paulus WJ. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 2008; **117**: 43–51.
42 Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res* 2000; **86**: 494–501.
43 Herrera BS, Martins-Porto R, Campi P, Holzhausen M, Teixeira SA, Mendes GD, Costa SK, Gyurko R, Van Dyke TE, Spolidório LC, Muscará MN. Local and cardiorenal effects of periodontitis in nitric oxide-deficient hypertensive rats. *Arch Oral Biol* 2011; **56**: 41–47.
44 Calderone A, Thaik CM, Takahashi N, Chang DL, Colucci WS. Nitric oxide, atrial natriuretic peptide, and cyclic GMP inhibit the growth-promoting effects of norepinephrine in cardiac myocytes and fibroblasts. *J Clin Invest* 1998; **101**: 812–818.
45 Ruiz-Hurtado G, Delgado C. Nitric oxide pathway in hypertrophied heart: new therapeutic uses of nitric oxide donors. *J Hypertens* 2010; **28**: S56–S61.
46 Takimoto E, Champion HC, Li M, Belardi D, Ren S, Rodriguez ER, Bedja D, Gabrielson KL, Wang Y, Kass DA. Chronic inhibition of cyclic GMP phosphodiesterase 5 A prevents and reverses cardiac hypertrophy. *Nat Med* 2005; **11**: 214–222.
47 Giannetta E, Isidori AM, Galea N, Carbone I, Mandosi E, Vizza CD, Naro F, Morano S, Fedele F, Lenzi A. Chronic inhibition of cGMP phosphodiesterase 5 A improves diabetic cardiomyopathy: a randomized, controlled clinical trial using magnetic resonance imaging with myocardial tagging. *Circulation* 2012; **125**: 2323–2333.
48 Falcão-Pires I, Hamdani N, Borbély A, Gavina C, Schalkwijk CG, van der Velden J, van Heerebeek L, Stienen GJ, Niessen HW, Leite-Moreira AF, Paulus WJ. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. *Circulation* 2011; **124**: 1151–1159.