REVIEW

Infective endocarditis and dental procedures : evidence, pathogenesis, and prevention

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Abstract : Infective endocarditis is a serious infection occurring on the endothelial surfaces of the heart, especially at the valves. Oral commensal bacteria are the important etiologic agents in this disease. Common dental procedures, even non-surgical dental procedures, can often cause bacteremia of oral commensals. Periodontally diseased patients are at risk from bacteremia even after brushing the teeth. Bacteremia itself rarely affect healthy people but they can result in mortal infective endocarditis in those who have a predisposed risk for this disease, such as those with heart valve diseases, pacemaker implantation, etc. Infective endocarditis is thus established when all the 3 conditions are present simultaneously, i.e., 1) a predisposing impairments in the heart, 2) the introduction of bacteria into the bloodstream, and 3) the virulence of bacteria. Antibiotics have to be adequately used to prevent this infection, however, their frequent uses generates drug-resistant mutant bacteria, which is a serious social problem. The development of novel alternative drugs to be used instead of the current antibiotics is thus highly desired. We are now using several types of combinatorial peptide libraries to search for small size molecular mimetics that can interfere with the adhesion of bacteria to the target organ. The use of such peptides is expected to lead to the development of compounds for a novel preventive drug which does not kill bacteria, thus making it safer and less likely to generate drug-resistant mutants. J. Med. Invest. 53 : 189-198, August, 2006

Keywords **:** *infective endocarditis, dental procedures, oral commensal bacteria, viridans streptococci, combinatorial libraries*

INTRODUCTION

Infective endocarditis is a life-threatening disease. It is always fatal if untreated, and it continues to cause substantial morbidity and mortality despite modern antimicrobial and surgical treatments. Substantial morbidity and mortality results from this infection (1), despite improvements in the outcome due to advances in antimicrobial therapy and an enhanced ability to diagnose and treat complications. Primary prevention is thus the most important. It was first suggested, at the beginning of the twentieth century, that oral bacteria are related to infective endocarditis (2, 3). Since then, interest has grown in the relationship between dental procedures and infective endocarditis, and bacteremia as a result of dental treatments has thus continued to be a subject of research interest. Antimicrobial chemotherapy is now widely advocated to protect at-risk patients, however, their

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frequent uses generates drug-resistant mutant bacteria, which has become a serious social problem (4).

This short review describes the current knowledge about the relationship between the dental procedures and infective endocarditis and the ongoing challenge to discover alternative candidate compounds for use as novel preventive drugs.

INFECTIVE ENDOCARDITIS; DEFINITION AND CLASSIFICATION

Infective endocarditis is an infection of the lining of the heart chambers (endocardium), usually the heart valves are involved. Fungi, chlamydia, rickettsia, etc can cause this infection, however, the most common causes of this disease are bacteria, and this phenomenon is therefore also called bacterial endocarditis (5). It has been classified into acute and subacute types, according to the natural history of the disease. Recently, as the number of cases with valve replacement surgery is increasing, the number of endocarditis cases associated with the prosthetic valves is increasing. Therefore, these diseases are also classified into "prosthetic valve endocarditis" and "native valve endocarditis". In addition, the categories of "intravenous drug abuse endocarditis" and "nosocomial endocarditis" associated with intravenous catheters have been reported (1).

PATHOGNENESIS AND TREATMENT

The establishment of infective endocarditis results from the adherence of microorganisms to wounded cardiac surfaces and their proliferation at the local site. Damaged heart valves as a sequela of rheumatic fever or previous endocarditis, acquired valve lesions, roughened cardiac surfaces as a result of a jet stream effect from blood crossing congenital cardiac lesions, such as a septal defect, and prosthetic heart valves are the usual predisposing clinical conditions for infective endocarditis. Sterile vegetations composed of platelet-fibrin clot and thrombus are initially formed on the damaged endothelial surfaces, and then, if bacteria are introduced into the bloodstream, the lesion can trap bacterial cells and thus act as an incubator. Subsequent growth of the infective vegetation causes local myocardial abscess that inhibits the valvular function, and finally results in congestive heart failure. In addition to the local problems of the heart, pieces of the infective vegetation may break off and travel through the patient's body through the blood circulation. These infective emboli can cause cerebral infraction and aneurysms, and thus producing infections in remote organs, such as kidney and spleen. The quick identification of etiologic microorganisms and antibiotic therapy based on the results of microbial sensitivity tests are therefore very much desired. However, blood cultures often provide negative results and the empiric selection of antibiotics is thus necessitated. Patients with symptoms of heart failure or with no improvement in their clinical conditions despite antibiotic treatments therefore have to undergo surgical treatment. The success rate of cardiac surgery for infective endocarditis has recently improved, however, the mortality rate still ranges 20 - 25% in Japan (6).

Men are more susceptible to infective endocarditis than women ; 1.2 - 3 times more susceptible for all ages and 2 - 8 times for people older than 60 years of age (7). The average age of the patients with this disease is gradually increasing and it is now over 55 years of age and about half of all patients are older than 60 (7). Although the progress of clinical medicine has succeeded in lowering the mortality of infective endocarditis, the incidence of this disease has recently been increasing, particularly in developed countries (8). This is reasonable since owing to the current progress in cardiac surgery, more patients are now surviving who would not have been rescued previously, this in turn increases the number of people at high risk from infective endocarditis.

ETIOLOGIC AGENTS OF INFECTIVE ENDOCARDITIS

The most common causative microorganisms for infective endocarditis are bacteria. Among the wide variety of bacteria, the leading cause of infective endocarditis is viridans streptococci (9, 10), particularly as the cause for the subacute form of this diseases. Viridans streptococci comprise the largest group in the member of streptococci, and they are the most dominant commensals in the oral cavity. The most frequently isolated viridans streptococci from the infective endocarditis patients is *S. sanguis* (31.9%), followed by *S. oralis* (29.8), the mutans group

of streptococci, which is notorious for cariogenicity (ability to cause dental caries = tooth cavities), can also cause infective endocarditis (9). In contrast, periodontopathic bacteria have been less frequently isolated from patients with infective endocarditis. *Actinobacillus actinomycetemcomitans* has also been reported to be a causative agent (11), but it is not as common as viridans streptococci. *Porphyromonas gingivalis*, the most important pathogen of adult periodontitis, has never been isolated from patients with infective endocarditis.

One should aware of the limitations of the methodology of bacterial cultures to identify the causes of infective endocarditis, although such methods have recently greatly improved. When clinical symptoms indicate the possibility of infective (bacterial) endocarditis, antibiotics may be empirically chosen and given to the patients before sampling their blood for bacterial cultures, and the antibiotic medications in the blood samples can interfere with the results of bacterial cultures. In addition, the conventional culture conditions are not suited for all kinds of bacteria. For example, nutritionally variant streptococci, one group of viridans streptococci and recently classified into genera *Abiotrophia* and *Granulicatella*, have been shown to be causes of so -called culture-negative bacterial endocarditis (12). These factors mentioned here may thus be associated with the low frequency of periodontopathic bacteria in infective endocarditis.

INDUCTION OF BACTEREMIA BY DENTAL PROCEDURES

The bloodstream is sterile under normal healthy conditions. The introduction of bacteria into the bloodstream is necessary for an intracardiac infection to occur. Such bacteremia occurs after tooth extractions and other oral surgery procedures. Bacteremia as a result of dental treatments has been a subject of research interest since the first indication at the start of the 20th century that oral bacteria may be related to infective endocarditis (2). Non surgical dental procedures have also been reported to cause bacteremia at significant frequencies. These include the administration of local anesthesia (13), orthodontic band placement (14), periodontal probing (15), dental prophylaxis (16), scaling and root planing (17), and even after daily tooth brushing (18) and flossing (19).

Although the American Heart Association (AHA) guidelines (5) do not recommend antibiotic prophylaxis for patients undergoing root canal treatments which do not go beyond the root apex, a recent paper (20) reported a marked frequency of bacteremia following non-surgical root canal treatment utilizing several modern reliable techniques to detect bacteria in the blood. Different results can be obtained for the diagnosis of bacteremia by the different methodologies for detecting bacterial existence and the timing of blood sampling.

Regarding the detection methods, there exist a lot of factors that need to be considered, e.g., cultures in aerobic vs. anaerobic conditions, in broths vs. on plates, and compositions of culture media. These are the points to be discussed when culture methods are utilized to detect the presence of bacteria. Recently, a highly sensitive polymerase chain reaction (PCR) technique for detecting bacterial DNA can be also utilized. The timing of blood sampling is another important consideration for detecting the bacteremia associated with dental procedures, because such bacteremia are known to be transient in healthy people who can be enrolled in studies for this kind of purpose. Savarrio *et al.* (20) have tried to minimize these problems ; they thus obtained samples at three different times regarding the dental procedures, 30 min before the dental treatment (considered as the negative control or the background), during the dental procedures, and 30 min after the end of the dental treatments. Taking these considerations into account, they have observed bacteremia either during or after non-surgical root canal treatment in 9 out of 30 patients (33.3%) (20). In their investigation, the most sensitive method to detect the presence of bacteria is shown to be the broth cultures of 15 ml blood both in aerobic and anaerobic conditions immediately after the sampling. The pour plate method using 5 ml blood and PCR detection using 0.2 ml of blood are shown to be much less sensitive than the broth culture method. They did not use a lysis filtration method, in which the host blood cells are lysed and then the samples are filtrated through membranes with 0.2 μm pore size, and bacteria trapped on the filter membrane cultured. This method is particularly useful for blood cultures from patients who are treated with antibiotics before blood sampling(21). The authors of this story(20) did not use the lysis filtration method, because the subjects were not given antibiotics; they rather attempted to maximize the detection sensitivity by immediate conventional culturing using the two culture techniques. How-

ever, they did not try to combine the lysis filtration method with PCR detection. The combination of the two methodologies, i.e., "lysis filtration method" and the "PCR method" allows one to use 15 ml of blood for PCR detection rather than 0.2 ml used in their study. This will consequently improve the sensitivity of the PCR method, which may surpass that of the immediate broth cultures using 15 ml blood.

EXPERIMENTAL INFECTIVE ENDOCARDITIS

Animal models of infective endocarditis have been established in rabbits (22) and rats (23). They are useful tools to investigate the effectiveness of different antibiotics, the pathogenesis of the disease and bacterial virulence. We previously investigated the virulence factors of nutritionally variant streptococci using experimental endocarditis in rats (24) and thus showed their ability to bind to host extracellular matrix proteins, particularly fibronectin (Figs. 1 and 2). In addition, in an animal model, which demonstrated the same conditions as those seen in human infective endocarditis, the requirement for the establishment of the disease are predisposing damage on the endothelial surfaces of the heart and the introduction of virulent bacterial cells into the bloodstream. Usually in the animal models, catheters are inserted from the carotid artery to thus injure the aortic valves 24 hours prior to the intravenous (i.v.) injection of live bacterial cells. The same i.v. injections of bacterial cells to unmanipulated animals produce no endocardial infection, nor does catheterization alone. It is also important that all bacteria are not equally virulent. As shown in Fig. 1, different strains isolated from oral cavities showed higher or lower pathogenic capacities, while strains from endocarditis patients regularly showed a high pathogenic capacity in the rat model. Hence, the three factors, namely 1) the predisposing impairment on the endocardium, 2) the introduction of bacteria in the bloodstream, and 3) the virulence of bacteria are thus considered to be necessities for the establishment of infective endocarditis in both humans and animals (Fig. 3).

PREVENTION OF INFECTIVE ENDOCARDITIS IN DENTAL PRACTICES

AHA shows, in 1997, the latest guidelines for the

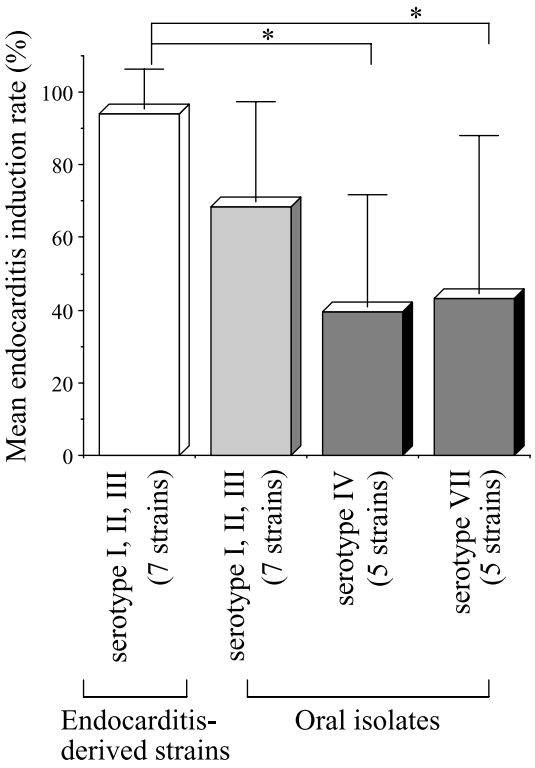

Fig. 1. Comparison of the endocarditis-inducing capacities of nutritionally variant streptococci. The strains derived from infective endocarditis patients and oral cavities of healthy volunteers were classified by their serotypes. The serotypes I, II and III have a higher capacity to induce endocarditis than IV and V. (29) *Significant difference ($P < 0.05$) by ANOVA with Tukey's adjustment.

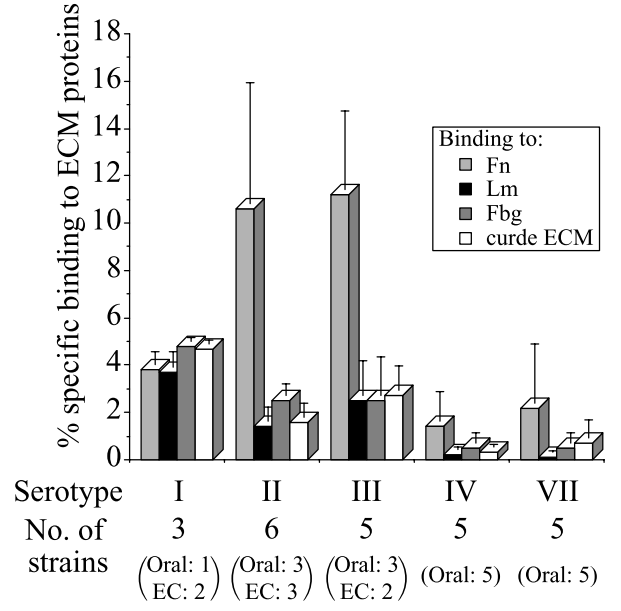

Fig. 2. Extracellular matrix binding of nutritionally variant streptococci strains. Serotype II (*Granulicatella adiacens*) and III strains specifically adhere to fibronectin while serotype I strains moderately to the ECM proteins tested (Fn: fibronectin, Lm: laminin, Fbg: fibrinogen). The number of strains included in each serotype and their origins are indicated at the bottom (EC: derived from endocarditis patients, oral: derived from healthy oral cavities) (29)

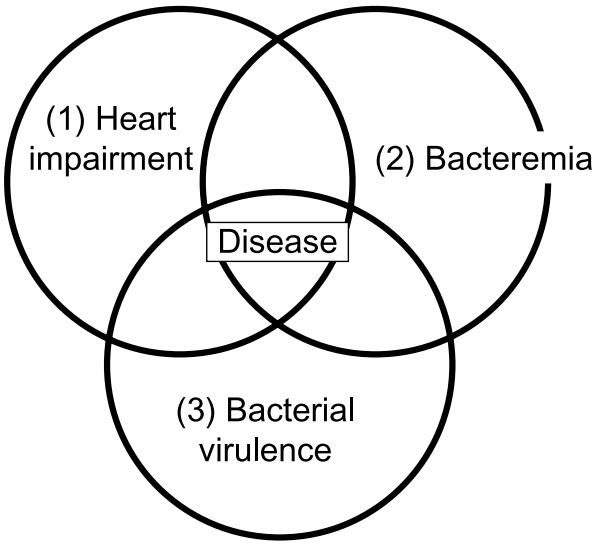

Fig. 3. The three conditions are needed to be assembled for induction of infective endocarditis; 1) predisposing impairment on the endocardium, 2) introduction of bacteria into the bloodstream, and 3) virulence of bacteria

prevention of infective (bacterial) endocarditis (5). Patients who are judged to be at risk based on medical interviews are thus considered to be appropriate subjects for antibiotic prophylaxis (Tables 1, 2, and 3). In Japan, the Japanese Circulation Society has established the guidelines for prevention and management of infective endocarditis in 2003 (JCS 2003) based on the results of a nation-wide hospital questionnaire survey (25). These guidelines are, in general, in close accordance with the AHA guidelines (5), however, JCS 2003 recommends antibiotic cover for people using pacemakers and implantable cardioverter defibrillators (ICD), which are not recommended in the AHA guidelines. Both guidelines suggest the use of Cephalexin and Cefadoxil for patients with histories of penicillin allergy, but the use of β-lactam agents for patients with penicillin allergy may be questioned ; other effective agents, such as Clindamycin or Azithromycin/Clarithromycin, should be selected earlier. Erythromycin has been recommended in the older guidelines (1990), but not in the current one.

Regarding the recommendation about dental procedures, the guidelines do not stipulate the necessity of antibiotic prophylaxis for patients who are undergoing non-surgical dentistry (Table 2). However, as already mentioned above, it has been shown that bacteremia can be induced by non-surgical dental procedures at significant frequencies. Therefore, dentists, physicians, and patients themselves should be aware of this fact and thus be as careful as possible when dental treatments are performed.

PERIODONTAL DISEASE AND INFECTIVE ENDOCARDITIS

The problem of whether patients with periodontal diseases are at higher risk from infective endocarditis than people who have healthy gingivae has not yet been fully addressed. However, several reports indicate that bacteremia is more frequently inducible in patients with severer periodontal diseases than those who have healthier periodontal tissue after tooth brushing and periodontal pocket probing (Table 4) (15, 26). Gum inflammation loosens the gingival epithelial tissues and it often becomes ulcerative at the inner part of periodontal pockets. It can thus provide oral bacteria the route for getting into the host circulation. Furthermore, some periodontopathic bacteria such as *A. actinomycetemcomitans* and *P. gingivalis* have the capacity to invade the host epithelial and connective tissues, and these characteristics are considered to be involved in the enlargement of inflammatory lesions. Periodontopathic bacteria which seem to be less important etiologic agents of infective endocarditis may play important roles in the induction of this disease by causing gum inflammation and opening a route toward the blood circulation for endocardiopathic viridans streptococci. Direct evidence for the relationship between the prevalence of periodontal disease and the incidence of infective endocarditis remains to be investigated. Cohort studies are expected to provide better evidence to elucidate this relationship.

PREVENTION OF INFECTIVE ENDOCARDITIS: ALTERNATIVES TO ANTIBIOTICS

Antibiotic prophylaxis is the only way to prevent infective endocarditis, as has already been mentioned above. However, the antibacterial spectrum is inevitably limited and, moreover, the frequent use of antibiotics results in the generation of resistant mutant bacteria, which has become a serious social problem. Therefore, the development of safer and hopefully more effective drug alternatives to antibiotics is highly desired. Bactericidal or bacteriostatic antibiotics which threaten the life of bacteria induce drug-resistant mutations in order to survive. If an agent allows bacteria to live at their

Table 1. Cardiac conditions associated with endocarditis (5)

Endocarditis prophylaxis recommended
High-risk category
Prosthetic cardiac valves, including bioprosthetic and homograft valves
Previous bacterial endocarditis
Complex cyanotic congenital heart disease (e.g., single ventricle states, transposition of the great arteries, tetralogy of Fallot)
Surgically constructed systemic pulmonary shunts or conduits
Moderate-risk category
Most other congenital cardiac malformations (other than above and below)
Acquired valvular dysfunction (e.g., rheumatic heart disease)
Hypertrophic cardiomyopathy
Mitral valve prolapse with valvular regurgitation and/or thickened leaflets
Endocarditis prophylaxis not recommended
Negligible-risk category (no greater risk than the general population)
Isolated secundum atrial septal defect
Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 mos)
Previous coronary artery bypass graft surgery
Mitral valve prolapse without valvular regurgitation
Physiologic, functional, or innocent heart murmurs
Previous Kawasaki disease without valvular dysfunction
Previous rheumatic fever without valvular dysfunction
Cardiac pacemakers (intravascular and epicardial) and implanted defibrillators

Table 2. Dental procedures and endocarditis prophylaxis (5)

Endocarditis prophylaxis recommended[a]
Dental extractions
Periodontal procedures including surgery, scaling and root planing, probing, and recall maintenance
Dental implant placement and reimplantation of avulsed teeth
Endodontic (root canal) instrumentation or surgery only beyond the apex
Subgingival placement of antibiotic fibers or strips
Initial placement of orthodontic bands but not brackets
Intraligamentary local anesthetic injections
Prophylactic cleaning of teeth or implants where bleeding is anticipated
Endocarditis prophylaxis not recommended
Restorative dentistry[b] (operative and prosthodontic) with or without a retraction cord[c]
Local anesthetic injections (non-intra-ligamentary)
Intra-canal endodontic treatment ; post placement and buildup
Placement of rubber dams
Postoperative suture removal
Placement of removable prosthodontic or orthodontic appliances
Taking of oral impressions
Fluoride treatments
Taking of oral radiographs
Orthodontic appliance adjustment
Shedding of primary teeth

[a] Prophylaxis is recommended for patients with high- and moderate-risk cardiac conditions.
[b] This includes the restoration of decayed teeth (filling cavities) and the replacement of missing teeth.
[c] Clinical judgment may indicate antibiotic use in selected circumstances that may create significant bleeding.

Table 3. Prophylactic regimens for dental, oral, respiratory tract, or esophageal procedures[a] (5)

Situation	Agent	Regimen
Standard general prophylaxis	Amoxicillin	Adults: 2.0 g ; children: 50 mg/kg orally 1 h before procedure
Unable to take oral medications	Ampicillin	Adults: 2.0 g IM or IV ; children : 50 mg/kg IM or IV within 30 min before procedure
Allergic to penicillin	Clindamycin	Adults: 600 mg; children: 20 mg/kg orally 1 h before procedure
	Cephalexin or Cefadroxil[b]	Adults: 2.0 g; children; 50 mg/kg orally 1 h before procedure
	Azithromycin or Clarithromycin	Adults: 500 mg; children: 15 mg/kg orally 1 h before procedure
Allergic to penicillin and unable to take oral medications	Clindamycin	Adults : 600 mg ; children : 20 mg/kg IV within 30 min before procedure
	Cefazolin	Adults: 1.0 g; children: 25 mg/kg IM or IV within 30 min before procedure

IM indicates intramuscularly, and IV, intravenously.
[a] Total children's dose should not exceed adult dose.
[b] Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins.

Table 4. Gingival conditions and induction of bacteremia

Author /year	Nation /number of subjects (gender)/ages	Measure for periodontal condition	Detection method of bacteremias	Results	Statistical relationship
Sliver 1977[a]	Canada 96 (44 males) 17～61 yrs	Gingival index (GI)	Blood sampling immediately after brushing teeth	GI 0～ 0.75 : 16% 2.2～3.0 : 68%	Yes
Daly 2001[b]	Australia 20 periodontitis (10 males)/43.0 yr 20 gingivitis (11 males)/35.5 yr	Alveolar bone level (radiographs)	Blood sampling immediately after pocket probing	Periodontitis : 40% Gingivitis 10%	Yes

[a] (26)
[b] (15)

commensal sites (such as the oral cavities) and just inhibit their attachment to a critical site in the body (such as the endocardium), they do not have to mutate for their survival. Such an agent is therefore promising to be a novel drug for prevention of infections. The adhesion of bacteria to fibronectin, which is a major extracellular matrix protein exposed on the wound endocardium, is considered to be important for the establishment of this infection (24, 27). We have found a novel mode of interaction between endocarditis-causing bacteria and human fibronectin (27). During the course of this study, monoclonal antibodies (mAb) which can inhibit the bacterial binding to fibronectin have been generated. The mAb could be the candidate leading compound of a novel drug to prevent infective endocarditis, however, antibody drugs are not feasible for the purpose of preventing infective endocarditis, since it would be very expensive, and the repeated use of an antibody drug will result in the generation of a neutralizing antibody by the host immune system. We therefore attempted to develop small size molecular mimetics of functional structures of fibronectin or mAb that can interfere with the bacterial-Fn interaction. For this purpose, several types of combinatorial peptide li-

braries have been constructed ; i.e.," positional scanning libraries" (Fig. 4) and" on-bead random peptide libraries". Although the real goal of this study, namely the development of new drugs is still far from being realized, we have nevertheless made some progress in the methodologies. The findings of some of our trials have been described elsewhere (28).

CONCLUSION

Common dental procedures, even non-surgical dental procedures, often cause bacteremia that can result in infective endocarditis in people who have a predisposing risk for this disease, such as valvular heart diseases including prosthetic valves, congenital heart diseases, cardiomyopathy, coronary artery disease, pacemaker implantation, etc. The infection is established when all 3 conditions simultaneously occur, i.e., a predisposing impairment in the heart, the introduction of bacteremia and the virulence of the introduced bacteria. Common dental procedures often cause bacteremia and periodontally diseased patients may even suffer

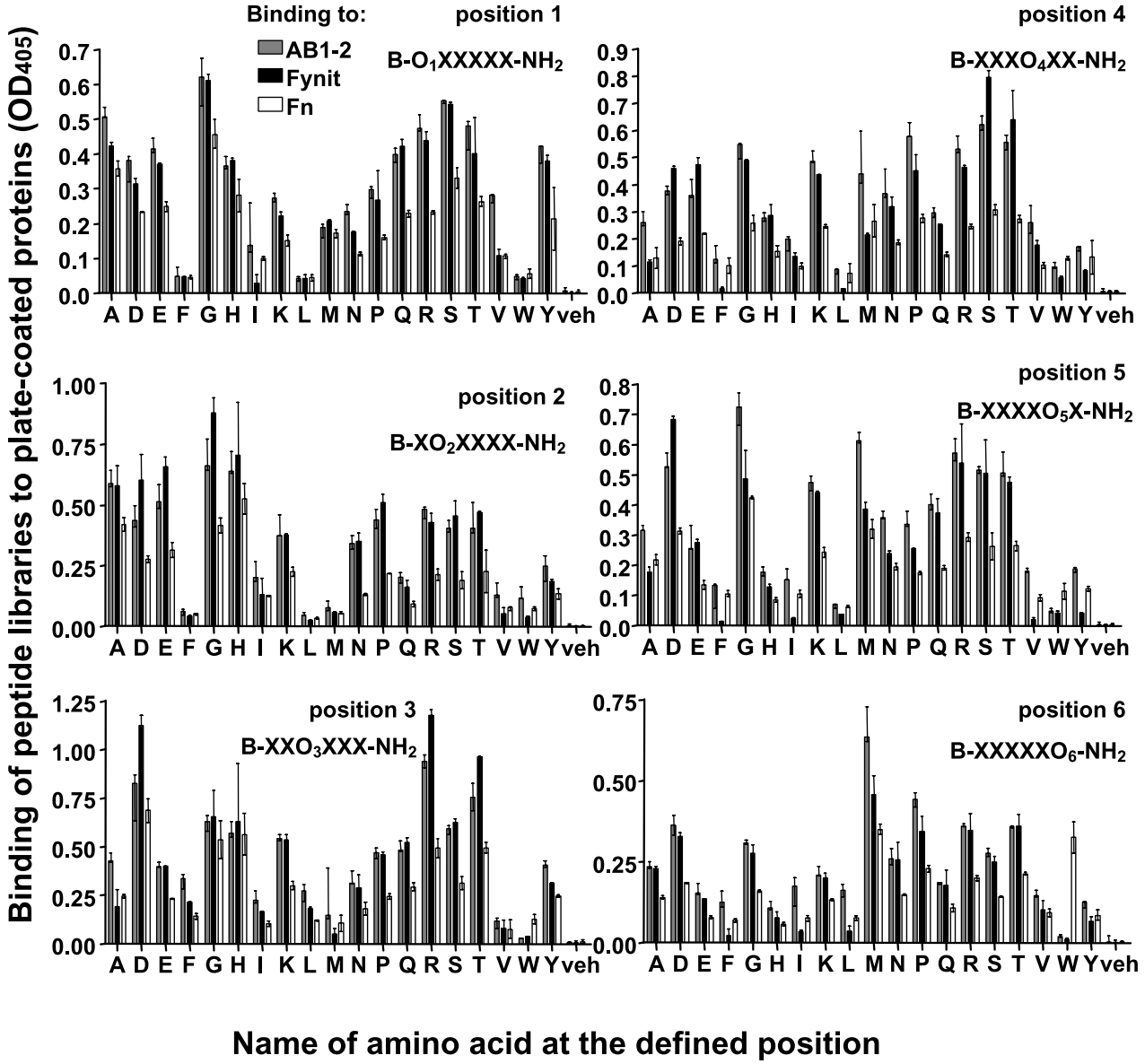

Fig. 4. The screening of a hexamer positional scanning peptide library by binding of the peptides to an anti-fibronectin mAbs Fynit-I 01, AB 1-2 (control mAb) and to Fn 105 kDa fragment (negative control protein). The library consists of 114 peptide mixtures (19 amino acids×6 positions, cysteine was omitted from the building block), where each position of the peptide is defined by the amino acid labeled on the x axis. Each peptide mixture contains 19^5=about 2.5×10^5 different sequences. Individual bars show the levels of binding of different peptide mixtures at 0.5 mM to the two mAbs and Fn fragment. The six sublibraries are thus expected to provide information about most important amino acid residues for the molecular recognition at each position (28).

from bacteremia after tooth brushing. Antibiotics have to be used adequately in order to prevent such infections during dental procedures, however, their frequent use can also generate drug-resistant mutant bacteria. The development of novel drugs to be used as an alternative to the current antibiotics is therefore highly desired.

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REFERENCES

1. Moreillon P: Endocarditis and endarteritis. In: Infectious diseases. Armstrong D, Cohen J, eds. Harcourt Publishers, London, 1999, pp. 2. 50. 1-2. 50. 9
2. Horder T : Infective endocarditis. Q J Med 11: 319-323, 1908
3. Rushton MA : Subacute bacterial endocarditis following the extraction of teeth. Guy's Hosp Rep 10 : 39-44, 1930
4. Mogi A, Nishi JI, Yoshinaga M, Harada H, Narahara S, Kawakami K, Maruyama I : Increased prevalence of penicillin-resistant viridans group streptococci in Japanese children with upper respiratory infection treated by beta-lactam agents and in those with oncohematologic diseases. Pediatr Infect Dis J 16 : 1140-1144, 1997
5. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, Gewitz MH, Shulman ST, Nouri S, Newburger JW, Hutto C, Pallasch TJ, Gage TW, Levison ME, Peter G, Zuccaro G : Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 277 : 1794-1801, 1997
6. Matsushita M, Tsuruya Y, Saitoh M : Myocaditis, pedicarditis, and infective endocarditis, their prognosis. Junkankika 51 (in Japanese) : 67-72, 2002
7. Dhawan VK : Infective endocarditis in elderly patients. Clin Infect Dis 34 : 806-812, 2002
8. Fonager K, Lindberg J, Thulstrup AM, Pedersen L, Schϕnheyder HC, Sϕrensen HT : Incidence and short-term prognosis of infective endocarditis in Denmark, 1980-1997. Scand J Infect Dis 35 : 27-30, 2003
9. Douglas CW, Heath J, Hampton KK, Preston FE : Identity of viridans streptococci isolated from cases of infective endocarditis. J Med Microbiol 39 : 179-182, 1993
10. Herzberg MC, Meyer MW, Kiliç A, Tao L : Host-pathogen interactions in bacterial endocarditis : streptococcal virulence in the host. Adv Dent Res 11 : 69-74, 1997
11. Chen YC, Chang SC, Luh KT, Hsieh WC : Actinobacillus actinomycetemcomitans endocarditis : a report of four cases and review of the literature. Q J Med 81 : 871-878, 1991
12. Ruoff KL : Nutritionally variant streptococci. Clin Microbiol Rev 4 : 184-190, 1991
13. Roberts GJ, Simmons NB, Longhurst P, Hewitt PB : Bacteraemia following local anaesthetic injections in children. Br Dent J 185 : 295-298, 1998
14. McLaughlin JO, Coulter WA, Coffey A, Burden DJ : The incidence of bacteremia after orthodontic banding. Am J Orthod Dentofacial Orthop 109 : 639-644, 1996
15. Daly CG, Mitchell DH, Highfield JE, Grossberg DE, Stewart D : Bacteremia due to periodontal probing : a clinical and microbiological investigation. J Periodontol 72 : 210-214, 2001
16. Fine DH, Korik I, Furgang D, Myers R, Olshan A, Barnett ML, Vincent J : Assessing pre-procedural subgingival irrigation and rinsing with an antiseptic mouthrinse to reduce bacteremia. J Am Dent Assoc 127 : 641-2, 645-6, 1996
17. Bender IB, Naidorf IJ, Garvey GJ : Bacterial endocarditis : a consideration for physician and dentist. J Am Dent Assoc 109 : 415-420, 1984
18. Sconyers JR, Crawford JJ, Moriarty JD : Relationship of bacteremia to toothbrushing in patients with periodontitis. J Am Dent Assoc 87 : 616-622, 1973
19. Faden HS : Letter: Dental procedures and bacteremia. Ann Intern Med 81 : 274, 1974
20. Savarrio L, Mackenzie D, Riggio M, Saunders WP, Bagg J : Detection of bacteraemias during non-surgicalroot canal treatment. J Dent 33 : 293-303, 2005
21. Heimdahl A, Hall G, Hedberg M, Sandberg

H, Soder PO, Tuner K, Nord CE .: Detection and quantitation by lysis-filtration of bacteremia after different oral surgical procedures. J Clin Microbiol 28 : 2205-2209, 1990

22. Baddour LM, Christensen GD, Lowrance JH, Simpson WA : Pathogenesis of experimental endocarditis. Rev Infect Dis 11 : 452-463, 1989
23. Kitada K, Inoue M, Kitano M : Experimental endocarditis induction and platelet aggregation by *Streptococcus anginosus, Streptococcus constellatus* and *Streptococcus intermedius*. FEMS Immunol Med Microbiol 11 : 25-32, 1996
24. Okada Y, Kitada K, Takagaki M, Ito H-O, Inoue M : Endocardiac infectivity and binding to extracellular matrix proteins of oral *Abiotrophia* species. FEMS Immunol Med Microbiol 27 : 257-261, 2000
25. Nakatani S, Mitsutake K, Hozumi T, Yoshikawa J, Akiyama M, Yoshida K, Ishizuka N, Nakamura K, Taniguchi Y, Yoshioka K, Kawazoe K, Akaishi M, Niwa K, Nakazawa M, Kitamura S, Miyatake K : Current characteristics of infective endocarditis in Japan : an analysis of 848 cases in 2000 and 2001. Circ J 67 : 901-905, 2003
26. Silver JG, Martin AW, McBride BC : Experimental transient bacteraemias in human subjects with varying degrees of plaque accumulation and gingival inflammation. J Clin Periodontol 4 : 92-99, 1977
27. Ito H-O, Soutome S, Nokihara K, Inoue M : Identification and characterization of bacterial -binding property in the type Ⅲ repeat domain of fibronectin. Biochem Biophys Res Commun 320 : 347-353, 2004
28. Ito H-O, Nokihara K, Soutome S, Ohyama T : Screening of peptides that inhibit bacterial binding to fibronectin using combinatorial peptide libraries. Int J Pept Res Ther (in press, 2006)
29. Okada Y, Ito H-O, Kitada K, Inoue M : Infectivity of nutritionally variant streptococci : capacity of endocarditis induction and extracellular matrix binding. In : Streptococci and Streptococcal diseases. Martin DR, Tagg JR, eds. Securacopy, Priura, New Zealand, 2000, pp.653-656