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Hypothesis

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Myocardial bridging is a potential risk factor of very late stent thrombosis of drug eluting stent

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Summary

Drug eluting stents have been implanted worldwide and used in nearly 90% of percutaneous coronary interventions in China. Although many randomized trials have confirmed the efficacy and safety profile of drug eluting stents, they were not powered to detect or exclude the effect of drug eluting stents on rare events such as stent thrombosis. Several mechanisms of very late stent thrombosis have been postulated, but are not widely accepted. Virchow's triad describes the 3 main factors of thrombus formation – stasis of blood flow, endothelial injury and hypercoagulability. Myocardial bridging is a common congenital anomaly. Modern anatomy and angiography regard myocardial bridging as widespread, but its pathophysiological response is always ignored. According to Virchow's triad, myocardial bridging negatively affect endothelial function, and the turbulent shear stress and intimal trauma predispose the vessel toward thrombus formation. Therefore, we question whether a relationship between myocardial bridging and very late stent thrombosis of drug eluting stents exists. Also, we propose that myocardial bridging might be a potential risk factor of very late stent thrombosis of drug eluting stents; coronary artery bypass grafting might be a promising and novel choice in the treatment of myocardial bridging with severe stenosis in the coronary artery.

key words: **myocardiol bridging • drug eluting stent • stent thrombosis**

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Background

Myocardial infarction from atherosclerotic coronary artery disease is a leading cause of mortality and morbidity worldwide. Emergent removal of the obstructive lesions and prevention of coronary artery disease is an imperative, ongoing challenge for scientists and cardiologists.

Percutaneous coronary intervention (PCI) was first introduced in 1977 by Andreas Gruentzig and by the mid-1980s it was promoted as an alternative to coronary artery bypass grafting (CABG). It has been used for over 3 decades and has been subjected to more randomized clinical trials than any other interventional procedure. In early 21st century, sirolimus- and paclitaxel-coated drug eluting stents (DES) were developed. Its role in the treatment of patients presenting with stable CAD is challenged by advances in medical treatment, referred to as optimal medical therapy, which include intensive lifestyle and pharmacological management. Although DES have mostly replaced bare metal stents (BMS) due to their decreased rates of restenosis and re-intervention rates [1], higher rates of very late stent thrombosis is the significant disadvantages of DES [2,3]. To prevent stent thrombosis in DES, current guidelines recommend up to 1 year of dual anti-platelet therapy [4]. Nevertheless, DESs still have been criticized for events of stent thrombosis occurring anywhere from 1 to 5 years after implantation [5–9]. Especially, many results have been reported on an increased risk of very late stent thrombosis with DES [10,11].

Then, how is stent thrombosis exactly classified? The Academic Research Consortium classifies stent thrombosis into 4 types: acute (within 24 h of stent placement), subacute (24 h to 30 days), late (after 30 days), and very late (12 months after stent placement).

Known risk factors for stent thrombosis include premature discontinuation of oral antiplatelet agents, long stents, renal failure, bifurcation lesions, diabetes mellitus, and low ejection fraction [12]. The most important histological risk factor for stent thrombosis is considered as lack of endothelial coverage or delayed arterial healing, and the risk decreases after a year due to nearly complete endothelialization [13]. Increased risk of acute, sub-acute and late stent thrombosis can be explained based on the presence of unhealed endothelium causing activation of platelets and thrombosis [14].

Several mechanisms of very late stent thrombosis have been postulated. Gaddam et al. [15] proposed the cause of very late stent thrombosis to be formation of a *de novo* atherosclerotic lesion in the proximal segment of a stented artery. Farb et al. [16] reported pathological descriptions and showed that stenting across branch ostia, disruption of adjacent vulnerable plaques, and extensive plaque prolapse could precipitate late stent thrombosis. Cook et al. [17] showed that very late stent thrombosis resulted from delayed hypersensitivity to components of the drug polymer device combination that caused necrotizing vasculitis and late malposition.

All of the above statements are not widely accepted. Is there any other explanation for late stent thrombosis of DES? Virchow's triad proposes the 3 main causes of thrombosis to be stasis of blood flow, endothelial injury and hypercoagulability [18]. Based on Virchow's triad, question whether a relationship between myocardial bridging (MB) and very late stent thrombosis of DES exists.

MB is a congenital coronary anomaly defined as the tunneling of a segment of a major epicardial artery that travels intramurally through the myocardium beneath a muscle bridge. The current gold standard for diagnosing MB is coronary angiography with characteristic features of the "milking effect" and a "step down, step up" phenomenon induced by systolic compression of the epicardial coronary vessel. Modern imaging techniques, such as intracoronary ultrasound and Doppler and intracoronary pressure-wires, have contributed significantly to the diagnosis of MB [19].

Why do we question that a relationship between MB and very late stent thrombosis of DES exists? Firstly, it is because modern anatomy and angiography consider MB as widespread. MB's prevalence has been reported to range between 5.4% and 85% in autopsy series and 0.5–29.4% on coronary angiography [20]. Although it is clinically silent in the majority of cases, approximately 20–30% of patients with cardiac chest pain have a normal coronary angiogram, and in about 5% of these patients an MB can be identified [21]. In other words, MB is common, but its pathophysiological response is always ignored. Secondly, we know that the mechanisms by which MB causes myocardial ischemia include compromised coronary blood flow, endothelial dysfunction, thrombus formation and a strong association with coronary vasospasm [22]. Based on the above 2 points and Virchow's triad, we propose MB is a potential risk factor of very late stent thrombosis of DES.

Hypothesis

We propose the following hemodynamic and pathological mechanisms by which MB is a potential risk factor of very late stent thrombosis of DES. Firstly, MB can cause compromised coronary blood flow, which leads to acceleration of distal blood flow and stasis of proximal blood flow. The stasis of blood flow can be considered as potential risk factor for stent thrombus formation. Secondly, we propose that the "milking effect" of MB segments causes increased shear stress [23] and the increased shear stress and high intravascular pressure in MB may appear to negatively affect endothelial function [24,25]. Furthermore, thrombus formation in MB segments has been reported in patients with myocardial bridging-related cardiac events. These reports suggest that turbulent shear stress and intimal trauma predispose the vessel toward thrombus formation [26]. Increased shear stress associated with MB also appears to reduce the production of vasoactive agents such as endothelial nitric oxide synthase, endothelin-1 and angiotensin-converting enzyme within the bridging segment. According to Virchow's triad, MB negatively affects endothelial function, and the turbulent shear stress and intimal trauma predispose the vessel toward thrombus formation. In summarize, the presence of MB distal to coronary lesions should be seriously considered in preprocedural evaluation of the lesions as a potential risk factor for intracoronary thrombus formation.

Which kind of treatment is most suitable for coronary heart disease patients with MB? Generally, medication, especially with beta-blockers or calcium channel blockers, is

recommended as a first-line strategy for symptomatic patients with MB [27]. Although some patients are responsive to medical therapy, the changes from aging, weight and internal environment and increase of cardiac load, may still upset the balance between myocardial oxygen supply and oxygen consumption, resulting in myocardial ischemia. When medical management fails to yield results in severely symptomatic patients, intracoronary stenting and surgical interventions such as myotomy and CABG will be adopted.

However, stenting is not recommended in myocardial bridging (MB) due to the high rate of thrombosis and restenosis [28–30]. If the patient with severe stenosis in coronary artery and long segment muscle bridge receives stenting therapy, the risk of very late stent thrombosis of DES will significantly increase. Taken together, we propose that CABG or myotomy maybe a better choice to target the lesion with MB than DES implanting.

Pratt et al. [31] reported 2 cases of symptomatic MB refractory to medical management that were treated by minimally invasive CABG without cardiopulmonary bypass, and concluded that minimally invasive coronary artery bypass techniques are appropriate alternatives to muscle bridge division, or aortocoronary grafting with cardiopulmonary bypass for the management of symptomatic MB. WU Qing-yu et al. [32] reported on 31 consecutive patients with MB who underwent surgical treatment, all patients survived and recovered uneventfully. Postoperative exercise testing in all patients failed to reveal any persistent ischemia. After 3–115 months (mean 31 months) follow-up time, angiographic studies in 21 patients (68%) demonstrated restoration of coronary blood flow and myocardial perfusion without significant residual compression of the artery, and all patients were symptom-free and currently in NYHA class I–II. They concluded that patients who were refractory to medication would actively undergo surgical procedures such as myotomy and CABG.

Overall, we propose that MB of DES is a cause of very late stent thrombosis. CABG might be a promising and novel choice in the treatment of MB with severe stenosis in the coronary artery. MB can cause unstable blood flow and increase the shear stress, which is considered as a potential risk factor for very late stent thrombus formation. More epidemiological investigation is needed to determine the incidence of MB in coronary heart disease patients with very late stent thrombosis. More laboratory and clinical studies are critically needed to determine dynamics changes in patients with MB, such as blood flow resistance and shear stress in the coronary. The question of how to choose the optimal treatment for coronary heart disease patients with MB needs further investigation.

Conclusions

Since MB of DES is a cause of very late stent thrombosis, CABG maybe a better choice than DES implanting to target the lesion with MB.

Conflicts of interest statement

None declared.

References:

1. Greenhalgh J, Hockenhull J, Rao N et al: Drugeluting stents versus bare metal stents for angina or acute coronary syndromes. Cochrane Database Syst Rev, 2010; 12(5): CD004587
2. Moreno R, Fernández C, Hernández R et al: Drug-eluting stent thrombosis. Results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol, 2005; 45(6): 954–59
3. Daemen J, Simoons ML, Wijns W et al: ESC forum on drug eluting stents European Heart House, Nice, 27–28 September 2007. Eur Heart J, 2009; 30(2): 152–61
4. Smith Jr SC, Feldman TE, Hirshfeld Jr JW et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force of Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention), 2005
5. Al-Dehneh A, Virk H, Alkhouri Y et al: Drug-eluting stent thrombosis 1659 days after stent deployment: case report and literature review. Tex Heart Inst J, 2010; 37(3): 343–46
6. Paturi A, Rothenberg M, Borzak S: Very late subacute thrombosis of a sirolimus-eluting stent after 57 months. J Invasive Cardiol, 2009; 21(12): E252–53
7. Korovesis S, Katritsis DG: Stent thrombosis four and a half years after implantation of a sirolimus-eluting stent. Hellenic J Cardiol, 2009; 50(5): 423–25
8. Layland J, Jellis C, Whitbourn R: Extremely late drug-eluting stent thrombosis: 2037 days after deployment. Cardiovasc Revasc Med, 2009; 10(1): 55–57
9. Nagrani T, Zaher M, Gaddam S et al: In-stent thrombosis after 68 months of implantation in spite of continuous dual antiplatelet therapy: a case report. Cases J, 2010; 3: 68
10. Spaulding C, Daemen J, Boersma E et al: A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med, 2007; 356(10): 989–97
11. Stone GW, Moses JW, Ellis SG et al: Safety and efficacy of sirolimus – and paclitaxel – eluting coronary stents. N Engl J Med, 2007; 356(10): 998–1008
12. Iakovou I, Schmidt T, Bonizzoni E et al: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA, 2005; 293(17): 2126–30
13. Finn AV, Joner M, Nakazawa G et al: Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation, 2007; 115(18): 2435–41
14. Joner M, Finn AV, Farb A et al: Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol, 200; 48(1): 193–202
15. Gaddam S, Rizvi M, Nimmagadda KC et al: Proximal atherosclerotic lesion as a cause of very late stent thrombosis. Med Hypotheses, 2011; 76(4): 500–2
16. Farb A, Burke AP, Kolodgie FD, Virmani R: Pathological mechanisms of fatal late coronary stent thrombosis in humans. Circulation, 2003; 108(14): 1701–6
17. Cook S, Ladich E, Nakazawa G et al: Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation, 2009; 120(5): 391–99
18. Gaddam S, Rizvi M, Nimmagadda KC et al: Proximal atherosclerotic lesion as a cause of very late stent thrombosis. Med Hypotheses, 2011; 76(4): 500–2
19. Cay S, Oztürk S, Cihan G et al: Angiographic prevalence of myocardial bridging. Anadolu Kardiyol Derg, 2006; 6(1): 9–12
20. Möhlenkamp S, Hort W, Ge J, Erbel R: Update on myocardial bridging. Circulation, 2002; 106(20): 2616–22
21. Möhlenkamp S, Eggebrecht H, Ebralidze T et al: Normal coronary angiography with myocardial bridging: a variant possibly relevant for ischemia. Herz, 2005; 30(1): 37–47
22. Vales L, Kanei Y, Fox J: Coronary artery occlusion and myocardial infarction caused by vasospasm within a myocardial bridge. J Invasive Cardiol, 2010; 22(4): E67–69
23. Herrmann J, Higano ST, Lenon RJ et al: Myocardial bridging is associated with Alteration in coronary vasoreactivity. Eur Heart J, 2004; 25(23): 2134–42
24. Huang A, Sun D, Kaley G, Koller A: Superoxide released to high intraarteriolar pressure reduces nitric oxide-mediated shear stress- and agonist-induced dilations. Circ Res, 1998; 83(9): 960–65

25. Ungvari Z, Csiszar A, Huang A et al: High pressure induces superoxide production in isolated arteries via protein kinase C-dependent activation of NAD(P)H oxidase. Circulation, 2003; 108(10): 1253–58

26. Teragawa H, Fukuda Y, Matsuda K et al: Myocardial bridging increases the risk of Coronary Spasm. Clin Cardiol, 2003; 26(8): 377-83

27. Bourassa MG, Butnaru A, Lespérance J, Tardif JC: Symptomatic myocardial bridges: overview of ischemic mechanisms and current diagnostic and treatment strategies. J Am Coll Cardiol, 2003; 41(3): 351–59

28. Berry JF, von Mering GO, Schmalfuss C et al: Systolic compression of the left anterior descending coronary artery: a case series, review of the literature, and therapeutic options including stenting. Catheter Cardiovasc Interv, 2002; 56(1): 58–63

29. Alegria JR, Herrmann J, Holmes DR Jr et al: Myocardial bridging. Eur Heart J, 2005; 26(12): 1159–68

30. Yan HB, Wang J, Zhu XL et al: Frequency of infarct-related artery with myocardial bridging in patients with ST-elevation myocardial infarction and its impact upon percutaneous coronary intervention. Chin Med J, 2006; 119(7): 539–43

31. Pratt JW, Michler RE, Pala J, Brown DA: Minimally invasive coronary artery bypass grafting for myocardial muscle bridging. Heart Surg Forum, 1999; 2(3): 250–53

32. Wu QY, Xu ZH: Surgical treatment of myocardial bridging: report of 31 cases. Chin Med J, 2007; 120(19): 1689–93