12.4: Viscosity and Laminar Flow; Poiseuille's Law

Learning Objectives

By the end of this section, you will be able to:

- Define laminar flow and turbulent flow.
- Explain what viscosity is.
- Calculate flow and resistance with Poiseuille's law.
- Explain how pressure drops due to resistance.

Laminar Flow and Viscosity

When you pour yourself a glass of juice, the liquid flows freely and quickly. But when you pour syrup on your pancakes, that liquid flows slowly and sticks to the pitcher. The difference is fluid friction, both within the fluid itself and between the fluid and its surroundings. We call this property of fluids *viscosity*. Juice has low viscosity, whereas syrup has high viscosity. In the previous sections we have considered ideal fluids with little or no viscosity. In this section, we will investigate what factors, including viscosity, affect the rate of fluid flow.

The precise definition of viscosity is based on *laminar*, or nonturbulent, flow. Before we can define viscosity, then, we need to define laminar flow and turbulent flow. Figure shows both types of flow. Laminar flow is characterized by the smooth flow of the fluid in layers that do not mix. Turbulent flow, or turbulence, is characterized by eddies and swirls that mix layers of fluid together.

Figure 12.4.1: Smoke rises smoothly for a while and then begins to form swirls and eddies. The smooth flow is called laminar flow, whereas the swirls and eddies typify turbulent flow. If you watch the smoke (being careful not to breathe on it), you will notice that it rises more rapidly when flowing smoothly than after it becomes turbulent, implying that turbulence poses more resistance to flow. (credit: Creativity103)

Figure shows schematically how laminar and turbulent flow differ. Layers flow without mixing when flow is laminar. When there is turbulence, the layers mix, and there are significant velocities in directions other than the overall direction of flow. The lines that are shown in many illustrations are the paths followed by small volumes of fluids. These are called *streamlines*. Streamlines are smooth and continuous when flow is laminar, but break up and mix when flow is turbulent. Turbulence has two main causes. First, any obstruction or sharp corner, such as in a faucet, creates turbulence by imparting velocities perpendicular to the flow. Second, high speeds cause turbulence. The drag both between adjacent layers of fluid

and between the fluid and its surroundings forms swirls and eddies, if the speed is great enough. We shall concentrate on laminar flow for the remainder of this section, leaving certain aspects of turbulence for later sections.

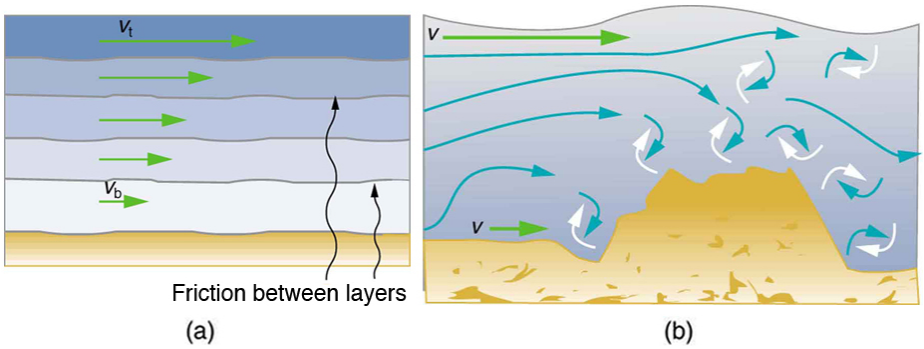

Figure 12.4.2: (a) Laminar flow occurs in layers without mixing. Notice that viscosity causes drag between layers as well as with the fixed surface. (b) An obstruction in the vessel produces turbulence. Turbulent flow mixes the fluid. There is more interaction, greater heating, and more resistance than in laminar flow.

Making Connections: Take-Home Experiment: Go Down to the River

Try dropping simultaneously two sticks into a flowing river, one near the edge of the river and one near the middle. Which one travels faster? Why?

Figure shows how viscosity is measured for a fluid. Two parallel plates have the specific fluid between them. The bottom plate is held fixed, while the top plate is moved to the right, dragging fluid with it. The layer (or lamina) of fluid in contact with either plate does not move relative to the plate, and so the top layer moves at while the bottom layer remains at rest. Each successive layer from the top down exerts a force on the one below it, trying to drag it along, producing a continuous variation in speed from to 0 as shown. Care is taken to insure that the flow is laminar; that is, the layers do not mix. The motion in Figure is like a continuous shearing motion. Fluids have zero shear strength, but the *rate* at which they are sheared is related to the same geometrical factors A and L as is shear deformation for solids.

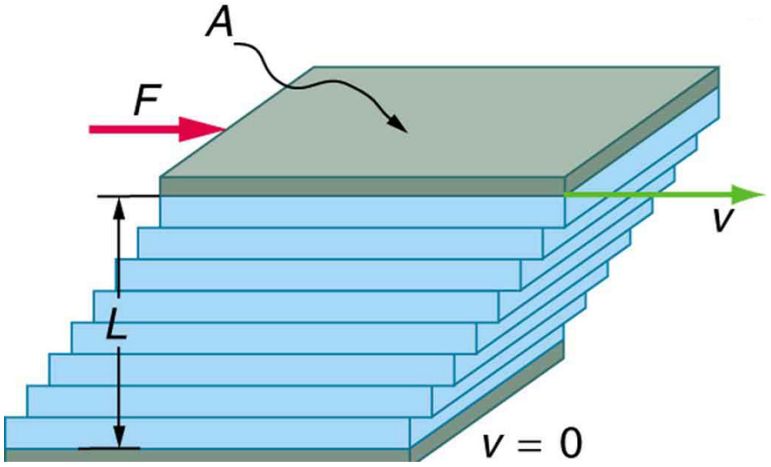

Figure 12.4.3: The graphic shows laminar flow of fluid between two plates of area A. The bottom plate is fixed. When the top plate is pushed to the right, it drags the fluid along with it.

A force F is required to keep the top plate in Figure moving at a constant velocity v, and experiments have shown that this force depends on four factors. First, F is directly proportional to v (until the speed is so high that turbulence occurs—then a much larger force is needed, and it has a more complicated dependence on v). Second, F is proportional to the area A of the plate. This relationship seems reasonable, since A is directly proportional to the amount of fluid being moved. Third, F is inversely proportional to the distance between the plates L. This relationship is also reasonable, L is like a lever arm, and the greater the lever arm, the less force that is needed. Fourth, F is directly proportional to *the coefficient of viscosity*, η. The greater the viscosity, the greater the force required. These dependencies are combined into the equation

$$F = \eta \frac{\nu A}{L}, \tag{12.4.1}$$

which gives us a working definition of fluid viscosity η. Solving for η gives

$$\eta = \frac{FL}{\nu A}, \tag{12.4.2}$$

which defines viscosity in terms of how it is measured. The SI unit of viscosity is

\[N \cdot m/[(m/s)m^2] = (N/m^2)s \, or \, Pa \cdot s\), Table lists the coefficients of viscosity for various fluids.

Viscosity varies from one fluid to another by several orders of magnitude. As you might expect, the viscosities of gases are much less than those of liquids, and these viscosities are often temperature dependent. The viscosity of blood can be reduced by aspirin consumption, allowing it to flow more easily around the body. (When used over the long term in low doses, aspirin can help prevent heart attacks, and reduce the risk of blood clotting.)

Laminar Flow Confined to Tubes—Poiseuille's Law

What causes flow? The answer, not surprisingly, is pressure difference. In fact, there is a very simple relationship between horizontal flow and pressure. Flow rate Q is in the direction from high to low pressure. The greater the pressure differential between two points, the greater the flow rate. This relationship can be stated as

$$Q = \frac{P_2 - P_1}{R}, \tag{12.4.3}$$

where P_1 and P_2 are the pressures at two points, such as at either end of a tube, and R is the resistance to flow. The resistance R includes everything, except pressure, that affects flow rate. For example, R is greater for a long tube than for a short one. The greater the viscosity of a fluid, the greater the value of R. Turbulence greatly increases R, whereas increasing the diameter of a tube decreases R.

If viscosity is zero, the fluid is frictionless and the resistance to flow is also zero. Comparing frictionless flow in a tube to viscous flow, as in Figure, we see that for a viscous fluid, speed is greatest at midstream because of drag at the boundaries. We can see the effect of viscosity in a Bunsen burner flame, even though the viscosity of natural gas is small.

The resistance R to laminar flow of an incompressible fluid having viscosity η through a horizontal tube of uniform radius r and length l such as the one in Figure, is given by

$$R = \frac{8\eta l}{\pi r^4}. \tag{12.4.4}$$

This equation is called Poiseuille's law for resistance after the French scientist J. L. Poiseuille (1799–1869), who derived it in an attempt to understand the flow of blood, an often turbulent fluid.

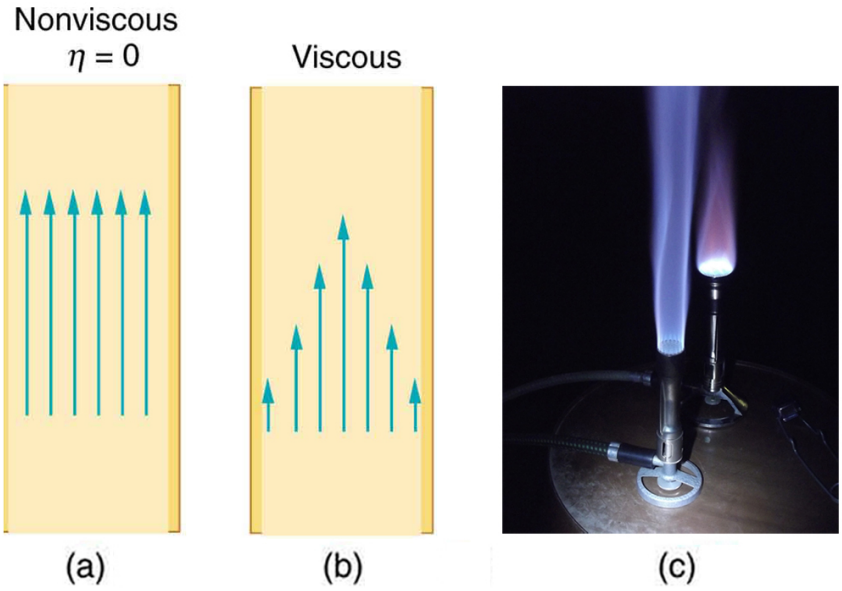

Figure 12.4.4: (a) If fluid flow in a tube has negligible resistance, the speed is the same all across the tube. (b) When a viscous fluid flows through a tube, its speed at the walls is zero, increasing steadily to its maximum at the center of the tube. (c) The shape of the Bunsen burner flame is due to the velocity profile across the tube. (credit: Jason Woodhead)

Let us examine Poiseuille's expression for R to see if it makes good intuitive sense. We see that resistance is directly proportional to both fluid viscosity η and the length l of a tube. After all, both of these directly affect the amount of friction encountered—the greater either is, the greater the resistance and the smaller the flow. The radius r of a tube affects the resistance, which again makes sense, because the greater the radius, the greater the flow (all other factors remaining the same). But it is surprising that r is raised to the *fourth* power in Poiseuille's law. This exponent means that any change in the radius of a tube has a very large effect on resistance. For example, doubling the radius of a tube decreases resistance by a factor of $2^4 = 16$.

Taken together, $Q = \frac{P_2 - P_1}{R}$ and $R = \frac{8\eta l}{\pi r^4}$ give the following expression for flow rate:

$$Q = \frac{(P_2 - P_1)\pi r^4}{8\eta l}. \tag{12.4.5}$$

This equation describes laminar flow through a tube. It is sometimes called Poiseuille's law for laminar flow, or simply Poiseuille's law.

Example 12.4.1: Using Flow Rate: Plaque Deposits Reduce Blood Flow

Suppose the flow rate of blood in a coronary artery has been reduced to half its normal value by plaque deposits. By what factor has the radius of the artery been reduced, assuming no turbulence occurs?

Strategy

Assuming laminar flow, Poiseuille's law states that

$$Q = \frac{(P_2 - P_1)\pi r^4}{8\eta l}. \tag{12.4.6}$$

We need to compare the artery radius before and after the flow rate reduction.

Solution

With a constant pressure difference assumed and the same length and viscosity, along the artery we have

$$\frac{Q_1}{r_1^4} = \frac{Q_2}{r_2^4} \tag{12.4.7}$$

So, given that $Q_2 = 0.5Q_1$, we find that $r_2^4 = 0.5r_1^4$.

Therefore, $r_2 = (0.5)^{0.25} r_1$ a decrease in the artery radius of 16%.

Discussion

This decrease in radius is surprisingly small for this situation. To restore the blood flow in spite of this buildup would require an increase in the pressure difference $(P_2 - P_1)$ of a factor of two, with subsequent strain on the heart.

12.4.1

Fluid	Temperature (ºC)	Viscosity (mPa·s)
Gases		
Air	0	0.0171
	20	0.0181
	40	0.0190
	100	0.0218
Ammonia	20	0.00974
Carbon dioxide	20	0.0147
Helium	20	0.0196
Hydrogen	0	0.0090
Mercury	20	0.0450
Oxygen	20	0.0203
Steam	100	0.0130
Liquids		
Water	0	1.792
	20	1.002
	37	0.6947
	40	0.653
	100	0.282
Whole blood[1]	20	3.015
	37	2.084
Blood plasma[2]	20	1.810
	37	1.257
Ethyl alcohol	20	1.20
Methanol	20	0.584
Oil (heavy machine)	20	660
Oil (motor, SAE 10)	30	200
Oil (olive)	20	138
Glycerin	20	1500
Honey	20	2000–10000
Maple Syrup	20	2000–3000
Milk	20	3.0
Oil (Corn)	20	65

The circulatory system provides many examples of Poiseuille's law in action—with blood flow regulated by changes in vessel size and blood pressure. Blood vessels are not rigid but elastic. Adjustments to blood flow are primarily made by varying the size of the vessels, since the resistance is so sensitive to the radius. During vigorous exercise, blood vessels are selectively dilated to important muscles and organs and blood pressure increases. This creates both greater overall blood

flow and increased flow to specific areas. Conversely, decreases in vessel radii, perhaps from plaques in the arteries, can greatly reduce blood flow. If a vessel's radius is reduced by only 5% (to 0.95 of its original value), the flow rate is reduced to about $(0.95)^4 = 0.81$ of its original value. A 19% decrease in flow is caused by a 5% decrease in radius. The body may compensate by increasing blood pressure by 19%, but this presents hazards to the heart and any vessel that has weakened walls. Another example comes from automobile engine oil. If you have a car with an oil pressure gauge, you may notice that oil pressure is high when the engine is cold. Motor oil has greater viscosity when cold than when warm, and so pressure must be greater to pump the same amount of cold oil.

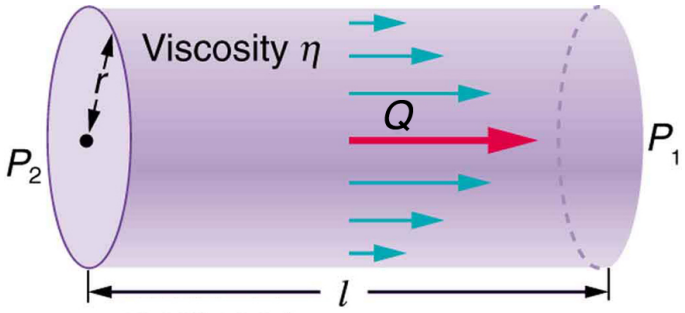

Figure 12.4.5:. Poiseuille's law applies to laminar flow of an incompressible fluid of viscosity η through a tube of length l and radius r. The direction of flow is from greater to lower pressure. Flow rate Q is directly proportional to the pressure difference $P_2 - P_1$, and inversely proportional to the length l of the tube and viscosity η of the fluid. Flow rate increases with r^4, the fourth power of the radius.

Example 12.4.2: What Pressure Produces This Flow Rate?

An intravenous (IV) system is supplying saline solution to a patient at the rate of $0.120\, cm^3/s$ through a needle of radius 0.150 mm and length 2.50 cm. What pressure is needed at the entrance of the needle to cause this flow, assuming the viscosity of the saline solution to be the same as that of water? The gauge pressure of the blood in the patient's vein is 8.00 mm Hg. (Assume that the temperature is $20^o\, C$.

Strategy

Assuming laminar flow, Poiseuille's law applies. This is given by

$$Q = \frac{(P_2 - P_1)\pi r^4}{8\eta l}, \tag{12.4.8}$$

where P_2 is the pressure at the entrance of the needle and P_1 is the pressure in the vein. The only unknown is P_2.

Solution

Solving for P_2 yields

$$P_2 = \frac{8\eta l}{\pi r^4} Q + P_1 \tag{12.4.9}$$

P_1 is given as 8.00 mm Hg, which converts to $1.066 \times 10^3\, N/m^2$. Substituting this and the other known values yields

$$P_2 = \left[\frac{8(1.00 \times 10^{-3} N \cdot s/m^2)(2.50 \times 10^{-2} m)}{\pi(0.150 \times 10^{-3}\, m^4)}\right](1.20 \times 10^{-7}\, m^3/s) + 1.066 \times 10^3\, N/m^2 \tag{12.4.10}$$

$$= 1.62 \times 10^4\, N/m^2 \tag{12.4.11}$$

Discussion

This pressure could be supplied by an IV bottle with the surface of the saline solution 1.61 m above the entrance to the needle (this is left for you to solve in this chapter's Problems and Exercises), assuming that there is negligible pressure drop in the tubing leading to the needle.

Flow and Resistance as Causes of Pressure Drops

You may have noticed that water pressure in your home might be lower than normal on hot summer days when there is more use. This pressure drop occurs in the water main before it reaches your home. Let us consider flow through the water main as illustrated in Figure 12.4.6. We can understand why the pressure P_1 to the home drops during times of heavy use by rearranging

$$Q = \frac{P_2 - P_1}{R} \tag{12.4.12}$$

to

$$P_2 - P_1 = RQ, \tag{12.4.13}$$

where, in this case, P_2 is the pressure at the water works and R is the resistance of the water main. During times of heavy use, the flow rate Q is large. This means that $P_2 - P_1 = RQ$ is valid for both laminar and turbulent flows.

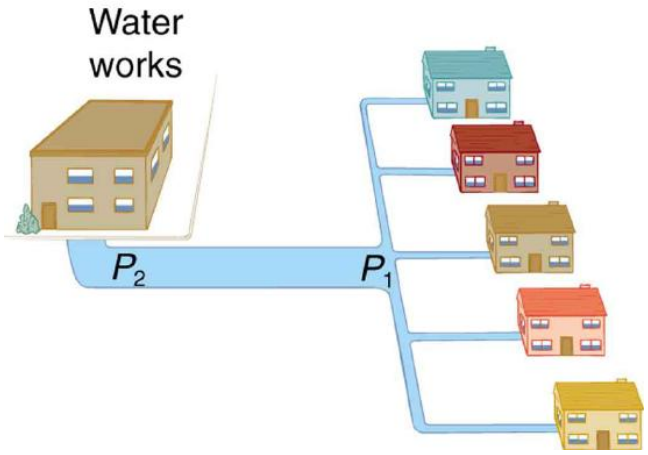

Figure 12.4.6: During times of heavy use, there is a significant pressure drop in a water main, and P_1 supplied to users is significantly less than P_2 created at the water works. If the flow is very small, then the pressure drop is negligible, and $P_2 - P_1$.

We can use $P_2 - P_1 = RQ$ to analyze pressure drops occurring in more complex systems in which the tube radius is not the same everywhere. Resistance will be much greater in narrow places, such as an obstructed coronary artery. For a given flow rate Q, the pressure drop will be greatest where the tube is most narrow. This is how water faucets control flow. Additionally, R is greatly increased by turbulence, and a constriction that creates turbulence greatly reduces the pressure downstream. Plaque in an artery reduces pressure and hence flow, both by its resistance and by the turbulence it creates.

Figure 12.4.7 is a schematic of the human circulatory system, showing average blood pressures in its major parts for an adult at rest. Pressure created by the heart's two pumps, the right and left ventricles, is reduced by the resistance of the blood vessels as the blood flows through them. The left ventricle increases arterial blood pressure that drives the flow of blood through all parts of the body except the lungs. The right ventricle receives the lower pressure blood from two major veins and pumps it through the lungs for gas exchange with atmospheric gases – the disposal of carbon dioxide from the blood and the replenishment of oxygen. Only one major organ is shown schematically, with typical branching of arteries to ever smaller vessels, the smallest of which are the capillaries, and rejoining of small veins into larger ones. Similar branching takes place in a variety of organs in the body, and the circulatory system has considerable flexibility in flow regulation to these organs by the dilation and constriction of the arteries leading to them and the capillaries within them. The sensitivity of flow to tube radius makes this flexibility possible over a large range of flow rates.

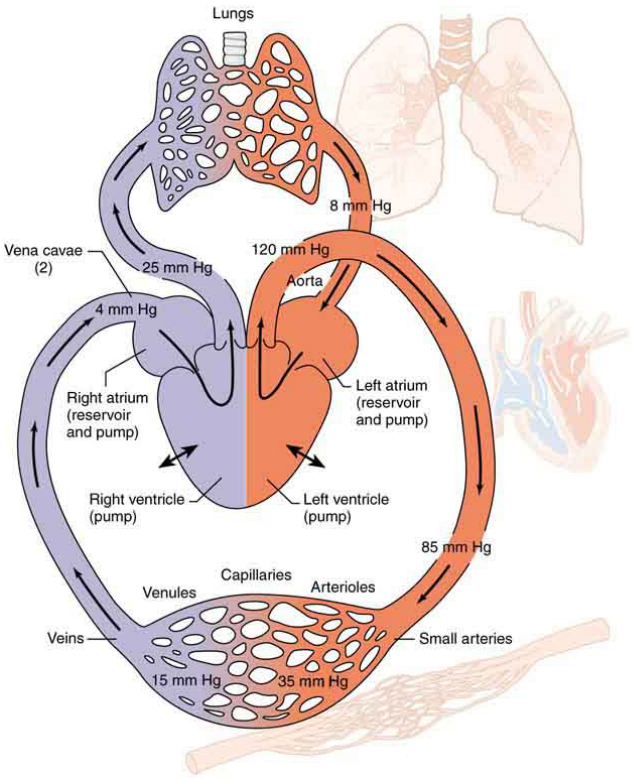

Figure 12.4.7: Schematic of the circulatory system. Pressure difference is created by the two pumps in the heart and is reduced by resistance in the vessels. Branching of vessels into capillaries allows blood to reach individual cells and exchange substances, such as oxygen and waste products, with them. The system has an impressive ability to regulate flow to individual organs, accomplished largely by varying vessel diameters.

Each branching of larger vessels into smaller vessels increases the total cross-sectional area of the tubes through which the blood flows. For example, an artery with a cross section of $1\,cm^2$ may branch into 20 smaller arteries, each with cross sections of $0.5\,cm^2$, with a total of $10\,cm^2$ In that manner, the resistance of the branchings is reduced so that pressure is not entirely lost. Moreover, because $Q = A\bar{v}$ and A increases through branching, the average velocity of the blood in the smaller vessels is reduced. The blood velocity in the aorta $(diameter = 1\,cm)$ is about 25 cm/s, while in the capillaries ($20\,\mu m$ in diameter) the velocity is about 1 mm/s. This reduced velocity allows the blood to exchange substances with the cells in the capillaries and alveoli in particular.

Section Summary

- Laminar flow is characterized by smooth flow of the fluid in layers that do not mix.
- Turbulence is characterized by eddies and swirls that mix layers of fluid together.
- Fluid viscosity η is due to friction within a fluid. Representative values are given in Table. Viscosity has units of (N/m^2)s or $Pa \cdot s$.
- Flow is proportional to pressure difference and inversely proportional to resistance:

$$Q = \frac{P_2 - P_1}{R}. \tag{12.4.14}$$

- For laminar flow in a tube, Poiseuille's law for resistance states that

$$R = \frac{8\eta l}{\pi r^4}. \tag{12.4.15}$$

- Poiseuille's law for flow in a tube is

$$Q = \frac{(P_2 - P_1)\pi r^4}{8\eta l}. \tag{12.4.16}$$

- The pressure drop caused by flow and resistance is given by

$$P_2 - P_1 = RQ. \tag{12.4.17}$$

Footnotes

1 The ratios of the viscosities of blood to water are nearly constant between 0°C and 37°

2. See note on Whole Blood.

Glossary

laminar
a type of fluid flow in which layers do not mix

turbulence
fluid flow in which layers mix together via eddies and swirls

viscosity
the friction in a fluid, defined in terms of the friction between layers

Poiseuille's law for resistance
the resistance to laminar flow of an incompressible fluid in a tube: $R = 8\eta l/\pi r^4$

Poiseuille's law
the rate of laminar flow of an incompressible fluid in a tube: $Q = (P_2 - P_1)\pi r^4/8\eta l$

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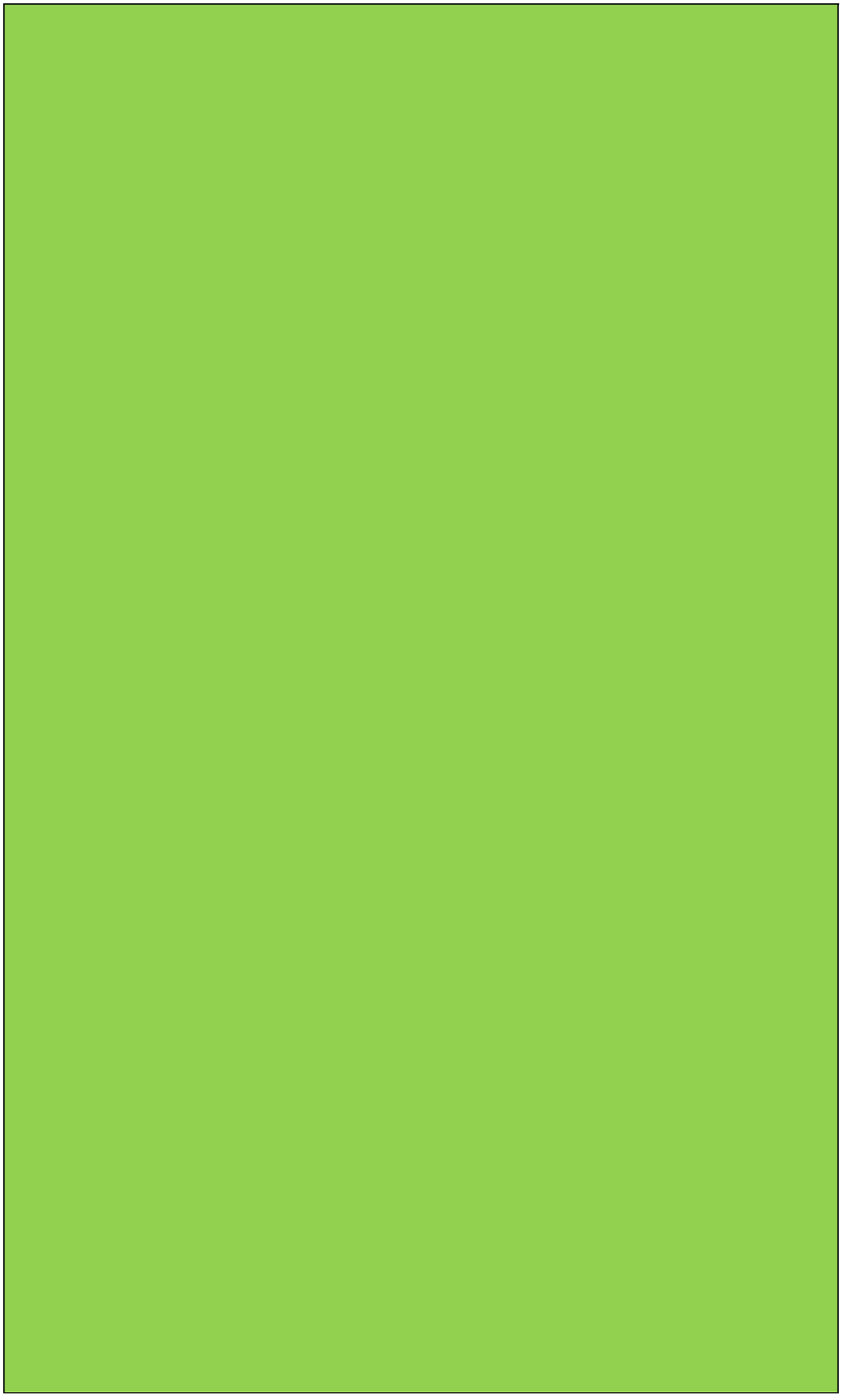

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SPECIAL SUPPLEMENT

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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 years[2] 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 Röentgen, 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 States[7] 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]

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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 ratio[10] 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 H_2O. Contrast media used in cardiovascular procedures are often referred to as high osmolar (HOCM,

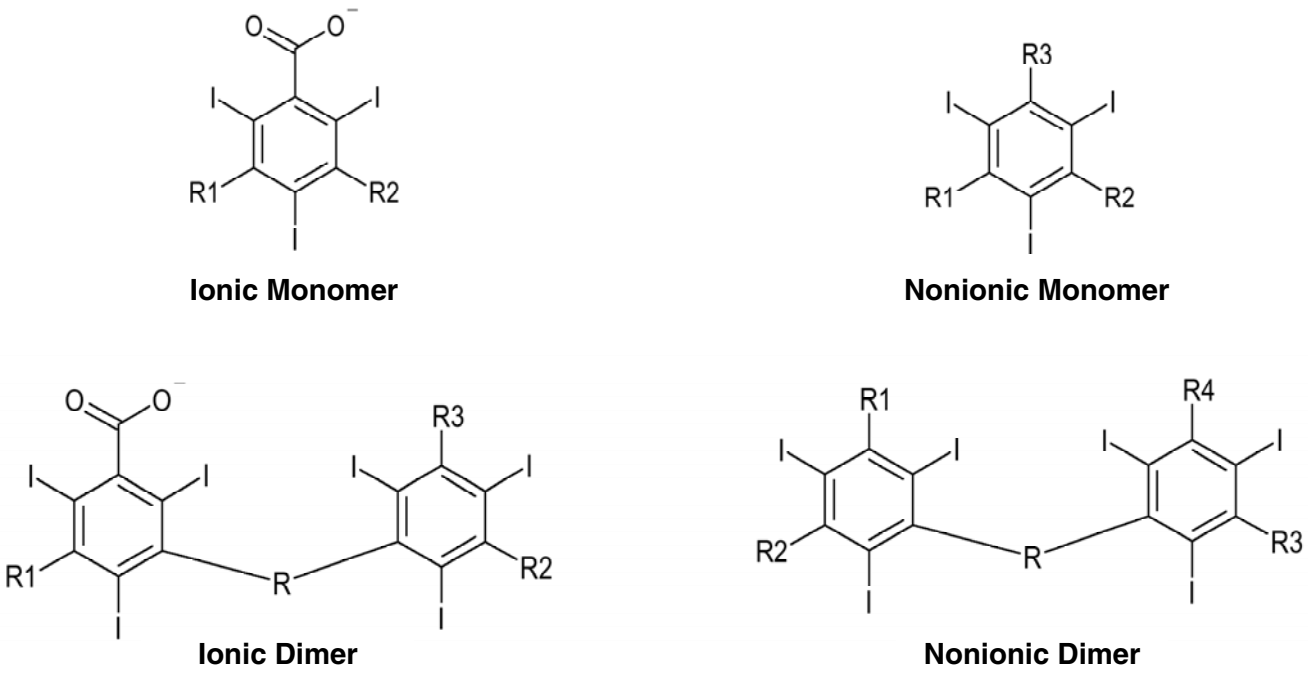

Figure 1. *Prototypic structures of contrast media.*

typical osmolality 1400–2016 mOsm/kg H_2O), low osmolar (LOCM, typical osmolality 600–844 mOsm/kg H_2O) or isoosmolar (290 mOsm/kg H_2O).

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.

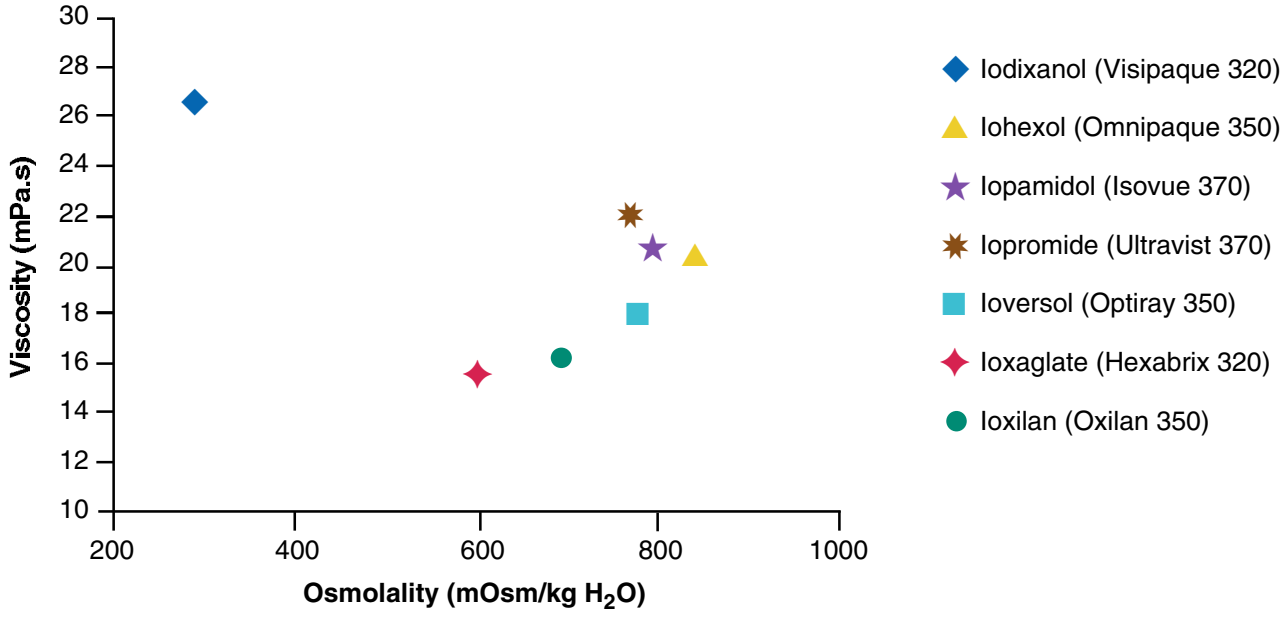

Figure 2. *Viscosity and osmolality of select contrast media at 20°C.*

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

Class			Chemical Name	Trade Name and Manufacturer†	Osmolality (mOsm/kg H_2O)	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 H_2O) 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 H_2O) 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/kgH_2O), 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 pharmaceuticals. Although they are among the safest known agents, a number of side effects exist.

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

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 nonionic 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 al[33] 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, Katzberg[34] 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 Patzak[35] 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 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 al[37] 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 al[38] compared the impact of the ionic dimer, ioxaglate, and the non-ionic dimer, iodixanol, on renal

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

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 al[43] 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, Mehran[47] 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]	• Improved renal medullary blood flow • Shorter duration of medullary hypoxia
Thromboembolic Events[83–85]	• 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]	• 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]	• 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, fibrinolysins, 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 al[91] 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 al[92] 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.

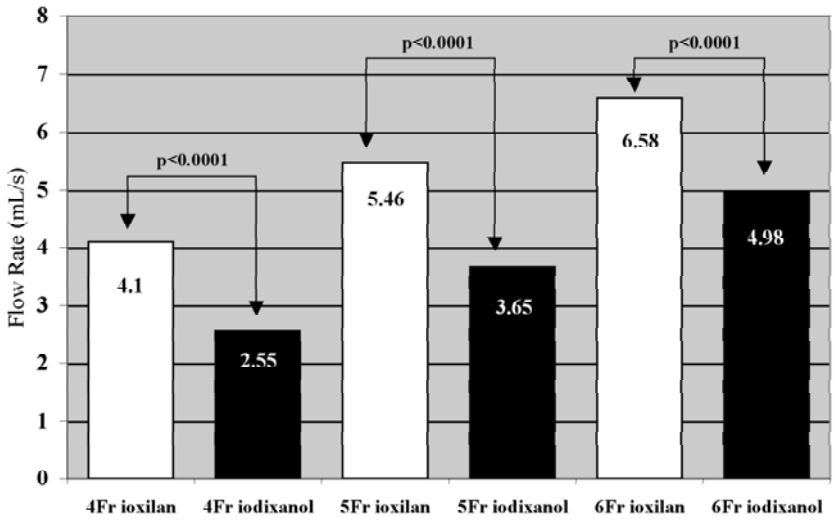

Figure 4. *Relationship between contrast media viscosity, catheter size and flow rate.*

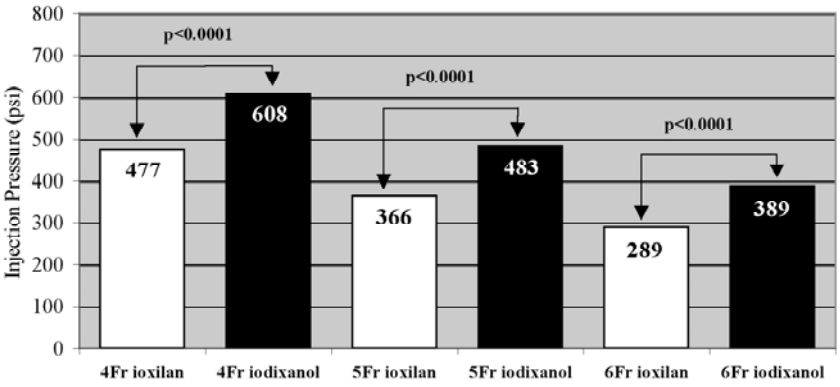

Figure 5. *Relationship between contrast media viscosity, catheter size and injection pressure.*

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 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 al[101] 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 al[102] 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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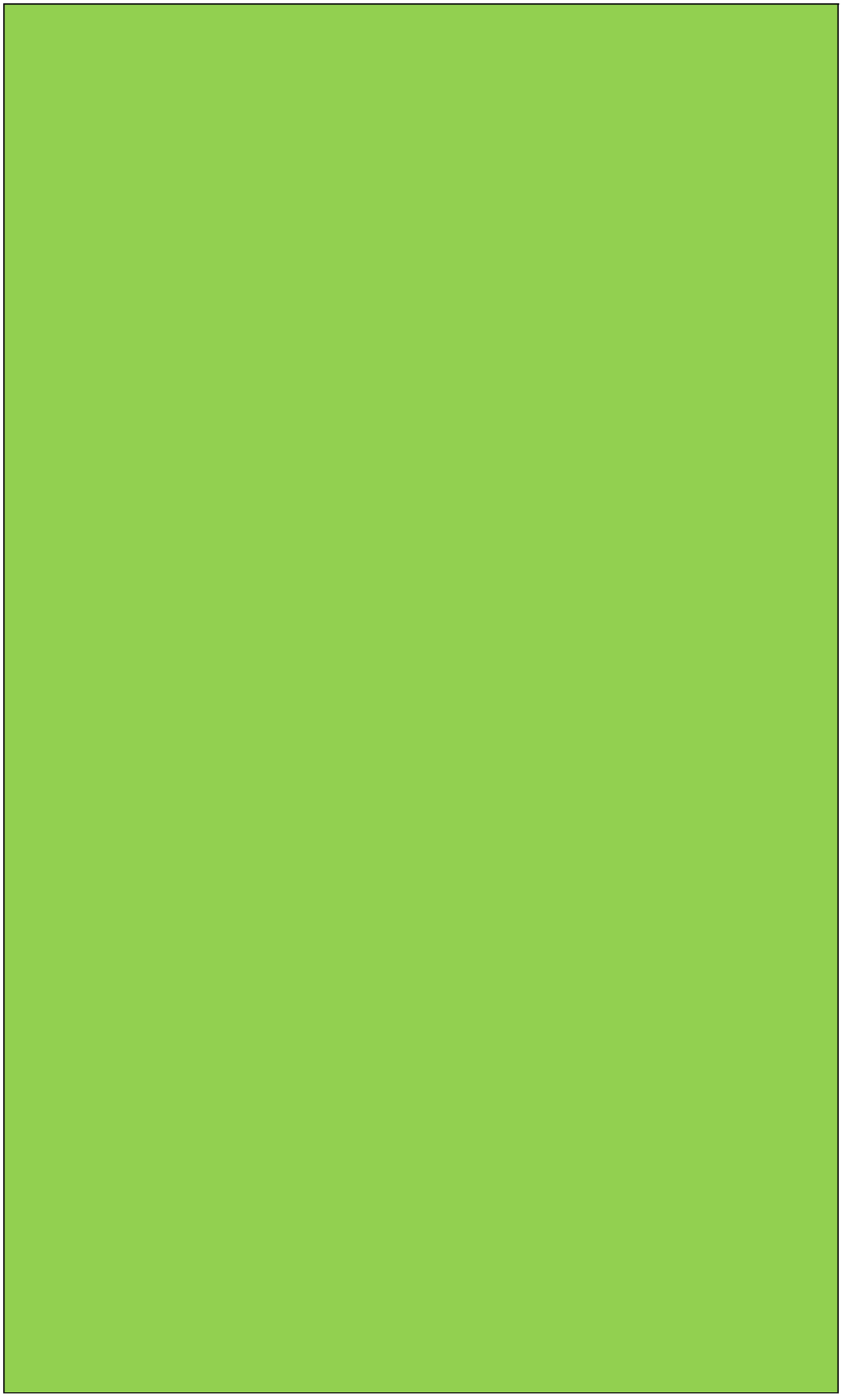

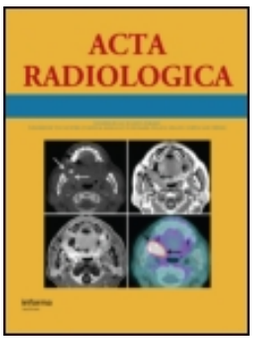

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Viscosity of Some Contemporary Contrast Media before and after Mixing with Whole Blood

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VISCOSITY OF SOME CONTEMPORARY CONTRAST MEDIA BEFORE AND AFTER MIXING WITH WHOLE BLOOD

Ö. SMEDBY

Abstract

The viscosity of 7 contrast media was measured using a rotational viscometer. When solutions with similar iodine concentrations were compared, the highest viscosities were found for the nonionic dimers iodixanol and iotrolan, the lowest for diatrizoate, iopamidol, and iopromide, and intermediate values for iohexol and ioxaglate. The viscosity of iohexol and ioxaglate was found to vary linearly with temperature and quadratically with concentration. Whole-blood viscosity was measured for 5 subjects at high and low shear rates before and after mixing with contrast media in various proportions. Low-shear viscosity was found to decrease and high-shear viscosity to increase with contrast medium concentration. It is concluded that the contrast media currently used may affect blood rheology less than previous agents, despite their higher viscosity.

Key words: Contrast media, comparative studies; —, experimental studies; iohexol; iopamidol; iopromide; iotrolan; iodixanol; ioxaglate.

Much of the interest in developing new radiographic contrast media (CM) stems from the physicochemical properties of the substances used, in particular their osmolality. Many of the side effects of CM injection are thought to be related to the hypertonic character of the preparations. The quest for less hypertonic solutions has led to the introduction of nonionic tri-iodinated compounds, such as iohexol, iopamidol, and iopromide, and of an ionic hexa-iodinated dimeric substance, ioxaglate. All of these have an iodine-to-particle ratio of 3. The same principle is carried even further in the nonionic hexa-iodinated dimers, e.g., iotrolan (10), which have an iodine-to-particle ratio of 6. In fact, polymerization as a means of reducing osmolality was suggested more than 20 years ago by ALMÉN (1) and tested empirically by BJÖRK et al. (7).

Another aspect of the physical chemistry of CM, also discussed by ALMÉN, concerns their viscosity. In the 1960's, FISCHER (12) and KROVETZ et al. (18) published studies on the viscosity of CM that were then in common use. Their primary concern was the problem of introducing in a limited time as much iodine as possible through a fine catheter. This problem has led to the practice of preheating CM before injection in order to make them less viscous (15). However, the value of this procedure has been questioned (16).

RAND & LACOMBE (23) studied how the viscosity of whole blood is affected by mixing it in varying proportions with hypo- and hypertonic solutions, including an angiographic CM. When the strongly hypertonic CM was injected in vivo, whole-blood viscosity rose drastically but plasma viscosity was unaffected (24). The same result was noted when a hypertonic solution of low viscosity was injected, whereas isotonic injections of high viscosity resulted in an increase in plasma viscosity only. This led these authors to the conclusion that the changes in whole-blood viscosity were related to the hypertonicity rather than to the viscosity of the CM. Later, similar measurements were performed by ASPELIN (3), who provided a detailed analysis of the effects of blood-CM mixing on hematocrit and whole-blood viscosity. Both these studies indicate that the viscosity of the blood-CM mixture cannot be easily predicted from the viscosities of the 2 components. This should not come as a surprise, in view of the effects that CM have on both red cell aggregation and crenation. According to ASPELIN (2), both ionic and nonionic CM can convert erythrocytes into crenated cells (echinocytes) and reduce their tendency to aggregate, though other researchers have observed increased aggregation (5, 19, 22).

Viscosity measurements of this kind are complicated by the fact that whole blood is a non-Newtonian fluid, i.e., its viscosity at a given temperature is not constant but varies with the shear rate. It is generally accepted that at high shear rates, the shearing deformation of the erythrocytes is

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Table 1

Contrast media studied

Generic name	Trade name	Manufacturer	Ionic/nonionic	Iodine content per molecule	Iodine-to-particle ratio	Concentrations mg I/ml
Iohexol	Omnipaque	Nycomed	nonionic	3	3	140, 180, 200, 240, 300, 350
Ioxaglate	Hexabrix	Guerbet	ionic	6	3	160, 200, 320
Iopromide	Ultravist	Schering	nonionic	3	3	300
Iopamidol	Iopamiro	Astra-Meditec	nonionic	3	3	300
Iotrolan	Isovist	Schering	nonionic	6	6	300
Iodixanol	–	Nycomed	nonionic	6	6	320
Diatrizoate	Urografin	Schering	ionic	3	1.5	290

the main determinant of whole-blood apparent viscosity, whereas at low shear rates, where viscosity is considerably higher, aggregation is the most important factor (9).

STÄUBLI et al. (27) have found that the viscosity of whole blood is increased, at both low and high shear rates, by mixing it with CM; rather less, however, with ioxaglate than with metrizamide and diatrizoate. SCHMID-SCHÖNBEIN et al. (26) compared iopamidol and diatrizoate and found the greatest effects with the latter substance.

Metrizamide (and to a large extent also the ionic media) has now been supplanted by the other media mentioned above. Viscosity figures are available for most of these media (13), but mostly from the manufacturers' own measurements on the basic substance at certain concentrations, not on the ready-made preparations available for clinical use, and the method of analysis is seldom described.

The intention with this investigation was to measure the viscosities of a number of currently used CM, including, for some of them, the effects of temperature and concentration, and to study how the viscosity of whole blood is affected by mixing it with such CM in varying proportions. This has direct implications for the feasibility of studying fluid mechanical phenomena in vivo using angiography.

Material and Methods

The CM studied are listed in Table 1. The tri-iodinated ionic substance diatrizoate was included for comparison with an older generation of CM.

Blood samples were obtained from the cubital veins of 5 healthy volunteers (3 males and 2 females, aged 27–44 years), using a tourniquet and dry-heparinized 10 ml vacutainer tubes. The tubes were stored in a water-bath at 37°C until analysis, which was completed within 7 hours. Mixture with CM and saline was performed with a pipette at 37°C.

For measurements of whole-blood viscosity, 2 types of rotational viscometer are in common use: couette (Fig. 1) and cone-on-plate (Fig. 2) viscometers. Both allow the shear rate to be varied in a controlled fashion by adjusting the rotational speed of the cup relative to the shaft while the torque exerted on the shaft is measured by an electromagnetic servo system. This torque is directly proportional to the shear stress resulting from viscous forces in the fluid.

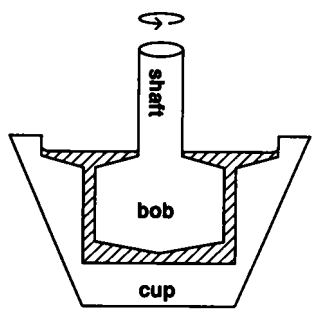

Fig. 1. Couette viscometer.

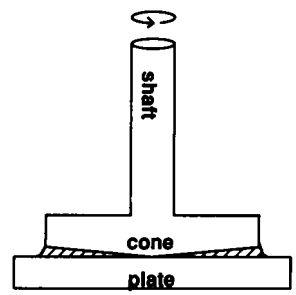

Fig. 2. Cone-on-plate viscometer.

Viscosity measurements were carried out with a Low Shear 30 couette viscometer (Contraves AG, Zürich, Switzerland), used for routine analysis of whole-blood and plasma viscosity (25). A comparative study by ERNST et al. (11) indicated that this instrument had the highest reproducibility among the 3 rotational viscometers tested. Calibration was performed by analysis of degassed pure water with a known viscosity of 0.695 mPa s at 37°C (14). All CM were analyzed at 25°C and 37°C; iohexol (300 mg I/ml) and ioxaglate (320 mg I/ml) were also measured at intermediate temperatures. The viscosity measurements on blood–CM mixtures were carried out at 2 shear rates, 1/s and 100/s, representing 2 extremes of the shear dependence of apparent viscosity. The CM concentrations studied for each subject were 0, 25, 50, 75, and 100% by volume.

Statistical comparisons were made using General Linear Models analysis with a 5% significance limit, treating duplicate measurements as separate observations (4). In 2 analyses, an alternative model with a logarithmic transformation of the viscosity values was also tested.

The reproducibility of repeated measurements on the same sample was assessed by computing the ratio of the sum of squares within subjects to the sum of squares between subjects (SS_w/SS_b). Blood viscosity measurements were repeated 5 times for each subject to control for drift with time. The trend over time was tested with a linear model correcting for the variability between patients.

The viscosity of blood–CM mixtures was analyzed with a linear model with 9 effects, each representing the concentration of one subject's blood or one CM (or saline). This

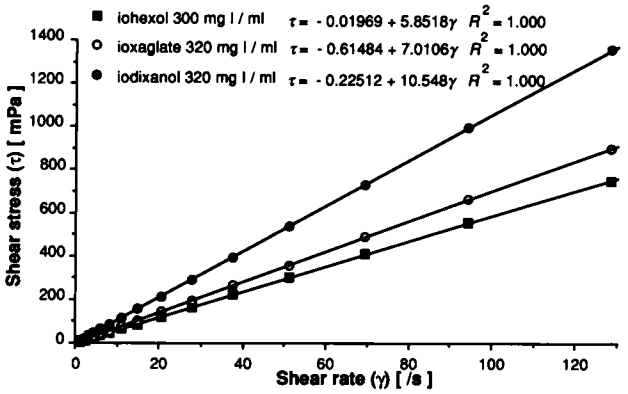

Fig. 3. Shear stress at varying shear rates for 3 CM.

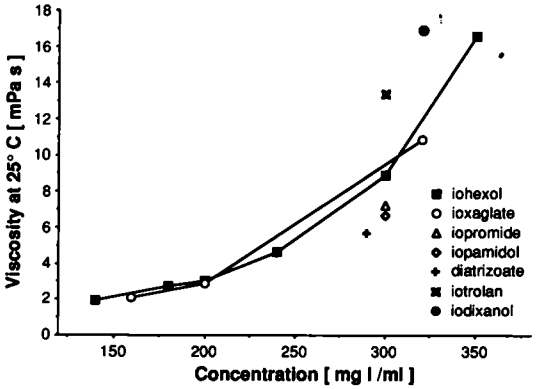

Fig. 4. Iodine concentration and viscosity at 25°C of various CM.

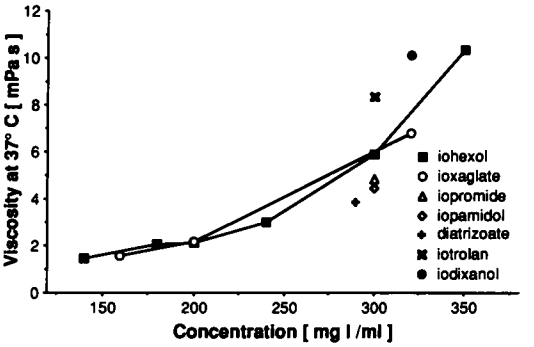

Fig. 5. Iodine concentration and viscosity at 37°C of various CM.

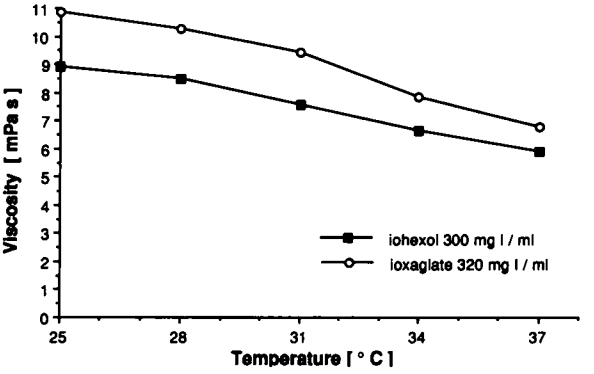

Fig. 6. Viscosity at varying temperature for 2 CM.

is equivalent to a multiple linear regression model with 9 independent variables and no intercept term. Explicitly, the model is given by the equation

$$\mu = \sum_{b=1}^{5} a_b C_b + \sum_{m=1}^{4} a_m C_m$$

where μ denotes viscosity, C_b ($b = 1...5$) the concentration of each individual's blood, C_m (m = 1...4) the concentration of each CM, and the coefficients a_b and a_m are chosen so that the agreement with the model (R^2 = proportion of variance explained by the model) is maximized. This procedure fits a straight line to the data of each pair of subjects and preparations.

Results

To test the hypothesis of Newtonian behavior of the CM, the relationship between shear rate and shear stress was studied for 3 of the media in the range between 1/s and 130/s. All these measurements were made at 37°C. The relationship was well described by a linear relation, thus verifying the hypothesis (Fig. 3). Since these CM represent the 3 major groups in the study, Newtonian behavior was assumed for all pure CM, and only one shear rate (38/s) was used for the subsequent viscosity measurements.

For iohexol and ioxaglate, which were studied at various concentrations, viscosity measured at 25°C varied strongly with concentration (Fig. 4), but no obvious difference was seen between the 2 substances at comparable concentrations. The remaining 2 nonionic monomers, iopromide and iopamidol, had, at 300 mg I/ml, somewhat lower viscosity values, approaching that of the ionic monomer diatrizoate. The nonionic dimers, on the other hand, displayed distinctly higher values. The highest value was found for iodixanol, which had a viscosity close to that of iohexol at its highest concentration (350 mg I/ml).

The corresponding data for 37°C (Fig. 5) had a similar appearance, although all viscosity values were lower. In this case, iohexol 350 had the highest viscosity. At neither temperature was there a significant difference between iohexol and ioxaglate when the dependence on concentration was taken into account, regardless of whether a linear or a quadratic model was assumed for this dependence.

For 2 of the media, iohexol (300 mg I/ml) and ioxaglate (320 mg I/ml), the temperature dependence was studied in some detail in the interval between 25°C and 37°C (Fig. 6). The viscosities of both CM decreased steadily with increasing temperature to a final value about 1/3 lower than the starting level. The slopes of the 2 regression lines were both significantly below 0. The small difference in slope between the 2 preparations was significant with a linear viscosity

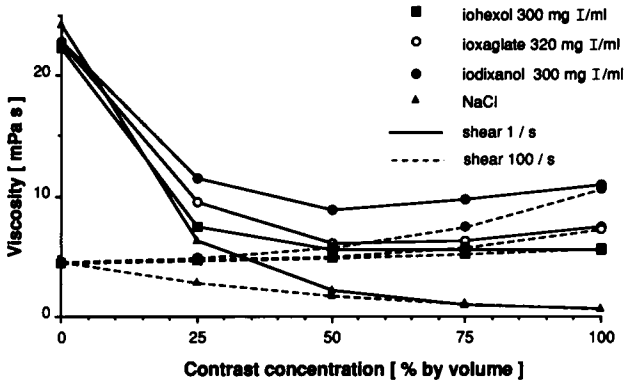

Fig. 7. Apparent viscosity at 2 shear rates for blood–CM mixtures and mixtures of blood with physiologic saline. Mean values for 5 subjects.

scale. After a logarithmic transformation of the viscosity axis, the slopes were still significantly negative, but the difference between them did not even approach significance. Thus the difference appears to be an effect of the proportionally higher values found for ioxaglate (320 mg I/ml).

The low-shear viscosity of pure blood for the 5 subjects ranged from 14.2 to 31.8 mPa s, and the high-shear viscosity from 3.6 to 5.6 mPa s, reflecting the differences in erythrocyte volume fraction (EVF), which varied between 40 and 52%. When reproducibility was tested for repeated measurements on the same subject's blood, an SS_w/SS_b value of 3.7% was found for low-shear viscosity and 3.0% for high-shear viscosity. This means that the variability (expressed as variance) between repeated measurements on the same subject is about 1/30 as large as the variability between subjects. No significant trend with time was found either for low- or for high-shear viscosity values.

The viscosity measurements on blood–CM mixtures are summarized in Fig. 7, which also includes corresponding data for mixtures of blood with a physiologic saline solution, illustrating the dilution effect. For pure blood there was a difference by a factor of about 5 between the values for low and high shear rates. With increasing CM concentration, this difference diminished until it had completely disappeared for the pure CM, which are Newtonian fluids.

At the low shear rate, there was already a marked reduction in apparent viscosity between 0 and 25% CM concentration (ranging from 50% for iodixanol to 66% for iohexol), after which the changes were smaller. The reduction was not as pronounced as with saline, though. At 100/s, on the other hand, the viscosity increased with increasing CM concentration, but most appreciably at concentrations above 50%. The high-shear viscosity was more than doubled with iodixanol. With iohexol and ioxaglate, however, the mean increase was 59% at most (range 5–98%), and when concentrations up to 50% were considered, the mean increase was no more than 9% (range 3–18%). The difference between the preparations was reflected at all concentrations, with iodixanol mixtures ranking highest and iohexol mixtures lowest (except for the saline mixtures) for each shear rate.

Table 2

Two models for the variation in low- and high-shear viscosity (μ) with different concentrations of blood (C_b) and contrast medium (C_m). The coefficients a_b and a_m are chosen so that they maximize the agreement with each model

Model	Shear rate 1/s R^2	Shear rate 100/s R^2
$\mu = \sum a_b C_b + \sum a_m C_m$	0.904	0.992
$\log \mu = \sum a_b C_b + \sum a_m C_m$	0.986	0.995

The variations in low- and high-shear viscosity were analyzed with the linear model described above. The proportion of total variance explained by the model (R^2) for low- and high-shear viscosity is given in Table 2. When the logarithmic model, motivated by the nonlinear appearance of the curves in Fig. 7, was tested, it yielded higher R^2 values, at least for the low shear rate.

Discussion

To a great extent, the findings presented above were expected. The Newtonian, viscous, character of pure CM could be anticipated with substances of molecular weight up to about 1 600.

Also as expected, all newer CM have higher viscosity values than the smallest molecule, diatrizoate. For 2 of the CM, however – iopromide and iopamidol – this difference is only small and may be partly explained by their differing iodine concentrations (cf. Figs. 4–5). The largest molecules – iodixanol and iotrolan – correspond, as expected, to the highest viscosity values at comparable concentrations, but the difference between these 2 substances of similar molecular size is notable, though it may also be an effect of the concentration difference.

The remaining 2 CM – ioxaglate and iohexol – seem to be equivalent as far as viscosity is concerned; differences between them correspond to the variations in iodine concentration. The relationship between viscosity and concentration, which is well known from practical work with the drugs, does not fit a straight line. It is better described by a 2nd degree polynomial, which can also be derived from physicochemical theory when particle-to-particle interactions are taken into account (17).

The question whether one should heat CM before injection to ascertain sufficient flow rates through the catheter cannot be answered unequivocally by this study. What can be accomplished by heating from room temperature to body temperature is a reduction in viscosity of 25 to 40% for all the preparations tested, and within this interval the reduction is proportional to the degree of heating, at least for iohexol and ioxaglate. As pointed out by BJÖRK et al. (6), delivery rates through angiography catheters are only to a small

extent affected by variations in viscosity of the CM. However, HALSELL (16), who made the same observation, found the greatest effects for the most viscid media he tested (such as ioxaglate 320 mg I/ml), and therefore one might expect heating to be of importance for the nonionic dimers, which have even higher viscosities. Only empirical testing with actual catheters can solve that problem.

A more intriguing question is what rheologic phenomena can occur once the CM has been injected into the vessel. Some information about this can be inferred from the measurements on blood–CM mixtures. These findings agree well with preliminary reports by STRICKLAND et al. (29) who also found that low-shear viscosity decreased and high-shear viscosity increased with increasing CM concentration. STÄUBLI et al. (27), who found an increase in low-shear viscosity, used a lowest shear rate of 5.8/s, which may be one explanation for the discrepancy between our results.

However, in large arteries commonly studied by angiography, typical shear rates will often exceed 100/s (8). Consequently, the high-shear viscosities will be of greater importance for these situations. If iohexol or ioxaglate is used, and if we assume the CM concentration in the vessel to be 50% at most, the small difference in high-shear viscosity is unlikely to have any substantial influence on the vessel's fluid mechanics. This, of course, presupposes that the CM is heated to body temperature.

The biologic variation between the blood of different subjects must also be taken into account; the strong dependence of whole-blood viscosity on EVF is well known (25). To be sure, the patient material in this study is small, but it does cover a wide range of EVF and whole-blood viscosities. The good agreement of the models with the data, as reflected by the high R^2 values, in particular after the logarithmic transformation, suggests that the findings remain valid within a wide range of native whole-blood viscosities.

The present study has revealed smaller effects of CM on high-shear whole-blood viscosity than have studies with older media (3, 23). Since the modern CM have lower osmolality, this is consistent with RAND & LACOMBE's conclusion (23) that the effects on whole-blood viscosity are related to hypertonicity. The somewhat higher values for the iodixanol mixtures seem to be an exception, where the inherent high viscosity of the CM outweighs the rather low osmolality.

The effects of CM injection on arterial fluid mechanics are, however, more complex than that. MORRIS et al. (21) observed that injection of a solution with higher viscosity than blood was followed by a transient increase in flow corresponding to the injected volume and then by a reduction in flow lasting for some 10 s, which they attributed to the arrival of the viscous fluid in the resistance vessels.

Later effects of CM injection on blood rheology have been studied by LLOYD et al. (20). They found that injection of diatrizoate 370 mg I/ml resulted in a significant increase in cardiac output and plasma osmolality, a significant decrease in hematocrit, and a nonsignificant decrease in blood viscosity measured at an intermediate shear rate (11.25/s). The changes were noted after 3 min and persisted for about 30 min. By the same token, STRECKER et al. (28), analyzing blood samples from patients undergoing angiography, found a significant decrease in whole-blood viscosity after CM injection. The decrease was smaller with iopromide than with diatrizoate, although this difference was not statistically significant. All these findings are consistent with an acute shift of fluid from the extracellular space to the intravascular compartment. Also this effect is expected to be less pronounced with CM that are less hypertonic.

In conclusion, the contemporary contrast agents included in this study, in particular the nonionic dimers, have higher viscosities than the CM formerly used. Nevertheless, they may still have less effect on blood rheology when used for angiography, because of their lower osmolality.

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