Rev Estomatol. 2024; 32(1):e13362 DOI: 10.25100/re.v32i1. 13362

Revista Estomatología

NARRATIVE REVIEW

The impact of *Porphyromonas gingivalis* and its virulence in cardiovascular diseases

El impacto de *Porphyromonas gingivalis* y su virulencia en enfermedades cardiovasculares

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Citation:

Parra Pérez A.S., Plaza D., Hoyos M.P., Gómez González S., Moreno Correa S. The impact of *Porphyromonas gingivalis* and its virulence in cardiovascular diseases. *Rev Estomatol*.2024; 32(1):e13594 DOI: 10.25100/re.v32i1.13362

Received: November 17th 2023
Evaluated: April 20th 2024
Accepted: September 22th 2024
Published: October 30th 2024

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Keywords: *Porphyromonas gingivalis;* Infection; Mechanisms; Heart Valve Diseases; Cardiovascular.

ABSTRACT

Aim: To describe the pathogenic mechanisms used by *P. gingivalis* to migrate to the heart and infect the heart valves.
Materials and methods: A systematic search of the information is carried out from the PRISMA Declaration to obtain sources of information, the MeSH health descriptors "*Porphyromonas gingivalis*", "Infection mechanisms" and "Valvular heart disease" are |obtained, which were combined through the boolean "AND" connector.
Results: Two types of searches were carried out, in which a total of 61 articles were analyzed, where four studies related to the chosen theme were found, including two original scientific research articles and two observational articles; a conventional PCR method was used to detect *P. gingivalis* in all the articles.
Conclusion: Several studies carried out in patients with periodontal disease with or without the presence of concomitant valvular disease have managed to isolate the periodontopathogen in heart valves, although its proportion is minimal compared to other pathogens, however, the pathogenic mechanism by which *P. gingivalis* infects heart valves has not been identified, and research is needed to obtain accurate information on the relationship between infection caused by *P. gingivalis* and valve disease.

INTRODUCTION

In the oral cavity as in the whole human body we have a microbiota which is the set of microorganisms that live in this anatomical niche without being pathogenic for the individual, the mouth is colonized by more microorganisms when the teeth develop and a symbiotic relationship that generates stability in it is generated. An imbalance in this can damage oral health which can lead to alterations in soft tissues and other diseases at a systemic level; in the case of *Porphyromonas gingivalis* which is a gram negative bacterium typical of the anaerobic gingival sulcus and member of the Bacteroidetes family that can cause periodontal disease which is a chronic inflammatory disease that compromises the integrity of the supporting tissues of the tooth has been related to inflammatory processes that affect the tissues generating the fall of teeth and bone loss. However, all this depends on its ability to evade host immunity, a process carried out by means of its virulence factors, among which the following have been identified: fimbriae, secreted proteins such as gingipains, lipopolysaccharides and capsules. These mechanisms allow and favor the survival of the bacteria within the organism and the inhibition of the immune response.[1]

Additionally, this has been related to a series of systemic diseases such as respiratory diseases, preterm birth, low birth weight, cardiovascular disease due to atherosclerosis,

increased cardiovascular risk since it has been found to favor a proinflammatory endothelial state by increasing inflammatory markers and chemotactic substances that facilitate bacterial invasion, favoring the accumulation of dead macrophages and LDLs. This alters endothelial and smooth muscle function, resulting in occlusion, narrowing and loss of flexibility of the blood vessel, triggering atherosclerotic diseases [2] and valvular diseases, because the heart receives blood from the organism and sends it to the lungs where the gaseous exchange is generated in order to obtain the necessary oxygenation for the different organs of the body and this is done by means of two atria and two ventricles that are separated by interatrial and interventricular septa and between these chambers there are four valves that can be identified as follows: mitral valve, tricuspid valve, tricuspid valve and tricuspid valve: mitral, tricuspid, aortic and pulmonary valves.[3] These valves function as gates that open and close to allow the passage of blood to another cavity and prevent it from going in the wrong direction,[4] when a lesion is generated in these valves, this can be reflected in stenosis or valvular insufficiency; where in the first case the passage of blood from one chamber to another is prevented and in the second case, when there is not an adequate closure, a return of blood that should not happen is generated and these two scenarios can cause an insufficient flow for the rest of the organism or generate pulmonary, hepatic or lower limb congestive symptoms due to the retention generated.[3]

Although *P. gingivalis* has been found in cardiac valves, the virulence mechanisms used by *P. gingivalis* to achieve this infection and trigger valvulopathy have not been studied in depth. Therefore, the objective of this article is to describe the pathogenicity mechanisms used by *P. gingivalis* to migrate to the heart and infect cardiac valves, considering as a hypothesis that the migration of this periodontopathogen to the valves may contribute to the progression of valvular disease.

MATERIALS AND METHODS

In this review of the literature, a systematized search of the information was carried out, based on the PRISMA Statement [5] to obtain sources of information. In this sense in MeSH on Demand through the guiding question "What are the infection mechanisms used by *Porphyromonas gingivalis* to infect heart valves", the MeSH health descriptors "*Porphyromonas gingivalis*", "Infection mechanisms" and "Valvular heart disease" were obtained, which were combined through the Boolean connector "AND".

In the MEDLINE database, through the PubMed search engine, a search was performed with the combinations "Porphyromonas gingivalis" AND "Valvular heart disease" without delimiting the time, using English and Spanish filters, from which 9 results were obtained. Another combination used was "P gingivalis" AND "heart disease" to which the time filter was applied, between 2012-2022, due to the density of the information and the English-Spanish language filter. This second search yielded 52 results. In total 61 articles were obtained, 7 articles were discarded because they were repeated, 17 because they did not relate periodontal disease to cardiovascular disease and 4 articles because they were related to the topic, however they did not answer the research question posed from the general objective. Finally, 33 articles were analyzed (Figure 1). It is worth clarifying that the key words were combined using the AND operator because the objective is to review the literature that relates both terms and it was necessary to filter the information more precisely so that it would be focused on the purpose of the present review.

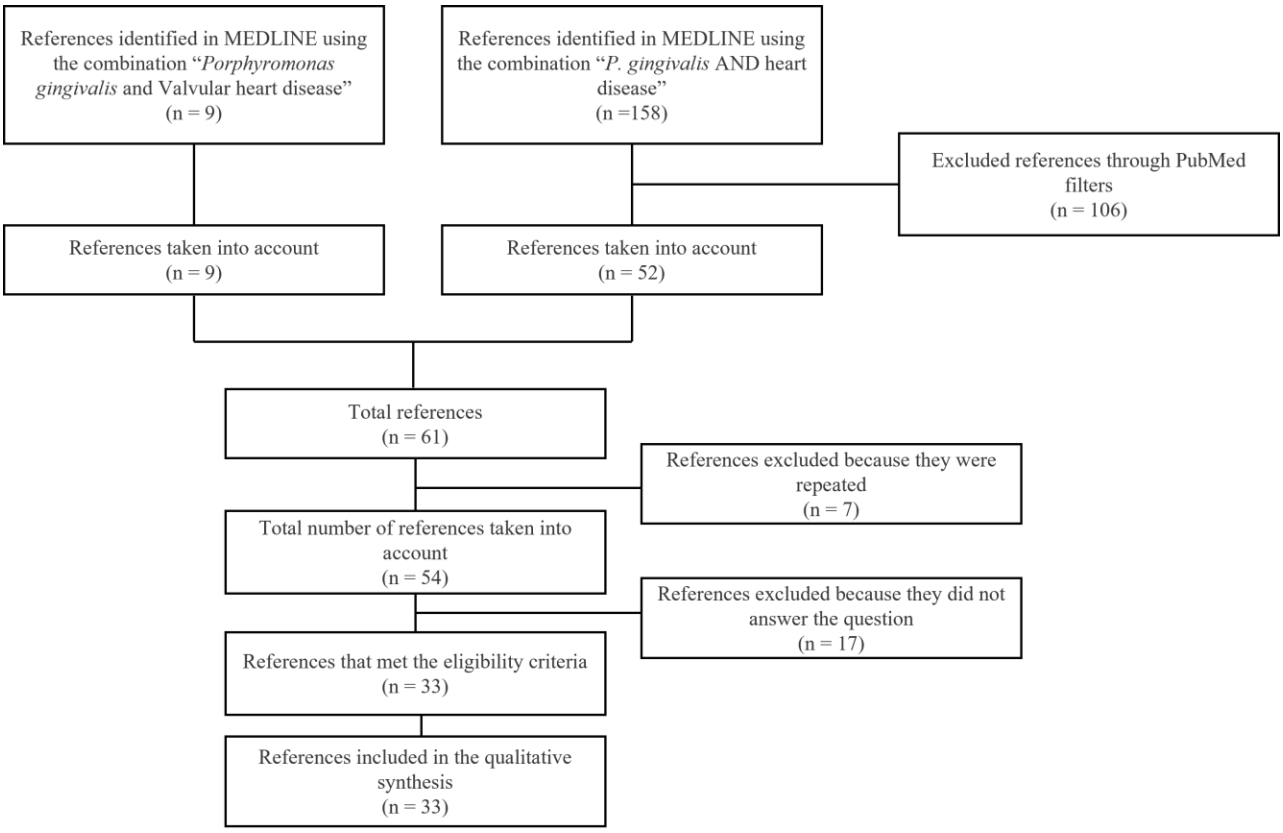

Figure 1. Flow diagram of the systematized search for information used in this literature review based on the PRISMA(5) statement.

RESULTS

Since the main objective of the article is to find the relationship between P. gingivalis and heart valve disease during the systematic review performed in Table 1, finally out of 33 articles included (Table 1), 4 studies related to the chosen topic were found within which there are two original scientific research articles and two observational ones; conventional PCR was used as detection method in the four studies and the samples were collected in the following way:

In the article by Moreno S et al. 30 samples of subgingival and valvular tissue were used, the one by Forte Oliveira et al. 42 patients were used were divided into dentate and edentulous, edentulous patients had saliva samples collected while dentate patients had supragingival tissue and plaque collected,[6] in the article by L Rafaelli and collaborators of 19 patients they collected valve tissue and whole blood samples, Malgorzata Radwan-oczko and collaborators used 30 patients who underwent valve surgery and from whom valve tissue and periodontal pockets were collected.[7]

Table 1. Table of search results.

Article Name	Conclusions	Relationship to Research Question
Porphyromonas gingivalis-Induced Cellular Hypertrophy and MMP-9 Activity via Different Signaling Pathways in H9c2 Cardiomyoblast Cells	The data obtained in the article cannot be associated to a specific virulence factor. however, P. gingivalis in the myocardium evidences increased MMP-9 along with multiple signaling pathways involving p38, ERK, JNK, PI3K and calcineurin, which link P. gingivalis in myocardiomyocyte hypertrophy being key in cardiac diseases such as heart failure, but this link is dose- and exposure-dependent and time-dependent and only certain periodontal pathologies associated with specific genes contribute to it.	The current findings provide a potential link between P. gingivalis and myocardial hypertrophy, suggesting that some virulence factors or metabolic byproducts of P. gingivalis directly affect myocardial cells and could be involved in cardiac pathologies, however, they do not specifically mention valvular disease.
Periodontal microbiota and microorganisms isolated from heart valves in patients heart valves in patients who underwent valve replacement surgery in a valve replacement surgery in a clinic in Cali, Colombia.	The periodontal microbiota of patients undergoing valve replacement surgery was composed of Gram negative species was composed of Gram-negative species that have been associated with infections in extraoral tissues. However, no periodontal pathogens were found in the valve tissues. valve tissues. Although there were samples from these tissues and subgingival tissues, positive for Gram-negative enteric bacilli, it is not possible to be certain that these Gram-negative enteric bacilli, it is not possible to ensure that they had the same phylogenetic origin.	In the article it was not possible to isolate *P. gingivalis* and therefore it is not mentioned as a causal microorganism of valvulopathy.
Molecular Analysis of Oral Bacteria in Heart Valve of Patients With Cardiovascular Disease by Real-Time Polymerase Chain Reaction	*P. gingivalis* has received special attention among periodontopathic bacteria with respect to its association with CVD, although it was found with low frequency in the present study. This bacterium is detected with high frequency in studies that investigate its investigate its presence in atherosclerotic plaques, and in vitro and in vivo experimental studies have shown that P. gingivalis accelerates the atherosclerotic plaque process through different mechanisms.	In the article, *P. gingivalis* was found in deep periodontal pockets and in heart valves of both edentulous and dentate patients, however, its presence was low compared to the other pathogens, with *S. mutans* being the main pathogen isolated.
Detection of oral bacteria in cardiovascular specimens	*S. mutans* and *A. actinomycetemcomitans*, are related to bacteremia and may be etiological factors for the development of cardiovascular diseases. As for other species, *S. sanguinis* other species, *S. sanguinis*, *P. gingivalis* and *T. denticola* were detected with frequencies ranging from 15 to 20 %, each of which was significantly lower than *S. mutans* ($P < 0.05$).	*P. gingivalis* was detected in cardiac valves, however, only in 5.6% in relation to *S. mutans* which is 78%.
Examination of periodontal pathogens in stenotic valve specimens and in whole blood samples in patients affected by aortic	Neither the 19 aortic valve samples nor the blood samples were positive for the genome of the selected periodontal pathogens. The selected periodontal pathogens did not colonize the aortic valve of patients affected by stenosis and the bacterial genome was not	It was not possible to isolate any of the selected microorganisms, including *P.gingivalis*, from the valves.

valve stenosis and chronic periodontitis	present in the whole blood samples.	
Level of serum antibody against a periodontal pathogen is associated with atherosclerosis and hypertension	The results suggest that an elevated level of antibodies against *P. gingivalis* indicates advanced periodontal disease and suggests progression of atherosclerosis and hypertension.	Mentions the relationship between *P. gingivalis* and the development of atherosclerotic disease but does not mention the mechanisms of virulence.
Molecular Analysis of Oral Bacteria in Heart Valve of Patients With Cardiovascular Disease by Real-Time Polymerase Chain Reaction	Se encontraron bacterias orales, especialmente S. mutans, en la válvula cardíaca en muestras de pacientes con alto índice de caries y gingivitis/periodontitis	El artículo menciona la enfermedad valvular cardiaca y la relación de diferentes patógenos en el desarrollo de la misma, sin embargo, llega solo hasta la detección de P gingivalis en las válvulas cardiacas
Assessment of Serum IgG Titers to Various Periodontal Pathogens Associated with Atrial Fibrillation in Acute Stroke Patients	*Porphyromonas gingivalis*, especially FimA type III and type V, could be associated with AF in stroke patients.	Although there is limited evidence of an association between Porphyromonas gingivalis mA figenotypes and systematic internal disease they reported that fimA type II and type IV were most frequently detected in heart valve or atheromatous plaque samples.
"Association of periodontopathic anaerobic bacterial co-occurrence to atherosclerosis" - A cross-sectional study	The results of this study strongly correlate periodontal bacterial co-occurrence and periodontal bacterial adhesion factor with atherosclerosis.	Recognizes that periodontal anaerobic agents can invade coronary vessels.
Dysregulation of miR-146a by periodontal pathogens: A risk for acute coronary syndrome	MicroRNA-146a is a key molecule that associates periodontitis with acute coronary syndrome.	The proinflammatory factor generated by *P. gingivalis* is related to SCA.
Periodontal pathogens and their role in cardiovascular outcome	Detection of *E. corrodens* was associated with a lower risk of adverse CV events in patients with CV disease. The pathophysiological background underlying this association should be investigated in further studies.	Different pathogens can generate an effect on cardiovascular disease but does not specify how P gingivalis does.
Periodontal pathogens in atheromatous plaque	A correlation was established between the putative bacteria contributing to atheroma plaques and the species associated with periodontal disease.	Confirmation that DNA from periodontal bacteria such as *P. gingivalis* is present in coronary atheromatous plaques.
Salivary IgA to MAA-LDL and Oral Pathogens Are Linked to Coronary Disease	The study highlights an association between salivary IgA to MAA-LDL and atherosclerosis.	Study shows how antibody levels increase with exposure to *P. gingivalis*
The association between subgingival periodontal pathogens and systemic inflammation	In these dentate men aged 60 to 70 years, the presence of *P. gingivalis* in the subgingival plaque was significantly associated with an elevated C-reactive protein level.	The study shows how there is an increase in inflammatory factors with the presence of *P. gingivalis.*

Periodontal pathogen load and increased antibody response to heat shock protein 60 in patients with cardiovascular disease	In cardiovascular patients, a higher burden of subgingival infection with elevated levels of *P. gingivalis* and *T. forsythia* is associated with modestly higher levels of anti-hHSP60.	The article mentions how the levels of antibodies against *P. gingivalis* are increased in patients with cardiovascular disease.
Oral Bacterial Signatures in Cerebral Thrombi of Patients With Acute Ischemic Stroke Treated With Thrombectomy	The common presence of streptococcus viridans bacterial DNA in thrombus aspirates from patients with acute ischemic stroke is evidenced. Streptococcal bacteria, mainly of oral origin, may contribute to the progression and thrombotic events of cerebrovascular diseases. *P. gingivalis* was not isolated in thrombi.	It was not possible to isolate p.gingivalis in the thrombi, however, its participation in thrombus formation is not excluded since it was isolated in the blood samples extracted.
Associations of Antibodies Targeting Periodontal Pathogens with Subclinical Coronary, Carotid, and Peripheral Arterial Atherosclerosis in Rheumatoid Arthritis	In our study, we did not observe an association of anti-Pg with any measure of atherosclerosis, which could indicate specificity in the effect related only to *Aggregatibacter* in RA. RA patients with evidence of exposure to *Aggregatibacter*, but not *P.gingivalis*, had higher levels of atherosclerosis across multiple vascular beds independent of other CVD risk factors.	The article found no association between anti-porphyromonas antibodies and any measure of atherosclerosis.
Porphyromonas gingivalis antibody levels and diagnosis of coronary artery disease in HIV-positive individuals	Periodontal bacteria may be contributing to the risk of CAD (coronary artery disease) in people with HIV. No correlations were found between inflammatory markers and antibody titers to periodontal pathogens although there was a trend toward such a relationship between CD14 and antibody titer against *P. gingivalis*.	This study demonstrates that periodontal bacteria may contribute to cardiovascular risk in HIV patients, where higher levels of anti-P. gingivalis were detected in those patients who went on to develop atherosclerosis.
Detection of periodontal microorganisms in coronary atheromatous plaque specimens of myocardial infarction patients: A systematic review and meta-analysis	The consistent detection of periodontal bacterial DNA in coronary atheroma suggests its systemic dissemination from periodontal sites. The consistent detection of the key periodontal bacterium, *P. gingivalis*, in atheromatous plaque samples collected from patients with myocardial infarction reinforces the concept of bacterial translocation from inflamed periodontal sites to coronary arteries, however, the mechanism of action to achieve this is not established.	The article concludes that *P. gingivalis* is consistently detected in atheromatous plaque samples collected from patients with myocardial infarction and therefore suggests that bacterial translocation from inflamed periodontal sites to coronary arteries is a possible mechanism involved.
Relationship of oral conditions to the incidence of infective endocarditis in periodontitis patients with valvular heart disease: a cross-sectional study	Patients with valvular disease and endocarditis may have severe periodontitis compared to patients without infective endocarditis, although mitigation will be necessary because this is based on only 7 patients with valvular disease with infective endocarditis.	An increase in *P. gingivalis* infection was associated with the occurrence of endocarditis in patients with valvular disease.
Endothelial committed oral stem cells as modelling in the relationship between periodontal and cardiovascular disease	Time-lapse experiments showed that LPS-G causes a rapid and sustained increase in ROS generation in e-hPDLSCs, negligible in undifferentiated cells. From the data obtained, by multi-parametric analysis	LPS-G causes a slowing of cell growth after 24 h and the release of IL6, IL8 and MCP1 molecules.
Prevalence of eight putative periodontal pathogens in atherosclerotic plaque of coronary artery disease patients and comparing them	It is concluded that subjects with atherosclerosis had a higher prevalence of periodontal pathogens in subgingival biofilms compared to non-cardiac subjects. subgingival biofilms compared to non-cardiac subjects.	The article mentions how P gingivalis achieves endothelial invasion and enhances the inflammatory response in humans through one of its virulence mechanisms which is fimA and how this may contribute to the formation of atherosclerotic disease.

with noncardiac subjects: A case-control study		
Specific Inflammatory Stimuli Lead to Distinct Platelet Responses in Mice and Humans	Using human studies and animal models, the results demonstrate that variable sources of inflammatory stimuli have the ability to influence the platelet phenotype in different ways. inflammatory stimuli have the ability to influence platelet phenotype in different ways, indicative of the diverse role of platelets in thrombosis, hemostasis and immunity.	Mentions the increase in antibodies and how this affects platelets.
Association between central and peripheral blood pressure and periodontal disease in patients with a history of myocardial infarction	There is an association between PE and increased central and peripheral BP, which may partially explain the cardiovascular risk associated with chronic PE. High titers of antibodies against P.g g gingipains were not related to increased central or peripheral BP.	There was no relationship with virulence factors of *P. gingivalis* and blood pressure, although it is related to periodontal disease, probably due to the chronicity of the inflammatory process.
Periodontitis and myocardial hypertrophy	Although other periodontal pathogens such as *A.actinomycetemcomitans* induce cardiac hypertrophy by increasing MMP2 synthesis, *P. gingivalis* does not accelerate hypertrophy by this pathway, however, in the isoproterenol-induced myocardial hypertrophy model in animal models, P.g. induces myocardial hypertrophy through Toll-like receptor-2 signaling and increased NOX4. An important finding observed in several studies by the authors and other reports is that the regulation of chronic inflammation induced by periodontitis could play a key role in the treatment of myocardial hypertrophy.	In animal studies: Increase of molecules such as TLR-2 and NOX4 in cardiomyocytes favoring their hypertrophy.
Periodontitis and the outcome of atrial fibrillation ablation: *Porphyromonas gingivalis* is related to atrial fibrillation recurrence	Elevated serum antibody titers against *P. gingivalis* type IV may be a predictor of late recurrence of PA in patients undergoing RFCA, as *P. gingivalis* type IV may be a pathogen related to the induction of PA recurrence.	In patients with periodontitis, P. gingivalis type IV major fimbriae may favor PA due to their endothelial adherence and proinflammatory potential.
Porphyromonas gingivalis and left atrial appendage spontaneous echo contrast in atrial fibrillation ablation candidates	Elevated serum *P. gingivalis* antibody titers (Fim A types II and IV) were associated with the severity of LAA SEC among AF ablation candidates who received adequate anticoagulation. *P. gingivalis* infection may exacerbate the prothrombotic state in LAA and measurement of serum *P. gingivalis* antibody titers may be useful in monitoring the risk of thromboembolic disease in patients with AF.	The presence of P. gingivalis in patients with periodontitis is related to the severity of LAA SEC in patients receiving PA.
Porphyromonas gingivalis in periodontal pockets and heart valves	There is no relationship between *P. gingivalis* infection and valvular degeneration.	Establishes that there is no relationship between *P. gingivalis* infection and valvular degeneration.

Relationship between past myocardial infarction, periodontal disease and *Porphyromonas gingivalis* serum antibodies: A case-control study	There was a relationship between chronic periodontal disease and a history of MI, as well as the presence of *P. gingivalis* anti-gingipain antibodies and a history of MI, which was independent of classic risk factors for cardiovascular disease.	The gingipains of *P. gingivalis* and the immune response induced against these virulence factors may be associated with IM in patients with periodontitis.
Antibodies to periodontal pathogens are associated with coronary plaque remodeling but not with vulnerability or burden	Plasma IgG and IgA against the main periodontal pathogens were not associated with the degree of coronary atherosclerosis (except for a trend in diabetics) or with coronary plaque vulnerability. IgA against periodontal pathogens was inversely associated with the extent of coronary remodeling. Taken together, these results do not add evidence for a substantial role of systemic exposure to periodontal pathogens in coronary artery disease.	Plasma levels of IgG and IgA against the four major periodontal pathogens were not associated with the extent of coronary atherosclerosis, nor with coronary plaque vulnerability as measured with IVUS-VH in a population of patients with established coronary artery disease.
Salivary biomarkers of bacterial burden, inflammatory response, and tissue destruction in periodontitis	Salivary concentrations of MMP-8, IL-1β, and *P. gingivalis* are associated with various clinical and radiographic measures of periodontitis. The CRS index, which combines all three salivary biomarkers, is more associated with periodontitis than any of the markers alone, regardless of the patients' coronary artery disease status.	Salivary concentrations of MMP-8, IL-1b and *P. gingivalis* are associated with periodontitis and several clinical and radiographic variables. They were more strongly associated with substantial periodontitis than any of the markers alone regardless of the patients' systemic disease.
Relationship between Periodontal disease, *P. gingivalis*, peripheral vascular resistance markers and Coronary Artery Disease in Asian Indians	Periodontal disease induces early changes in peripheral blood vessels. The presence of Pg in patients with periodontal disease. cardiovascular risk factors and CAD indicates the importance of oral hygiene in disease control.	No direct relationship with cardiovascular disease is evident.
The Prevalence of Periodontal Pathogenic Bacteria in Atherosclerotic Cardiovascular Disease	It is not possible to establish a cause-effect relationship between Pg infection in valves and valvular disease because other factors are involved.	The article explains how different pathogens can affect the cardiovascular system, however, it specifies that a cause and effect between *P. gingivalis* and the development of valvular disease cannot be established.

Furthermore, in the results of these articles there are differences in the findings. On the one hand, *P. gingivalis* is found in low presence, while in different studies it was not possible to isolate any microorganism and in others it is found in the periodontal pockets, but not in the cardiac valves. As can be seen, the presence of *P. gingivalis* in cardiac valves has been limited, however, various authors have found the relationship of this microorganism with cardiovascular diseases because through its virulence mechanisms it has the ability to migrate and make bacteremia generating the activation of the LPS-Toll type receptor that leads to nuclear translocation of NFκB and the induction of genes related to inflammation, in addition, in other literatures it is found that *P. gingivalis* through its fimbria fimA increases the expression of genes for inflammatory response in endothelial cells and aortic tissue generating atherosclerotic disease Figure 2).[8]

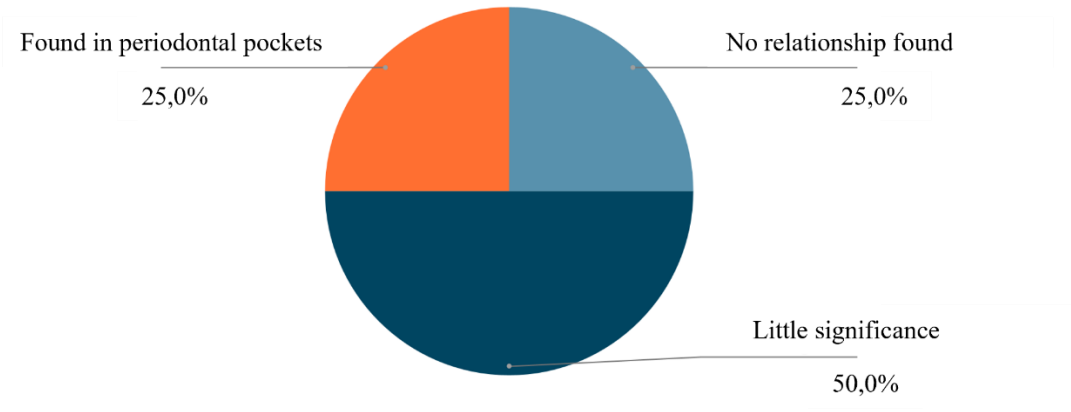

Figure 2. Presence of *P. gingivalis* in cardiac valves.

On the other hand, within the search there are articles that find antibodies against P. gingivalis which means that there is an immune response of the host to this microorganism, within these 9 articles were found in which it is detected in a study by Yohsuke Hanaoka and collaborators studied 127 patients with ischemic heart disease, serum antibody levels were measured against *P. gingivalis* and found that elevated antibody levels indicate advanced periodontal disease as well as atherosclerosis and hypertension;[9] Tomohisa N et al. sampled using ELISA against 9 periodontal pathogens in acute stroke patients registered in 2 hospitals and found a relationship of fimA type III and V with AF in these patients; also, Akhi R et al. studied 451 patients, took IgA antibodies in saliva against MAA-LDL, Rgp 44 and Aa-HSP60 in patients with CAD and acute coronary syndrome and found reactive salivary IgA was associated with cross-reactivity with oral pathogens;[10] Leishman SJ et al. obtained data from 74 patients with CAD in which serum antibodies against pathogens, Gro ELand hHSP60 by ELISA were used in which it is found that the higher the infection load of *P gingivalis* and *T. forsythia* there are higher levels of hHSP60;[11] Giles Jon and collaborators analyzed sera for antibodies directed to *Porphyromonas gingivalis* (Pg), *Aggregatibacter actinomycetemcomitans* serotype B (Aa) and Aa-derived leukotoxin A (LtxA), where finally no association is found between P gingivalis infection and increased antibodies;[12] Berquist V. L. and collaborators studied 24 patients with HIV where antibodies were taken against whole cells of the periodontal pathogens *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum*, as well as the inflammatory markers sCD14, CXCL10 and high sensitivity C-reactive protein, however no correlations were found between the inflammatory markers and antibody titers of the pathogens;[13] Radoslaw P and collaborators took 220 patients who were separated into groups of cases and controls in which the group of cases are the patients who have a history of myocardial infarction and the other those who have no history but have risk factors, all patients underwent periodontogram and blood sampling for analysis of anti gingipain antibodies of *P. gingivalis*, and found a relationship between these two groups. *P. gingivalis* and a relationship was found between chronic periodontal disease and a history of myocardial infarction, as well as the presence of P. gingivalis anti gingipain antibodies and a history of myocardial infarction;[14] Sanneke P. M and collaborators between 2008 and 2011 studied 581 patients in which IgG and IgA were measured against P. gingivalis, A. actinomycetemcomitans, *T. forsythia* and *P. intermedia*, the result of which showed that immunoglobulins were not associated with the degree of atherosclerosis, nor with the vulnerability of coronary plaque.[15]

Finally, it can be seen that *P. gingivalis* generates an increase in antibodies in most of the cases that are related to cardiovascular disease; however, in three cases there is no significant relationship between the infection and atherosclerotic disease; what is repeated in all the studies is how *P. gingivalis* generates an inflammatory response that is associated with cardiovascular disease (Figure 3).

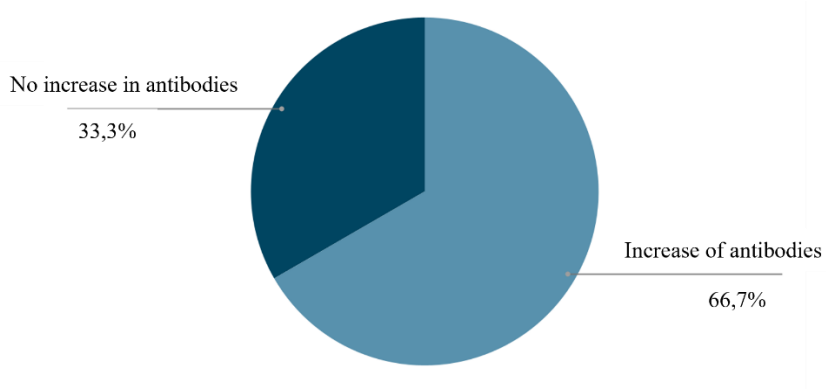

Figure 3. Relationship between P. gingivalis infection and increased antibodies in patients with cardiovascular disease.

DISCUSSION

The discussion of the present article was divided into five sections where we argue about how P. gingivalis contributes to the development of diseases of the cardiovascular system and finally what is its role in heart valve diseases.

Pathophysiology of migration to cardiovascular tissues

Porphyromonas gingivalis is a gram-negative bacterium that tends to inhabit the oral cavity; however, like all bacteria, it possesses pathogenicity factors that allow it to invade tissues and generate damage to the host when an alteration occurs with said host, causing dysbiosis. This bacterium is characterized by having facultative structures that confer its pathogenicity such as its capsule, capsular polysaccharide, secretion proteins and type A fimbriae. It is through these structures that it allows tissue damage and subsequent colonization. This pathogenic process is mediated by the use of fimbriae that allow tissue adhesion through the extracellular matrix to induce virulence by favoring the exchange of bacterial DNA, creating diverse phenotypes of fimbriae and increasing the pathogenicity of the bacteria by creating different polymorphisms of these structures. [16,17]

Likewise, it has been found that the capsule contains intracellular vesicles that facilitate the coaggregation and colonization of the bacteria to the host cells, using enzymes that degrade vital components of the extracellular matrix such as collagen, elastin and fibrinogen. Together with the capsular polysaccharide it helps to mediate this adhesion, favors the evasion of the immune system and decreases the inflammatory response.[16] Accompanied by proteins such as hydrolases and proteases, it will be in charge of allowing the survival of the bacteria in the middle of the colonization process. Through the hydrolyzation of host proteins providing amino acids to the bacteria as a nutritional source, it neutralizes the host immune system, degrades the extracellular matrix that would be the

periodontal support, produces hemodynamic changes such as the increase of coagulases, mediates cell adhesion, modifies the receptors for bacteria on oral surfaces and modulates the fixation of other bacteria and their colonization in subgingival sites. Likewise, endotoxic lipopolysaccharides (LPS) induce alterations and destruction of periodontal tissue including attachment loss, collagen degradation and alveolar bone loss, thus inducing bacteremia in the host.[16,18]

Therefore, to have systemic implications the bacteria must enter the bloodstream. Once here, it is transformed into thrombogenic agents that produce platelet adhesion and aggregation by mimicry of type I and III collagen binding sites. Through its fimbriae, it adheres to and invades epithelial and endothelial cells, entering by endocytosis into these cells and multiplying inside them. Likewise, it uses LPS to mobilize within the blood and express adhesion molecules to allow it to adhere and enter the subendothelium and colonize monocytes reinforcing the evasion of the immune response. Similarly, they can bind to low density lipoproteins (LDL) for transport and then bind to the CD14 receptor of immune cells such as macrophages, so that they become activated, release more adhesion molecules and gradually secrete proinflammatory cytokines. These macrophages begin to accumulate triglycerides in the smooth muscle, which favors the formation of atheromatous plaques. Similarly, it is known that bacteria in blood can increase viscosity by increasing the leukocyte count, CRP and fibrinogen, which together with the interaction of Von Willebrand factor and LPS cause platelet aggregation, favoring thrombogenic activity.[19] Therefore, it is through the previously mentioned mechanisms that allow invasion and subsequent bacteremia that have been studied and related to periodontal disease and cardiovascular diseases.

Presence of *P. gingivalis* in atheromas

Atherosclerosis is defined as the accumulation of cellular debris and cholesterol forming what is known as atheroma plaque, which is the basis of most cardiovascular pathologies. Traditional risk factors include hypertension, dyslipidemia, diabetes and smoking; however, emerging evidence suggests that inflammation in response to specific pathogens is an additional risk factor for atherosclerosis. Taking this into consideration, periodontal disease is caused by infection predominantly with Gram-negative bacteria, including *P. gingivalis*, which causes inflammation and is associated with the development of atherosclerosis and cardiovascular disease.[9]

Several studies have demonstrated the presence of *P. gingivalis* in atheromatous formations present in areas of the cardiovascular system other than the heart valves, which has contributed to establish a possible relationship between the presence of this periodontal pathogen in cardiovascular diseases. Nakano K. and collaborators conducted a study of 203 individuals from which samples were obtained from mitral valve, aortic valve and the wall of abdominal, thoracic and thoracoabdominal aortic aneurysms, from which it was possible to isolate the periodontal pathogen *Phorphyromonas gingivalis* with a frequency between 15% to 20% being significantly lower than Streptococcus mutans ($P < 0.05$), however, it is far from being the most common.[20]

The local inflammatory response by periodontal pathogens promotes their passage into the bloodstream whose cause seems to be associated with the performance of invasive dental procedures or even normal daily activities, such as brushing teeth or eating food.[21] Mahendra J. and collaborators reported in a study that took into account 51 cardiac and non-cardiac subjects with coronary artery disease, samples

of subgingival plaque and atheromatous plaque present in the coronary arteries were taken, in which the percentage of periodontal bacteria detected in the atheromatous plaque correlated significantly with periodontal pathogens among which P. gingivalis is found, suggesting its main role in the progression of atherogenesis.[22] Bacteremia and/or endotoxins from periodontal pathogens induce the expression of inflammatory cytokines and increase endothelial adhesion molecules leading to a prothrombotic environment, which may promote inflammatory changes in vessel walls and thus support Cardiovascular remodeling processes. This being the case, it raises the possibility that this is the common interface for periodontal and cardiovascular diseases.[21]

On the contrary, Gode S. and collaborators carried out a case-control study in which they included 96 patients with a diagnosis of valvulopathy due to atherosclerosis and 85 patients with advanced aortic valve stenosis due to rheumatic fever who underwent aortic valve replacement, finding DNA of *P. gingivalis* in one (1.04 %) and three (3.13 %) of 96 samples of atherosclerotic tissue; in the remaining 85 samples the microorganism was not isolated. It has been established that systemic inflammation induced by *P. gingivalis* has a relationship between atherosclerosis and periodontal disease, although it is not possible to determine a causal relationship between periodontal pathogenic bacteria and the formation of atherosclerosis, because inflammation may be affected by other factors such as ethnicity, dietary habits, nutritional availability and lifestyle.[23]

Recent studies have shown that periodontal disease can produce numerous changes in systemic health with changes in blood chemistry with increased inflammatory mediators, serum proteins and lipids. Periodontitis has been proposed to have an etiologic or modulatory role in cardiovascular and cerebrovascular disease, diabetes, respiratory disease, adverse pregnancy outcomes, and rheumatoid arthritis.

Rath SK et al. conducted a study in 7 patients undergoing coronary endarterectomy from which atheromatous plaque samples were obtained and *P. gingivalis* was found to be present in 71.43%.[24] On the other hand, Joshi C. and collaborators in a meta-analysis in which they took into account 14 studies reported the presence of *P. gingivalis* fimbriae in 21 coronary atheromatous samples and fimA type II was detected in 11 samples. In 10 of these atheromatous samples belonged to patients with periodontitis, while only one subject was completely healthy, which supports the relationship between the presence of fimbriae as an adhesion mechanism of the bacterium that favors its proliferation in atheromatous plaques.[25]

P. gingivalis: Factor or risk indicator?

According to different studies, infection by the presence of *P. gingivalis* and, in general, periodontal disease, increases the risk of suffering cardiovascular diseases by 20%.[7] Likewise, some studies indicate that the abundance of periodontal pathogens in the subgingival microbiota increases the probability of their entry into the circulation, which contributes to the pathogenesis of atheromatous plaques in atherosclerotic disease. It has also been identified that gingipains from *P. gingivalis* can increase the inflammatory response which can lead to increased blood pressure; however, it has been found that the increase in antibodies against *P. gingivalis* is not related to the increase in central and peripheral blood pressure, nor is it related to acute myocardial infarction.[14]

On the other hand, it has been shown that infection by this bacterium can exacerbate the prothrombotic state and serum *P. gingivalis* antibody levels are useful for controlling the risk of thromboembolic disease in patients with atrial fibrillation.[10] Thus, *P. gingivalis* infection can be associated with the development of cardiovascular diseases, since, as described above, it is pathophysiologically related to inflammatory and

atheromatous processes and is even involved in generating a prothrombotic state in patients with atrial fibrillation, but not in all cases the increase of these antibodies is related to a greater increase in the risk of these diseases.[10]

P. gingivalis in relation to heart valves

Different studies have been carried out where *P. gingivalis* has been identified in the heart valves, however, the virulence mechanism by which it manages to reach that area has not been described. Just as the presence of this bacteria has been described, other pathogens such as *S. mutans*; A study carried out by Moreno and collaborators analyzed specimens obtained from aortic and mitral valves, from which cultures were performed where microorganisms such as *P. acnes*, Gram-negative enteric rods, *Parabacteroides merdae* and *C. bifermentans* were found, however they report that in a study carried out by Radwan et al. the capacity of *P. gingivalis* to colonize heart valves through its virulence mechanisms is found but they do not find its DNA in the heart valves but in the periodontal pocket unlike *propionibacterium acnes* in which its appearance in the heart valves is explained by surgical procedures that facilitate its dissemination from the skin and its capacity to form biofilms.[6] However, the author Oliveira and collaborators report that the most frequent microorganisms detected in the heart valve samples were *S. mutans* with 89.3%, followed by *P. intermedia* with 19.1%, *P. gingivalis* represented in 4.2% and finally *T. denticola* with the lowest percentage 2.1%.[31, 17]

On the other hand, *L. Raffaelli* and collaborators carried out a study in 19 patients diagnosed with aortic valve stenosis and chronic periodontitis in order to observe the presence of DNA of periodontopathogens by PCR for *F. nucleatum*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, *A. actinomycetemcomitans*, *C. rectus*, *E. corrodens*, *T. denticola*. The study was concluded after examining the aortic valves and blood samples

Radwan-Oczko M. et al. examined 31 valve samples removed during cardiac surgery and periodontal pocket samples for the detection of periodontopathogenic *Porphyromonas gingivalis* DNA by PCR testing, thereby evaluating a possible association between the presence of *P. gingivalis* DNA in periodontal pockets and degenerated heart valves. *P. gingivalis* DNA from periodontal pockets was detected in 15 patients, all with periodontitis, however, DNA from these bacteria was not present in any of the mitral/aortic valves collected. Several studies have shown that *P. gingivalis* has properties that can promote atherosclerosis, invade endothelial cells and enhance atheroma formation, although the lack of DNA of these bacteria in heart valves with calcified degenerations may indicate that there is no relationship between the presence of *P. gingivalis* and valvular dysfunction, so that this oral pathogen may not play any role in the damage or inflammation of the heart valves.[21,33,24]

CONCLUSION

P. gingivalis is a periodontopathogen that, through its virulence mechanisms, generates numerous changes in systemic health and blood chemistry with an increase in inflammatory mediators, proteins and lipids in the serum. In turn, bacteremia and/or endotoxins from periodontal pathogens increase endothelial adhesion molecules that lead to a prothrombotic environment, which leads to inflammatory changes in the vessel walls supporting cardiovascular remodeling processes. It also promotes atherosclerosis by invading endothelial cells and enhancing the formation of atheroma, which is the interface that connects periodontal disease with cardiovascular diseases. However, the pathogenic mechanism by which *P. gingivalis* migrates and infects heart valves has not been established. Most studies have found *P. gingivalis* in the periodontal pockets of patients with valvular disease, but its identification in heart valves is limited compared to other microorganisms. Therefore, considering the difficulties in determining *P. gingivalis* in valvular samples and the lack of knowledge about its pathogenesis, there is a need to increase the number of investigations

that allow obtaining in-depth and accurate information on the relationship between infection caused by *P. gingivalis* and the affectation of heart valves, as well as the pathogenic mechanism by which it manages to migrate and reach them.

CONFLICT OF INTEREST

There is no conflict of interest.

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