Chapter from the book *Advances in the Diagnosis of Coronary Atherosclerosis*
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1. Introduction

Since its introduction several decades ago, coronary angiography and intervention has become a widely and ever increasingly popular diagnostic and therapeutic modality. However, it is not devoid of occasional systemic and local complications, and their immediate detection and management are crucial to achieving a favourable clinical course. This chapter focuses on the mechanism, diagnosis and treatment of the inherent risks of coronary angiography and intervention.

2. Systemic complications

Coronary angiography and intervention comprise local procedures performed via a percutaneous vascular approach. Untoward hemodynamic and systemic hormonal changes and toxic effects of the contrast agents used might occur during and after procedures. Patient’s general status, comorbid conditions and degree of systemic atherosclerosis are the most important factors predisposing to the development of systemic complications. Effective pre-procedural preparation and immediate proper treatment help prevent event occurrence and its subsequent deterioration to permanent sequelae.

2.1 Side effects of contrast agent

Use of contrast agents has a long history since the introduction of X-ray technology in 1895, and progressive changes after Douglas Cameron of Minnesota recommended the use of sodium iodide for retrograde phelography reduced toxicity leading to current angiography practices. The side effects of contrast agents are related to their osmolarity, hydrophilicity and viscosity, and there currently are different kinds of contrast media available which can be classified according to their chemical characteristics (Table 1).

Osmolarity is the most important characteristic of contrast agents, which thereby are classified into high-osmolar (~2,000 mOsm/kg), low-osmolar (600~800 mOsm/kg) and iso-osmolar (290 mOsm/kg) contrast media. Commonly, high osmolar contrast agents induce fluid shift into vessels, which can cause a febrile sensation and pain. Also, high osmolar contrast media take cellular fluid from cells including red blood cells and therefore lead to dehydration and morphological changes. Hemodilution and hypervolemia can further
aggravate heart failure when present. In the past 60 years, high-osmolar contrast media with osmolarity 5–8 times higher than that of plasma have been replaced by low-osmolar contrast media having osmolarity 2–3 times higher than that of plasma.

<table>
<thead>
<tr>
<th>Osmolarity</th>
<th>Molecular structure</th>
<th>Component</th>
<th>Iodine concentration (mg/mL)</th>
<th>Osmolarity (mOsmol/kg)</th>
<th>Viscosity at 37°C (cps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-osmolar</td>
<td>Ionic monomer</td>
<td>Sodium iothalamate</td>
<td>320–370</td>
<td>1,500–2,100</td>
<td>2.75–5.0</td>
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<tr>
<td></td>
<td></td>
<td>Meglumine diatrizoate</td>
<td></td>
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<tr>
<td>Low-osmolar</td>
<td>Ionic dimer</td>
<td>Meglumine ioxaglate</td>
<td>320</td>
<td>580</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iopamidol</td>
<td>300</td>
<td>520–672</td>
<td>4.5–6.3</td>
</tr>
<tr>
<td></td>
<td>Nonionic dimer</td>
<td>Iotrolan</td>
<td>240</td>
<td>320</td>
<td>8.1</td>
</tr>
<tr>
<td>Iso-osmolar</td>
<td></td>
<td>Iodixanol</td>
<td>320</td>
<td>290</td>
<td>11.4</td>
</tr>
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</table>

Table 1. Characteristics of contrast media

Cell membranes consist of phospholipid bilayers which are resistant to hydrophilic molecules. Therefore hydrophilic contrast agents are safer than hydrophobic ones. Viscosity increases as iodine concentration increases and temperature decreases; therefore, contrast agents should be heated from room temperature to body temperature before use. Early ionic contrast agents were associated with high incidence of early systemic side effects such as nausea, urticaria, pain, and heat sensation by comparison to non-ionic agents. Therefore, ionic agents have been replaced with non-ionic agents. However, the incidence of late skin reaction, i.e., 24 hours after injection of non-ionic dimeric agents is relatively high as compared to monomeric agents (Sutton et al 2001).

The side effects of contrast media are divided into anaphylactoid and non-anaphylactoid reactions. Most of the adverse effects occur within 20 minutes after administration of contrast agents. Therefore, the patient’s systemic symptoms, blood pressure, heart rate and rhythm, and respiratory status should be carefully monitored early after contrast injection. Furthermore, the catheterization laboratory always should be ready for cardiopulmonary resuscitation.

2.1.1 Anaphylactoid reactions

Anaphylactoid reaction is a life-threatening side-effect of contrast media which occurs within 20 minutes and requires immediate, intensive therapy; the incidence of use of high osmolar contrast agent is approximately 1–3 % and a fatal reaction has been estimated at 0.9 cases per 100,000 exposures (Krause 2010). The term anaphylactoid reaction refers to a syndrome that albeit clinically similar to anaphylaxis differs from true hypersensitivity reactions by mast cell or basophil degranulation which is independent from immunoglobulin-E mediation, not requiring previous sensitisation, and not consistently recurring in an experienced patients (Hong et al 2002). Mild symptoms include urticaria,
pruritus, dizziness, mild dyspnea, nausea and vomiting and these are usually self-limiting and resolving with minimal medical therapy. In severe cases, symptoms such as hypotension, bronchospasm, laryngeal edema, abdominal cramps, pulmonary edema, syncope, and serious arrhythmias can occur and lead to death and therefore require intensive treatment. In patients who are at high risk of an anaphylactoid reaction to contrast media, H1 antihistamines and corticosteroids prior to the administration of ionic contrast may be useful in preventing anaphylactoid reactions to contrast agents (Delaney et al 2006). The treatment of anaphylactoid reactions depends on the severity of symptoms and clinical findings. Monitoring of the respiratory status and oxygen concentration is very important. If mild bronchospasm occurs, patient can be treated with oxygen supplementation and/or bronchodilator inhalation. In moderate cases, 0.1-0.3 mL of 1:1000 epinephrine should be subcutaneously administered carefully, especially in patients with cardiac disease. In more severe cases, 1 mL of 1:10,000 epinephrine can be administered intravenously for 5 minutes, which can be repeated every 10 minutes. Additionally, antihistamines may be administered. Hypotension is another serious side effect of contrast agents. Immediate oxygen supplementation and isotonic fluid supplement is necessary, and if ineffective, dopamine at an infusion rate of 2-20 μgm/kg/min can be administered.

2.1.2 Non-anaphylactoid reactions

Early (<24 hours) and late (24 hours ∼ 7 days) reactions may occur after injection of contrast agents. The mechanisms of the late reactions are unknown and their manifestations are very diverse and non-specific, including flulike symptoms such as general weakness, headache, fever, chill, vomiting, abdominal pain, constipation or diarrhea, pruritus and rash. Most symptoms are self-limiting and respond well to symptomatic treatment and fluid administration.

Hypotension and bradycardia as consequence of vasovagal stimulation associated with high-osmolar contrast infusion are common. Isotonic fluid and atropine administration (0.5~1 mg, intravenously, repeated every 3-5 minutes) are effective in most cases. Life threatening cardiac arrhythmias such as ventricular tachycardia and ventricular fibrillation can occur after rapid injection of contrast media, especially in patients with acute myocardial infarction. Careful ECG monitoring after first contrast injection and immediate cardioversion or defibrillation should be performed.

Contrast-induced nephropathy (CIN), an important complication in the use of contrast media, is associated with increased frequency of late cardiovascular events after coronary intervention as well as increased risk of death. The commonly used definition of CIN is a rise in serum creatinine level of 0.5 mg/dL or a 25% increase from baseline value, assessed at 48 hours after angiography (Solomon et al 2010). The incidence of CIN in patients undergoing coronary intervention varies depending on the definition, preventive management, baseline renal function and procedures, and it ranges between 2~37% (Solomon et al. 2010, Gruberg et al 2000). There are several known risk factors for CIN (Table 2). The type of contrast media used is one of the important factors for the development or aggravation of renal failure. A meta-analysis showed that low-osmolarity contrast media was associated with significantly lower rates of CIN than high-osmolarity contrast media, especially in patients with pre-existing renal failure (Barrett et al 1993). Also, iso-osmolar contrast media have been shown to be associated with a lower risk of CIN than low-osmolar contrast media in patients with high risk for the development of CIN.
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Patient comorbidities

- Diabetes mellitus
- Congestive heart failure
- Acute hypotension
- Anemia
- Myocardial infarction
- Nephrotoxic drugs
- Volume depletion
- Reduced renal function (eGFR < 60 mL/min/1.73 m²)

Procedural factors

- Contrast volume
- Type of contrast
- Periprocedural hypotension

Table 2. Risk factors for contrast-induced nephropathy (Solomon et al. 2010, McCullough 2008)

The pathophysiology of CIN remains unknown; however, it is believed to result from release of acute vasoconstrictors induced by adenosine, endothelin, prostaglandin leading to ischemic injury and death of renal tubular cells (McCullough 2008). Although more clinical studies are needed, some effective preventive measures have been suggested based on postulated mechanisms and clinical trial results (Table 3). Volume expansion is the easiest and most effective method although there are limited data on optimal solution and volume. Although many pharmacological agents including antioxidants, ascorbic acid, statins, prostaglandins, aminophylline/theophyllines and N-acetylcysteine (NAC) have been suggested for the prevention of CIN, none has been proven effective. Also, there are inconsistent data regarding the renal protective effect of hydration, N-acetylcysteine, and theophylline. Among them, NAC is considered as a cost effective and safe agent, and the combination of volume expansion and NAC is more effective than NAC alone (Briguori et al 2007). A meta-analysis showed N-acetylcysteine as more renoprotective than hydration alone; theophylline also might reduce risk for contrast-induced nephropathy however the detected association did not achieve statistical significance (Kelly et al 2008).

<table>
<thead>
<tr>
<th>Pre- and post-procedure</th>
<th>Hold nephrotoxic agents</th>
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<tbody>
<tr>
<td></td>
<td>- Anti-inflammatory drugs</td>
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<td></td>
<td>- High dose diuretics</td>
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<td></td>
<td>- Aminoglycosides</td>
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<tr>
<td>Volume expansion (Isotonic saline with/without bicarbonate solution)</td>
<td>1.0 mL/kg/hr, 12 hours before and 12 hours after procedure</td>
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<td></td>
<td>- Urine flow : &gt;150 mL/hr</td>
</tr>
<tr>
<td></td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td></td>
<td>- 1200 mg oral bid pre-and post-procedure</td>
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<table>
<thead>
<tr>
<th>During procedure</th>
<th>Use iso- or low-osmolar contrast</th>
</tr>
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<tr>
<td></td>
<td>Lowest dose of contrast</td>
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<table>
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<tr>
<th>Post-procedure</th>
<th>Dialysis and hemofiltration</th>
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</table>

Table 3. Suggestive preventive measures for contrast-induced nephropathy in patients at risk
2.2 Cholesterol embolization syndrome
Cholesterol embolization syndrome (CES), known as blue toe syndrome, is caused by systemic embolization of cholesterol crystals from aortic atherosclerotic plaques. CES is suggested by the gradual onset of peripheral cutaneous manifestations, livedo reticularis, accompanied by progressive increases in blood urea nitrogen and creatinine levels following an arterial catheterization procedure. The aortic plaques easily come off the aortic wall and embolize to the brain, eyes, kidneys and extremities. Eosinophilia which is present in up to 80% of cases might be an important clue to early detection of cholesterol embolization syndrome (Wilson et al 1991). The clinical incidence is 0.09∼1.4%, varying according to the aggressiveness of procedures such as diagnostic angiography, coronary intervention and peripheral vascular intervention (Fukumoto et al 2003, Scolari et al 1996). Elevation of baseline plasma C-reactive protein (CRP) level is a risk factor independently associated with CES indicating an important association between systemic inflammation and CES (Fukumoto et al. 2003). The clinical presentation varies from asymptomatic to multi-organ failure. In-hospital mortality is 16% which is increased to 70~90% in patients with diffuse embolism and multi-organ failure (Fine et al 1987). When CES is suspected, it is recommended to discontinue anticoagulation because several case reports have suggested that patients are more likely to develop CES when they are anticoagulated (Bruns et al 1978). Most of the treatments are supportive with symptomatic measures.

2.3 Stroke
The cerebral embolism rate associated with coronary angiography is dependent on the clinical characteristics of the patients, catheterization methods, imaging modalities for the diagnosis, and clinical severity. In one series, silent ischemic cerebral lesions detected by diffusion-weighted MRI were found in 5-22% patients after cardiac catheterization (Hamon et al 2006, Busing et al 2005). After diagnostic coronary angiography via femoral approach, stroke occurred in 0.11%, with a persistent neurological defect in only 0.04% (Ammann et al 2003). Although radial access for coronary angiography is more prone than femoral access to generating more particulate cerebral microemboli which can pass the right middle cerebral artery, femoral and radial access are associated with similar rates of stroke.

3. Local complications
Local vascular puncture and closure necessary in all catheterization procedures can cause a variety of local complications, ranging from minor problems resolving with time to major complications with long-term sequelae. For the individual patient, the risk is dependent upon cardiovascular anatomy, the experience of the operator, and the type of procedure being performed. Immediate detection and proper treatment is vital for the prevention of catastrophic events.

3.1 Local hematoma and bleeding
Local bleeding and hematoma at the arterial puncture site are the most common complications of angiography. Small hematomas at the femoral puncture site are relatively common and usually insignificant; however, severe bleeding and hematoma requiring transfusion occur in 1.5∼5.8% of the cases. Most hematomas occur within 12 hours after sheath removal. Immediate bleeding occurring after sheath insertion is induced by arterial laceration at the site of the atherosclerotic vessel wall. Otherwise, delayed bleeding after sheath removal is due to inappropriate compression or coagulation disorders. Clinically,
risk factors are old age, female gender, high blood pressure, use of large sized sheaths, long procedural times and use of anticoagulants and glycoprotein IIb/IIIa receptor antagonists before or after procedures. Many arterial closure devices are available as an alternative to traditional mechanical compression. Although these devices have the potential to reduce the time to hemostasis, facilitate patient mobilization and decrease hospital length of stay, the incidence of access-site-related complications is similar or somewhat higher compared with mechanical compression (Nikolsky et al 2004, Biancari et al 2010). Local bleeding is transformed to hematoma, which spontaneously resolves in 1–2 weeks in small hematomas, or in several weeks or months in large hematomas. Table 4 describes the general recommendations for postprocedural hemostasis after femoral artery access listed in the American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on Cardiac Catheterization Laboratory Standards (Bashore et al 2001).

<table>
<thead>
<tr>
<th>Situation</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Following hemostatic closure device</td>
<td>1–2 h recumbent in position of comfort, then ambulate 3 30 min before discharge</td>
</tr>
<tr>
<td>Following removal of venous sheath</td>
<td>1 h with leg straight, then ambulate 3 30 min before discharge</td>
</tr>
<tr>
<td>Following removal of femoral arterial sheath (ACT, 175 s)</td>
<td></td>
</tr>
<tr>
<td>Manual compression</td>
<td>10–20 min (until hemostasis achieved)</td>
</tr>
<tr>
<td>Clamp</td>
<td>15 min to 1 h to achieve hemostasis</td>
</tr>
<tr>
<td>Bedrest</td>
<td>Leg straight, slight head elevation X 2–6 h</td>
</tr>
<tr>
<td>Ambulation</td>
<td>30 min to 1 h before discharge</td>
</tr>
</tbody>
</table>

Table 4. General recommendations regarding postprocedural hemostasis after prior femoral artery access (Bashore et al. 2001)

3.2 Pseudoaneurysm

After removal of the sheath and compression, the puncture site is surrounded and blocked by local hematoma. Inappropriate compression favours come-and-go blood flow between artery lumen and aneurysm surrounded by hematoma. Femoral pseudoaneurysm is the second most common complication occurring in 0.1% to 0.2% of diagnostic angiograms and 3.5% to 5.5% of interventional procedures (Demirbas et al 2005, Kronzon 1997). If hemostasis is achieved using manual compression, the pseudoaneurysm rate is higher in superficial femoral artery than common femoral artery access, however rates are similar when using closure devices (Gutzeit et al 2011). In patients with acute coronary syndrome who are undergoing emergency angiography and possible intervention, pseudoaneurysm rate needing closure is lower in radial compared with femoral angiography (HR 0.30, 95% CI 0.13–0.71; p=0.006) (Jolly et al 2011). Small femoral pseudoaneurysm is usually filled with clots and does not require treatment, however, larger femoral pseudoaneurysms may lead to secondary complications including rupture, local pain and compression of the adjacent femoral vein or nerve (Kronzon 1997). Color Doppler ultrasonography is the best diagnostic tool with a positive diagnostic rate of 95%, however other imaging modalities such as 3-dimensional CT angiography and angiography are useful. Using color-Doppler ultrasonography, flow inside the aneurysm sac and the “to-and-fro flow” at the neck of the lesion is definitely diagnostic. Application of good external compression after sheath
removal, selecting a small-bore introducer and sheath removal at a low activated clotting time (<200 sec) are important factors preventing pseudoaneurysm. Ultrasonography guided compression of the communicating canal of the pseudoaneurysm stops the blood flow and leads to clotting and obliteration with a success rate of 84-93% in patients without anticoagulation (Lange et al 2001, Gabriel et al 2007, Schaub et al 1994). Ultrasound-guided thrombin injection is another effective means with a success rate of 97-100% (Schneider et al 2009, Weinmann et al 2002). Other endovascular approaches, such as stent graft repair and coil embolization, are also available. Open surgical repair should be considered after nonsurgical procedure failure.

Fig. 1. Doppler ultrasonography image showing a flow jet from superficial femoral artery to pseudoaneurysm surrounded by huge hematoma

Fig. 2. Computerized tomographic (CT) findings of pseudoaneurysm in a patient who underwent coronary angiography. A: Contrast enhanced pseudoaneurysm (arrow) is seen at anterior aspect of the superficial femoral artery. B: Three-dimensional reconstruction of the same patient showing saccular pseudoaneurysm (arrow), superficial femoral artery and anteria profunda femoris.
3.3 Arteriovenous fistula
Although iatrogenic femoral arteriovenous fistula is very rare with an incidence of 0.22%, it is a significant complication after femoral puncture technique (Sidawy et al 1993). The fistulas originating at the superficial femoral artery or at the profunda femoris artery drain to the superficial femoral, profunda femoris vein or its lateral circumflex branch. Below the femoral artery bifurcation, profunda femoralis vein crosses laterally behind the proximal superficial femoral artery and then lies in a posterior location to the profunda femoris artery. Therefore, it is important to avoid a low groin puncture by identifying the level of the inguinal ligament or localizing the distal half of the femoral head by fluoroscopy (Sidawy et al. 1993, Lamar R 1990). Early angiography and surgical correction are recommended for optimal results.

3.4 Retroperitoneal hematoma
Retroperitoneal hematoma occurs in less than 1% of cases of percutaneous coronary intervention. Clinical signs and symptoms include decreased haematocrit, back or inguinal pain, abdominal pain, diaphoresis, bradycardia and hypotension. Early recognition of retroperitoneal hematoma is very important because the diagnosis is often delayed as symptoms are nonspecific and difficult to recognize because blood silently tracks in the loose retroperitoneal fatty tissue. Factors predisposing to retroperitoneal hematoma are female gender, low body surface area, and higher femoral artery puncture (Farouque et al 2005). It can be easily detected on computerized tomography as an abnormal, high-density soft-tissue mass originating at the puncture site and contiguous with the retroperitoneum with resultant compression or distortion of the normal retroperitoneal structures. There is lack of clinical evidence for the best management of retroperitoneal haematoma. Inguinal compression is not effective in most cases. Retroperitoneal hematoma after femoral artery puncture can usually be treated by volume replacement, correction of coagulopathy and blood transfusion. A small subset of patients who are unresponsive to volume resuscitation require open repair of bleeding vessel (Kent et al 1994).

Fig. 3. Angiographic findings of pseudoaneurysm before (A) and after (B) coil embolization.
3.5 Spasm
Arterial spasm near the puncture site occurs when arterial size is too small for the sheath. The transradial approach for coronary angiography or angioplasty is increasingly being used as an alternative to femoral access due to its low rate of local complications. Arterial spasm is the most common complication of this technique especially in female patients. Use of hydrophilic coated sheath, but not long sheath, reduces the incidence of radial artery spasm during transradial coronary procedures (Rathore et al 2010). Intra-arterial or subcutaneous infusion of nitroglycerin reduces arterial spasm and facilitates introduction of catheters (Candemir et al 2009).

4. Conclusion
It is critical to make every attempt at minimizing occurrence of complications during and after coronary angiography and interventional procedures; beyond operator’s experience and the patient factors noted, this involves care and attentiveness. The impact of improved understanding and techniques in intervention should be added to management considerations. Coronary angiography and intervention is continuously evolving and knowledge acquired through clinical experience and availability of new devices should therefore allow safer procedures in the future.

5. References


Krause RS (2010). Anaphylaxis: e-Medicine from WebMD


Coronary artery disease (CAD) and its consequences are most important morbidity and mortality reasons in the developed and developing countries. To prevent hard end-points, early definitive diagnosis and optimum therapy play significant role. Novel advanced diagnostic tests which are biomarkers of inflammation, cell adhesion, cell activation and imaging techniques provide to get the best result in the detection and characterization of calcified or uncalcified atherosclerotic plaques. In spite of last developments in the imaging methods, coronary catheterization is still frequently performed. Following the first cardiac catheterization performed in 1844, date by date historical developments and the mechanics of cardiac catheterization techniques, risks associated with coronary angiography, and also, preventions and treatments of possible complications have been presented in this book. Other important issue is radiation exposure of patients and staff during coronary angiography and scintigraphy. Radiation dose reduction techniques, general radiation protection principles have been discussed in related chapters.

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