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The Important Properties of Contrast Media: Focus on Viscosity 1A

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The Important Properties of Contrast Media: Focus on Viscosity

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Introduction

Iodinated contrast media (CM) are utilized in an estimated 80 million diagnostic and interventional cardiovascular and non-cardiovascular procedures worldwide, annually.¹ In the United States alone, the number of inpatient cardiac catheterizations and percutaneous coronary interventional procedures increased by > 300% in the last 20 years² to more than 2 million procedures by 2003. Since opacification is the primary measure by which CM are judged, other important properties that may influence their relative efficacy and safety, including ionicity, chemical structure, osmolality, and viscosity, are less frequently recognized. Of these properties, the influence of viscosity on visualization, hemodynamics, platelets, thrombogenicity, contrast-induced nephropathy, other clinical outcomes and procedural technique has perhaps been the least appreciated. The aim of this article is to review the history and physical and biochemical properties of CM, with a focus on the importance of viscosity and its impact on procedural outcomes.

Brief History of Contrast Media

Soon after the discovery of X-rays by Röntgen, it was recognized that iodine was radio-opaque. The attenuation of X-rays by iodine-containing media during radiographic examinations resulted in the name “contrast” media. In 1901, Marcel Guerbet, Professor of Toxicology at the School of Pharmacy in Paris, developed Lipiodol, the first organic contrast compound.³ However, it was not until 1921–1922 that this iodinated oil compound was used in radiology procedures, following myelography studies by Jacques Forestier and Jean-Athanase Sicard.⁴ In 1928, Moses Swick developed the first water-soluble iodinated CM suitable for intravenous use. After his initial attempts to find a soluble and stable CM compound, Swick and colleagues went on to develop a number of more effective, safer compounds.⁵

The first use of CM in cardiac catheterization was by Sven-Ivar Seldinger,⁶ a young radiologist working at the Karolinska Clinic in Stockholm in 1956. By that time, the forerunner of contemporary CM containing a tri-iodinated benzene ring compound (sodium diatrizoate) had been produced.

Early CM were ionic, monomeric and high osmolar. In 1968, the first nonionic, monomeric, low-osmolar CM, metrizamide, was developed by a Swedish radiologist, Torsten Almén, in an effort to improve the safety profile of CM.⁵ He believed

that the dissociation of ionic CM in solution and the resulting effects on the osmolality of the solution were primarily responsible for their untoward hemodynamic effects. Since metrizamide was unstable in solution, other low-osmolar CM were developed. One of the first stable low-osmolar CM, ioxaglate, was marketed in the United States⁷ in 1985. More recently, nonionic, dimeric, iso-osmolar CM were developed in an attempt to further reduce their osmolality to that approaching plasma. However, the dimeric structure of these agents resulted in a substantial increase in their viscosity.⁸

Physicochemical Properties of Contrast Media

Contrast media have traditionally been classified by their physical and biochemical properties, including structure, ionicity, osmolality and viscosity.⁹ Although intimately related, these properties are distinct and are best discussed separately.

Structure is related to the number of benzene rings per molecule. The basic structure of all currently used CM consists of a 2, 4, 6 tri-iodinated benzene ring. The structural composition of iodinated CM is either a single tri-iodinated benzene ring (monomer) or 2 bound benzene rings (dimer). Monomers and dimers can be either ionic or nonionic depending on their side chain constituents.

Ionicity refers to the conjugation of the benzene ring structure (anion) with a non-radio-opaque cation resulting in a water-soluble compound. Ionic monomeric CM dissociate (ionize) in solution (*i.e.*, in the bloodstream) into 1 anion and 1 cation, resulting in an iodine-to-particle ratio of 3:2 (3 iodine atoms for 2 ions). Nonionic monomeric CM consist of tri-iodinated benzene rings with hydrophilic hydroxyl groups and organic side chains placed at the 1, 3, 5 positions, which do not ionize in solution, resulting in an iodine to particle ratio¹⁰ of 3:1. Dimeric CM can be composed of either 2 bound nonionic monomers or a bound nonionic and ionic monomer, resulting in iodine-to-particle ratios of 6:1 and 6:2, respectively. The iodine-to-particle ratio and the concentration of iodine-bearing molecules in solution affect the osmolality and amount of radio-opacity of a given CM, respectively.

Based upon these differences in structure and ionicity, iodinated CM are often grouped into 4 major categories: ionic monomers, nonionic monomers, ionic dimers, and nonionic dimers.¹¹ The chemical structures of these prototypic CM are illustrated in Figure 1.

Osmolality refers to the concentration of osmotically active particles in a solution. The normal osmolality of blood is 280–295 mOsm/kg H₂O. Contrast media used in cardiovascular procedures are often referred to as high osmolar (HO-CM,

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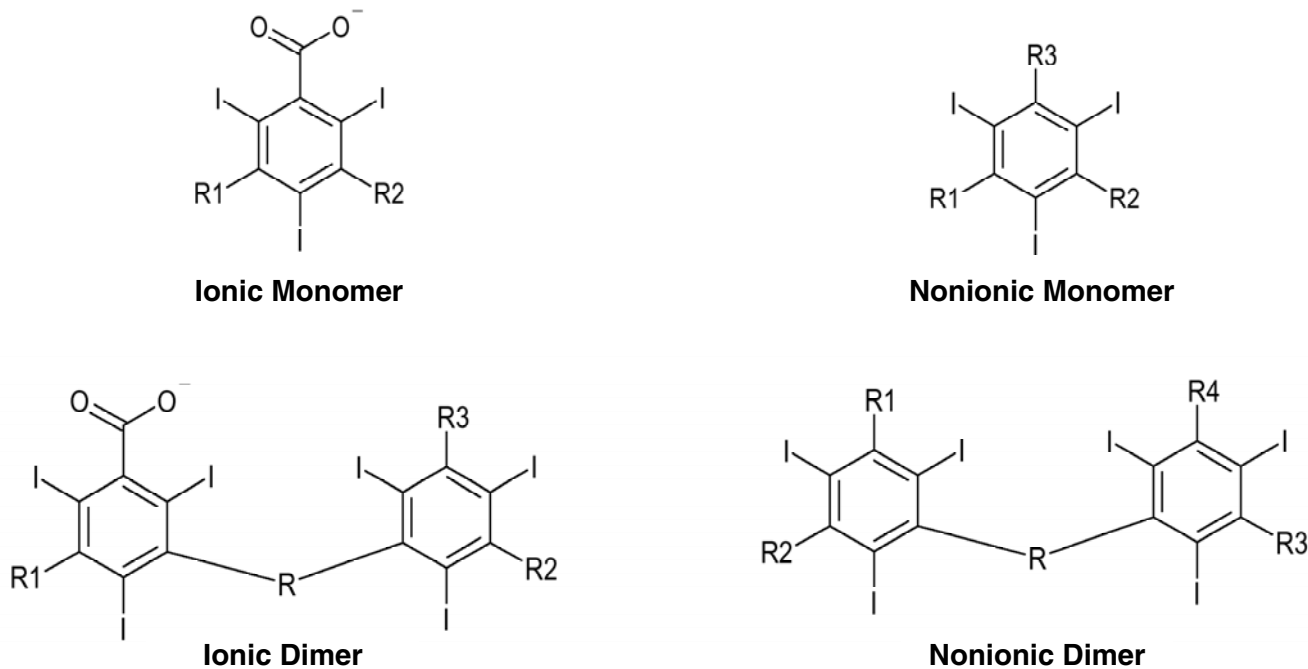


Figure 1. Prototypic structures of contrast media.

typical osmolality 1400–2016 mOsm/kg H₂O), low osmolar (LOCM, typical osmolality 600–844 mOsm/kg H₂O) or iso-osmolar (290 mOsm/kg H₂O).

Viscosity refers to the intrinsic resistance of a material to changing form and is determined primarily by the chemical structure of CM, differences in organic side chain composition, iodine concentration and temperature. Factors, such as molecular size and complexity of side chains, may lead to steric hindrance of bond torsion angles, restricting rotation and resulting

in a more rigid molecule with higher viscosity. In general, viscosity is directly related to particle size and inversely related to osmolality. As with osmolality, CM may be categorized as high-viscosity CM (HVCM) or low-viscosity CM (LVCM). The viscosities of select currently available CM for iodine concentrations used in cardiac catheterization and percutaneous coronary intervention (PCI) vary widely from 15.7–26.6 mPa.s at 20°C. The relationship between viscosity and osmolality of select LOCM is summarized in Figure 2.

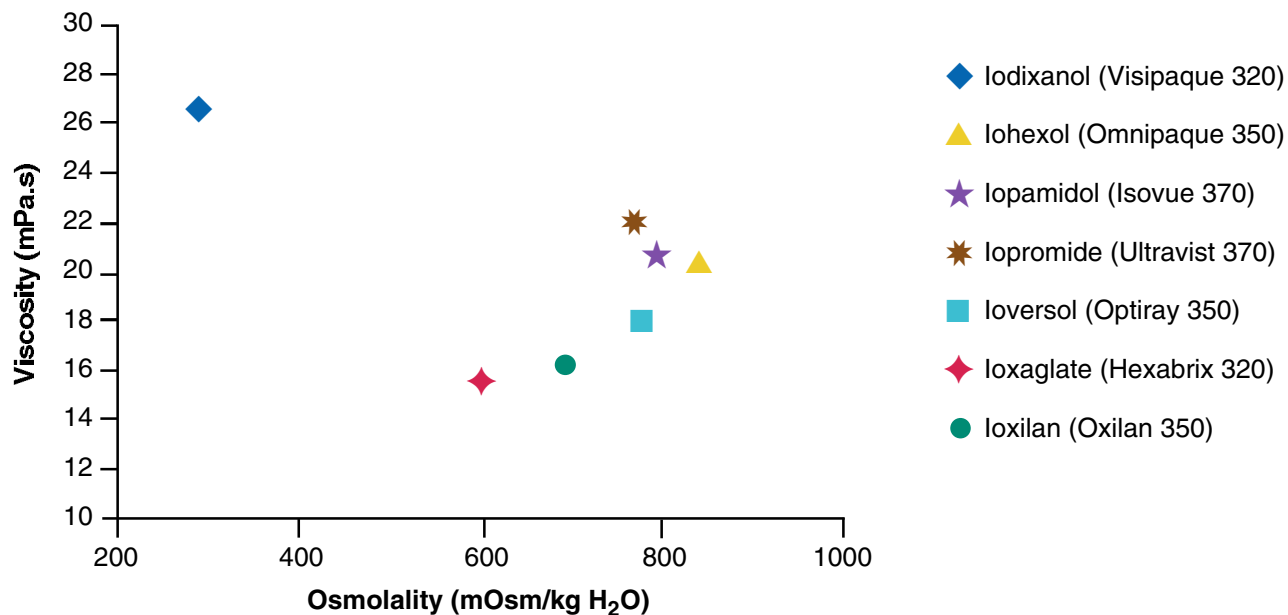


Figure 2. Viscosity and osmolality of select contrast media at 20°C.

Table 1. Classification of select contrast media* used for cardiac procedures.

| Class | | Chemical Name | Trade Name and Manufacturer† | Osmolality (mOsm/kg H ₂ O) | Viscosity (mPa.s at 20°C) | |
|---------------------|-----------------------|-------------------|------------------------------|---------------------------------------|---------------------------|------|
| High-Osmolar (HOCM) | | Ionic Monomers | Diatrizoate | Hypaque® (GEH) | 2016 | n/a§ |
| | | | | RenoCal-76® (B) | 1870 | n/a§ |
| | | | | MD-76®R (M) | 1551 | n/a§ |
| | | | Iothalamate | Conray® (M) | 1400 | n/a§ |
| Low-Osmolar (LOCM) | High-Viscosity (HVCM) | Nonionic Dimer | Iodixanol | Visipaque™ 320 (GEH) | 290 | 26.6 |
| | | Nonionic Monomers | Iopromide | Ultravist® 370 (Br) | 774 | 22.0 |
| | | | Iopamidol | Isovue® 370 (B) | 796 | 20.9 |
| | | | Iohexol | Omnipaque™ 350 (GEH) | 844 | 20.4 |
| | | | Ioversol | Optiray® 350 (M) | 792 | 18.0 |
| | Low-Viscosity (LVCM) | Ioxilan | Oxilan® 350 (G) | 695 | 16.3 | |
| | | Ionic Dimer | Ioxaglate | Hexabrix® 320 (G-M)‡ | 600 | 15.7 |

* Approved in the United States
† Manufacturer: B: Bracco; Br: Berlex; G: Guerbet; GEH: GE-Healthcare; M: Mallinckrodt
‡ Outlicensed by Guerbet to Mallinckrodt
§ Not available

Types of Contrast Media

Contrast media differ significantly with regard to their physical and biochemical properties. The properties of select CM used in cardiac procedures are summarized in Table 1.

Ionic monomers include diatrizoate, iothalamate, metrizoate and ioxithalamate and were the first class of CM agents.¹⁰ These agents are HOCM. Due to their high osmolality, ionic monomers result in a number of side effects and now account for less than 3% of intravascular CM used in the United States.

Nonionic monomers include iohexol, iopamidol, ioversol, iopromide and ioxilan.¹⁰ These agents are LOCM and are available in iodine concentrations of 240–370 mgI/mL. The viscosities of nonionic monomers vary widely, depending upon their specific chemical structure as well as iodine concentration. Ioxilan is unique due to a small hydrophobic region within its hydrophilic side chain that leads to molecular aggregation and a reduction in the number of osmotically active particles in solution.¹² This results in the lowest osmolality (695 mOsm/kg H₂O) and viscosity (16.3 mPa.s at 20°C) of the nonionic monomers; thus, ioxilan is classified as a LOCM and LVCM.

Ionic dimers available in the United States are limited to ioxaglate. Ioxaglate, like ioxilan, is a balanced LOCM (600 mOsm/kg H₂O) and LVCM (15.7 mPa.s at 20°C) at the 320 mgI/mL concentration.

Nonionic dimers available in the United States include only iodixanol at present. Iotrolan, another nonionic dimer, was previously withdrawn from the Japanese and European markets due to late adverse reactions.¹⁰ Iodixanol is an iso-osmolar CM (290 mOsm/kgH₂O), but its large, bulky molecular structure also makes it a HVCM (26.6 mPa.s at 20°C). The result is a CM with the lowest osmolality but the highest viscosity of the available CM. In addition, the high viscosity associated with iodixanol limits its usable iodine concentration to 270–320 mgI/mL.

Side Effects of Contrast Media

Iodinated CM are widely used intravascularly administered

Table 2. Adverse reactions to contrast media.¹⁵

| | HOCM | LOCM | p |
|--------------------------------|--------|--------|--------|
| Total Adverse Reactions | 12.66% | 3.13% | < 0.01 |
| Severe Adverse Reactions | 0.22% | 0.04% | < 0.01 |
| Very Severe Adverse Reactions* | 0.04% | 0.004% | < 0.01 |

* Requiring anesthesia or hospitalization

pharmaceuticals. Although they are among the safest known agents, a number of side effects exist.

Adverse reactions to CM can occur in patients of all ages but tend to be more severe in patients age > 50 years.¹³ With regard to frequency, adverse reactions are more common in patients between 20 and 40 years of age, a phenomenon that may be related to immune system priming and peak levels of immunoglobulin E, although other mechanisms have been proposed.¹⁴ These reactions may manifest as allergic reactions, hemodynamic effects, thrombogenicity and contrast-induced nephropathy. In a survey of 337,647 patients receiving CM, the prevalence of adverse drug reactions (including severe and very severe reactions) was higher with the use of ionic HOCM compared to nonionic LOCM (Table 2).¹⁵ Similarly, data from the US Food and Drug Administration from 1990 to 1994 revealed that the incidence of reactions (including severe reactions) and death was significantly higher with HOCM compared with non-ionic LOCM.¹⁶

Anaphylactoid reactions to CM, although appearing clinically similar to allergic responses, do not represent true allergies, as there is no clear evidence that they are mediated by immunoglobulin E. These complications range in severity from mild skin reactions to catastrophic, fatal events. There is no relationship between CM dose and either the likelihood or severity of an anaphylactoid response.¹⁷ These reactions can be characterized by urticaria, warmth, swelling, dyspnea, bronchospasm, hypotension and circulatory collapse (Table 3).¹⁸ Risk factors for

$$Q = \Delta P r^4 \pi / 8 \eta l$$

Q = rate of flow
 ΔP = pressure gradient
 r = radius of tube
 η = viscosity of fluid
 l = length of tube

Figure 3. Poiseuille's law of flow.

the development of anaphylactoid reactions include previous adverse reaction to CM, asthma, underlying atopy/allergy, pre-existing cardiovascular or renal disease and use of beta-blocking agents. There have been a number of proposed mechanisms for the etiology of these complications (Table 4).^{10,19,20}

Contrast-induced nephropathy (CIN) is the third leading cause of acute renal failure in hospitalized patients and is associated with a mortality rate of up to 34%.^{21,22} The true incidence of CIN is unknown — it varies with the population studied and is complicated by lack of a universal definition. Most authorities define CIN as either an increase in serum creatinine of > 25% above baseline or an absolute rise in creatinine of > 0.5 mg/dL within 48–72 hours of CM administration, although peak impairment of renal function may be delayed by 3–5 days or more.²³ The incidence of CIN is thought to be negligible in patients with normal baseline renal function and is higher among patients with pre-existing conditions including advanced age, pre-existing renal dysfunction (glomerular filtration rate of < 60 mL/min), diabetes mellitus and hypovolemia.²⁴ Contrast-

induced nephropathy is usually a self-limited, transient process with serum creatinine levels peaking at 3–5 days after CM administration and returning to baseline within 10 days.^{24–27}

A number of potential mechanisms have been proposed for CIN. First, it is believed that CM administration may lead to vasoconstriction in the renal medulla with diminished medullary blood flow.^{1,28–30} In addition to this vasoconstrictive effect and its resultant ischemic changes to the renal tubules, CM may directly injure the tubular epithelial membrane.^{31,32} Recent experimental data from Heinrich et al³³ indicate that although hyperosmolality plays a major role in the cytotoxic effects of HOCM on proximal renal tubular cells, it has only a minor role with LOCM. Their data revealed that with the use of LOCM and iso-osmolar CM, direct cytotoxic effects may be the most important factor. Furthermore, dimeric CM result in significantly greater cytotoxic effects than monomeric LOCM, and these effects are independent of osmolality. In the accompanying editorial, Katzberg³⁴ stated that this was “convincing evidence of a direct cellular toxicity of contrast agents independent of either hemodynamic mechanisms or osmolality.” He elegantly proposed that attention should be focused on the “contrast medium molecule itself and on direct cellular mechanisms for elucidation of the pathophysiology of contrast-induced acute renal failure and, thus, on the potential for a solution.” Persson and Patzak³⁵ have also supported the view that, based upon the available experimental data, iso-osmolar CM would not be expected to result in a lower risk of CIN compared to LOCM. In addition to these potential

Table 3. Anaphylactoid reactions associated with contrast media.^{10,15,16,18,74,105}

| Severity | Associated Physical Signs/Symptoms |
|---|---|
| Mild Treatment: antihistamines, benzodiazepines, analgesics | Urticaria Pruritis Rhinitis Cough Injection site pain Flushing Headache |
| Moderate Treatment: IV fluids, antihistamines, albuterol, benzodiazepines, hydrocortisone | Nausea/vomiting Bronchospasm Dyspnea Facial edema Chest pain Tachycardia/bradycardia |
| Severe Treatment: resuscitation, respiratory and cardiovascular support, IV fluids, epinephrine, vasopressors | Hypotension Laryngeal edema Cardiac arrest Cardiac arrhythmias |

mechanisms of CIN, CM administration leads to production of oxygen-free radicals, including reactive oxygen species.³⁶ Finally, CM viscosity may also have a significant impact on renal outcomes. Poiseuille's law states that viscosity is inversely related to flow (Figure 3). Therefore, a reduction in flow associated with HVCM may lead to diminished renal perfusion. In 1999, Lancelot et al³⁷ evaluated this concept in a rat study and reported that the HVCM, iodixanol, was associated with decreased inner medullary and cortical blood flow compared to LVCM. Furthermore, when iodixanol was heated, thereby lowering the viscosity of the agent, this effect was attenuated. Similarly, a 2002 study by Lancelot et al³⁸ compared the impact of the ionic dimer, ioxaglate, and the non-ionic dimer, iodixanol, on renal

Table 4. Proposed mechanisms of anaphylactoid reactions to contrast media.^{10,19,20}

| | |
|------------------------------|--|
| Enzyme inhibition | Cholinesterase (deactivates acetylcholine) leading to increased concentration of acetylcholine with vagal hyperstimulation |
| Vasoactive substance release | Histamine, serotonin, bradykinin |
| Cascade system activation | Complement activation, kinin activation, coagulation activation and fibrinolytic activation |
| Immune system disturbances | No widely accepted proposed mechanisms |
| Psychological disturbances | Anxiety, apprehension and fear with resultant hypothalamic response |

medullary blood flow in dogs, confirming several previous animal studies reporting the deleterious effects of CM viscosity associated with HVCM.³⁹⁻⁴¹ The HVCM, iodixanol, was associated with a longer duration of medullary hypoxia when injected directly into the canine renal artery. These findings suggest that HVCM, such as iodixanol, may have deleterious effects on blood flow in the renal medulla.

Several trials have studied CIN, most frequently comparing CM of differing osmolalities. Although there appears to be little or no benefit of LOCM over HOCM in the lowest risk patients (those with normal renal function), the use of LOCM in patients with pre-existing renal insufficiency is associated with a reduction in the risk of CIN.^{24,42} More recent studies have attempted to further define the impact of osmolality on CIN by comparing LOCM and iso-osmolar CM. In a Swedish registry of 57,925 patients undergoing cardiac catheterization and/or PCI, Liss et al⁴³ reported that the incidence of clinically significant renal failure (defined as rehospitalization with a diagnosis of renal failure or dialysis) was higher for patients receiving the iso-osmolar agent, iodixanol, compared to the LOCM, ioxaglate (1.7% vs. 0.8%, $p < 0.001$). Dialysis was more frequently required in patients who received iodixanol versus ioxaglate (0.2% vs. 0.1%, $p < 0.01$). In the Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media (NEPHRIC) study,⁴⁴ the mean peak increase in creatinine was less with the iso-osmolar agent, iodixanol, compared to the LOCM, iohexol (0.13 vs. 0.55 mg/dL, $p = 0.001$) in patients with diabetes and baseline renal insufficiency undergoing angiography. However, other prospective, randomized trials involving patients without diabetes with baseline renal insufficiency have not supported these findings.^{45,46} Furthermore, 2 recent late-breaking trials presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2006 Scientific Symposium failed to demonstrate that the iso-osmolar CM, iodixanol, resulted in a reduction in the incidence of CIN over LOCM in high-risk patients. In the Ionic Versus Nonionic Contrast to Obviate Worsening of Nephropathy After Angioplasty in Chronic Renal Failure Patients (ICON) trial, Mehran⁴⁷ reported that iodixanol did not significantly reduce the increase in serum creatinine levels after coronary catheterization or PCI compared to ioxaglate. In addition, rates of in-hospital and 30-day outcomes did not differ between the 2 agents. In the Cardiac Angiography in Renally Impaired Patients (CARE) trial presented by Solomon,⁴⁸ there was no difference in the incidence of CIN (using multiple definitions) in patients with an estimated glomerular filtration rate < 60 mL/min undergoing coronary angiography randomized to iodixanol or iopamidol. The lack of difference between these 2 agents persisted in patients who underwent PCI and in those with diabetes mellitus. Interestingly, patients who received iodixanol actually had a higher mean rise in peak serum creatinine levels compared to iopamidol. Therefore, based upon the available data, there is insufficient evidence to suggest that iso-osmolar CM reduce the risk of CIN compared to LOCM, even in high-risk patients.

Currently, no well-established standard exists for CIN prevention or treatment. Early trials based on the concept that

increased urinary output would improve CM excretion and reduce CIN were disappointing. Similarly, the administration of mannitol was not associated with an improvement in outcomes, and furthermore, the use of furosemide led to an increase in CIN.⁴⁹ The only interventions that clearly decrease CIN risk are intravenous hydration and minimization of CM volume.^{23,24,27} Intravenous fluid administration leads to increased extracellular volume and improved medullary perfusion as well as decreased contrast concentration in the kidney, thereby diminishing direct and indirect toxic effects of CM on the renal medulla.¹ The administration of the antioxidant N-acetylcysteine, in an effort to decrease generation of reactive oxygen species, has been associated with varied results.^{24,50-53} Efforts to increase renal perfusion with vasodilators, such as dopamine, fenoldopam and theophylline, have yielded conflicting data.⁵⁴⁻⁶² The role of hemodialysis, which effectively removes CM, has been evaluated as a measure for CIN prophylaxis; however, the results of the few small trials performed in the past several years have revealed no benefit to hemodialysis, and 1 study even suggested some harm from this intervention.⁶³⁻⁶⁵ Finally, a single-center study suggests that pre-procedural hydration with sodium bicarbonate, due to its ability to alkalinize the renal tubular fluid and urine, may result in improved CIN outcomes compared to IV normal saline;⁶⁶ however, the benefits of bicarbonate have been recently challenged.⁶⁷ Further study and eventual standardization of the pretreatment approach to patients at high-risk for CIN is critical in order to improve outcomes.

Thromboembolic events associated with CM administration, perhaps more notably with nonionic CM, have been well documented. In a study by Davidson et al,⁶⁸ thromboembolic events were reported to complicate 0.18% of coronary angiographic procedures using nonionic CM. All CM affect the intrinsic and extrinsic coagulation cascade pathways, platelet function and/or vascular endothelial function to varying degrees.⁶⁹ Although early data suggested that ionic CM may have greater anticoagulant properties and inhibition of platelet aggregation than nonionic CM, pre-clinical and clinical trial results have been equivocal.⁷⁰⁻⁷⁸ Traditionally, the clinical marker for significant thromboembolic outcomes has been a composite of major adverse cardiac events (MACE), and several studies have compared MACE rates in patients treated with ionic versus nonionic CM with conflicting results. A number of trials have failed to demonstrate any differences between ionic and nonionic CM with regard to clinical outcomes.^{75,76,79,80} In a meta-analysis of 5,129 patients undergoing PCI, there was no significant difference in the 30-day composite endpoint of death, myocardial infarction and urgent revascularization between ionic and nonionic CM.⁸¹ In a study of 3,990 patients undergoing PCI, acute and subacute stent closure rates were higher with the use of nonionic CM, and MACE rates at 1 year were lower with the use of ionic CM.⁸² With regard to the potential effects of viscosity on red blood cells, platelets and coagulation and complement systems, the LVCM, ioxilan, did not substantially affect erythrocyte morphology or osmotic fragility compared to the HVCM, iopamidol and iohexol, in an *in-vitro* evaluation by Parvez et al.⁸³ In addition, ioxilan reduced platelet aggregation to a significantly greater degree than iohexol

Table 5. Proven and potential benefits of low-viscosity contrast media.

| | |
|---|--|
| Contrast-Induced Nephropathy ³⁶⁻⁴¹ | <ul style="list-style-type: none"> • Improved renal medullary blood flow • Shorter duration of medullary hypoxia |
| Thromboembolic Events ⁸³⁻⁸⁵ | <ul style="list-style-type: none"> • Does not affect erythrocyte morphology or osmotic fragility • Greater inhibition of platelet aggregation • Does not activate coagulation system • Does not activate complement system • Fewer alterations in laminar flow patterns |
| Improved Visualization ^{90,91} | <ul style="list-style-type: none"> • Higher flow rates • Lower injection pressures required to achieve similar flow rates • Facilitated injection using smaller catheters |
| Facilitation of Minimally Invasive Approach ^{93,97-104} | <ul style="list-style-type: none"> • Ability to utilize smaller French-sized catheters • Radial access site • Earlier ambulation • Earlier discharge (potentially same-day for PCI) • Decreased use of closure devices • Reduced cost • Improved patient satisfaction and quality-of-life indices |

and iopamidol and did not activate coagulation or complement systems. Whether these findings are due to differences in viscosity or mediated by other unique properties of CM is unknown. In an evaluation of 37 patients undergoing left ventriculography by Ogawa et al,⁸⁴ there was a significant decrease in platelet aggregation among patients receiving ioxilan or iomeprol compared to iohexol. In a recent study of 498 patients undergoing PCI, thrombus-related events were more frequent with the HVCM, iodixanol (nonionic dimer), compared to the LVCM, ioxaglate (ionic dimer), both for in-hospital MACE (4.8% vs. 0.3%, $p < 0.005$) and the appearance of a large thrombus during PCI (6.0% vs. 0.3%, $p < 0.0001$).⁸⁵ In addition, shear stress, disruption of laminar flow and endothelial injury may contribute to differences in the thromboembolic profile of CM.

Cardiovascular effects of CM vary based upon osmolality, ionicity, viscosity and electrolyte composition.^{13,86-88} On a cellular level, changes in red blood cells and direct endothelial injury may result in release of vasoactive substances, such as histamine, serotonin, fibrinolytics, leukotrienes and complement, leading to changes in the microcirculation.⁵ Furthermore, injection of CM is associated with a number of hemodynamic changes, including decreased cardiac contractility and cardiac output, increased pulmonary artery pressure and increased plasma volume.⁵ Similarly, CM injection causes alterations in cardiac conduction ranging in severity from non-specific ST-segment changes and QT-interval prolongation, to bradyarrhythmias and asystole, to life-threatening ventricular arrhythmias. These microcirculatory, hemodynamic and conduction system changes are more significant with the use of HOCM, whose osmolality may exceed that of human plasma by 5–7 fold.^{5,89} In an early evaluation by Lembo et al,⁷⁵ the ionic monomer, diatrizoate, was compared to the nonionic monomer, iopamidol. Patients treated with diatrizoate were more likely to experience ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, compared to those receiving iopamidol. Compared with HOCM, the low concentration of electrolytes (in particular sodium) of some LOCM may increase the risk of ventricular fibrillation. However, the addition of sodium citrate to ioxilan has

been shown to reduce its arrhythmogenic potential, without inducing negative inotropic effects.^{86,87} The use of LOCM in the overwhelming majority of patients is based upon a reduction in the risk of cardiovascular and other side effects of HOCM.

Benefits of Low-Viscosity Contrast Media

The focus of much of the CM literature on the properties of structure, ionicity and osmolality has perhaps resulted in an under-appreciation of the importance of viscosity. Contrast media viscosity is inversely related to opacification due to its negative impact on both flow rate and injection pressure. The use of LVCM improves flow rate and injection pressure, which should result in superior opacification and safety. These beneficial effects may allow for modifications in diagnostic and interventional procedural technique, resulting in improved outcomes in areas far beyond those traditionally attributed to CM. The proven and potential benefits of LVCM are summarized in Table 5.

Flow rate is inversely related to CM viscosity and directly related to opacification. In an *in-vitro* comparison of several CM by Kern et al,⁹⁰ mean peak radiographic density (opacification) of static arterial phantoms was highest for the lowest viscosity CM. The authors concluded that the use of LVCM may result in superior opacification, particularly with smaller-sized diagnostic or interventional catheters, and that opacification could be approximated by the iodine concentration divided by CM viscosity. In our unpublished *in-vitro* analysis, 32%–61% higher flow rates (mL/s) were achieved using the LVCM, ioxilan, compared to the HVCM, iodixanol, when injected through 4, 5 and 6 French (Fr) diagnostic coronary catheters using a power injector (Figure 4). Furthermore, when ioxilan was injected through a 1-Fr-size smaller catheter (*i.e.*, 5 Fr), similar flow rates were achieved compared to iodixanol injected through a 1-Fr-size larger catheter (*i.e.*, 6 Fr), indicating that flow rate was maintained with LVCM (compared to HVCM) despite catheter “down-sizing.” The use of HVCM, such as iodixanol, makes injection more difficult, especially with smaller diameter catheters.

Injection pressure is directly related to CM viscosity and opaci-

fication. Roth et al⁹¹ concluded that CM viscosity was a major determinant of injection pressure, especially through catheters less than 6 Fr in diameter, and concluded that LVCM provides an advantage when using smaller diameter catheters. Our study presented at Cardiovascular Revascularization Therapies 2007 in Washington, DC, by McDaniel et al⁹² supported these findings and revealed that the HVCM, iodixanol, required 27%–35% higher injection pressures in pounds per square inch (psi) versus the LVCM, ioxilan, to achieve similar flow rates when injected through 4, 5 and 6 Fr diagnostic coronary catheters using a power injector (Figure 5). The ability to achieve adequate flow rates with lower injection pressures with the use of LVCM may improve opacification and have safety advantages.

The favorable flow rates and injection pressures achieved by LVCM may have significant implications. First, the use of LVCM should improve visualization during the increasing number of cardiac diagnostic and interventional procedures performed with smaller catheters, as lesser angiographic quality is a recognized limitation of their use.⁹³ Impaired visualization is also seen during interventional procedures, where guiding catheters are often partially obstructed by wires, stents and other equipment.

Second, more frequent and further reductions in catheter size may be achieved if flow rates and injection pressures are improved with the use of LVCM. Minimizing catheter and sheath size in diagnostic and interventional procedures has significant impact in reducing vascular and bleeding complications, as these events correlate with sheath size. In the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial, sheath size was an independent predictor of vascular site bleeding or surgery in 2,058 patients undergoing PCI.⁹⁴ In turn, hemorrhagic complications are independent predictors of ischemic complications and mortality in PCI and acute coronary syndromes (ACS).⁹⁵ In an analysis of 7,789 patients with ACS undergoing PCI from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial by Manoukian et al,⁹⁶ major bleeding was a frequent complication (5.9%). Importantly, composite ischemic events (24.2% vs. 7.8%, $p < 0.0001$) and mortality rates (5.4% vs. 0.8%, $p < 0.0001$) were significantly higher in patients with major bleeding compared to those without major bleeding. In addition to these risks, vascular bleeding complications also increase the length, complexity and cost of hospitalization.⁹⁷ Therefore, the ability to utilize smaller catheters and sheaths, if facilitated by improved opacification with LVCM, would be

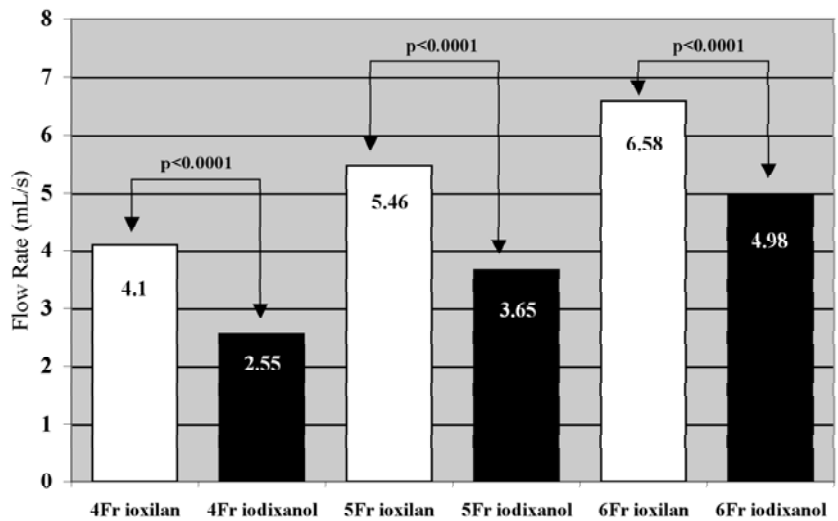


Figure 4. Relationship between contrast media viscosity, catheter size and flow rate.

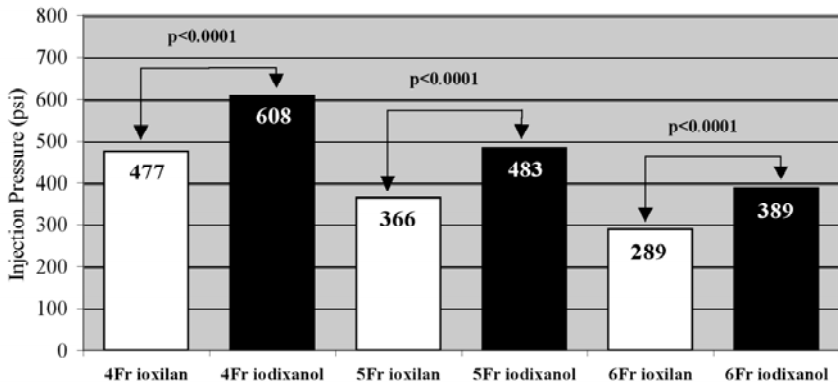


Figure 5. Relationship between contrast media viscosity, catheter size and injection pressure.

expected to result in a reduction in bleeding, associated events and cost.

Third, improved visualization might encourage a further increase in the number of diagnostic and interventional procedures performed via the radial approach. Radial procedures have been associated with a reduction in vascular access complications and bleeding compared with the femoral approach.⁹⁸ In addition, improved opacification might lead to further reductions in catheter size for procedures utilizing the radial approach, which has also been associated with a reduction in vascular complications, including loss of the radial pulse.⁹⁹

Finally, due to these reasons, LVCM facilitates the “minimally invasive” approach to diagnostic and interventional procedures. This technique would ideally include some or all of the following: minimal catheter size, use of the radial access site, low hemorrhagic risk anticoagulant strategies, direct stenting, no closure devices, early ambulation, short post-procedural observation times and early (possibly same-day) discharge.¹⁰⁰ Hamon et al¹⁰¹ popularized this concept in their evaluation of the safety and feasibility of direct stenting using 5-Fr guiding catheters via the transradial approach in 119 patients with ACS. In this study,

there were no vascular access site complications, and “upsizing” to 6-Fr guiding catheters occurred in only 3% of patients. Lasevitch et al¹⁰² described the feasibility of a 5-Fr transfemoral approach in 100 patients undergoing PCI with immediate arterial sheath removal (without the use of closure devices) followed by early discharge within 8–12 hours. The ideal minimally invasive approach could positively impact outcomes, procedural and ancillary costs and quality-of-life indices.^{103,104}

Conclusion

Viscosity is an important property of CM, which, in addition to its potential effects on CIN, thrombogenicity and hemodynamics, is a major determinant of opacification due to its impact on flow rate and injection pressure. The use of LVCM improves opacification and possibly safety by increasing flow rate and achieving lower injection pressures, respectively. Improved visualization may allow for modifications in procedural technique, such as reduced catheter size and increased use of the radial access site, thereby facilitating a minimally invasive approach to diagnostic and interventional procedures. This minimally invasive approach has been associated with improved outcomes, reduced cost and a positive impact on quality of life. The selection of CM needs to be an active choice, extending beyond opacification and including consideration of all the properties of these unique agents, including viscosity.

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