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Advances in the study of the effects of chronic periodontitis on cardiac arrhythmias

Chen Hong[1,*], Wenxian Fan[2], Mirigul·Mahsut[1], Madina·Abdullam[1], Nurjan·Wresdem[1], Merhaba·Yasen[1], Xinshang Li[1,2]

[1]Department of Endodontics, The First Affiliated Hospital of Xinjiang Medical University (Affiliated Stomatological Hospital), Urumqi, 830054, China
[2]Institute of Stomatology, Xinjiang Uygur Autonomous Region, Urumqi, 830054, China
[*]Corresponding author: 330630787@qq.com, 1589694153@qq.com

Abstract: *Periodontitis is a disease that is currently receiving urgent attention in public health because its prevalence reaches 50% worldwide and it can affect almost all age groups, including adolescents, adults, and the elderly. The prevalence of periodontal disease is predicted to be increasing annually because of the aging population growth, with periodontitis being more likely to occur in the elderly group. The high prevalence of periodontitis will increase the global burden, which has increased more than 50% from 11 years ago. This paper outlines how oral diseases such as periodontitis and periapical periodontitis may be linked to cardiovascular disease, atrial fibrillation and cardiac arrhythmia. We undertake a systematic review of the literature focused on acute dental infection and types of cardiac arrhythmia and also describe an illustrative case where an acute dental infection diagnosed as periapical periodontitis was associated with the occurrence of atrial fibrillation.*

Keywords: *Arrhythmia; chronic periodontitis; oral microbiome; atrial fibrillation*

1. Systemic inflammation and AF

A variety of factors, such as the age, other structural heart diseases, the blood pressure, the alcohol intake, obesity, and genetic factors, have been reported to play a role in modifying the electrophysiological substrate of AF[1]. Systemic inflammation has also been suggested as one of the modifying factors of AF, which was corroborated by the increased inflammatory markers in the patients with AF. A case–control study reported that the circulating CRP level was higher in patients with AF than in those without AF. A population-based study revealed that the serum CRP level was independently associated with the new occurrence of AF as well as baseline AF[2]. Additionally, AF is associated with elevated pro-inflammatory IL-6 levels, and left atrial diameters were positively associated with CRP and IL-6 levels, which suggested that the inflammation might promote atrial remodeling[3]. A basic research has suggested the interaction between the release of inflammatory cytokines, such as tumor necrosis factor-alpha and IL-6, and the remodeling of the atrial muscle, leading to the development of AF substrates. In the present study, although a numerical value of CRP level was not correlated with AF recurrence in Cox proportional hazard models, the patients with mildly elevated CRP $\geq$ 0.1 mg/dL showed a higher recurrence rate than the counterpart (CRP < 0.1 mg/dL) [4]. Periodontal disease is not only evident in periodontitis itself, it increases the risk for the emergence of other systemic diseases; from 1980 to present, 57 systemic diseases have been reported to be associated with periodontal disease. Periodontitis is a chronic multifactorial inflammatory disease identical to immune dysfunction that was previously induced by bacterial infection, mainly anaerobic gram-negative bacteria, which causes progressive damage to the soft and hard tissues supporting the Periodontal bacterial infection increases systemic inflammatory markers, which also initiates various systemic diseases, including Stroke is considered the most common cause of death due to periodontal disease and is currently a massive epidemic in numerous developed and developing countries[5].

2. PD and AF

In animal models, induced PD led to an inflammatory response and remodeling of the atrial myocardium, facilitating AF inducibility [6]. In addition, previous studies have reported the presence of periodontal pathogens in human atheromatous lesions and the association of those pathogens with

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myocardial damage, which suggested that periodontal pathogens may infiltrate into arterial wall or myocardium. Thus, the direct infiltration of periodontal bacteria also may be a potential mechanism of atrial remodeling and predisposition to AF. A Taiwanese nationwide population-based cohort study showed an association between PD and the future development of AF or atrial flutter. PD was associated with future arrhythmic events, including AF, atrial tachycardia, and atrial premature beat, and thromboembolic events during the long-term follow-up of the patients with AF[7]. Nevertheless, the association of PD with arrhythmia recurrence after CA has not been elucidated. A recent study has shown the association between serum antibody levels to one of the periodontal pathogens and the recurrence of AF. This study is the first to demonstrate the association between actual oral health conditions examined in detail by periodontists or dentists and arrhythmia recurrence after CA for PAF, which supports the results of previous studies[8]. An interesting finding of this study is the recurrence-free rate curves in the Kaplan–Meier analysis of the PD and non-PD groups separated in the long-term (after 1 year) rather than in short-term. A recent study reported that electrical left atrial remodeling and non-PV triggers were more common in long-term recurrence of AF than in short-term recurrence, whereas PV reconnections were dominant in short-term recurrence. In other words, short-term recurrence is mainly associated with procedure-related factors while long-term recurrence is more affected by atrial remodeling, which may develop slowly[9]. This may explain how PD and subsequent systemic inflammation may have an impact on long-term recurrence through atrial remodeling rather than on short-term outcomes. Although the present study could not show the association of PD with the evidence of atrial remodeling such as enlarged atrial dimension or greater atrial low voltage area because of the small sample size and lack of 3D imaging data or voltage map, future prospective studies may address the impact of PD on electrophysiological findings in AF[10].

3. Relationship between PD, Oral Inflammatory Diseases, and Atrial Fibrillation

Previous studies have shown that the relationship between oral inflammatory diseases such as PD and atrial fibrillation is inconclusive. Aoyama[11]et al. found that the detection rate of P. gingivalis in atrial fibrillation patients aged 71～90 years was significantly higher than that in patients with bradyarrhythmia. Miyauchi[12] et al. found that serum anti-P. gingivalis antibody type IV was an independent predictor of atrial fibrillation recurrence after catheter ablation (OR 1.937, 95% CI 1.301–2.884, and P=0.002). The abovementioned two studies indirectly suggested that oral inflammatory diseases such as PD may promote the occurrence, development, and recurrence of atrial fibrillation. Holm-Pedersen[13] et al. found that patients with one to two active coronal caries lesions had 2.8 times higher odds (95% CI 1.1–7.0) of arrhythmia than those without active coronal caries, but there was no association between arrhythmia and periodontal disease. And this study did not further analyze the relationship between active coronal caries, periodontitis, and atrial fibrillation. In the recent years, a number of large retrospective cohort studies and prospective cohort studies have suggested that oral inflammatory diseases such as periodontitis may be associated with an increased risk of atrial fibrillation, but the causal relationship still needs to be further verified[14]. This study did not conduct a pooled analysis about the relationship between oral inflammatory diseases and atrial fibrillation because few studies could be included, with a large span of publication years, large differences in sample size, different design (included retrospective cohort study, prospective cohort study, and cross-sectional study), different outcome indicators (only recurrence of atrial fibrillation and recurrence of atrial fibrillation/atrial flutter), adjusted confounding factors, and varying follow-up time[15]. In addition, different characteristics of the study population may also affect the results of the study. For example, the prevalence rate of new-onset atrial fibrillation of male patients may be higher than that of female patients, and the prevalence rate of the elderly patients is significantly higher[16] . The differences of underlying diseases may also affect the results, such as heart failure, diabetes, chronic kidney disease, and coronary artery disease. A Mendelian randomization study, which intended to verify the causal relationship between PD and cardiovascular diseases, such as atrial fibrillation, showed that there was no causal relationship between dental caries, PD, and cardiovascular diseases such as atrial fibrillation, and the correlation between PD and atrial fibrillation may be related to the common etiological pathway in the investigation study[17] . PD shared the same genetic and environmental risk factors with cardiovascular diseases such as atrial fibrillation and hypertension. Although confounding factors were adjusted in the abovementioned studies, it cannot be ruled out that other potential confounding factors may have influenced the study results[18]. Genetic polymorphisms, a possible confounding factor that is very difficult to control for, could increase the predisposition to atrial fibrillation and other cardiovascular diseases. Combined with the current research results, it is not easy to conclude whether PD and other oral inflammatory diseases affect the risk of new-onset atrial fibrillation. Future research is still needed to clarify the potential confounding factors between PD and atrial fibrillation, and more rigorous longitudinal studies will be needed to evaluate the association and

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specific causal relationship between oral inflammatory diseases such as PD and new-onset atrial fibrillation.Sen[19]et al. revealed that severe PD significantly increased the occurrence risk of atrial fibrillation (RR = 1.31, 95% CI 1.06–1.62, *P*=0.01). This finding was supported by the results of Struppek et al., which also found that the atrial fibrillation incidence in male was higher than in female. Only one prospective cohort study and one cross-sectional study elaborated the relationship between severe PD and atrial fibrillation in this review. However, considering that approximately 10% of the global population suffers from severe PD, approximately 16.3% of severe PD is associated with atrial fibrillation. Therefore, more attention should be given to the occurrence risk of atrial fibrillation with severe PD. In the future, more large prospective studies are needed to evaluate the impact of different degrees of PD and other oral inflammatory diseases on the occurrence risk of atrial fibrillation. In addition, a cross-sectional study suggested that the prevalence of new-onset atrial fibrillation in PD patients increases with age, and male patients at the same age were more likely to develop atrial fibrillation. Advanced research will be needed to evaluate the effects of severe PD on atrial fibrillation in different ages and sexes. In clinical practice, elderly male patients with severe PD should be considered[20].

4. Effects of Tooth Brushing and Oral Care on Atrial Fibrillation

Other important findings were that compared with long-term nonbrushing or tooth brushing <3/d, long-term ≥3/d tooth brushing significantly improved the occurrence risk of atrial fibrillation; compared with no oral hygiene or occasional oral hygiene, regular dental cleanings or oral care ≥1/year could significantly reduce the occurrence risk of atrial fibrillation[21]. Although the current studies have not confirmed the correlation and causality between oral health and atrial fibrillation, the positive effect of oral care in reducing the risk of atrial fibrillation suggests that a better oral environment appears to be beneficial in improving the occurrence of atrial fibrillation[22]. The current study found the advantages of tooth brushing and oral care in improving new-onset atrial fibrillation but failed to confirm whether brushing frequency ≥3 times per day and oral hygiene at different frequencies had inconsistent effects on new-onset atrial fibrillation. In addition, Chen[23] et al. reported that dental cleanings 0–2/year were a protective factor for atrial fibrillation compared with patients without oral care (HR 0.39, 95% CI 0.38–0.41), but dental cleanings >2/year were a risk factor for atrial fibrillation (HR 6.06, 95% CI 5.38–6.83). This may be associated with preexisting periodontitis in patients with dental cleanings >2/year or recall bias in self-report questionnaires. Abovementioned results may suggest that proper oral hygiene appears to be important in improving the risk of atrial fibrillation, but the findings still need to be further validated in future studies, and more rigorous large-scale prospective studies are needed to explore the relationship between different frequency of oral care and the incidence of atrial fibrillation[24].

In addition, Omori et al. showed that in hospitalized patients with heart disease complicated with periodontitis, six-step oral hygiene enhancement can improve the occurrence of atrial fibrillation after cardiac surgery. All of the abovementioned studies suggested that regular tooth brushing and oral care had an advantage in improving the occurrence and recurrence of atrial fibrillation. Therefore, the importance of long-term tooth brushing and oral hygiene should be emphasized in clinical practice and health promotion. At the same time, more studies are needed in the future to confirm the impact of different tooth brushing frequencies or oral care on the occurrence and recurrence of atrial fibrillation and whether high-frequency oral care increases the risk of atrial fibrillation[25-26].

5. Conjecture about Related Underlying Mechanisms

Although the causal relationship between PD and atrial fibrillation remains unclear, studies have shown that oral pathogens and inflammatory mediators may increase the occurrence risk and recurrence risk of atrial fibrillation, and the underlying mechanisms are as follows: First, regarding the role of oral pathogens, the oral cavity is a reservoir for many kinds of bacteria and microorganisms, and P. gingivalis can release lipopolysaccharide, downregulate the expression of L-type calcium channels in cardiomyocytes, and shorten the atrial effective refractory period. P. gingivalis can increase the expression of toll-like receptor 2 (TLR-2) and toll-like receptor 4 (TLR-4), which can induce atrial fibrosis, reduce the transient outward potassium ion current, promote atrial structural remodeling and electrical remodeling, and increase the occurrence risk and recurrence risk of atrial fibrillation. Aggregator actinomycetes could promote inflammatory cell infiltration and induce cardiac remodeling, which may play an important role in increasing the occurrence risk of atrial fibrillation. Second, regarding the roles of inflammatory mediators and systemic inflammation, periodontal disease could cause a

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persistent inflammatory response or bacteremia, release inflammatory mediators such as C-reactive protein and interleukin-6, stimulate myocardial cell hypertrophy and apoptosis, promote myocardial fibrosis, and shorten the atrial effective refractory period, which could increase the occurrence risk and recurrence risk of atrial fibrillation. As the main virulence factor of P. gingivalis, fimbriae can regulate bacterial adhesion and invasion and stimulate a long-term chronic inflammatory response, inhibit interleukin-12 expression, and reduce the host's ability to clear inflammation. Third, regarding immune response, periodontal pathogens can stimulate the release of large amounts of matrix metalloproteinases (MMPs) from lymphocytes and promote the occurrence of cardiovascular diseases. In addition, antibodies against heat shock protein 60 (HSP-60) expressed by periodontal pathogens can cross-react with hSP-60 in the host body to activate T cells, leading to endothelial damage and atherosclerotic plaque formation and mediating cardiovascular disease. However, whether MMPs or HSP-60-related immune responses of periodontal pathogens play important roles in atrial fibrillation remains unclear[27-29].

Regular tooth brushing and oral hygiene could reduce the colonization and accumulation of pathogenic bacteria, reduce the levels of C-reactive protein, interleukin-6, and other inflammatory mediators, and reduce the systemic inflammatory response, which may play important roles in preventing the occurrence and development of atrial fibrillation. Some studies have shown that periodontal therapy can alleviate elevated blood pressure, decrease white blood cell count and oxidative stress response, and reduce the expression of MMPs. In addition, periodontal treatment can reduce serum total cholesterol, low-density lipoprotein, oxidized low-density lipoprotein, and other lipid levels. The role of these mechanisms in preventing the occurrence and progression of atrial fibrillation remains unclear[30-32].

6. Summary and Outlook

At present, considering the high recurrence rate and the high risk of thromboembolism after the occurrence of atrial fibrillation, the guidelines for atrial fibrillation gradually focus on the primary prevention of atrial fibrillation. To evaluate the effects of different degrees of PD, oral hygiene, and tooth brushing on the risk of atrial fibrillation, this study included clinical studies related to oral inflammatory diseases such as PD, oral care, and atrial fibrillation. Eight clinical trials were included based on multiple database searches, and studies have shown that PD and other poor oral health condition may increase the risk of atrial fibrillation, of which severe PD has the highest risk, but the correlation and causality remained to be further verified. Patients with better oral health seemed to have a positive impact on preventing AF or reducing AF recurrence. Regular and moderate oral care and tooth brushing 2–3 times per day are effective measures for improving oral health and preventing AF[33,34]. Oral health and oral disease prevention should be an important part of preventing new-onset atrial fibrillation. It is recommended to strengthen oral health publicity in future atrial fibrillation-related education. There are several limitations in this study. First, this is a single-center observational study. Although consecutive patients were enrolled in the study, potential selection bias cannot be ruled out. Further studies are required to prove a causal relationship between PD and AF. Second, this study comprised relatively small number of patients which precluded the assessment of the impact of each component of periodontal status on the arrhythmia recurrence after CA. In addition, because of limited sample size, it was difficult to determine the interaction and collinearity of PD with other clinical factors related with arrhythmia recurrence[35]. Likewise, relatively small number of cases in our study may not have had sufficient statistical power to demonstrate significant associations of known risk factors with AF recurrence. Future studies will have to prospectively explore collinearity and interaction of PD and known predictors of recurrent AF with sufficient sample size. Third, arrhythmia recurrence after CA was diagnosed based on electrocardiogram documentation or recording of a 24-h Holter or a 1-week event loop recorder. Thus, asymptomatic recurrence may have been missed by examinations, and the recurrence rate might have been underestimated. Fourth, changes in the periodontal status before and after index CA were not assessed, and the information on the periodontal treatment was also lacking, which may have affected the clinical outcomes. Fifth, strategies in CA procedures were left to the operators' discretion, which may have affected the outcomes. Finally, this study excluded patients with persistent AF because of a different recurrence rate from PAF.

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