**Introduction**

Iodinated contrast media are widely used either to visualize blood vessels (angiography) or to enhance the density of the parenchyma of different organs. In both instances, they are administered intravascularly and ideally their effects on blood and endothelium should be minimal. However, all contrast media have some effects on the endothelium, blood, and its constituents. There is a vast literature on these effects both in vitro and in vivo. The present chapter summarizes the effects from a clinical perspective in order to clarify whether there are important differences between the types of iodinated contrast media in current clinical use.

Iodinated contrast media may be either ionic or nonionic and they all produce various effects on blood components. These effects are thought to be caused by the chemical nature of contrast media, their electrical charge, and by the viscosity and the osmolality of the solution in which they are given. Different contrast media have varying effects on the many components of the blood.

The hematologic effects of iodinated contrast media have been divided into the following categories: red blood cells, white blood cells, endothelium, platelets, coagulation, and fibrinolysis.

**Red Blood Cells**

The effect of contrast media on red blood cells can be divided into the effects on morphology, aggregation, and rheology (flow properties of the blood). When iodinated contrast media come into contact with red blood cells, the normal discoid shape of the red
blood cells changes (Aspelin et al. 1980; Nash and Meiselman 1991). Two changes caused by extraction of water may occur: either shrinkage of the red blood cells producing a dessicocyte, or changes in shape called echinocyte or stomatocyte deformation.

17.2.1 Red Cell Morphology

Dessicocyte formation is an in vitro effect of dehydration of the red blood cell and is proportional to the osmolality of the contrast media to which it is exposed (Aspelin et al. 1980). It is observed only in a fraction of red blood cells if exposed to almost undiluted high-osmolar contrast medium.

Echinocyte formation in vitro is dependent on the chemotoxicity (including electrical charge, pH, or salt concentration) (Chronos et al. 1993) and not on the osmolality of the contrast agent. All contrast media including the iso-osmolar dimers may induce some degree of echinocyte formation (Hardeman et al. 1991; Aspelin et al. 1987).

17.2.2 Red Blood Cell Aggregation

Contrast media in vitro cause disaggregation of red blood cell rouleaux and not aggregation as sometimes believed (Aspelin et al. 1987). The reason for the misunderstanding could be that contrast media make red cells more rigid causing precapillary stasis, which can be mistaken for increased red blood cell aggregation (Aspelin and Schmid-Schönbein 1978; Aspelin 1992).

17.2.3 Blood Rheology

The combined effect of the dessicocyte, echinocyte, and stomatocyte is reduced plasticity of the red blood cells as compared with normal red blood cells (Aspelin and Schmid-Schönbein 1978; Aspelin 1992; Losco et al. 2001). Plasticity is essential for the smooth flow of red blood cells through small capillaries and when it is lost there is a decrease in blood flow especially after intra-arterial injections (Dawson et al. 1983; Le Mignon et al. 1988; Strickland et al. 1992b; Pugh 1996). Pure echinocyte and stomatocyte formation without any dehydration of red blood cells produces only minor rheological change (Aspelin et al. 1980; Nash and Meiselman 1991). However, the overall in vivo effect is a mixture of the effect of contrast media on red blood cell morphology, rigidity, viscosity, and vascular tone. Contrast media can induce both vasoconstriction and vasodilatation in different organs (Morcos et al. 1998; Mills et al. 1980; Almén et al. 1980; Liss et al. 1996). In the pulmonary circulation, contrast media can induce red cell rigidity and pulmonary arterial vasoconstriction, leading to an increase in pulmonary vascular resistance (Pugh 1996; Morcos et al. 1998; Mills et al. 1980; Almén et al. 1980). In the kidney, contrast media can reduce the blood flow in the vasa recta in the medulla (Liss et al. 1996). It is not clear whether this effect is mainly caused by stasis due to vasoconstriction or by increased red blood cell aggregation in vivo. The morphological red cell changes may also affect the capacity for oxygen delivery and pH buffering (Galtung et al. 2002). However, these effects have not been proven to be of importance in clinical studies (Strickland et al. 1992a).

The overall effect of contrast media on red blood cells has not been shown to be of clinical importance.

17.3 White Blood Cells

The function of the white blood cells is mainly host defense, but their interactions with the endothelial cells and platelets are also important. White blood cells must be able to adhere to the endothelium and migrate through the vessel wall in order to phagocytize and inactive toxic products. This involves adherence, chemotaxis, degranulation, and phagocytosis. In vitro studies have shown that all these processes are affected by contrast media.

17.3.1 Phagocytosis

Contrast media reduce the ability of white blood cells to exhibit phagocytosis (Rasmussen et al. 1988, 1992b; Rasmussen 1998). This effect has been studied only with ionic, high-osmolar contrast media. It may also be caused by calcium chelating agents in the solution. The clinical importance of these in vitro observations is not known.
17.3.2 Chemotaxis, Granulocyte Adherence, and Inflammation

Contrast media have been shown in vitro to inhibit the chemotoxic response of white blood cells. In vivo studies have not shown this finding to be significant (Rasmussen et al. 1992c). All contrast media decrease the adherence property of white blood cells (Rasmussen et al. 1992a; Barani et al. 2002; Blann et al. 2001; Zhan et al. 1998). Contrast media may interfere with the inflammatory response of white blood cells in the body (Hernanz-Schulman et al. 2000; Fanning et al. 2002; Laskey and Gellman 2003).

There are no clinical data to suggest that any of these interactions between contrast media and white blood cells are of clinical importance.

17.4 Endothelium

Endothelial cells contribute to the regulation of many aspects of vascular homeostasis, including coagulation, fibrinolysis, and platelet function. In addition, they are important modulators of vascular tone, primarily by the regulated secretion and rapid clearance of powerful vasoactive mediators such as prostacyclin, nitric oxide, endothelin, and adenosine. The endothelium also controls solute permeability and leukocyte movement during the generation of inflammatory and immune responses (Pearson 1991).

Endothelial cells are exposed transiently to high concentrations of contrast media following intravascular administration. The endothelial effects of contrast media may contribute to the hemodynamic disturbances, thrombosis, and pulmonary edema associated with the intravascular use of these agents.

Modulation of the production of endothelial vasoactive substances plays an important role in mediating the hemodynamic effects of contrast media particularly in the kidney (Morcos 1998). Contrast media can increase the release and expression of the potent vasoconstrictor peptide endothelin by the endothelial cells (Oldroyd and Morcos 2000). In addition, contrast media may decrease the endothelial production of nitric oxide by reducing the activity of the enzyme nitric oxide synthase which is responsible for the endogenous synthesis of this vasodilator (Schwartz et al. 1994; Heyman et al. 1998). How contrast media increase the release of endothelin or reduce the production of nitric oxide is not fully understood.

Contrast media, particularly high-osmolality ionic agents, have cytostatic and cytotoxic effects on endothelial cells which may precipitate thrombosis (Barstad et al. 1996; Wilson and Sage 1994; Laerum 1983; Morgan and Bettmann 1989; Fauser et al. 2001; Gabelman et al. 2001; Sumimura et al. 2003). In addition, contrast media can induce apoptosis (programmed cell death) of endothelial cells (Zhang et al. 2000). An increase in the frequency of apoptosis in the endothelium may alter vascular homeostasis including coagulant and thrombotic properties, permeability and tone of the blood vessel wall, as well as vessel growth and angiogenesis (Zhang et al. 2000).

The biocompatibility of contrast media is influenced both by osmolality and chemical structure, particularly the presence of carboxyl groups in the molecules of the ionic agents. In nonionic media, the absence of carboxyl groups and the presence of many hydroxyl groups that increase hydrophilicity markedly improve biocompatibility and significantly reduce cytotoxicity (Heptinstall et al. 1998; Éloy et al. 1991; Labarthe et al. 2003; Albanese et al. 1995). Ionic contrast media, in particular high-osmolar agents, have greater effects on enzymes and higher affinity to proteins and lipids in comparison to nonionic media, and can induce injury to cell membranes and interfere with cell metabolism (Krause and Niehues 1996; Dawson 1996). In addition, contrast media can penetrate endothelial cells, forming dense granules on the luminal surface and pinocytotic vesicles (Nordby et al. 1989).

Ionic contrast media may increase vascular endothelial permeability leading to pulmonary edema (Morcos 2003; Furuta et al. 2001, 2002; Sendo et al. 2000; Tominaga et al. 2001; Emery et al. 2001). Subclinical pulmonary edema without obvious signs or symptoms of respiratory distress is thought to be common after intravascular use of contrast media but its true incidence is difficult to establish (Idée et al. 2002). Pulmonary edema produced by contrast media could also be responsible for the increase in the pulmonary vascular resistance (PVR) caused by these agents (Morcos 2003). Experimental studies have shown that ioxaglate induced the largest increase in PVR of the isolated rat lung preparation and more marked pulmonary edema compared to other classes of contrast media (Furuta et al. 2001, 2002; Sendo et al. 2000; Tominaga et al. 2001; Emery et al. 2001). However,
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these experimental observations have not been confirmed in larger clinical studies (Idée et al. 2002).

The endothelial effect of high-osmolar ionic contrast media is of clinical importance in phlebography because of the increased frequency of thrombosis after the procedure.

17.5

Platelets

Briefly, platelets adhere to exposed collagen, von Willebrand factor, and fibrinogen at the site of arterial injury (adhesion step). Adherent platelets are then activated by mediators such as thrombin, collagen, adenosine diphosphate (ADP), serotonin, etc. (activation step). Activated platelets degranulate and secrete chemotaxins, clotting factors, and vasoconstrictors, thereby promoting thrombin generation, vasospasm, and additional platelet accumulation (aggregation step) (Ferguson et al. 2000; Becker 2001). Therefore, when the interaction of contrast media with platelets is assessed, each step of platelet physiology should be evaluated separately.

17.5.1

Experimental Effects

17.5.1.1

Platelet Adhesion

Grabowski et al. (1991a, b) showed that in vitro platelet adhesion/aggregation was inhibited in the order diatrizoate > ioxaglate > iohexol > saline. However, these effects were rapidly diminished because of hemodilution. In a baboon study (Markou et al. 2001), contrast media were found to inhibit platelet deposition on stents in the order ioxaglate > iohexol > iodixanol > saline. Thus, all contrast media inhibit platelet adhesion, with ionic agents being more potent than nonionic ones.

17.5.1.2

Platelet Activation by Thrombin

In vitro platelet activation by thrombin was inhibited by low-osmolar ionic contrast media, whereas non-ionic monomeric and dimeric contrast media did not affect it (Li and Gabriel 1997).

17.5.1.3

Direct Platelet Activation

Direct activation of platelets (i.e., degranulation and release of the procoagulant content of dense bodies and α-granules) was induced in vitro by nonionic monomeric contrast media. Lesser activation was caused by high-osmolar ionic contrast media and there was no activation by low-osmolar ionic and non-ionic dimeric contrast media (Chronos et al. 1993; Corot et al. 1996). Chronos et al. (1993) showed that blood from patients anticoagulated with heparin and pretreated with aspirin in preparation for percutaneous coronary angioplasty (PTCA) showed the same pattern of nonionic monomeric contrast-medium-induced platelet activation as normal subjects.

17.5.1.4

Platelet Aggregation

An inhibitory effect of contrast media on platelet aggregation was first described by Zir et al. (1974) and has been widely investigated since. Both high-and low-osmolar ionic contrast media inhibit in vitro platelet aggregation (induced by mediators such as thrombin, ADP, or collagen) more than nonionic agents (monomeric or dimeric) (Heptinstall et al. 1998; Elory et al. 1991). Potentiation of the antithrombotic effects of clopidogrel, an antiaggregant drug, has been found in rats with an ionc low-osmolar contrast medium but not with a nonionic monomer (Labarthe et al. 2003).

17.5.2

Clinical Pharmacology Studies

Clinical pharmacology studies comparing the different categories of contrast media, however, led to more equivocal conclusions than in vitro or animal studies.

In one study of patients, no significant platelet activation (P-selectin expression) was found following left ventriculography or coronary angiography with iohexol (Albanese et al. 1995). Similarly, Arora et al. (1991) and Brzoko et al. (1997) did not find a significant difference between ionic and non-ionic contrast media when platelet degranulation markers were measured in peripheral venous samples. Polanowska et al. (1992) reported an increase in the venous level of β-thromboglobulin following arteriography with a high-osmolar contrast agent.
Conversely, in another study (Jung et al. 2002), following cardiac catheterization, no platelet activation was found with ioxaglate, whereas serotonin release was detected following injection of a nonionic monomer. Most of these studies, with the exception of that of Albanese et al. (1995), evaluated peripheral venous and not local blood samples. It is known that arterial catheterization itself may activate platelets.

With respect to platelet aggregation, most clinical pharmacology studies have shown a higher antiaggregatory effect for ionic agents than nonionic monomers, as confirmed by Dalby et al. (2002) and Eloy et al. (1991). However, one study did not show a difference between these categories of contrast media (Stormorken et al. 1986).

The clinical impact of these in vitro and experimental in vivo changes is debatable and is discussed in the section on coagulation.

In summary, there are no clinical data to suggest that the effect of nonionic contrast media on platelets induces increased coagulation. The mechanisms responsible for the effects of contrast media on platelets are still unclear and clinically significant effects have not been shown.

17.6 Coagulation

17.6.1 In Vitro Effects of Contrast Media

All contrast media inhibit blood coagulation but to different extents. Prothrombin time, reptilase time, activated partial thromboplastin time, and recalcification clotting time are significantly increased in proportion to the dose of the contrast media (Eloy et al. 1991). Comparison of assays of fibropeptide A and thrombin–antithrombin complex between ionic agents (both monomeric and dimeric) and nonionic monomers showed that coagulation times were shorter for nonionic monomers, but were always longer than in the controls (Idée et al. 2002; Corot et al. 1989; Engelhart et al. 1988; Grabowski et al. 1991a, b; Parvez and Moncada 1986; Parvez and Vik 1991; Rausli et al. 1989).

The ionic dimer ioxaglate shows an anticoagulant activity similar to that of the ionic monomers (Eloy et al. 1991). In one study, the nonionic dimer iodixanol was found significantly less anticoagulant than the nonionic monomer iohexol (Corot et al. 1996), while in another study it was reported that iodixanol affects the bleeding time similar to nonionic monomers (Melton et al. 1995). However, the precise mechanisms responsible for this inhibition are still unclear. It has been suggested that the main factors are inhibition of activation of factor X, which leads to the formation of thrombin from prothrombin (Eloy et al. 1991; Fay and Parker 1998; Idée and Corot 1999) and inhibition of fibrin polymerization (Stormorken et al. 1986; Fay and Parker 1998; Dawson et al. 1986; Dawson 1999). Al Dieri et al. (2001, 2003) showed that ioxaglate blocks feedback activation of factors V and VIII, significantly inhibits platelet-dependent thrombin generation, and boosts the effect of abciximab, whereas iodixanol does not. Interference with the assembly of fibrin monomers by contrast media results in poor fibrin stabilization of clots (Chronos et al. 1993; Engelhart et al. 1988).

Therefore, ionic monomers and dimers have similar anticoagulant activity in vitro, which is more pronounced than that of nonionic monomers and dimers. Nonionic monomers probably have more anticoagulant effect than nonionic dimers.

17.6.2 Clinical Trials

Clinical data are less easy to evaluate because of patient-related and procedure-related variability (state of the hemostatic system, condition of the vessel wall, use of guidewires, catheters, balloons, stents). Because of the rapid clearance of contrast media, their anticoagulant effect is local rather than systemic and their effect may be not significant if measured in distant peripheral blood vessels.

Following the in vitro observation by Robertson (1987) of more frequent clot formation in blood contaminated syringes with nonionic monomers than with ionic agents, a few case reports of thrombotic complications in diagnostic angiography with nonionic monomers have been published (Bashore et al. 1988; Grollman et al. 1988; Millet and Sestier 1989). However, trials have shown no clinical evidence of significant differences in thrombotic complications when ionic agents are compared to nonionic monomers for coronary angiography (Davidson et al. 1990; Schrader 1998).

Randomized trials comparing ioxaglate to nonionic monomers during PTCA have produced
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conflicting results (Piessens et al. 1993; Grines et al. 1996; Esplugas et al. 1991; Malekianpur et al. 1998; Schrader et al. 1999; Fleisch et al. 1999; Danzi et al. 2003). In the two studies with the largest number of patients, one showed no significant difference between ioxaglate and iomeprol in the incidence of sudden vessel occlusion (Schrader et al. 1999), whereas the other showed a trend toward less thromboembolic complications with ioxaglate compared to ioversol (Fleisch et al. 1999). Scheller et al. (2001) reported that patients undergoing stent placement had fewer acute and subacute stent occlusions when imaged using ioxaglate (vs. multiple nonionic agents). However, Danzi et al. (2003) reported that nonionic monomers (iopamidol and iopromide) did not adversely affect stent patency when compared to ioxaglate. The considerable periprocedural use of anti-platelet agents may explain their results. A meta-analysis comparing nonionic monomers to ioxaglate showed a significant reduction of coronary vessel abrupt occlusions with ioxaglate (Cucherat and Leizorovicz 1999). Iodixanol was compared to ioxaglate in three trials. In one, no significant differences with regard to major adverse cardiac events (MACE) were detected (Bertrand et al. 2000). In the second, high-risk patient group, less abrupt vessel occlusions (p = 0.05) were found with iodixanol (Davidson et al. 2000). This difference was more significant in patients who did not receive GpIIb/IIIa blockers. In the third, no significant differences between the two media were found and there was no clear advantage with the use of an ionic contrast agent in a large population of patients undergoing percutaneous coronary intervention for both stable and unstable coronary artery disease (Sutton et al. 2002).

17.6.3 Contrast Media Interactions with Angiographic Devices

Interactions of contrast media with angiographic devices have been investigated both in vitro and in vivo. The syringe material greatly influenced the possibility of clot formation in syringes containing contrast media and blood. Glass was a more powerful activator of coagulation than plastic, and among the plastic syringes those made of styrene acrylonitrile activated coagulation more than those made of polypropylene. Furthermore, clots formed only in situations where there was very poor angiographic technique (Dawson et al. 1986).

Teflon-coated catheters and guidewires are more thrombogenic than polyurethane materials and much more than polyethylene materials (Dawson 1999). Idée and Corot (1999) comprehensively reviewed the many factors influencing clotting in catheters, including the length of the procedure, blood/catheter contact time, volume of blood in the catheter, size and type of the catheter, type of contrast material, and degree of blood/contrast medium mixture in the catheter. Some of these factors are difficult to control or standardize in clinical studies.

Therefore, catheter and guidewire materials probably play a significant role in clinical studies of contrast media and coagulation. The use of equipment with technically improved surfaces will probably largely overcome this problem.

17.7 Fibrinolysis

Contrast media impede fibrinolysis and delay the onset of lysis by recombinant tissue-type plasminogen activator (rt-PA), urokinase, and streptokinase (Dehmer et al. 1995). This effect is reduced by increasing the concentration of the lysis agent. Contrast media cause fibrin to form in long/thin fibrils, which have a lower mass/length ratio and are more resistant to fibrinolysis (Gabriel et al. 1991; Parvez et al. 1982). In vitro studies have shown that diatrizoate and iohexol delay the onset of lysis induced by all lysis agents. However, ioxaglate delayed the onset of lysis by rt-PA and urokinase but not by streptokinase (Dehmer et al. 1995). Another in vitro study showed that thrombi formed with iodixanol and iohexol are larger and more resistant to thrombolysis when compared to thrombi formed with ioxaglate (Jones and Goodal 2003). In vivo studies in dogs showed that alteplase-induced thrombolysis could be delayed by iohexol and amidotrizoate, whereas ioxaglate had no significant effect (Pislaru et al. 1998). In a small group of patients undergoing pulmonary angiography, iohexol significantly increased plasma levels of PAI-1, an inhibitor of t-PA and urokinase, while ioxaglate did not (van Beek et al. 1994). Other effects on fibrinolysis caused by interactions of contrast media with concomitantly given drugs are described in more detail in Chap. 20.
Conclusion

All contrast agents may alter the morphology and function of red blood cells. However, the overall effect of contrast media on red cells has not been shown to be of clinical importance. Similarly, the effect on white blood cells has not been shown to be clinically important.

In vitro studies have shown that nonionic monomers cause more activation of platelets than ionic contrast media. Iso-osmolar dimeric contrast media have not been shown to activate platelet function. Clinical studies have not confirmed these in vitro observations.

Contrast media have cytostatic, cytotoxic, and apoptotic effects on endothelial cells. These effects are more evident with ionic contrast media, in particular high-osmolar agents, than with nonionic media. Contrast media-induced endothelial injury may play a role in the pathophysiology of the effects of contrast media. These include hemodynamic effects, thrombosis, and contrast media-induced pulmonary edema.

The risk of thrombosis induced by contrast media relates to the combined effect on platelets, endothelial cells, and coagulation factors. In clinical practice, high-osmolar contrast media can induce thrombosis after intravenous injection, mainly because of endothelial injury produced by high osmolality. This effect is less with nonionic low-osmolar and iso-osmolar contrast media.

All contrast media have anticoagulant properties, and ionic media are more anticoagulant than nonionic compounds. Acute and subacute thrombus formation remains a topic of debate, including the use of low-osmolar ionic contrast media in preference to low-osmolar nonionic contrast media in coronary interventions. However, the general consensus is that a good angiographic technique is the most important factor in reducing thrombotic complications. Drugs and interventional devices that decrease the risk of thromboembolic complications during interventional procedures minimize the importance of the effects of contrast media (AGUIRRE et al. 1997).

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