

# Radiographic contrast media and thrombosis: the more we know, the more we need to know

**Key words:** radiographic contrast media; clotting

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### Abstract

The diverse effects of radiographic contrast media (RCM) on virtually all organ systems extend to the haemostatic system. Before the advent of non-ionic RCM, little controversy surrounded these effects, i.e. inhibition of thrombin generation, disruptive effects on arterial endothelium and inhibition of platelet aggregation. Thus, ionic high osmolar contrast media (HOCM) were viewed as having 'anti-coagulant' and 'anti-thrombotic' properties. The fact that these inhibitory properties were chiefly *in vitro* phenomena, that significant dilution occurred in the circulation resulting in any local (inhibitory) effects being transient and that differentiation of effects caused by ionicity or osmolality were limited by the availability of RCM other than HOCM all contributed to the origin of the 'clotting controversy' when non-ionic RCM was introduced.

The following review takes its motivation from the clinical perspective. Thrombosis is viewed as the end result of the pathological interaction of vessel wall, blood flow and formed elements of the blood. The interaction of ionic and non-ionic RCM with each of these elements is discussed. While consensus exists with respect to the *in vitro* and *in vivo* anti-coagulant properties of RCM (inhibition of thrombin formation), less consensus focuses on the *in vitro* and *in vivo* effects of RCM on platelet function. Furthermore, extension of the *in vitro* data to the clinical setting is problematic given the lack of clinical data suggesting a pro-thrombotic effect of non-ionic RCM. As many of the potentially deleterious effects on endothelial and/or platelet function are the result of either RCM ionicity or osmolality, the results of studies with non-ionic, iso-osmolar RCM are discussed.

### Introduction

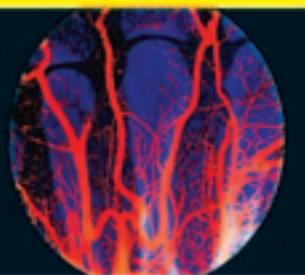
Radiographic contrast media (RCM) are among the most widely used pharmaceutical agents in cardiovascular medicine. However, RCM have only one desirable feature – the enhancement of radiographic contrast – and a plethora of undesirable effects.

Fortunately, the majority of the latter are transient in nature and do not pose a clinically significant hazard to the patient. Serious adverse effects of RCM may be categorised by organ specificity, e.g. RCM-related nephropathy, or more generally by system specificity, e.g. cardiovascular effects. In this review, the focus will be on the interaction of RCM with those elements of the haemostatic system in man that have clinical relevance. A basic distinction between clotting and thrombosis is made at the outset: clotting is physiological and best assessed *ex vivo*; thrombosis is distinctly pathological and very much an *in vivo* process.

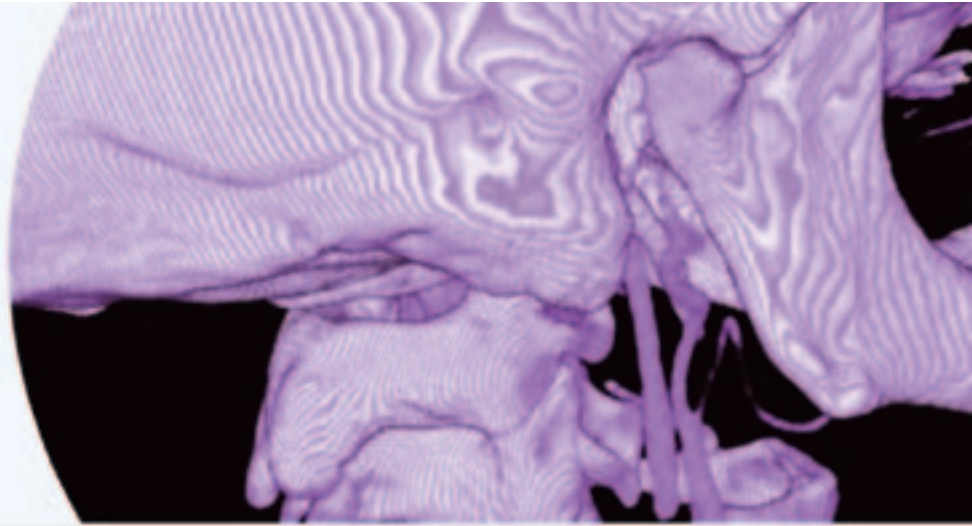
Virchow's triad – the hypothesis that thrombosis is the end result of the interaction of the blood vessel wall, blood flow and formed elements of the blood – remains central to our thinking, notwithstanding the exponential increase in the knowledge base in all three areas. In fact, our increasing understanding of the inter-relationship between thrombosis and inflammation can be seen as an extension of Virchow's seminal observations. Therefore, the following discussion of the issue(s) surrounding RCM and thrombosis will focus on the three elements of Virchow's triad.

### RCM and the vessel wall

The least intensively studied of the properties of RCM – their interaction with vessel wall components – has perhaps the most important clinical implications for thrombosis. Ionic RCM, irrespective of osmolality, exhibit the most disruptive effects on normal endothelium *in vitro*<sup>1</sup> and *ex vivo*<sup>2</sup> while non-ionic iso-osmolar dimers appear least disruptive.<sup>1</sup> Not surprisingly, in the setting of abnormal endothelium, the effects of RCM should be even more pronounced. Specifically, these effects extend from abnormal histological appearance, including destruction,<sup>1,3</sup> to the inhibition of nitric oxide production.<sup>4</sup> The specific effects of RCM on endothelial cell release of inflammatory cytokines and, conversely, the effects of cytokines on endothelial functions are only beginning to be appreciated. Given the increasingly



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evident inter-dependence between inflammation and thrombosis,<sup>5</sup> the potential for RCM to contribute to both local thrombosis and inflammation superimposed on abnormal endothelium is of immediate relevance. Activation of von Willebrand factor and release of intercellular adhesion molecules and pro-inflammatory cytokines have all been detected in clinical studies<sup>6-10</sup> and confirm *in vitro* observations.

Injured or denuded endothelium predisposes to thrombosis via a number of pathways, most notably the activation of Factor VII by tissue factor. The critical role of platelet activation and aggregation will be discussed below but is mentioned here given the fundamental role of platelet activation by damaged endothelium. Furthermore, the ionicity and/or osmolality of RCM may be critical in the dynamic balance between local thrombosis and lysis. Controversy exists with respect to effects of RCM on the fibrinolytic system with some studies suggesting activation<sup>11</sup> and others indicating inhibition<sup>12</sup> of the lytic system. Differences between *in vitro* and *in vivo* data further confound this issue.

#### **RCM and blood flow**

In regions of high flow velocity and shear stress, platelet activation is likely to occur.<sup>13</sup> These abnormal haemodynamics are also seen in association with endothelial cell injury and dysfunction. Conversely, in regions of low velocity flow and low shear, stasis and activation of the clotting cascade are likely to occur. In fact, observation of the clotting cascade activation led to many of the initial concerns surrounding the facilitation of clot formation with non-ionic RCM.<sup>14</sup> However, the clinical implications of clot formation in static blood admixed with RCM<sup>14</sup> are unclear. Additional studies have shown that the anticoagulant effects of RCM were preserved in both glass and plastic syringes, irrespective of ionicity.<sup>15</sup> It should be emphasised that, at both extremes of shear stress, the *sine qua non* for thrombosis in man is the presence of an 'abnormal surface' – thus highlighting, again, the importance of endothelial integrity.

In one of the few areas of concordance between *in vivo* and *in vitro* data, both ionic and non-ionic RCM inhibit the 'clotting cascade' and, ultimately, thrombin formation.<sup>16</sup> Prolongation of clotting times correlate with the extent of inhibition of thrombin formation *in vitro*. Ionic RCM, irrespective of osmolality, consistently possess greater anticoagulant properties *in vitro* compared with non-ionic RCM.<sup>16,17</sup> The relevance of this observation to the patient receiving systemic thrombin inhibitors is less clear. From a theoretical standpoint, the viscosity of RCM might contribute to altered blood flow patterns and, therefore, shear stress. However, given the extensive dilution undergone by RCM during a first pass, with resultant local concentrations generally under 1%, any significant alteration in local viscosity is unlikely.<sup>18</sup>

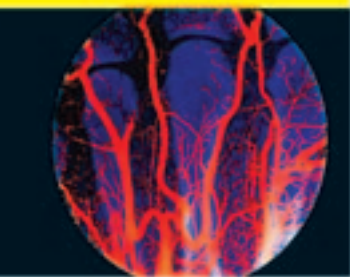
#### **RCM and formed elements of the blood**

Given the central role of the platelet in physiological haemostasis and pathological thrombosis, the extensive literature on the effects of RCM on platelet function is appropriate. However, no greater area of controversy surrounding the effects of RCM exists than in the interaction of platelets with RCM. Here again, differences among *in vitro* studies as well as between *in vitro* and *in vivo* studies have led to considerable uncertainty about the implications of these interactions (or lack thereof) as well as their clinical relevance.

Studies *in vitro* were spurred by the inception of non-ionic RCM and concerns surrounding their 'pro-thrombotic' potential.<sup>14,19,20</sup> Unfortunately, inter-study differences in methodology, definitions and experimental conditions resulted in conflicting data with respect to the effects of RCM on 'platelet function'. This term, however, encompasses platelet adhesion, activation, degranulation and, ultimately, aggregation. It is also important to note that, in addition to these diverse measures of platelet function, clinically relevant differences exist in the extent of activation by various agonists (e.g. collagen, thrombin

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or thromboxane). Thus, although ionic RCM inhibited thrombin-mediated platelet 'activation' to a greater extent than non-ionic RCM, neither class of RCM activated platelets by themselves.<sup>21</sup> There is evidence of a 'platelet-activating effect' associated with non-ionic low osmolal RCM (degranulation and surface antigen expression) but not with ionic low osmolal RCM.<sup>22</sup> However subsequent studies using more physiological means of assessing platelet function (e.g. flowing blood platelet aggregometry) demonstrated the independence of degranulation and ionicity and the over-riding importance of osmolality.<sup>23</sup> In addition, again using a platelet function assay simulating more physiological conditions, Sakariassen *et al.* demonstrated a lack of concordance between degranulation and platelet thrombus formation.<sup>24,25</sup>

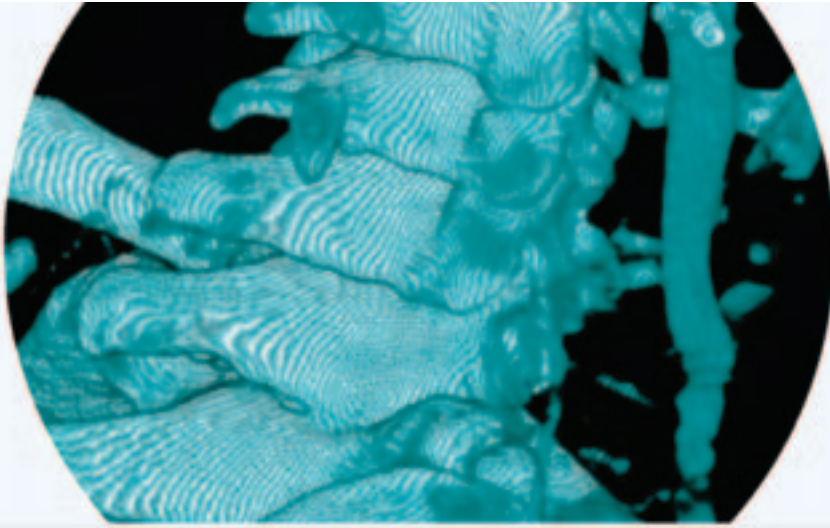
Data obtained *in vivo* tend to support the results of studies of platelet function under 'physiological' conditions, i.e. no evidence of pro-thrombotic potential for non-ionic RCM.<sup>18,26</sup> The clinical literature provides strong support for the safety of non-ionic RCM during cardiac angiography<sup>27</sup> as well as a lack of evidence of enhanced thrombogenicity.<sup>28</sup> It is noteworthy that the act of vascular invasion, *per se*, is associated with systemic evidence of activation of coagulation and inflammation;<sup>29-31</sup> factors rarely controlled for in any study. Presently, the controversy centres on the role of RCM during coronary interventional procedures. These clinical circumstances represent a most extreme pro-thrombotic milieu and should facilitate the detection of the pro-thrombotic potential of RCM.

A meta-analysis of studies reported before 1999 found a reduced rate of abrupt vessel closure during interventional procedures with use of a low osmolal ionic agent (ioxaglate) compared with non-ionic low osmolal agents.<sup>32</sup> However, in this study no difference

was observed in rates of abrupt closure between ioxaglate and the iso-osmolar, non-ionic dimer iodixanol. Furthermore, despite the large sample size, this study failed to identify a difference in an overall composite rate of serious adverse events between ioxaglate and non-ionic comparators.<sup>32</sup> Therefore, it is worth noting that several recent large-scale, multi-centre, randomised, controlled trials have demonstrated the safety of non-ionic RCM during coronary interventional procedures.<sup>33,34</sup>

Expanding on the importance of osmolality as well as ionicity, the Contrast Media Utilization in High Risk PTCA (COURT) trial demonstrated enhanced safety of the non-ionic, iso-osmolal dimer iodixanol compared with the ionic, low osmolal dimer ioxaglate during coronary interventional procedures.<sup>35</sup> These intriguing findings were also noted in the Visipaque™ (iodixanol) vs. Isovue® (iopamidol) in Cardiac Catheterization (VICC) trial<sup>36</sup> – a more contemporary version of the COURT trial. In the VICC trial, in-hospital adverse event rates during coronary intervention were lower with iodixanol compared with a non-ionic, low osmolal RCM, iopamidol. From a practical standpoint, it becomes increasingly difficult to demonstrate RCM-specific platelet dysfunction given the universal use of potent 'anti-platelet' agents during coronary intervention. Nevertheless, it remains intuitive that RCM, with the least likelihood of interfering with platelet and endothelial function, would be the most desirable, particularly in 'high-risk' settings.

The interaction of RCM with white blood cells is another area of clinical relevance. As white blood cells are rich sources of chemokines and cytokines that are both pro-inflammatory and pro-thrombotic, the effects of RCM osmolality and ionicity may have relevance at the local level. Osmolality, as a major stimulator of MAP kinase and NFκB,<sup>37,38</sup> may exacerbate local inflammation and thrombosis.



Such a result might be reflected in acute and/or short-term adverse sequelae, despite systemic anti-coagulation and anti-platelet treatment.

### Conclusions

In summary, a considerable database of preclinical information indicates that all RCM possess anti-coagulant activity, i.e. they inhibit thrombin formation, and that ionic RCM exhibit greater inhibition of thrombin formation than non-ionic RCM. Furthermore, RCM have variable effects on specific measures of platelet function and although no agents are frankly pro-thrombotic, ionic RCM exhibit greater morphological and functional deterioration in endothelial cells compared with non-ionic

agents, and the osmolality of RCM may be an important (negative) determinant of their pro-thrombotic potential.

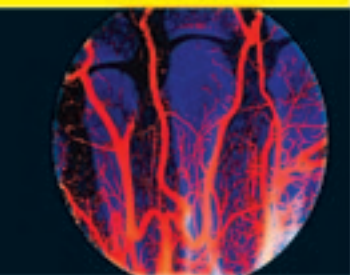
The clinical literature supports the overall safety of non-ionic RCM during cardiac angiography. Recent randomised controlled clinical trials indicate that the use of the non-ionic, iso-osmolar dimer iodixanol during high-risk coronary interventional procedures is associated with a measurable benefit compared with either ionic or non-ionic RCM. Given the complexity of the relationship between vascular endothelial function, inflammation and thrombosis, further study of the effects of RCM on these determinants of procedural outcomes is needed.

### Key Learning

- This article reviews the pathological basis for thrombosis
- The effects of RCM on the elements of thrombosis are reviewed from the standpoint of ionicity and osmolality
- RCM can exert effects on blood vessel walls, blood flow and formed elements of the blood
- Areas of consensus regarding the effects of RCM are noted:
  - RCM inhibit thrombin formation and disrupt endothelial cells (ionic > non-ionic agents)
  - Clinical data indicate safety of low osmolar non-ionic RCM in diagnostic cardiac angiography
  - Clinical data indicate safety of iso-osmolar non-ionic RCM in coronary intervention
- Areas where a lack of consensus exists reflect differences between *in vivo* and *in vitro* data:
  - RCM effects on fibrinolysis and platelet function are variable
  - Ionicity and osmolality of RCM are important negative determinants in interactions with platelets and white blood cells
- The relationship between endothelial function, thrombosis and inflammation is viewed as essential to the understanding of the influence of contrast media on thrombosis

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