【学会発表】

1. Fujita D, Ogawa N, Imai Y, Nishimura H, Kato M, Shimada S, Taketani T, Morota T, Hirata Y, Nagai R. Phenotype and genotype correlations in Japanese Marfan population. 76th Japanese Society of Circulation, 2012.3.16-18, Fukuoka
2. 第 59 回日本心臓病学会（神戸, 2011. 09. 23-25）

① 藤田大司，今井靖，小川直美，西村敬史，加藤昌義，嶋田正吾，竹谷剛，師田哲郎，青木美穂子，平田恭信，永井良三：マルファン症候群専門外来からみた日本人マルファン症候群の臨床像

② 青木美穂子，今井靖，藤田大司，加藤昌義，西村敬史，小川直美，竹谷剛，師田哲郎，鈴木淳一，平田恭信，永井良三：マルファン症候群における口腔所見の意義　歯周病は極めて高頻度

③ 藤田英雄，安東治郎，木下修，川島大，大野貴之，小野稔，高本眞一，平田恭信，永井良三：糖尿病網膜症における冠動脈疾患と中期治療成績

④ 志賀太郎，絹川弘一郎，波多野将，今村輝彦，稲葉俊郎，牧尚孝，八尾厚史，西村隆，平田恭信，許俊鋭，小野稔，永井良三：左室補助人工心臓植え込み術前の中心静脈圧-肺動脈楔入圧比は、術後に右室補助人工心臓が必要となる患者のリスク評価に有用である

⑤ 安東治郎，大野貴之，川島大，木下修，重枝崇志，加藤聡，藤田英雄，平田恭信，小野稔，高本眞一，永井良三：糖尿病網膜症患者における重症冠動脈疾患の頻度と SYNTAX Score

⑥ 荷見映理子(東京大学医学部附属病院/循環器内科)，岩田洋，興梠貴英，真鍋一郎，絹川弘一郎，安東治郎，澤城大悟，高橋政夫，藤田英雄，平田恭信，永井良三:Diagnostic Implication of Change in B-type Natriuretic Peptide for Prediction of Subsequent Target Lesion Revascularization (TLR) Following Deployment of Drug-Eluting Stent (DES)

3. 84th American Heart Association Scientific Sessions 2011 (Orland, USA, 2011.11.12-16)

① Matsumoto R, Suzuki J, Ogawa M, Watanabe R, Muto S, Itai A, Hirata Y, Nagai R, Isobe M: Inhibition of I{kappa}B phosphorylation by a novel IKK inhibitor IMD-1041 attenuates myocardial dysfunction after infarction

② Aoyama N, Suzuki J, Ogawa M, Watanabe R, Izumi Y, Hirata Y, Nagai R, Isobe M: A periodontal pathogen accelerates the progression of abdominal aortic aneurysm via Toll-like receptor-2 signaling

③ Hanatani T, Suzuki J, Ogawa M, Aoyama N, Izumi Y, Hirata Y, Nagai R, Isobe M: Deterioration of myocardial infarction in mice infected with periodontal pathogens, Aggregatibacter Actinomycetemcomitans

④ Kobayashi N, Suzuki J, Ogawa M,

Aoyama N, Hirata Y, Nagai R, Izumi Y, Isobe M: A periodontal pathogen promotes neointimal formation after arterial injury through Toll-like receptor-2 signaling

⑤ Watanabe R, Suzuki J, Ogawa M, Muto S, Itai A, Hirata Y, Nagai R, Isobe M: A specific IKK inhibitor suppresses experimental autoimmune myocarditis in rats

⑥ Hamaya R, Suzuki J, Ogawa M, Watanabe R, Muto S, Itai A, Hirata Y, Nagai R, Isobe M: A Novel IKK inhibitor prevents progression of neointimal formation after arterial injury in mice

⑦ Hamaya R, Suzuki J, Ogawa M, Watanabe R, Hirata Y, Nagai R, Isobe M: PAI-1 has a significant role in arterial remodeling after mechanical injury in mice

4. 松本 玲央奈、兵藤 博信、永松 健、小松 篤史、吉田 志朗、山下 隆博、亀井 良政、藤井 知行、上妻 志郎、武谷 雄二：Ｍａｒｆａｎ症候群合併妊娠の妊娠分娩管理について　第 63 回日本産婦人科学会学術講演会　2011 年 8 月　大阪

5. 師田哲郎，縄田寛，竹谷剛，小野稔，高本眞一：Marfan 外来設立による診療科横断的診療体制　第 111 回日本外科学会　ワークショップ，2011

6. 師田哲郎，縄田寛，竹谷剛，北村律，小野稔：Stanford A 型急性大動脈解離の治療成績　―偽腔閉鎖型の予後―　第 39 回日本血管外科学会、2011

7. 竹谷剛，木下修，縄田寛，嶋田正吾，益澤明広，河田光弘，保科克行，師田哲郎，小野稔：胸部大動脈破裂例に対する緊急ステントグラフト内挿術　第 41 回日本心臓血管外科学会，2011

8. Hyodo H, Kamei Y, Yamashita T, Fujii T, Kozuma S, Taketani Y: The exploration of the risk factors of the aortic dissection in pregnant women with Marfan syndrome. The 20th FIGO World Congress of Gynecology and Obstetrics, Rome, Italy, Oct, 2012.

9. 松本玲央奈、兵藤博信、永松健、小松篤史、吉田志朗、山下隆博、亀井良政、藤井知行、上妻志郎、武谷雄二：Marfan 症候群合併妊娠の妊娠分娩管理について．第 63 回日本産婦人科学会学術講演会　大阪　2011 年 8 月

10. 師田哲郎，竹谷剛，縄田寛，小前兵衛，小野稔：弓部大動脈全置換術　―手技の tips―　第 72 回日本臨床外科学会ビデオ手術手技，2010

11. 縄田寛，小野稔，本村昇，師田哲郎，村上新：マルファン症候群合併僧帽弁閉鎖不全症に対する僧帽弁形成術　第 72 回日本臨床外科学会　ビデオ手術手技，2010

12. 竹谷剛，縄田寛，河田光弘，師田哲郎，小野稔，高本眞一：マルファン症候群女性患者の結婚・妊娠　第 63 回日本胸部外科学会　プレナリーセッション，2010

13. 師田哲郎：MDCT による Reimplantation 法の Valsalva 形態評価

第 63 回日本胸部外科学会，2010

14. 師田哲郎:「胸部大動脈瘤手術の基本と up to date」基部再建　第 53 回関西胸部外科学会　教育シンポジウム，2010
15. 縄田寛、師田哲郎，竹谷剛，河田光弘，本村昇，齋藤綾，西村隆，許俊鋭，村上新，小野稔：大動脈基部再建術の遠隔成績　第 38 回日本血管外科学会シンポジウム，2010
16. 本村昇，師田哲郎，齋藤綾，竹谷剛，小野稔：感染性大動脈疾患に対する Allograft を用いた外科治療　第 40 回日本心臓血管外科学会　ディベートセッション，2010
17. 北村律，川島大，木下修，縄田寛，久木基至，斉藤綾，竹谷剛，西村隆，師田哲郎，許俊鋭，本村昇，小野稔：僧帽弁閉鎖不全症に対する近年の手術適応拡大の妥当性に関する検討　第 63 回日本胸部外科学会定期，2010
18. 小前兵衛，師田哲郎，縄田寛，竹谷剛，小野稔：大動脈食道瘻に対する治療戦略の検討　第 63 回日本胸部外科学会定期，2010
19. 縄田寛，師田哲郎，竹谷剛，斉藤綾，北村律，西村隆，久木基至，木下修，本村昇，小野稔：Stanford A 型偽腔閉塞型急性大動脈解離の治療成績　第 63 回日本胸部外科学会，2010
20. 河田光弘，師田哲郎，竹谷剛，縄田寛，小野稔:ポリエステル製(通称 Dacron)人工血管の耐久性に関しての検討　第 38 回日本血管外科学会，2010
21. 縄田寛，師田哲郎，竹谷剛，小野稔，本村昇，村上新，高本眞一：自己弁温存大動脈基部置換術の中期遠隔成績　第 40 回日本心臓血管外科学会，2010
22. Uno K, Suzuki T, Kawakami N, Tsuji T, Matsumoto M, Watanabe K, Takeshita K, Ito M, Taneichi H, Hirano T, Yanagida H, Yamazaki K, Yamamoto T, Imagawa S, Minami S. The effect of early fusion at ten years or earlier for early onset scoliosis - comparison between 43 early fusion patients and 39 growing rod patients. 46th Annual Meeting of Scoliosis Research Society, Sep 14th-17th, 2011, Louisville, Kentucky, USA.
23. Yamada K, Matsudaira K, Hara N, Nakamura K, Takeshita K. The prevalence and characteristics of low back pain as the most disabling pain in Japan. EuroSpine 2011, Oct 19th-20th, Italy
24. Masuda K, Hara N, Chikuda H, Takeshita K, Yasunaga H, Horiguchi H, Matsuda S, Nakamura K. Factors affecting the occurrence of postoperative pulmonary embolism following spinal surgery. Annual Meeting of International Society for the study of the lumbar spine, June 14th-18th, 2011, Gothenburg, Sweden.
25. Hara N, Masuda K, Morii J, Tonosu J, Takeshita K, Nakamura K, Matsudaira K. Normal value of the Japanese version of the Zurich Claudication Questionnaire (ZCQ). Annual Meeting

of International Society for the study of the lumbar spine, June 14th-18th, 2011, Gothenburg, Sweden.

26. Tonosu J, Hara N, Matsudaira K, Masuda K, Takeshita K, Nakamura K. Normal Value of the Japanese version of the Oswestry Disability Index (ODI). Annual Meeting of International Society for the study of the lumbar spine, June 14th-18th, 2011, Gothenburg, Sweden.
27. Kato S, Takeshita K, Chikuda H, Hara N, Nakamura K. Normative score and cut-off value of the neck disability index. 2nd Annual Meeting of Cervical Spine Research Society Asia Pacific Section, Apr 28-30, 2011, Busan, Korea.
28. Nawata K, Tetsuro M, Taketani T, Ono M, Takamoto S. Midterm results of valve-sparing aortic root replacement for annuro-aortic ectasia. 8th International Research Symposium on Marfan Syndrome (Warrenton,VA USA 2010/9/11-14)
29. 第 58 回日本心臓病学会（東京, 2010.09.17-19)

① 今井靖、小川直美、武田憲文、西村敬史、加藤昌義、森田啓行、縄田寛、竹谷剛、師田哲郎、髙本眞一、平田恭信、永井良三:マルファン症候群に対する遺伝子診断と包括的診療体制

② 藤田英雄、大野貴之、木下修、安東治郎、重枝崇志、加藤聡、平田恭信、髙本眞一、永井良三: 冠危険因子としての糖尿病網膜症：糖尿病に対する新たなアプローチ

③ 安東治郎、小栗淳、森田敏宏、藤田英雄、山下尋史、平田恭信、永井良三、本村昇、小野稔:非保護左主幹部病変に対するシロリムス溶出性ステント留置の初期および中期治療成績 −PCI と CABG の比較検討−

④ 中島敏明、蔵野美葉、飯田陽子、高野治人、長谷川貴亮、森田敏宏、福田平、前村浩二、平田恭信、永井良三：急性高強度筋力トレーニングは顆粒球の PTX3 及び myeloperoxidase（MPO）を放出する

⑤ 目黒美葉、麻生妙子、飯田陽子、福田平、目黒健太郎、森田敏宏、平田恭信、永井良三、中島敏明：長期有酸素運動は虚血性心疾患患者の酸化ストレスを改善する

⑥ 小川真仁、鈴木淳一、平田恭信、磯部光章、永井良三：レニンアンジオテンシン系の活性化はマウス腎不全合併心筋梗塞の進展において重要な役割を担っている

⑦ 鈴木淳一、小川真仁、櫻井馨、平田恭信、磯部光章、永井良三：歯周病菌感染による血管リモデリングの促進とその機序の解明

⑧ 荷見映理子、岩田洋、興梠貴英、安東治郎、澤城大悟、高橋政夫、藤田英雄、平田恭信、永井良三：薬剤溶出性ステントを用いた経皮的冠動脈インターベンション（ PCI）症例における血漿 BNP 値経過の再狭窄予測因子としての有用性

⑨ 今井靖、柳元伸太郎、亀山祐美、飯島勝矢、秋下雅弘、安東治郎、藤田英雄、酒造正樹、Guillaume Lopez、森田啓行、矢作直樹、平田恭信、永井良三、山田一郎：脈波伝播速度法を応用した持続収縮期血圧モニタリング法の有用性

⑩ 岩田洋、安東治郎、興梠貴英、澤城大悟、高橋政夫、藤田英雄、平田恭信、永井良三：経皮的冠動脈インターベンション（PCI）施行症例の中・長期予後に対するシロスタゾール投与の効果検討

⑪ 長田太助、明城正博、平田恭信：ARBによるNO産生増加作用の機序の検討

⑫ 縄田寛、師田哲郎、竹谷剛、本村昇、村上新、小野稔、髙本眞一、今井靖、小川直美、西村敬史、加藤昌義、平田恭信、兵藤博信：挙児希望のあるマルファン症候群患者に対する自己弁温存大動脈基部置換の適応及び周産期管理に関する考察

⑬ 志賀太郎、絹川弘一郎、波多野将、八尾厚史、西村隆、平田恭信、許俊鋭、小野稔、永井良三：TOYOBO型左室補助人工心臓からの離脱試験では負荷時の心係数の評価が重要である

⑭ 鈴木淳一、小川真仁、平田恭信、磯部光章、永井良三：クラリスロマイシンはMMP活性阻害により心筋虚血再灌流後心室リモデリングを抑制する

⑮ 鈴木淳一、小川真仁、平田恭信、磯部光章、永井良三：プロスタグランジンE2受容体EP4作動薬による心筋炎後心室リモデリングの制御

⑯ 中山敦子、森田啓行、安東治郎、藤田英雄、平田恭信、永井良三：腹部大動脈未破裂瘤の最大短径とアンジオテンシン変換酵素阻害薬とアンジオテンシンII受容体拮抗薬との関係について

⑰ 中山敦子、森田啓行、安東治郎、藤田英雄、重松邦宏、宮田哲郎、平田恭信、永井良三：腹部大動脈瘤破裂と冠動脈疾患との関連についての検討

⑱ 澤城大悟、高橋政夫、藤田英雄、平田恭信、永井良三： PCI（経皮的冠動脈インターベンション）後、慢性期の高感度 CRP 高値と長期予後の関連についての検討

29. 第 33 回日本高血圧学会（福岡，2010.10.15-7）
平田恭信：配合薬時代の薬物療法の進め方−ARB/利尿薬合剤の有用性

30. 83th American Heart Association Scientific Sessions 2010 (Chicago, USA, 2010.11.7-10)

① Suzuki J, Masumura M, Nagashima A, Ogawa M, Shichiri M, Hirata Y, Nagai R, Isobe M: A critical role of salusin-β in suppressing angiogenesis after myocardial infarction and ischemia reperfusion injury.

② Suzuki J, Ogawa M, Hirata Y, Nagai R, Isobe M: A direct renin inhibitor significantly improves survival and cardiac remodeling after myocardial infarction in the condition of renal failure.

③ Tanaka K, Nagata D, Hirata Y, Tabata Y, Nagai R, Sata M: Enhanced angiogenesis in adventitia promotes

plaque formation in abdominal aorta of apolipoprotein E-deficient mice.

④ Hasumi E, Iwata H, Kohro T, Ando J, Sawaki D, Takahashi M, Fujita H, Hirata Y, Nagai R: Change in levels of B-type natriuretic peptide (BNP) during follow up predicts in stent restenosis after drug-eluting stent (DES) implantation.

⑤ Iwata H, Sata M, Ando J, Fujita H, Sawaki D, Takahashi M, Hirata Y, Nagai R: Significant correlation between primitive cells in intracoronary thrombi in patients with myocardial infarction and lesion progression.

⑥ Nakajima T, Kurano M, Takano H, Iida H, Fukuda T, Meguro K, Shiga T, Sagara M, Maemura K, Hirata Y, Yamasoba T, Nagai R: Acute high-intensity exercise releases myeloperoxidase and pentraxin3 from peripheral neutrophils in healthy subjects.

⑦ Suzuki J, Ogawa M, Hishikari K, Takayama K, Hirata Y, Nagai R, Isobe M: The anti-inflammatory mechanism of prostaglandin E2 receptor 4 activation in rat experimental autoimmune myocarditis.

⑧ Matsumoto K, Suzuki J, Ogawa M, Watanabe R, Hirata Y, Nagai R, Isobe M: Regulatory T lymphocyte transfer attenuates cardiac dysfunction after myocardial ischemia in mice.

31. 加藤敦子、辻原寛子、張 京浩、兵藤博信、山田芳嗣：マルファン症候群合併妊娠の危険性について考える−産褥期に大動脈解離およびくも膜下出血を発症し救命し得なかった自験例と、文献的考察− 第 114 回 日本産科麻酔学会 2010 年 12 月 横浜

32. 縄田寛、師田哲郎、竹谷剛、本村昇、村上新、小野稔、高本眞一、今井靖、小川直美、西村敬史、加藤昌義、平田恭信、兵藤博信：挙児希望のマルファン症候群患者への手術介入基準と周産期管理 第 58 回 日本心臓病学会 2010 年 10 月 東京

33. 小倉さやか、兵藤博信、福田友彦、亀井良政、藤井知行、上妻志郎、武谷雄二：産褥期に広範なくも膜下出血を起こし死亡した Marfan 症候群合併妊娠の 1 例 第 119 回日本産科婦人科学会関東連合地方部会 2010 年 6 月

34. 縄田寛，小野稔，本村昇，師田哲郎，村上新：マルファン症候群合併僧帽弁閉鎖不全症例に対する僧帽弁形成術 第 72 回日本臨床外科学会(横浜市、2010.11.21～23)

35. 加藤敦子、辻原寛子、張京浩、兵藤博信、山田芳嗣：マルファン症候群合併妊娠の危険性 z について考える−産褥期に大動脈解離およびくも膜下出血を発症し救命し得なかった自験例と、文献的考察−. 第 114 回 日本産科麻酔学会 横浜 2010 年 12 月

36. 小倉さやか、兵藤博信、福田友彦、亀井良政、藤井知行、上妻志郎、武谷雄二：産褥期に広範なくも膜下出血を起

こし死亡した Marfan 症候群合併妊娠の 1 例. 第 119 回日本産科婦人科学会関東連合地方部会学術集会　東京 2010 年 6 月

H. 知的所有権の出願・取得状況

なし

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Ghent基準-改訂前後の対比

表1

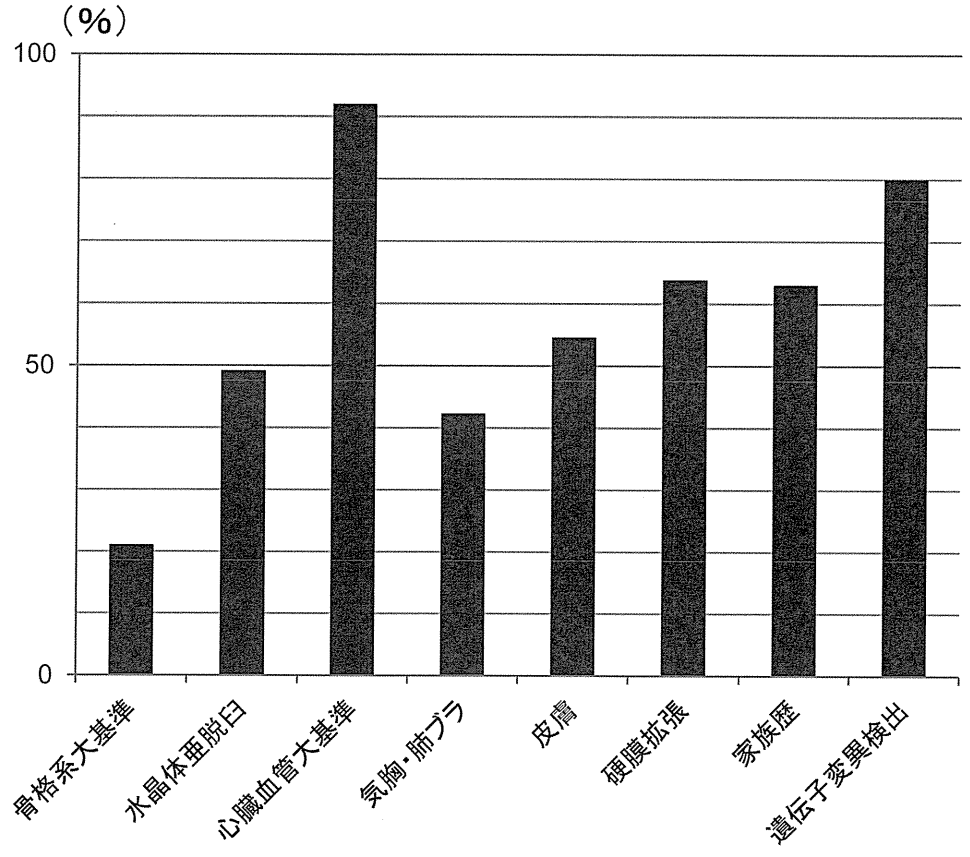
	改訂Ghent 陽性	陰性	systemic score	
旧Ghent基準				
陽性	121	10	5.50±3.03	全体としては約92%の一致
陰性	11	180	2.23±1.91	

FBN1変異の有無で新旧Ghent基準を評価

	FBN1変異(+)	FBN1変異(-)	systemic score	
Ghent基準				
陽性	49+8	16	5.61±2.88	旧Ghent 8例、改訂Ghent 9例においてFBN1が診断の決め手となった。
陰性	6	26	2.44±1.91	
改訂Ghent				
陽性	48+9	14	**5.44±3.02**	
陰性	6	28	2.68±2.24	

図1

マルファン症候群における表現型
―東大病院マルファン外来―



高頻度に認められる所見：

大動脈拡大・解離	92%
硬膜拡張	65%
手首・親指サイン	67%
高口蓋	47%
皮膚萎縮線条	52%

ほとんど認められなかった所見：

僧帽弁輪石灰化	0%
反復するヘルニア	5%

欧米と差を認める症候

指端長(arm span)/身長比＞1.05	23% (欧米55%)
気胸	19% (欧米 7%)

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
師田哲郎, 小野稔	Marfan症候群における治療Update.	Heart View	14	1042-1045	2010
Suzuki J, Aoyama N, Ogawa M, Hirata Y, Izumi Y, Nagai R, Isobe M.	Periodontitis and cardiovascular diseases.	Expert Opin Ther Tar.	14	1023-1027	2010
Takeshita K, Maruyama T, Nakao Y, Ono T, Taniguchi Y, Chikuda H, Shoda N, Oshima Y, Higashikawa A, Nakamura K.	Aorta movement in patients with scoliosis after posterior surgery.	Spine (Phila Pa 1976).	35	E1571-1576	2010
Takeshita K, Maruyama T, Ono T, Ogihara S, Chikuda H, Shoda N, Nakao Y, Matsudaira K, Seichi A, Nakamura K.	New parameters to represent the position of the aorta relative to the spine for pedicle screw placement.	Eur Spine J.	19	815-820	2010
Kono AK, Higashi M, Morisaki H, Morisaki T, Tsutsumi Y, Akutsu K, Naito H, Sugimura K.	High prevalence of vertebral artery tortuosity of Loeys-Dietz syndrome in comparison with Marfan syndrome.	Jpn J Radiol.	28	273-277	2010
Akutsu K, Morisaki H, Okajima T, Yoshimuta T, Tsutsumi Y, Takeshita S, Nonogi H, Ogino H, Higashi M, Morisaki T.	Genetic analysis of young adult patients with aortic disease not fulfilling the diagnostic criteria for Marfan syndrome.	Circ J.	74	990-997	2010

Ogawa N, Imai Y, Takahashi Y, Nawata K, Hara K, Nishimura H, Kato M, Takeda N, Kohro T, Morita H, Taketani T, Morota T, Yamazaki T, Goto J, Tsuji S, Takamoto S, Nagai R, Hirata Y.	Evaluating Japanese Patients With the Marfan Syndrome Using High-Throughput Microarray-Based Mutational Analysis of Fibrillin-1 Gene.	Am J Cardiol.	108	1801-7	2011
青木美穂子, 今井靖, 藤田大司, 小川直美, 加藤昌義, 西村敬史, 鈴木淳一, 平田恭信, 永井良三	：マルファン症候群では歯周病は極めて高頻度に認められる。	呼吸と循環	59	939-942	2011
藤田大司, 今井靖, 平田恭信	：【大動脈疾患の最新知見】 非動脈硬化性遺伝性疾患　Marfan症候群と関連疾患。	最新医学	66	1655-1663.	2011
Takeshita K, Maruyama T, Sugita S, Oshima Y, Morii J, Chikuda H, Ono T, Nakamura K.	Is a right pedicle screw always away from the aorta in scoliosis?	Spine (Phila Pa 1976).	36	E1519-24.	2011

治す 14

Marfan症候群における治療Update

Recent advances in treatment of patients with Marfan syndrome

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Marfan症候群（Marfan syndrome；MFS）の主たる生命予後規定因子は心臓血管病変にあり，無治療での自然予後は寿命約37歳と推定されるように，きわめて不良である[1]。しかしながら，診断・治療技術の進歩した現代においては，慎重な経過観察により適切な時期に適切な介入が行われた場合には，健常人と同等の生命予後が期待できる[2]ことも判明している。
MFSに伴う大動脈疾患とは，まずは大動脈瘤，特に大動脈基部の拡張病変である大動脈弁輪拡張症（annuloaortic ectasia；AAE），であり，次いで大動脈解離である。本稿では，近年急速に普及しつつあるAAEに対する新しい術式：自己弁温存大動脈基部置換術に関し，最新の知見を述べることに主眼を置いた。また，論文テーマからははずれるが，MFSに伴う僧帽弁逸脱症および心室性不整脈に関しても一部スペースを割いて解説した。一方，大動脈解離に関する最近の進歩といえば血管内治療であり，これに関しては別稿にも詳述されているが，MFSへの適用に関し若干の配慮が必要であるため言及した。

大動脈弁輪拡張症の治療

(1)大動脈基部置換術式の変遷

AAEに対する手術術式としては，古典的には，Wheat法[3]とよばれる上行大動脈人工血管置換＋大動脈弁置換が報告されたが，残存するValsalva洞の拡大・破裂が問題となった。1968年にBentall原法[4]が発表され，病的大動脈壁を完全に切除する術式として確立された。その後Piehler法[5]やCabrol変法[6]，button法[7]などの修飾を受け，約40年を経た現在も標準術式として通用している。1992年，AAEの大多数の症例においては大動脈弁閉鎖不全症が合併していても大動脈弁尖形態は

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保たれていることに着目し，自己弁を温存したまま拡張した大動脈壁－Valsalva洞－のみを切除し人工血管に置換する術式が発表された。いわゆるDavid手術(aortic root reimplantation)と称される，直管状人工血管を左室流出路側より刺入した縫合糸で大動脈弁輪に固定して，その内側に大動脈弁尖を縫着する術式である[8]。次いで1993年，弁輪縫合を省いて舌状に切り込みを入れた人工血管でValsalva洞を置換するYacoub手術(aortic root remodeling)が発表され[9]，自己弁温存術式はこの両術式をもって広く普及した。

(2)自己弁温存大動脈基部置換術の論点

第一の論点は，“DavidかYacoubか？”ということである。David手術においては当初，比較的小径の人工血管が用いられることが多く，弁開放時に弁尖が人工血管壁と干渉して変性をきたす危険性が危惧された。一方のYacoub手術では舌状の人工血管がValsalva洞様のふくらみを形成するため，生理的な形態が保たれることが利点とされた。しかし，Yacoub手術では弁輪への介入がなされないため，遠隔期に弁輪拡張による弁逆流再発が問題となった。弁輪への補強縫合を別個に追加する改良も考案されたが成績としては不確実で，またDavid手術の二重の縫合ラインに対してYacoub手術では1ラインのみであるため出血の危険性も高いという弱点も指摘された。そこで，今日ではValsalva洞形態を付加した人工血管でDavid手術を行う，David-V手術が最も信頼性のある術式と考えられるようになった(**表1**)。

表1　自己弁温存術式の変遷(C. Millerによる命名)

David－Ⅰ	reimplantation
David－Ⅱ	remodelingと同様の術式
David－Ⅲ	弁輪への補強を追加したreimplantation
David－Ⅳ	大径人工血管を用い，ST-junction部を縫縮
David－Ⅴ	Valsalva洞形態を再現したreimplantation

もう一つの論点は，術式の前提となる“弁尖は正常”であることが，本当にMFSのAAEにもあてはまるのか，という疑問である。David自身は，MFSでも遠隔成績に問題はないとしている[10]。しかし，症例数の豊富なStanfordからは，やはり弁の耐久性に問題があること，弁輪拡大の観点からDavid手術が望ましいこと，が報告されている[11]。またJohns Hopkinsの報告では，Bentall手術と比べると再手術のリスクが高くてもイベント発生率と遠隔生存率で有利[12]とされており，結論を得るに至っていない。それでも，ある程度の－生体弁の耐久性を上回るべきだが－長期間にわたり抗凝固療法なく生活できるならば，少なくとも若年女性，特に妊娠・挙児希望のある女性には大きな利点のある術式であることは異論のないところである。

(3)当科での術式：David－V UT modification

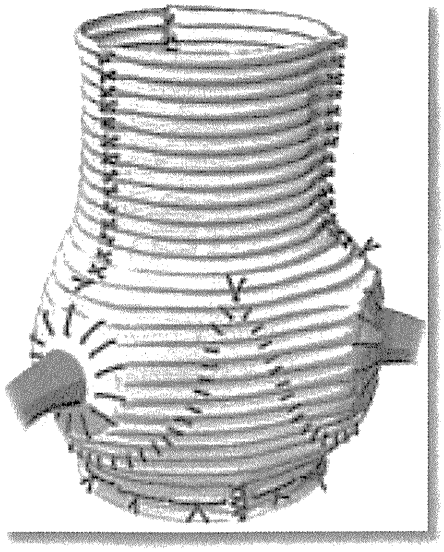
当科では1998年に自己弁温存術式を導入し，当初はMFSにはDavid手術を，non-MFSにはYacoub手術を選択していた。2004年より自己弁温存全症例にDavid-V手術の東京大学変法：David-V UT modification[13]を標準術式として適用している。これは径32～34mmの大径人工血管を用い，弁尖縫着後にST-junctionから遠位側吻合部までの人工血管を3カ所で縫縮してValsalva洞を形成する方法で，特別な人工血管を必要とせず，かつデザイン自由度の高い術式である(**図1**)。2010年5月までに45例のDavid-V UT modificationを施行し，手術死亡なし，現時点での平均AR Ⅰ度，弁置換なし，と成績は良好である。しかし，遠隔死亡が3例：不整脈死2，分娩後脳出血1，とMFS特有の疾患で失っており，今後の経過観察上での大きな問題と捉えている。

MFSにおけるその他心疾患治療の変貌

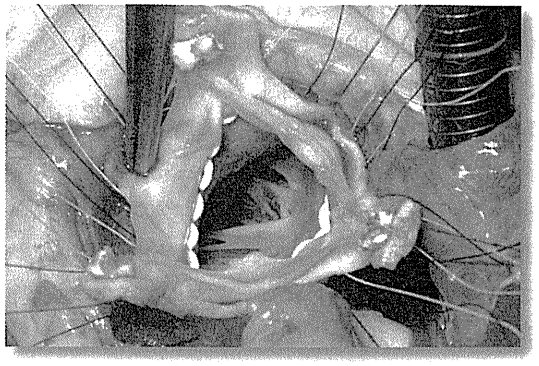
(1)僧帽弁逸脱症の治療

MFSに合併する僧帽弁逸脱症の頻度は，従来は40～80%といわれてきたが，昨今の厳密な診断基準では30%程度と

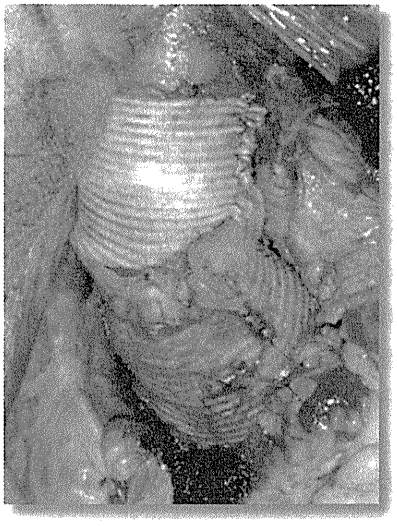
a：人工血管のデザインと完成模式図



b：弁輪への縫合糸



d：残存上行大動脈のラッピング



c：接合良好となった弁尖

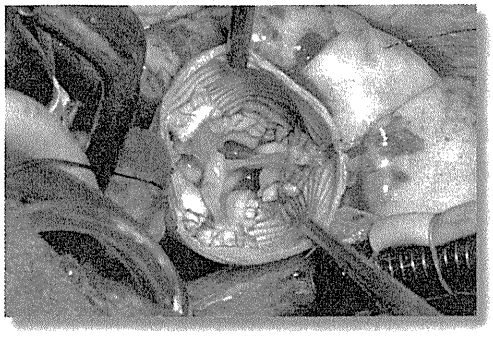
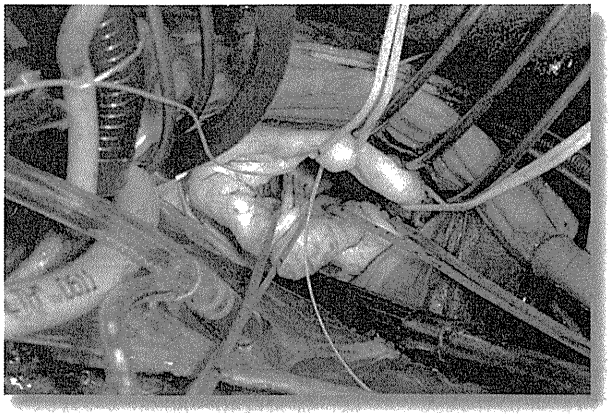


図1　David−V UT modification

a：前後尖の広範逸脱



b：人工腱索で逆流は消失した

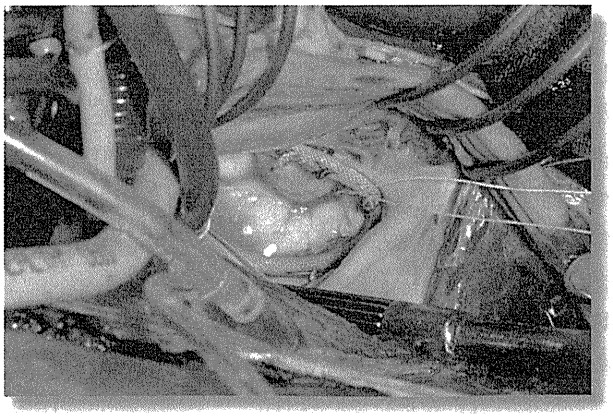


図2　人工腱索を用いた僧帽弁形成術

考えられている[14]。前後尖の広範な逸脱を呈することが多く，これまでは多くの症例で人工弁置換術が施行されてきた。僧帽弁に関しても大動脈弁と同様に弁形成技術の進歩は著しく，人工腱索の長期遠隔成績が実証されるに至って，広範逸脱や小児期の重症僧帽弁閉鎖不全症にも形成術が適用されるようになり，良好な長期成績をあげている[15]（図2）。大動脈弁・僧帽弁ともに人工弁使用を回避できることの意義は大きいと考えられる。

(2)心室性不整脈

MFS患者の生命予後を規定する重要な因子として，心室性不整脈が注目されている[16]。当科でも，大動脈基部と僧帽弁の修復がされながら不整脈死を遂げた症例を複数経験しており，リスクの予知と防止が課題となっている。DCGに代表される従来の検査法だけではなく，TDIを用いた心筋障害の検出[17]などの今後の発展に期待したい。

MFSにおけるステントグラフト治療の問題点

胸部下行大動脈瘤および解離において，従来の開胸手術に対する血管内治療（thoracic endovascular aneurysm repair；TEVAR）の施行比率は急速に上昇している。低侵襲性は当然のこととして，企業製デバイスの供給により合併症も減少し遠隔成績も向上してきている。しかし，現時点ではMFSへの積極的適応を示唆するエビデンスには乏しく，高率なエンドリークや新規解離発症などの報告も多く，遠隔成績はいまだ不明である[18-20]。TEVARは“健常部にランディングする”ことが基本であり，びまん性の中膜病変を有するMFSへの適用，特に解離への適用には慎重な配慮が必要と思われる。

文献

1) Van Karnebeek, DD, Naeff MS, Mulder BJ, et al: Natural history of cardiovascular manifestations in Marfan syndrome. Arch Dis Child 84: 129-137, 2001.
2) Judge DP, Dietz HC: Therapy of Marfan syndrome. Annu Rev Med 59: 43-59, 2008.
3) Wheat MW, Wilson JR, Bartley TD: Successful replacement of the entire ascending aorta and aortic valve. JAMA 188: 717-719, 1964.
4) Bentall H, DeBono A: A technique for complete replacement of the ascending aorta. Thorax 23: 338-339, 1968.
5) Piehler JM, Pluth JR: Replacement of the ascending aorta and aortic valve with a composite graft in patients with nondisplaced coronary ostia. Ann Thorac Surg 33: 406-409, 1982.
6) Cabrol C, Pavie A, Mesnildrey P, et al: Long-term results with total replacement of the ascending aorta and reimplantation of the coronary arteries. J Thorac Vasc Surg 91: 17-25, 1986.
7) Kouchoukos NT, Marshall WG, Jr, Wedige-Stecher TA: Eleven-year experience with composite graft replacement of the ascending aorta and aortic valve. J Thorac Cardiovasc Surg 92: 691-705, 1986.
8) David TE, Feindel CM: An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. J Thorac Cardiovasc Surg 103: 617-622, 1992.
9) Sarsam MAI, Yacoub M: Remodeling of the aortic valve annulus. J Thorac Cardiovasc Surg 105: 435-438, 1993.
10) David TE, Armstrong S, Maganti M, et al: Long-term results of aortic valve-sparing operations in patients with Marfan syndrome. J Thorac Cardiovasc Surg 138: 859-864, 2009.
11) Miller DC: Valve-sparing aortic root replacement in patients with the Marfan syndrome. J Thorac Cardiovasc Surg 125: 773-778, 2003.
12) Patel ND, Weiss ES, Alejo DE, et al: Aortic root operations for Marfan syndrome: a comparison of the Bentall and valve-sparing procedures. Ann Thorac Surg 85: 2003-2010, 2008.
13) Takamoto S, Nawata K, Morota T: A simple modification of 'David-V' aortic root reimplantation. Eur J Cardiothorac Surg 30: 560-562, 2006.
14) Taub CC, Stoler JM, Perez-Sanz T, et al: Mitral valve prolapse in Marfan syndrome: An old topic revisited. Echocardiography 26: 357-364, 2009.
15) Everitt MD, Pinto N, Hawkins JA, et al: Cardiovascular surgery in children with Marfan syndrome or Loeys-Dietz syndrome. J Thorac Cardiovasc Surg 137: 1327-1332, 2009.
16) Yetman AT, Bornemeier RA, McCrindle BW, et al: Long-term outcome in patients with Marfan syndrome: is aortic dissection the only cause of sudden death? J Am Coll Cardiol 41: 329-332, 2003.
17) Rybczynski M, Koschyk DH, Aydin MA, et al: Tissue Doppler imaging identifies myocardial dysfunction in adults with Marfan syndrome. Clin Cardiol 30: 19-24, 2007.
18) Cooper DG, Walsh SR, Sadat U, et al: Treating the thoracic aorta in Marfan syndrome: surgery or TEVR? J Endovasc Ther 16: 60-70, 2009.
19) Nordon IM, Hinchliffe RJ, Holt PJ, et al: Endovascular management of chronic aortic dissection in patients with Marfan syndrome. J Vasc Surg 50: 987-991, 2009.
20) Russo BL, La Palombara C, Rosati M, et al: Stent graft repair of descending aortic dissection in patients with Marfan syndrome: an effective alternative to open reoperation? J Thorac Cardiovasc Surg 138: 1108-1114, 2009.

Periodontitis and cardiovascular diseases

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Periodontitis is characterized by gingival inflammation and periodontopathic bacteria generate immunological inflammatory responses. Recent epidemiological reports suggest that periodontitis is one of the key risk factors for the onset of cardiovascular diseases. Several studies reported that periodontal bacteria in cardiovascular specimens were frequently detected. We revealed that patients with acute coronary syndrome showed significantly higher serum IgG titers to a strain of periodontopathic bacteria compared with patients with chronic coronary disease. Periodontopathic bacteria were also present in a high percentage of specimens of diseased arteries from patients with Buerger disease or abdominal aortic aneurysm. Although periodontopathic bacteria may play a role in the development of cardiovascular diseases, the influence of these bacteria on the disease has not yet been proven. In this article, we review the relationship between periodontopathic pathogens and cardiovascular diseases to conduct further clinical and experimental investigations in near future.

Keywords: aorta, bacteria, cytokine, inflammation, periodontitis

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1. Introduction

Periodontitis is a chronic inflammatory disease that degrades the attachment apparatus of the teeth, leading to tooth loosening. Clinical signs of the disease are often seen in middle age and it is a very common disease in adults [1,2]. Epidemiological studies showed that periodontitis significantly increased the risk of cardiovascular disease (CVD) [3-6]. Although data was adjusted for known CVD risk factors such as smoking, diabetes, hypertension and socioeconomic conditions, other points might still explain the apparent association. Levels of risk markers for CVD have been reported to be elevated in patients with periodontitis. Furthermore, animal studies demonstrated an association between the prevalence of periodontal pathogens, bacterial products, periodontitis and the incidence of CVD-related events [7,8]. Although DNA from oral bacteria has been found in atherosclerotic plaque in animal experimental models [9] and humans [10], the contribution of these bacteria to plaque formation remains unknown. Periodontal pathogens and their products were reported to be a trigger of the atherosclerotic process in animal studies [7,8]. However, their effects in the human system remain unclear. The release of host-derived inflammatory mediators, such as cytokines from the chronically inflamed periodontal tissues into the circulation, may provide a link between periodontal disease and CVD [11,12]. Altered serological profiles of risk markers in patients with periodontitis may result from an invasion of bacteria. Additionally, entry of their products from the periodontal lesion into the blood stream and the consequential induction and maintenance of a chronic inflammatory state also contribute to the progression of CVD.

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In this small article, we review pathological and immunological influence of periodontal pathogens to CVD and some promising methodologies for prevention of the disease.

2. Coronary arterial disease and periodontitis

Recent studies suggest that chronic inflammation plays an important role in the development of coronary arterial disease (CAD). Because periodontal disease is an enhancer of several chronic inflammatory factors such as MMPs [13-15], an etiological relationship between periodontal disease and CAD was proposed. For these reasons, there is strong interest in evaluating whether periodontal disease is independently associated with CAD [16-18]. Humphrey *et al.* revealed that periodontal disease is associated with increased risk of CAD using a meta-analysis [19]. They concluded that periodontal disease is a risk factor or marker for CAD, and is independent of traditional CAD risk factors. Nakajima *et al.* also revealed that periodontitis is associated with increased risk of CAD through dysfunction of endothelial cells, induced by either periodontopathic bacteria or their products [20]. CRP concentrations were higher among patients who subsequently developed myocardial infarction compared with those without the disease. However, there was no report to elucidate the relationship between specific gingival bacteria infection and CAD.

We recently revealed that there is an association between periodontitis and CAD, particularly acute coronary syndrome (ACS). A total of 28 CAD patients participated in the study. Coronary angiography, periodontal examination and dental radiography were performed in all patients. Subgingival plaque, saliva and blood samples were analyzed for the periodontopathogens *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* and *Prevotella intermedia* using PCR. Specific serum antibody titers to the five periodontal pathogens were determined by ELISA. We found that 33% of the ACS patients harbored *A. actinomycetemcomitans* in oral samples, whereas no *A. actinomycetemcomitans* was found in the patients with chronic CAD. Furthermore, ACS patients showed significantly higher serum IgG titers to *A. actinomycetemcomitans* compared with chronic CAD patients. Thus, we concluded that a specific periodontal pathogens may play a crucial role in the development of ACS [21].

3. Peripheral arterial disease and periodontitis

There are several papers demonstrating the relationship between peripheral arterial disease (PAD) and periodontitis. Buhlin *et al.* revealed the association by determining the plasma levels of some risk markers for PAD in cases with periodontitis [22,23]. Statistical analyses revealed a significant association between periodontitis and high levels of C-reactive protein (CRP), fibrinogen, IL-18 and antibodies against heat shock protein (Hsp) 65 and 70. They also showed the effect of infection control of periodontitis on the prevalence of the risk factors. One year after the initial treatment, IL-18 and other levels decreased. Thus, standard treatment for periodontal disease induces systemic changes in several biochemical markers that reflect the risk for PAD.

Chen *et al.* also revealed that periodontitis was associated with PAD using tissue specimens [24]. They identified *P. gingivalis, T. denticola, A. actinomycetemcomitans, P. intermedia* in tissue specimens taken from the anastomotic site of distal bypasses PCR. In the study, periodontopathic bacteria were detected in 52% of atherosclerotic specimens. Severe (Fontaine grade III or IV) patients showed higher detection frequency of *P. gingivalis* than mild (Fontaine grade II) patients. After adjusting for age, sex, diabetes and smoking, periodontitis increased fivefold the risk of having PAD. They also showed that periodontitis was associated with increased serum IL-6 and TNF-α concentrations.

Buerger disease also showed the significant relationship to periodontitis. Iwai *et al.* revealed that DNA of oral bacteria was detected in 13 of 14 arterial samples and all oral samples of patients with Buerger disease [25]. While *T. denticola* was found in 86% of the arterial samples, other pathogens were found in 14 to 43% of the samples. A pathological examination revealed that arterial specimens showed the characteristics of an intermediate-chronic-stage or chronic-stage lesion of Buerger disease. They reported that the patients with Buerger disease had high prevalence of severe periodontitis with higher serum IgG titers against *T. denticola, P. gingivalis* and *A. actinomycetemcomitans* [26]. They also found that the patients had increased titers of serum anti-cardiolipin antibody compared with healthy subjects [27]. These results suggest that periodontitis influences the development of PAD.

4. Aortic aneurysm and periodontitis

Abdominal aortic aneurysm (AAA) is a common and lethal disorder in the aging population [28,29]. Inflammation and MMPs appear to play a critical role in AAA development and progression [30]. Human AAA tissue samples demonstrated severe inflammatory infiltrates in both the media and adventitia [31,32]. An increased expression of MMPs has been observed in human aneurysm tissue specimens [33-37]. It is well known that MMPs play key roles in periodontal diseases. Periodontopathic bacteria generate host immunological inflammatory responses, thus resulting in the secretion of cytokines and MMPs [38], and eventually leading to the extracellular matrix destruction of the periodontal tissues [39]. Some studies reported the detection of periodontal bacteria in AAA specimens. Periodontopathic bacteria, especially *P. gingivalis* was present in a high percentage of specimens of AAA and were also found throughout the whole aneurysmal wall [40]. Thus, periodontopathic bacteria may play a role in the development of AAA, but the influence of these bacteria on the aneurysmal wall has not yet been

proven. To determine the effect of the periodontal microorganism on the AAA, we made a novel murine AAA model, which was produced by the periaortic application of 0.25 M $CaCl_2$. The mice received inoculations of either live *P. gingivalis*, *A. actinomycetemcomitans* or vehicle. Four weeks after the application of $CaCl_2$, the *P. gingivalis*-challenged mice showed a significant increase in the aortic diameter in comparison with the vehicle control mice while the *A. actinomycetemcomitans*-challenged mice showed no significant increase. Immunohistochemically, the CD8- and MOMA2-positive cells and the level of MMP-2 in the aneurysmal samples of *P. gingivalis*-challenged mice were also significantly higher than that inoculated with vehicle. We found that the *P. gingivalis*, but not *A. actinomycetemcomitans*, infection accelerated the progression of AAA due to the increased expression of MMPs (Aoyama N, unpublished).

5. Vitamin D is a key factor for periodontitis and cardiovascular diseases

Although vitamin D is well known to regulate calcium and phosphorus metabolism, it also has a physiological effects beyond its role in skeletal homeostasis. Recently, it was revealed that vitamin D is an immunomodulator which targets various immune cells, and modulates both innate and adaptive immune responses. Thus, vitamin D plays a crucial role in maintenance of immune homeostasis [41]. Several epidemiological studies have linked inadequate vitamin D levels to a higher susceptibility to immune-mediated disorders [42,43], including cardiovascular diseases [44]. It is believed that maintaining adequate vitamin D levels might in part prevent these common diseases [45]. It has been reported that low serum vitamin D levels were independently associated with periodontal and cardiovascular diseases [46,47]. Notably, vitamin D insufficiency is associated with increased circulating CRP levels, and vitamin D supplementation decreases circulating CRP levels [48]. Thus, the elevated CRP levels observed in periodontal and cardiovascular disease might be a surrogate for vitamin D insufficiency.

6. Conclusion

In this brief article, we have demonstrated the relationship between periodontopathic pathogens and cardiovascular diseases. We have also elucidated that each gingival bacterium caused different condition of cardiovascular diseases.

7. Expert opinion

Although several periodontopathic bacteria play a serious role in the development of cardiovascular diseases, the influence of these bacteria has to be elucidated because of the lack of appropriate investigations. Thus, further experimental and clinical studies should be conducted to elucidate the pathophysiology and relationship between periodontitis and cardiovascular diseases. Meanwhile, clinicians should optimize the periodontal conditions in patients with cardiovascular risk factors for primary and/or secondary prevention. Finally, it is plausible that this simple treatment of periodontitis might provide as much or even more benefit than the standard treatments for cardiovascular diseases.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Boehm TK, Scannapieco FA. The epidemiology, consequences and management of periodontal disease in older adults. J Am Dent Assoc 2007;138:26S-33S
2. Jain N, Jain GK, Javed S, et al. Recent approaches for the treatment of periodontitis. Drug Discov Today 2008;13:932-43
3. Friedewald VE, Kornman KS, Beck JD, et al. The American Journal of Cardiology and Journal of Periodontology Editors' Consensus: periodontitis and atherosclerotic cardiovascular disease. Am J Cardiol 2009;104:59-68

• **This article shows a standard consensus for physicians and dentists.**

4. Andriankaja OM, Genco RJ, Dorn J, et al. Periodontal disease and risk of myocardial infarction: the role of gender and smoking. Eur J Epidemiol 2007;22:699-705
5. Bahekar AA, Singh S, Saha S, et al. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a metaanalysis. Am Heart J 2007;154:830-7
6. Cairo F, Castellani S, Gori AM, et al. Severe periodontitis in young adults is associated with sub-clinical atherosclerosis. J Clin Periodontol 2008;35:465-72
7. Herzberg MC, Meyer MW. Dental plaque, platelets, and cardiovascular diseases. Ann Periodontol 1998;3:151-60
8. Dorn BR, Dunn WA, Progulske-Fox A. Invasion of human coronary artery cells by periodontal pathogens. Infect Immun 1999;67:5792-8
9. Zhang MZ, Li CL, Jiang YT, et al. Porphyromonas gingivalis infection accelerates intimal thickening in iliac arteries in a balloon-injured rabbit model. J Periodontol 2008;79:1192-9
10. Gaetti-Jardim E Jr, Marcelino SL, Feitosa AC, et al. Quantitative detection of periodontopathic bacteria in atherosclerotic plaques from coronary arteries. J Med Microbiol 2009;58:1568-75
11. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. AtheroGene investigators. Impact of infectious burden on extent and long-term prognosis of atherosclerosis. Circulation 2002;105:15-21
12. Desvarieux M, Demmer RT, Rundek T, et al. Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). Circulation 2005;111:576-82
13. Sorsa T, Tjaderhane L, Konttinen YT, et al. Matrix metalloproteinases: contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. Ann Med 2006;38:306-21
14. Sorsa T, Tjaderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral Dis 2004;10:311-18
15. Olsen I. Update on bacteraemia related to dental procedures. Transfus Apher Sci 2008;39:173-8
16. Nakib SA, Pankow JS, Beck JD, et al. Periodontitis and coronary artery calcification: the Atherosclerosis Risk in Communities (ARIC) study. J Periodontol 2004;75:505-10
17. Higashi Y, Goto C, Hidaka T, et al. Oral infection-inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. Atherosclerosis 2009;206:604-10
18. Zaremba M, Gorska R, Suwalski P, Kowalski J. Evaluation of the incidence of periodontitis-associated bacteria in the atherosclerotic plaque of coronary blood vessels. J Periodontol 2007;78:322-7
19. Humphrey LL, Fu R, Buckley DI, et al. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med 2008;23:2079-86
20. Nakajima T, Yamazaki K. Periodontal disease and risk of atherosclerotic coronary heart disease. Odontology 2009;97:84-91
21. Sakurai K, Wang D, Suzuki J, et al. High incidence of Actinobacillus actinomycetemcomitans infection in acute coronary syndrome. Int Heart J 2007;48:663-75
22. Buhlin K, Hultin M, Norderyd O, et al. Risk factors for atherosclerosis in cases with severe periodontitis. J Clin Periodontol 2009;36:541-9
23. Buhlin K, Hultin M, Norderyd O, et al. Periodontal treatment influences risk markers for atherosclerosis in patients with severe periodontitis. Atherosclerosis 2009;206:518-22
24. Chen YW, Umeda M, Nagasawa T, et al. Periodontitis may increase the risk of peripheral arterial disease. Eur J Vasc Endovasc Surg 2008;35:153-8
25. Iwai T, Inoue Y, Umeda M, et al. Oral bacteria in the occluded arteries of patients with Buerger disease. J Vasc Surg 2005;42:107-15
26. Chen YW, Iwai T, Umeda M, et al. Elevated IgG titers to periodontal pathogens related to Buerger disease. Int J Cardiol 2007;122:79-81
27. Chen YW, Nagasawa T, Wara-Aswapati N, et al. Association between periodontitis and anti-cardiolipin antibodies in Buerger disease. J Clin Periodontol 2009;36:830-5
28. Ernst CB. Abdominal aortic aneurysm. N Engl J Med 1993;328:1167-72
29. Alcorn HG, Wolfson SK Jr, Sutton-Tyrrell K, et al. Risk factors for abdominal aortic aneurysms in older adults enrolled in The Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 1996;16:963-70
30. Longo GM, Xiong W, Greiner TC, et al. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. J Clin Invest 2002;110:625-32
31. Bobryshev YV, Lord RS, Parsson H. Immunophenotypic analysis of the aortic aneurysm wall suggests that vascular dendritic cells are involved in immune responses. Cardiovasc Surg 1998;6:240-9
32. Pearce WH, Koch AE. Cellular components and features of immune response in abdominal aortic aneurysms. Ann NY Acad Sci 1996;800:175-85
33. Freestone T, Turner RJ, Coady A, et al. Inflammation and matrix metalloproteinases in the enlarging abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol 1995;15:1145-51

34. Davis V, Persidskaia R, Baca-Regen L, et al. Matrix metalloproteinase-2 production and its binding to the matrix are increased in abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 1998;18:1625-33

35. Rizas KD, Ippagunta N, Tilson MD III. Immune cells and molecular mediators in the pathogenesis of the abdominal aortic aneurysm. Cardiol Rev 2009;17:201-10

36. Takagi H, Manabe H, Kawai N, et al. Circulating matrix metalloproteinase-9 concentrations and abdominal aortic aneurysm presence: a meta-analysis. Interact Cardiovasc Thorac Surg 2009;9:437-40

37. Aziz F, Kuivaniemi H. Role of matrix metalloproteinase inhibitors in preventing abdominal aortic aneurysm. Ann Vasc Surg 2007;21:392-401

38. Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases. J Clin Periodontol 2005;32(Suppl 6):108-29

39. Ashley RA. Clinical trials of a matrix metalloproteinase inhibitor in human periodontal disease. SDD Clinical Research Team. Ann NY Acad Sci 1999;878:335-46

40. Kurihara N, Inoue Y, Iwai T, et al. Detection and localization of periodontopathic bacteria in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2004;28:553-8

41. Baeke F, Takiishi T, Korf H, et al. Vitamin D: modulator of the immune system. Curr Opin Pharmacol 2010: published online 27 April 2010, doi:10.1016/j.coph.2010.04.001

42. Pilz S, Tomaschitz A, Obermayer-Pietsch B, et al. Epidemiology of vitamin D insufficiency and cancer mortality. Anticancer Res 2009;29:3699-704

43. Shoenfeld N, Amital H, Shoenfeld Y. The effect of melanism and vitamin D synthesis on the incidence of autoimmune disease. Nat Clin Pract Rheumatol 2009;5:99-105

44. Judd SE, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. Am J Med Sci 2009;338:40-4

45. Goldstein MR, Mascitelli L, Pezzetta F. Peridontitis, atherosclerotic cardiovascular disease and vitamin D. Am J Cardiol 2009;104:1164

46. Dietrich T, Joshipura KJ, Dawson-Hughes B, et al. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr 2004;80:108-13

47. Kendrick J, Targher G, Smits G, et al. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis 2009;205:255-60

48. Elliott P, Chambers JC, Zhang W, et al. Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA 2009;302:37-48

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