



## Radial artery access site complications during cardiac procedures, clinical implications and potential solutions: The role of nitric oxide

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### Abstract

Percutaneous coronary intervention for the treatment of coronary artery disease is most commonly performed in the UK through the radial artery, as this is safer than the femoral approach. However, despite improvements in technology and techniques, complications can occur. The most common complication, arterial spasm, can cause intense pain and, in some cases, procedural failure. The incidence of spasm is dependent on several variables, including operator experience, artery size, and equipment used. An anti-spasmodic cocktail can be applied to reduce spasm, which usually includes an exogenous nitric oxide (NO) donor (glyceryl trinitrate). NO is an endogenous local vasodilator and therefore is a potential target for anti-spasm intervention. However, systemic administration can result in unwanted side-effects, such as hypotension. A method that adopts local delivery of NO might be advantageous. This review article describes the mechanisms involved in radial artery spasm, discusses the advantages and disadvantages of current strategies to reduce spasm, and highlight the potential of NO-loaded nanoporous materials for use in this setting.

**Key words:** Radial artery; Cannulation; Spasm; Nitric oxide; Vasodilation; Nanoporous material

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**Core tip:** Radial access during interventional cardiology procedures is much safer than femoral access although complications can still arise. However, the radial artery is more prone to spasm which can cause pain for the patient and lead to procedural failure.

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Current strategies to avoid spasm include administration of an anti-spasmodic cocktail. Several disadvantages towards the use of this “cocktail” leaves a gap in the industry for a new product to dilate the artery without any systemic effects.

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## INTRODUCTION

Coronary artery disease is a major cause of mortality and morbidity worldwide<sup>[1,2]</sup>. The underlying disease process, atherosclerosis, results in the accumulation of lipid plaque in the arterial intima. Atherosclerosis is triggered by endothelial dysfunction and can lead to reduced coronary blood flow, resulting in angina or myocardial infarction with a reduction in patient survival and quality of life<sup>[3-5]</sup>. Treatments for occlusive coronary artery disease are divided into three major categories: Medical therapy alone, concomitant coronary artery bypass grafting, or concomitant percutaneous coronary intervention (PCI). PCI was introduced in 1977 by Grüntzig *et al*<sup>[7]</sup> and is now the most common procedure used to treat diseased coronary arteries<sup>[6]</sup>, improving symptoms and reducing mortality in certain patients<sup>[6,7]</sup>.

There have been considerable technological advances in PCI since its inception, with the introduction of improved delivery equipment, intracoronary stents, improvement in stent design and introduction of anti-proliferation stent coatings, resulting in improved procedural success and patient outcomes. In the United Kingdom, PCI is most commonly performed through the radial artery (RA) because this is considered to be safer than the femoral approach. However, despite these developments, complications associated with PCI persist. These include vascular access site complications, coronary artery complications and procedure-related complications, such as embolism or renal dysfunction caused by radio-opaque contrast<sup>[8]</sup>. The most common complications are related to the vascular access site.

This review article describes the mechanisms that are involved in RA spasm and discusses strategies to reduce spasm and improve outcomes, with a particular focus on the potential for novel nitric oxide (NO) materials in this setting.

## PCI ACCESS SITES

Vascular access can be achieved via the femoral artery or, more recently, the RA<sup>[9-11]</sup>. Although femoral artery access is still used, it has several disadvantages compared to the RA approach, including longer bed rest, difficult access through the tortuous aorta, the need for puncture site compression after the procedure, and vascular complications of arteriovenous fistula and haematoma<sup>[9]</sup>. Furthermore, the femoral artery is an ‘end artery’ with limited alternative vascular pathways to contribute to lower limb perfusion. As a result, vascular complications can lead to limb loss<sup>[12]</sup>. The RA approach was introduced in 1989 by Campeau *et al*<sup>[13]</sup> and has been used increasingly for interventional and diagnostic cardiology over the last thirty years.

Studies have shown that, compared with the femoral approach, the radial method has reduced bleeding risk, earlier hospital discharge, lower cost, reduced haematoma formation, lower mortality and morbidity, and is preferred by most patients<sup>[14-18]</sup>. However, it carries technical challenges, not least on account of the small RA diameter, which hinders instrument insertion and increases artery-instrument contact, heightening the risk of disruption to the endothelial surface, which increases the risk of spasm.

As the RA approach is becoming more commonly used, there is a greater need to reduce the risk of complications.

## THE RADIAL ARTERY: ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

### Anatomy

The RA runs along the lateral part of the front of the forearm beside the superficial branch of the radial nerve<sup>[19,20]</sup>. Variation in the anatomy of the RA is less frequent in the distal forearm, where arterial cannulation is commonly performed<sup>[18,19,21]</sup>. Arterial blood flow is provided to the hand through a dense anastomotic network of four arches created from the radial and ulnar arteries. The complexity of the anatomy of the RA ensures substantial collateral blood flow is instrumental in ensuring that cannulation (and occlusion) is generally well-tolerated.

The RA has a thick tunica media composed of mainly smooth muscle cells with a high density of  $\alpha 1$  adrenoceptors (Figure 1). High density sympathetic innervation, coupled with a thick, muscular wall makes the RA highly susceptible to spasm; the predominance of  $\alpha$ -adrenoceptors leads to rapid vasoconstriction in response to stress-induced local release of the catecholamine, noradrenaline<sup>[22,23]</sup>. Anomalous radial artery anatomy and small artery diameter are major predisposing factors which can determine the development of spasm<sup>[24]</sup>. During cannulation, spasm can cause the vessel to “clamp” onto the guide catheter, which can result in pain for the patient and procedural difficulty for the operator, limiting successful completion. Spasm then exacerbates friction between the arterial wall and the sheath, which acts to intensify the spasm and induce a positive feedback loop (Figure 1). This continuous cycle of events can lead ultimately to intimal tear and thrombus formation in the artery<sup>[25,26]</sup>. Once catheters are inserted through a sheath, spasm can occur at other sites at any level from the RA to the subclavian artery<sup>[26]</sup>.

### NO - a powerful endogenous local vasodilator and anti-platelet agent

NO is an endogenous biological signalling molecule that mediates a variety of biological functions in the cardiovascular, immune and nervous systems<sup>[5]</sup>. NO mediates vasodilatation, cell proliferation and inhibition of platelet adhesion<sup>[27-29]</sup>.

The importance of NO in biological processes was first realised when it was identified as an endothelium-derived relaxing factor that is released by the vascular endothelium and mediates vasodilation. It has long been known that endogenous NO is reduced or absent in coronary arteries affected by atherosclerosis<sup>[27,30]</sup>. NO is now recognised to play a critical role in pathologic processes that culminate in the development of atherosclerotic lesions. Endothelial dysfunction is one of the earliest processes identified in atherosclerosis development. The normal homeostatic function of the endothelium requires NO, which has decreased bioavailability in patients with developing atherosclerosis<sup>[28]</sup>. Deficiency in NO generation or functional availability is a fundamental feature of atherosclerosis and many other processes associated with cardiovascular disease, including thrombosis, intimal hyperplasia and aneurysm<sup>[28,29]</sup>.

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## COMPLICATIONS FROM RADIAL ARTERY CANNULATION

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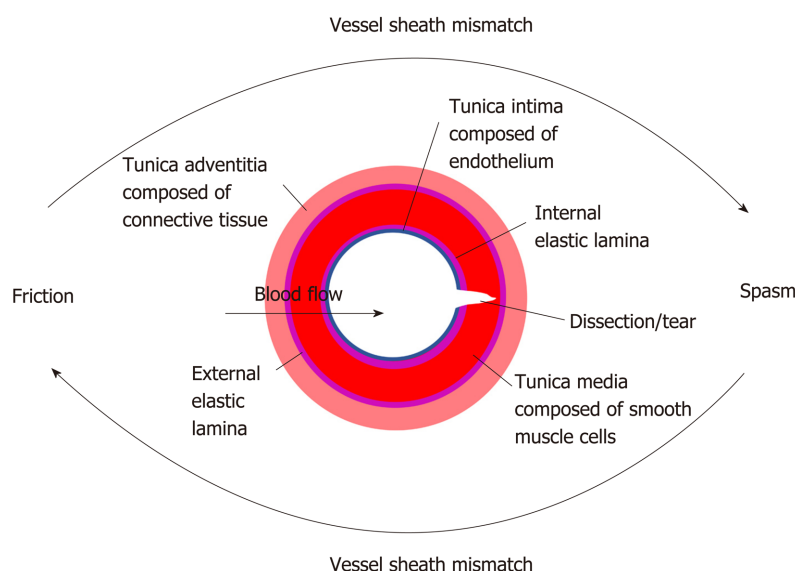
Table 1 summarises the complications associated with radial artery cannulation.

### Spasm

During RA cannulation, an early occurrence of RA spasm can result in difficulty to advance the sheath or guide catheter within the artery, or failure to cannulate altogether. RA spasm as a specific consequence of RA cannulation can occur at any stage of the procedure. Spasm at the end of the procedure can result in difficult and painful sheath removal. A report in 2004 indicated that severe spasm occurred in over 50% of patients that received transradial catheterization; incidence was inversely correlated with arterial diameter<sup>[33]</sup>. However, most recent studies report a much lower rate (1%-34%)<sup>[11,18,19,24,26,34-36]</sup>, presumably due to improved technique. The large range in reported RA spasm incidence (Table 1) is likely due to a combination of factors, including sheath size, vessel size, procedural differences, experience of the interventionalist, and the different definitions of spasm<sup>[24]</sup>. RA spasm is more common in females, smaller patients and patients with vaso-occlusive disorders such as diabetes<sup>[22]</sup>. Spasm in the RA is generally temporary and resolves spontaneously, but more prolonged spasm can occur, leading to trapping of the catheter and increased risk of RA occlusion.

### Other complications

It is out with the scope of this current review to discuss in detail other potential complications that can arise from RA cannulation, however their frequency is shown in Table 1. In summary, reported rates of RA occlusion vary greatly from 1%-3% to up to 19.7% (temporary occlusion)<sup>[11,19,24,26,35-37]</sup>. Perforation or rupture of the artery is a rare complication that can lead to forearm haematoma<sup>[24]</sup>. More serious complications, such as compartment syndrome, can occur<sup>[26,36]</sup>. Pseudoaneurysm is an extremely rare



**Figure 1 Composition of the radial artery.** The thick layer of tunica media contributes to the increased incidence of radial artery spasm. Vessel sheath mismatch induces spasm and friction. Spasm promotes friction which in turn induces more spasm, creating a continuous loop. The increased friction and spasm can lead to dissection of the artery lining.

complication in the RA approach (more common in transfemoral procedures) and occurs when an artery wall is injured, resulting in possible haemorrhage and haematoma in the surrounding tissue<sup>[11,26]</sup>. RA cannulation can also cause direct damage to the endothelium, which can affect RA function<sup>[38,39]</sup> impairing endothelium-dependent vasodilatory, anti-thrombotic and anti-mitogenic properties.

## PREVENTING COMPLICATIONS

Administration of vasodilators, either alone or in an anti-spasmodic cocktail is the most common approach to the prevention or management of spasm (Table 2). However, hydrophilic coatings and structural alterations of the sheaths are alternative strategies that are available<sup>[32,37]</sup>.

It is well recognised that RA spasm rates are lower in procedures conducted by experienced operators with good technique and patient preparation is recognised to be key to a successful procedure. Intraprocedural anticoagulation (usually heparin) is routinely administered to prevent thrombotic occlusion of the RA; the occlusion rate is inversely correlated to activated clotting time<sup>[15]</sup>. In selected cases, sedatives such as short acting benzodiazepines can be used (or at least offered to patients) as a means of reducing the incidence of spasm. Low dose sedation (opioid/benzodiazepine) has been shown to reduce spasm (2.6% in treatment group *vs* 8.3% in control group)<sup>[40]</sup>.

Vasodilators, such as NO donor drugs and calcium channel blockers can be used alone, or in combination with other compounds, to form an anti-spasmodic radial “cocktail”, to prevent or reduce RA spasm<sup>[26,28,32,34]</sup>. However, on account of the risk of systemic vasodilatory effects of spasmolytic drugs used in this setting, there are side-effects associated with systemic hypotension and this approach is contra-indicated in patients with pre-existing hypotension<sup>[15]</sup>. The use of a radial “cocktail” is based on the operator’s preference but is common practise in many units<sup>[37]</sup>.

Depending on the unit, the cocktail components and concentrations differ (Table 2), along with their reported effectiveness. The L-type calcium channel antagonist, verapamil is reported to be the most widely used agent for preventing spasm<sup>[15,41]</sup>. Nitroglycerin [glyceryl trinitrate (GTN)] is also widely used in RA catheterisation. GTN is metabolised to release NO in smooth muscle, resulting in smooth muscle relaxation through activation of guanylate cyclase and increased cyclic guanosine monophosphate.

A recent review of individual drugs and drug cocktails found that the use of verapamil (5 mg) alone or in combination with GTN (100-200 µg) was effective at achieving a significant but modest reduction in the incidence of spasm (9% compared to 12% for placebo)<sup>[41]</sup>. Despite these reported benefits of verapamil in this setting, there is concern about the negative chronotropic and inotropic effect of verapamil,

**Table 1 Complications from radial artery puncture**

Complication	Frequency (%)
Radial artery spasm <sup>[11,18,19,24,26,34-36]</sup>	1-34
Radial artery occlusion <sup>[11,19,24,26,35-37]</sup>	Up to 19.7
Haematoma <sup>[11,19,24,35]</sup>	Up to 14.4
Dissection <sup>[35,36]</sup>	Very rare (0.4)
Compartment Syndrome <sup>[26,36]</sup>	Very rare
Pseudoaneurysm formation <sup>[11,19,26,35,36]</sup>	Very rare up to 2.78
Infection <sup>[19,35]</sup>	Up to 3.4
Perforation <sup>[26,36]</sup>	Very rare

especially in those patients with left ventricular dysfunction, hypotension and bradycardia. It has been suggested that verapamil may not necessarily be required by high-volume trans-radial-operators<sup>[42]</sup>. GTN is thought to have a more favourable side-effect profile compared to verapamil and carries the additional benefit of inhibiting platelet aggregation. However, there are contraindications of GTN in certain patients (*e.g.*, severe aortic stenosis or severe hypotension<sup>[15,42]</sup>).

Development of a prophylactic vasodilator, with effects entirely localised to the vasculature affected by spasm would be a distinct advantage.

### **Sheath type and materials**

It has been suggested that the success rate of the RA approach is influenced by the ratio of sheath diameter to vessel diameter. The anatomy of the RA varies between patients, so vessel sheath mismatch is a potential issue<sup>[37]</sup>. In clinical practice, operator experience and personal preference largely controls catheter selections<sup>[15]</sup>. Operators will generally use the smallest sheath possible and therefore there is limited opportunity to further reduce sheath size. Several trials have evaluated the impact of different sheaths and catheters on occurrence of RA spasm. Several investigations have studied the impact of sheath length and coating, or the impact of sheath coating alone. In a study conducted by Rathore *et al*<sup>[35]</sup>, the application of 4 different introducer sheaths were examined: A long (23 cm) hydrophilic-coated, long uncoated, short (13 cm) hydrophilic-coated, and short uncoated. The results of this study showed that the hydrophilic sheath coating caused significantly less RA spasm (19% *vs* 39.9%) and patient discomfort (15.1% *vs* 28.5%), with no difference observed between long and short sheaths. Interestingly, RA occlusion was observed in 9.5% of patients but this was unaffected by sheath coating or length. One advantage of hydrophilic coatings is that larger sheaths can be used in smaller arteries<sup>[37]</sup>. Similar results have been found in other studies, but despite these approaches and advancements, RA spasm continues to affect a sizable proportion of patients, even with experienced operators.

### **Opportunity for a novel approach**

The application of a novel sheath coating could be advantageous in the cardiovascular setting, although the components of the coating would have to be carefully designed to produce the desired effect without any adverse systemic effects. A sheath design that dilates the vessel without the use of vasodilator drugs would not only minimise the risk of RA spasm, but also reduce the risk of any unintended side-effects of the drugs used. The application of NO to the sheath used in RA approach might provide the local dilating effects of NO with the potential to avoid any unwanted systematic effects. It would be essential that NO is delivered in appropriate quantities for a suitable time scale, to prevent adverse effects and optimise vasodilation. The use of a NO releasing coating of a sheath could prevent local vasospasm without prompting systemic vasospasm, reducing patient pain and anxiety. The delivery of NO through this mechanism could also inhibit any platelet aggregation prompted by catheterisation, preventing thrombosis during the procedure. Novel nanoporous materials such as metal organic frameworks (MOFs) or zeolites are excellent gas storage and release materials. Zeolites are inorganic, microporous materials often used for large-scale catalytic applications<sup>[45,46]</sup>. MOFs are organic- inorganic crystalline microporous materials made up of organic spacers which connect metal ions<sup>[47,48]</sup>. MOFs and zeolites have attracted interest for use in drug storage and delivery due to the ability to tune their structure and function<sup>[45-48]</sup>. NO storage in both nanoporous materials has been studied extensively with very promising results. However, cytotoxicity of these compounds is yet to be examined in the cardiac setting.

**Table 2 Variations of anti-spasmodic cocktail components**

Ref.	Radial cocktail ingredients	Concentration	Drug class
Kiemeneij <i>et al</i> <sup>[32]</sup>	Verapamil	5 mg	Calcium channel blocker <sup>1</sup>
	Nitroglycerin	0.2 mg	Nitrate <sup>2</sup>
Pancholy <i>et al</i> <sup>[44]</sup>	Nitroglycerin	0.2 mg	Nitrate <sup>2</sup>
	Diltiazem	5 mg	Calcium channel blocker <sup>1</sup>
Hizoh <i>et al</i> <sup>[43]</sup>	Verapamil	5 mg	Calcium channel blocker <sup>1</sup>
He <i>et al</i> <sup>[23]</sup>	Heparin	2500 units	Anticoagulant <sup>3</sup>
	Nitroglycerin	0.2 mg	Nitrate <sup>2</sup>
	Verapamil	2.5 mg	Calcium channel blocker <sup>1</sup>
Ruiz-Salmerón <i>et al</i> <sup>[24]</sup>	Heparin with	5000 units	Anticoagulant <sup>3</sup>
	Verapamil or	2.5 mg	Calcium channel blocker <sup>1</sup>
	Phentolamine	2.5 mg	Alpha-adrenergic antagonist <sup>1</sup>

<sup>1</sup>Disrupts the movement of calcium through calcium channels, Causing vasodilation.

<sup>2</sup>Activates guanyl cyclase and increases cyclic guanosine monophosphate causing vasodilation;

<sup>3</sup>Inhibits coagulation, preventing thrombus formation.

Previous work examining NO-loaded zeolites showed evidence that these high capacity NO stores could inhibit platelet aggregation over several hours. NO release profiles could be easily tuned through manipulation of the metal ion, along with the composition and nature of the polymer used for production. Stability studies also found that NO-loaded zeolites were very stable in the absence of water, suggesting a long shelf life of months to years under vacuum<sup>[46]</sup>. These data show promise for potential use in a sheath coating. More recent developments in NO storage materials have focused on the use of MOFs. MOFs have an advantage over zeolites due to the infinite number of possible frameworks that can be synthesised. This ability to fine-tune their structures provides an opportunity to alter chemical characteristics the suit the required function. Many MOF structures have been developed to store and release NO. Previous work has examined the capability of storage and release of NO in MOFs with different incorporated metal ions. The alteration of metal ions allows for the delivery of biologically active, but non-toxic levels of NO. It has been shown that the use of Ni<sup>2+</sup> as a dopant can improve the NO release performance of a MOF (CPO-27), delivering an appropriate bio-active concentration of NO. The results from this study highlights a significant advance in the development of a NO storage and delivery compound<sup>[47]</sup>. A 2017 study examined the release of NO from vascular catheters to prevent bacterial infection using a NO donor<sup>[49]</sup>. Results showed inhibition of bacterial adhesion without any cytotoxic effects towards mammalian cells. Another study investigated the release of NO from a coronary stent using a NO donor<sup>[50]</sup>. Results showed the promising positive effect of NO as a releasing agent to suppress or prevent restenosis and thrombosis. Authors proposed further investigations using other NO carriers or donors to further improve NO release pattern.

The tuneable nature of these materials could allow for an appropriate release of NO over a desired period thus excluding any toxic effects that may occur from overexposure of NO. The effects of the NO released should ensure a larger intraluminal diameter making the procedure safer and easier for the operator. The localised nature of the NO release should inhibit inflammation and thrombosis at the site of access without any adverse systemic effects. The development of these nanoporous materials has the potential for long-lasting, low level NO generation that mimics endothelial NO, with the potential to both inhibit spasm and prevent localised thrombosis. The use of a nanoporous material in the coating of a sheath could prevent local vasospasm without prompting systemic vasospasm, reducing patient pain and anxiety. Overall the procedure efficiency and effectiveness could be improved.

This application might not only benefit cardiac catheterisation, but other situations where catheter thrombosis or platelet aggregation can be problematic such as peripheral and central venous cannulae.

## CONCLUSIONS

The use of the RA instead of the femoral artery has reduced complications at the time of coronary artery procedures. However, despite improvement in cannulation

techniques, minimisation of sheath size, hydrophilic coatings and use of radial “cocktails” complications still occur, most commonly RA spasm, in a proportion of patients resulting in pain, procedural failure and RA damage. Novel approaches in sheath materials, perhaps to include NO releasing materials such as MOFs and zeolites might offer an exciting new target for improvement in outcomes.

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