Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 14, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.01.019

Mechanisms, Pathophysiology, and Clinical Aspects of Incomplete Stent Apposition

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Incomplete stent apposition (ISA) is characterized by the lack of contact of at least 1 stent strut with the vessel wall in a segment not overlying a side branch; it is more commonly found in drug-eluting stents than bare-metal stents. The accurate diagnosis of ISA, initially only possible with intravascular ultrasound, can currently be performed with higher accuracy by optical coherence tomography, which also enables strut-level assessment due to its higher axial resolution. Different circumstances related both to the index procedure and to vascular healing might influence ISA occurrence. Although several histopathology and clinical studies linked ISA to stent thrombosis, potential selection bias precluded definitive conclusions. Initial studies usually performed single time point assessments comparing overall ISA percentage and magnitude in different groups (i.e., stent type), thus hampering a comprehensive understanding of its relationship with vascular healing. Serial intravascular imaging studies that evaluated vascular response heterogeneity recently helped fill this gap. Some particular clinical scenarios such as acute coronary syndromes, bifurcations, tapered vessels, overlapping stents, and chronic total occlusions might predispose to ISA. Interventional cardiologists should be committed to optimal stent choices and techniques of implantation and use intravascular imaging guidance when appropriate to aim at minimizing acute ISA. In addition, the active search for new stent platforms that could accommodate vessel remodeling over time (i.e., self-expandable stents) and for new polymers and/or eluting drugs that could induce less inflammation (hence, less positive remodeling) could ultimately reduce the occurrence of ISA and its potentially harmful consequences. (J Am Coll Cardiol 2014;63:1355–67) © 2014 by the American College of Cardiology Foundation

Incomplete stent apposition (ISA), also described as stent malapposition, is a morphological characteristic defined by the lack of contact between at least 1 stent strut and the underlying intimal surface of the vessel wall in a segment not overlying a side branch. Due to the lack of sufficient resolution and the inability of providing cross-sectional images, angiography does not allow the diagnosis of ISA, whereas high-resolution intravascular imaging modalities, such as intravascular ultrasound (IVUS) (axial resolution of approximately 150 μm) and optical coherence tomography (OCT) (axial resolution of approximately 10 to 15 μm) do allow diagnosis (1). According to the time that ISA is diagnosed relative to the index procedure, ISA is labeled as acute (i.e., diagnosed post-procedure), persistent (i.e., diagnosed post-procedure and persistent at follow-up assessment), and acquired (i.e., not present post-procedure, but identified at follow-up assessment). In the absence of baseline intravascular imaging assessment, it is described simply as late ISA (2,3). Several factors are responsible for this pathological phenomenon and its different presentations, as follows: 1) inadequate stent implantation—in this setting, there are basically 2 possibilities: a) marked mismatch between stent size selection and luminal dimensions (i.e., stent diameter smaller than reference lumen diameter), a situation in which, regardless of optimal stent expansion, ISA will occur (4); or b) stent underexpansion despite an adequate stent–artery ratio due to several different factors, such as inadequate pressure of implantation and/or plaque-related factors (Fig 1); 2) chronic stent recoil (5); 3) thrombus dissolution after primary percutaneous coronary intervention (PCI) (6); 4) positive vessel remodeling (6–11); and 5) inadequate (i.e., insufficient and/or delayed) neointimal hyperplasia (12–15).

Incomplete Stent Apposition and Potential Relationship With Adverse Clinical Outcomes

A clear relationship between ISA and adverse cardiovascular events is still controversial. Although some studies have

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Manuscript received October 21, 2013; revised manuscript received December 12, 2013, accepted January 7, 2014.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
ISA = incomplete stent apposition
IVUS = intravascular ultrasound
OCT = optical coherence tomography
OLP = overlapping
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
ST = stent thrombosis
SES = sirolimus-eluting stent(s)
ZES = zotarolimus-eluting stent(s)

failed to demonstrate such connections (7,16–18), others have done so (12,19–24) (Table 1). Lee et al. (25) demonstrated that among 30 patients with very late stent thrombosis (ST), 73.9% of the drug-eluting stent (DES) group exhibited ISA (among whom 64.7% had late acquired ISA), whereas none of the bare-metal stent (BMS) group had ISA. Although the results showed a higher incidence of ISA in patients with DESs compared with BMSs, confirming data from previous reports (20), they also highlighted that ISA is not an isolated factor responsible for DES thrombosis (i.e., 26.1% of DES patients had stent thrombosis without evident ISA) (25). Guagliumi et al. (26) demonstrated by combined IVUS and OCT assessments that the presence and magnitude (i.e., area and distance) of ISA were significantly higher in patients with DES thrombosis compared with those without DES thrombosis. In addition, these investigators implicated 1 mechanism that led to ISA (i.e., positive remodeling) and another mechanism that could be a consequence of ISA (i.e., uncovered stent struts) as independent predictors of DES thrombosis (Fig. 2). Eosinophilic-rich inflammatory infiltrates associated with positive remodeling were also demonstrated (27). Alfonso et al. (27) also identified ISA in patients with ST using IVUS and OCT (ISA was identified in 40% and 47% of patients, respectively). Kang et al. (28) performed OCT imaging in 33 patients with very late ST and found that in the DES group, 52% and 64% had ISA and thrombi, respectively, whereas no patients presented with ISA in the BMS group. ISA was also more frequently found in 124 patients with very late definite DES versus BMS thrombosis (52% vs. 16%, respectively, $p = 0.005$) in a multicenter registry. Notably, greater ISA area was also demonstrated in the DES group compared with the BMS group. Moreover, among the DES group, a higher prevalence of ISA was identified in sirolimus-eluting stents (SES) compared with paclitaxel-eluting stents (PES) (58% vs. 37%, respectively, $p = 0.02$) (29). More recently, higher rates of ISA were revealed in 34 patients with DES (56%) and BMS (11%) thrombosis in Italy (30). Although extremely insightful, cautious interpretation of these results is crucial due to potential selection bias.

Understanding the underlying mechanisms involved in ISA is of paramount importance to the interventional cardiologist because it enables the identification of which features are potentially modifiable and which resources should be utilized during the index intervention to optimize implantation quality and minimize the likelihood of having ISA and its potentially harmful consequences (31–33). Although physiological vascular healing after stent implantation leads to progressive reduction of ISA over time (12–14,34,35), recent serial OCT assessments elucidated this complex mechanism more clearly, showing that the greater the acute ISA (i.e., after the index procedure), the higher the possibility of its persistence at follow-up (14,15). Furthermore, these studies demonstrated that acute ISA affects the overall vascular response negatively, ultimately leading to delayed stent strut coverage (12–15) and even to ST (12). The comprehension of this complex scenario, moreover, is key for investigators and biomedical engineers so that they can actively search for constant improvements in mechanical (i.e., stent platforms) (36) and biological (i.e., antirestenotic drugs, polymers) (37) components of coronary artery scaffolds.

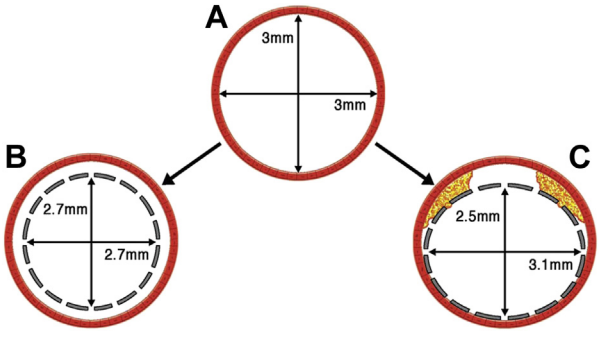

Figure 1 ISA in Vessels With Similar Dimensions

(A) A perfectly rounded vessel **(red circle)** with 3-mm diameter is depicted. **(B)** The **gray-dashed lines** correspond to a representation of a 2.5-mm stent implanted with high pressure, reaching 2.7 mm. In this situation, although the stent is very well and evenly expanded, incomplete stent apposition (ISA) occurred because there is a clear stent–vessel mismatch. **(C)** Conversely, a 3.0-mm stent also implanted with high pressure is seen, in which the horizontal diameter reaches 3.1 mm, but the vertical diameter is only 2.5 mm as the consequence of calcified plaques **(yellow with red dots)** that impair proper expansion, therefore, leading to ISA in some regions of the stent. Figure is by Craig Skaggs.

Histopathology Investigations

Histopathology studies have been instrumental in enabling a better understanding of mechanisms that lead to ISA. The pivotal demonstration by Virmani et al. (37) that Cypher (Cordis, Johnson & Johnson, New Brunswick, New Jersey) SES thrombosis was linked to hypersensitivity reactions and to a complex proinflammatory milieu raised the initial concerns regarding the safety issues of DESs (37). The investigators identified the presence of ISA with thick layers of fibrin thrombus separating stent struts from the vessel wall. In a larger series of patients, Joner et al. (38) ratified the complexity of the multifactorial scenario (i.e., procedural and clinical related features) associated with DES failure, describing the presence of ISA coupled with delayed arterial