The Physiologic Effect of Contrast Media Used for Angiography

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The deaths from angiography at Wisconsin General Hospital were reviewed and found to be two per cent of 249 patients. These 5 deaths are reported briefly. Investigation was carried out to determine the hemodynamic effects of contrast substances on 12 dogs. In general, there was a temporary increase in right atrial and pulmonary arterial pressure followed by a rather marked decrease in systemic arterial pressure and tachycardia. The significance of these findings is discussed in relation to shunts within the heart or between the aorta and pulmonary artery.

Death following administration of a contrast substance for the purpose of angiography leaves an indelible impression upon the clinician and radiologist. Several investigators have evaluated this problem as related to specific angiographic contrast substances and considerable experimental work has been done. It has been shown that Diodrast in high concentration produces an increase in the heart's force of contraction and an increase in coronary blood flow in the isolated rabbit heart. In dogs, Diodrast given intravenously in doses equivalent to those used in clinical angiography produces a fall in peripheral arterial pressure, a rise in heart rate, an increase in venous pressure and transient changes in the QRS complex and T wave of the electrocardiogram. The permeability of the cerebral vessels to trypan blue is increased in rabbits after the intracarotid injection of Diodrast and petechial hemorrhages may occur in the brain. Convolusions have been produced by intracarotid injection of Diodrast. The injection of Diodrast into peripheral arterial vessels produces dilatation. Investigations in patients given Diodrast have shown a fall in systemic arterial blood pressure and frequent electrocardiographic changes. Neo-iopax in high concentration has been shown to decrease the output of the heart-lung preparation and to depress the isolated rabbit heart. Frequently following this initial depression in cardiac function, there occurred an improvement that went beyond the control level and was attributed to the coronary vasodilatation with increased myocardial blood supply. Respiration increased in rate and amplitude after Neo-iopax, unless the dosage was very high and then depression occurred. When given rapidly through the carotid artery, apnea, convulsions and death could be produced by Neo-iopax. Thrombosis may be produced in vessels into which this substance is injected. In patients undergoing angiography with Neo-iopax, marked hypotension frequently occurs and electrocardiographic irregularities have been reported. Intravenous injection of Urokon, in large doses, produces hyperpnea, vomiting, defecation, convulsions, collapse and sometimes death.

Deaths following angiography are
most common in patients with congenital heart disease of the cyanotic variety,7,12,13 and vary greatly in incidence from one individual's experience to another's. Dotter and Jackson12 reported that, in two large series of angiographic examinations, totaling 2,500 consecutive studies, no deaths occurred. Data collected by these authors13 from Sweden revealed one death in approximately 450 studies. Morgan reported 6 fatalities in 600 angiograms,13 Dimond and Gonlbol, 2 deaths in 100 angiograms,14 and Carnegie,16 4 deaths in 172 cases.

Since deaths are more common in patients with cyanosis and since cyanosis due to shunts is dependent upon the dynamics in both right and left sides of the heart, the present study was undertaken to investigate simultaneously the effects of contrast substance on the right and left sides of the heart.

**Methods and Materials**

All the cases of fatal reaction to angiocardiography in the University Hospitals were reviewed. Four cases who died at the time of angiocardiography or in the succeeding 24 hours were accepted for study. One additional case (number 1), in whom there can be no reasonable doubt concerning the etiologic relation of contrast substance, was included even though death occurred five days after the angiocardiogram.

Angiocardiography is performed in this institution with the patient in the recumbent position. One milliliter of contrast substance is given intravenously as a sensitivity test and the procedure is completed only if no adverse reaction occurs. When required, a minimal effective concentration of anesthetic agent is given by the open-drop method. Angiocardiograms have been performed 283 times in 249 patients with 5 deaths apparently resulting from the procedure. Neo-iopax is the substance customarily used in this hospital and was used in all the fatal cases. The fatalities occurred in 3 patients with atrial septal defects, (one isolated and 2 complicated), one with rheumatic mitral disease, and one with tetralogy of Fallot. Regardless of the outcome, injection of the radiopaque material frequently produces a profound reaction characterized by cutaneous flushing, tachycardia, and a varying period of apnea followed by hyperpnea. In case 1 this reaction was quantitated by determining pulmonary and brachial artery pressures during the angiocardiogram. A brief summary of each fatal case is appended.

In the experimental study 12 mongrel dogs weighing 8 to 24 kilograms were anesthetized with 3 mg./Kg. of morphine followed, in one hour, by 12 mg./Kg. of sodium pentobarbital. The external jugular vein was exposed and Goodale-Lubin cardiac catheters were inserted into the right atrium and the pulmonary artery. A needle was placed in the femoral artery and a cannula was tied in a peripheral vein of an anterior extremity. The blood pressures were transmitted through short flexible plastic tubes to Statham strain gages and recorded by the Sanborn Poly-Viso. Simultaneous pressures were recorded from the pulmonary artery, right atrium and femoral artery. Mean blood pressures were determined by planimetric integration of the pressure tracings. An electrocardiogram was recorded continuously during the experimental study. After a short control observation, each dog was given 1 ml./Kg. of physiologic saline solution, 75 per cent Neo-iopax, 70 per cent Diodrast or 70 per cent Urokon rapidly intravenously. Each of these agents was administered, after the total demonstrable effect of the preceding injection was completed. Use of each of these agents in each animal is believed important, since the response is, to a degree, an individual matter; being either more or less pronounced to all substances in certain animals. The sequence of administration of the four substances was varied from animal to animal in an attempt to minimize any influence of a prior injection on the effect of each substance. A limited number of observations were made with the injection of contrast substance into the pulmonary artery through a no. 9 cardiac catheter. In an attempt to find a control for effects due to the viscosity of the contrast substances, observations were made following the injection of 1 ml./Kg. of 50 per cent glucose into the pulmonary artery in 2 dogs. Even though the viscosity of all these substances may not be identical, for this purpose they seemed similar enough and the pharmacologic effect of 50 per cent glucose is certainly most evident after its passage through the great vessels and dissemination in body tissues.

**Results**

The results of the experimental study are summarized in table 1 and diagrammed in figure 3. Figure 1 illustrates a mild response to the injection of Neo-iopax into a peripheral vein and figure 2, a more pronounced response with nodal bradycardia on injection of Neo-iopax through a cardiac catheter into the pulmonary artery.

The administration of saline solution produced no significant changes. All contrast substances, however, produced rather marked responses that were similar but less pronounced, when injection was in a peripheral vein, compared with Neo-iopax injection into
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Fig. 1. This tracing shows a rather mild response to injection of 1 ml./Kg. Neo-iopax into the peripheral vein of a dog. Planimetric integration of the area beneath the pressure curve revealed no significant change in right atrial pressure possibly because of the effects of inspiration indicated by the arrows. The pulmonary arterial mean pressure rose from 10 mm. Hg to 13 in 10 seconds, then to 14 in 25 seconds and finally returned to 11 mm. Hg at 70 seconds and 3 minutes. Changes in systemic arterial pressure are obvious to the unaided eye.

Fig. 2. A much more pronounced change produced by injection of 1 ml./Kg. of Neo-iopax into the pulmonary artery of a dog. The electrocardiogram, upper line, revealed a sinus pause followed by a ventricular premature contraction, several nodal beats and return to sinus rhythm. The dynamic effects on pressure are clearly revealed.

The usual effect on respiration was marked hyperpnea, which produced inspiratory decreases in the right atrial pressure. In spite of this respiratory effect, the average mean right atrial pressure was elevated 0.4 to 1.0 mm. after the injection of the contrast substances and fell during the following three minutes to the control level in most instances. The right atrial pressure fell 0.2 to 0.9 mm. Hg in five instances, remained unchanged in 2 cases, and rose 0.2 to 7.6 mm. Hg (average +1.7 mm. Hg) in 32 instances (82 per cent). The most significant datum, the true relation of right to left atrial pressure, is not shown. Since, normally, all intracardiac pressures are decreased during deep inspiration, small rises in right atrial pressure or even failure to fall, may be significant under these circumstances.
The pulmonary artery pressure was subject to similar respiratory variation, but showed statistically significant elevation (p < 0.05 – < 0.01) subsequent to administration of each of the contrast substances. An increase occurred in each instance, the range being +1 to +11 mm. Hg, with an average of +4 mm. Hg. This elevation occurred slightly after that of right atrial pressure and often had not returned to the control level by the end of the three minute period of continual pressure recording. This should be compared to the pulmonary arterial pressure response in case 1, whose systolic rose 27 mm. Hg and whose diastolic rose 20 mm. Hg.

Femoral arterial pressure, on the other hand, showed no change during the early postinjection phase. A considerable fall in peripheral
arterial pressure occurred at approximately 25 seconds, accompanied with, and followed by, persisting tachycardia. Because the peripheral arterial pressure did not always return to normal by the end of the three minutes, it was sometimes necessary to delay the next injection until pulmonary and systemic artery pressure returned to the control levels. These changes in right atrial and pulmonary artery pressures were similar with injection of 50 per cent glucose, and are therefore attributed, at least partially, to the physical characteristics of the solution. In one instance, rapid administration of 50 per cent glucose into the pulmonary artery produced transient nodal bradycardia. The 50 per cent glucose produced no remarkable effect on peripheral arterial pressure, the hypotensive changes produced by the contrast substances are therefore presumed to be a pharmacologic effect.

**CASE REPORTS**

**Case 1.** This 50 year old woman was admitted to the hospital for consideration of mitral valvulotomy. A heart murmur and mild exertional dyspnea had been present for 30 years, but progressive congestive failure began six months prior to hospitalization. Physical examination revealed moderately severe congestive failure and cardiomegaly with systolic and diastolic apical murmurs. The electrocardiogram showed right ventricular hypertrophy.

Subsequent to therapy with relief of the congestive failure, cardiac catheterization with a no. 9 catheter revealed the pulmonary artery pressure to be 115/52 and the mean "wedge" pressure 25 mm. Hg. Through this catheter 40 ml. of 75 per cent Neo-ipoax was injected manually as rapidly as possible into the right pulmonary artery in an attempt to outline the left side of the heart without overlying right-sided opacification. An immediate severe reaction occurred with cough, dyspnea, tachycardia, and marked apprehension. The brachial artery pressure (directly recorded) fell from 116/77 to 54/36 and then rose to 160/116, while the pulmonary artery pressure fell from 120/53 to 87/67 and then rose to 147/73. With coughing the pulmonary artery systolic pressure exceeded 210 mm. Hg. One hundred per cent oxygen therapy was immediately administered, but progressive dyspnea continued. Numerous rales in the right lung were noted followed by signs of consolidation and a friction rub over the right lower lobe. The angiocardiogram showed the Neo-ipoax to remain in the right pulmonary artery throughout the 20 second sequence of films. A subsequent chest film showed massive edema of the right lung with congestion of the left lung unchanged from its appearance prior to catheterization. The patient's course was that of progressive deterioration and she died five days after angiocardiography.

At postmortem examination, the right lung weighed 1,450 Gm. and there was a diffuse fibrinous exudate overlying the hemorhagically infarcted upper, middle and lower lobes. The heart weighed 380 Gm. The pericardium over the right atrium showed a fibrinous deposit that was seen to overlie an antemortem thrombus. Near the clot in the right atrium was a small round subintimal hemorrhage. The right ventricular myocardium measured 0.5 cm. in thickness and the left 1.5 cm. Atherosclerotic plaques were present in the pulmonary artery. The mitral valve was a rigid, calcific slit 12 mm. long and 2 mm. wide with calcium extending from the...
Respiration admitted valve into the chordae tendineae and papillary muscles.

Case 2. A 12 month old, 15 pound white female, admitted to the hospital for diagnostic evaluation of congenital heart disease thought to be an atrial septal defect. She had had repeated respiratory infections but no cyanosis. Physical examination revealed bulging of the precordium with a well-marked bilateral Harrison's sulcus. The cardiac impulse was 1 cm, outside the midclavicular line and a systolic thrill was palpable near the third left chondrosternal junction. A harsh systolic murmur was heard over the entire precordium with transmission to the left axilla and the interscapular region.

Cardiac fluoroscopy revealed that the heart was enlarged, the enlargement being predominantly of the right chambers with elevation of the apex above the diaphragm. Pulmonary vascularization was increased. The clinical diagnosis was congenital heart disease with a left-to-right shunt, but the location of this shunt could not be identified.

Angiocardiography was done without difficulty under vinyl ether anesthesia, using 10 ml. of 75 per cent Neo-iopax. The patient was permitted to awaken from anesthesia. The films were not satisfactory, however. Thirty minutes later anesthesia with vinyl ether was induced and a second angiocardiogram was performed using 14 ml. of Neo-iopax. Respiration ceased almost immediately after injection of the contrast substance and no pulse could be found. Although artificial respiration was given, the patient did not recover.

Permission for postmortem examination was not granted. The angiocardiogram was interpreted as being compatible with an atrial septal defect.

Case 3. A 7 month old, 11 pound boy, admitted to the hospital because of congenital heart disease. His history was that of repeated respiratory infections, chronic cough and cyanosis accentuated by crying.

Physical examination revealed a grayish-blue cyanosis and slight clubbing of the fingers. There was precordial bulging. A systolic thrill and a grade 3 systolic murmur were maximum at the left sternal border in the third interspace.

The electrocardiogram was normal. Cardiac fluoroscopy and x-ray film of the chest revealed that the heart was enlarged, both to the right and left. The left atrium and the left ventricle were considerably enlarged. The pulmonary arteries pulsed on fluoroscopy.

Angiocardiography was performed at 2:15 p.m. under vinyl ether anesthesia giving 10 ml. of 75 per cent Neo-iopax. There was no immediate untoward reaction. At 3:30 p.m. his color was reasonably good; however, at 5:00 p.m. his respirations were rapid and irregular and oxygen therapy was started. By 6:00 p.m. he was gray and cyanotic, his legs were cold and his temperature had risen to 105 F. At 7:00 p.m. the patient had rales in both sides of the chest with marked tachycardia and tachypnea. In spite of Digoxin and oxygen administration, and tracheal aspiration, the patient expired approximately five hours after angiocardiography.

X-rays of the chest taken after death suggested acute congestive heart failure. Postmortem examination revealed 100 ml. of fluid in the pleural cavities. There was an atrial septal defect with anomalous pulmonary vein drainage into the right atrium. Right ventricular hypertrophy and slight pulmonary edema were present.

Case 4. This 11 month old, 13 pound girl was referred to the hospital because of occipital meningoencephalocoele, Klippel-Feil syndrome and congenital heart disease characterized by cyanosis and a heart murmur. Physical examination revealed generalized cyanosis. A grade 3 systolic murmur and a thrill were present in the second and third left interspace parasternally. The electrocardiogram was normal. The chest roentgenogram revealed gross cardiac enlargement predominantly to the left, with the left hemithorax almost completely obscured by the heart shadow. The pulmonary vascular markings were increased. An episode of congestive failure during hospitalization was successfully treated with digitalis and Mercuhydrin.

An angiocardiogram was done under vinyl ether anesthesia with 10 ml. of 75 per cent Neo-iopax. However, the rate of injection was slow and the angiocardiogram was unsatisfactory. After a delay of 10 days the study was repeated under vinyl ether anesthesia. This time a satisfactory angiocardiogram was obtained at 3:30 p.m. with 10 ml. of 75 per cent Neo-iopax. The films showed an atrial septal defect, but a completely satisfactory diagnosis was not established. At 4:30 p.m. a small amount of emesis was noted. At 6:00 p.m. the temperature was 102.6 F. and the apical cardiac rate was 146. By 8:00 p.m. the fever had increased to 105 F. and marked dyspnea was evident. Oxygen was given without benefit and death occurred 12 hours after the administration of contrast substance. Permission for postmortem examination was not obtained.

Case 5. A 7 pound, 4 month old boy was admitted for evaluation of cyanotic congenital heart disease. Recurrent attacks of paroxysmal dyspnea with severe cyanosis had required morphine for their relief. On physical examination, the heart was found to be of normal size. There was a systolic precordial murmur. X-ray films revealed decreased pulmonary vascularity and elevation of the cardiac apex. An angiocardiogram was done to confirm the diagnosis of tetralogy of Fallot, since it appeared that the need for surgical intervention was urgent. Seven milliliters of 75 per cent Neo-iopax was given rapidly, intravenously, and this was followed by immediate cessation of respiration and apparently asystole, since no heart beat could be heard for approximately three minutes. Artificial respiration was given.
When the heart began beating again its rate was 40 to 50 per minute. The patient continued to have irregular respiration, periods of apnea and bradycardia. Epinephrine, morphine, Coramine and digitalis were used without success; the baby died 81/2 hours after angiocardiography, never having recovered from the initial reaction. Postmortem diagnosis was tetralogy of Fallot. The ductus arteriosus was partially thrombosed.

**DISCUSSION**

Dotter and Steinberg\(^7\) and Howarth\(^8\) have previously determined the effects of intravenous injection of contrast substance on the peripheral arterial pressure and heart rate in man. Their findings are, in general, the same as those reported here, in that there tends to be a precipitous drop in systemic blood pressure accompanied by marked and apparently compensatory tachycardia. This effect would appear to be largely due to the vasodilating action of these agents.\(^1\) Conclusive comparison of the physiologic properties of these different substances cannot be drawn from this number of observations. The demonstrated physiologic effects of Diodrast would not appear to justify the greater number of deaths reported subsequent to its use compared to those reported after the use of Neo-iopax or Urokon. This, as stated by Dotter and Steinberg,\(^7\) appears to be related to the greater frequency of utilization of Diodrast compared to the other compounds.

An atrial septal defect may be demonstrated angiographically when evaluation by clinical means indicates only a left-to-right shunt. In a series of acyanotic patients with atrial septal defect who underwent cardiac catheterization in this laboratory and in whom the left atrium was catheterized, the left-to-right pressure gradient averaged +1.4 mm. Hg. In 40 per cent of our animal studies, injection of contrast media elevated the right atrial pressure 1.5 mm. Hg or more; even without a decrease in left atrial pressure due to deep inspiration such an elevation might be expected to reverse the usual gradient.

The changes observed in pulmonary artery pressure would not seem to be clinically significant if they are of the same degree in the human subject as they are in the experimental animal. The one fatality in which hemodynamic studies were performed during angiocardiography (case 1) revealed marked elevation in pulmonary artery pressure prior to the injection of Neo-iopax, and it became much higher after the injection. The response of the pulmonary arterial pressure may be related to already existing pulmonary vascular damage and to the capacity of the pulmonary arterioles to dilate, so as to permit a viscous substance to pass through them. In these animal experiments, pressure increases were more marked in the right atrium and pulmonary artery when the contrast substance was delivered directly into the pulmonary artery. This presumably is due to the decreased dilution under such circumstances.

Immediate death after angiocardiography may be related to right-to-left shunts which cause venous blood and contrast substance to enter the systemic vessels and precipitate fatal medullary depression.\(^7\) It would appear that our experimental observations support the shunt portion of this concept. The elevation of right atrial pressure produced by administration of a contrast substance may be sufficient to reverse a left-to-right interatrial shunt. Since the elevation in right atrial pressure may persist for 25 seconds, the reversed shunt might last for a comparable period. By the time the right atrial pressure has returned to normal, the contrast substance has produced a decreased peripheral arterial pressure. This would tend to prolong and increase right-to-left shunting at the ventricular level or from the pulmonary artery to the aorta. In such conditions as tetralogy of Fallot, Eisenmenger's complex, and patent ductus arteriosus or aortic window with pulmonary hypertension, the expected effect of the drop in peripheral arterial pressure might be a hazardous increase of the right-to-left shunt at the expense of the already reduced pulmonary blood flow. A fatal cardiac arrhythmia or central nervous system depression under such circumstances would not be surprising.

Nearly all the angiocardiograms in this series were done with Neo-iopax, and as already noted, 5 deaths occurred with this substance.
following 283 angiocardiograms in 249 patients. This experience should be contrasted with 6,824 angiocardiograms collected by Dotter and Steinberg in which 26 deaths occurred,\(^7\) an incidence of 0.4 per cent. Included in this group were over 700 angiocardiographic studies done with Neo-iopax by Dotter and Steinberg without a death.\(^7\) Many of the patients in the present series were critically ill; in this regard other deaths in this hospital not included in the series are of interest. One patient, anesthetized for angiocardiography, died before any contrast substance was given. Another died prior to anesthesia during the exposure of a suitable vein for angiocardiography. Two others developed cerebral thrombosis after the procedure, and subsequently died. It could not be stated unequivocally in either case that the thrombosis was precipitated by the angiocardiographic examination, although the capacity of Neo-iopax to cause thrombosis of vessels is well known.\(^11\)

It is always difficult, with patients as ill as these, to determine the immediate factors precipitating death, but those here reported seem to be clearly related to the angiocardiogram. Only in case 2 was death immediate, and it appears that fatal cardiac arrest must have occurred. Temporary cardiac arrest also occurred in case 5 and probably precipitated the fatal result. In case 1 there was massive infarction of the right lung, possibly due to a specific sensitivity reaction. The other 2 cases had terminal febrile episodes associated with dyspnea and pulmonary congestion suggesting either pulmonary edema from the contrast medium or acute cardiac failure. Failure may result from the degree of pulmonary hypertension that occurred in case 1; however, since the pulmonary artery pressure was not measured in these patients, no causal relationship was established. In addition, petechial hemorrhages in the brain similar to those described by Broman and Olsson\(^1\) may have occurred to explain the hyperpyrexia and pulmonary edema. Dissection of the central nervous system was not performed in these postmortem examinations.

**Conclusions**

1. Five deaths subsequent to Neo-iopax administration for angiocardiography are reported.

2. Experimental observations in dogs concerning the physiologic effects of several contrast substances on heart rate, and pressure in the right atrium, pulmonary and femoral artery, are described.

3. Each of these contrast substances may produce elevation in right atrial and pulmonary artery pressures followed by systemic hypotension and tachycardia.

4. The effects of these alterations in the presence of abnormal circulation are discussed.

**Summario in Interlingua**

1. Es reportate cinque mortes post administrationes de Neo-iopax in examines angiocardiographic.

2. Es describite observationes experimental in canes in re le effectos physiologic exercite per varie substantias de contrasto super le velocitate del corde e le pressiones dextero-arterial, pulmono-arterial, e femoro-arterial.

3. Omne iste substantias de contrasto pote producere un elevation del pressiones del atrio dextere e del arteria pulmonary, sequite per hypotension systemic e tachycardia.

4. Es discutite le effectos de iste alterationes in le presentia de un circulation anormal.

**REFERENCES**


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