Hemodynamic Consequences of the Injection of Radiopaque Material

By G. C. Friesinger, M.D., Jochen Schaffner, M.D., J. Michael Criley, M.D.,
Robert A. Gaertner, M.D., and Richard S. Ross, M.D.

Angiocardiography and cineangiocardiography are employed with increasing frequency for the diagnosis of cardiovascular diseases. These commonplace techniques of cardiovascular radiology depend upon the rapid injection of radiopaque materials into the heart or central circulation. A wide variety of substances are in use, but all are hypertonic and some are considerably more viscous than blood. A variety of studies are available to indicate that the hemodynamic effects can be related to chemical structure, but as newer and safer agents have become available it seems clear that the pharmacodynamic effects are related most importantly to the hypertonicity of these compounds. The effects of the injection of contrast media can therefore be considered to be the effects of hypertonicity on the circulation, and the study of these effects assumes considerable practical importance.

Numerous reports are available that deal with the effects of hypertonic (and radiopaque) materials injected into the right heart and pulmonary circulation in animals, but comparable systematic studies in man are not available. The hemodynamic consequences associated with the injection of radiopaque materials into the left heart and aorta in man can be quite different from those following right-sided injection and have not been well documented. We have observed significant and consistent changes in a variety of hemodynamic parameters as a consequence of the injection of radiopaque materials into the left atrium, left ventricle and aorta in patients undergoing diagnostic cineangiocardiography. These clinical observations, supplemented by related animal experiments, form the subject of the current report.

Materials and Methods

The records of 101 patients undergoing cineangiographic studies have been analyzed. All patients were studied by technics previously described. The electrocardiogram and intracardiac pressures were recorded before and after the injection of radiopaque material in every case. Left atrial pressure was recorded for at least 15 minutes after left atrial injections of contrast material in 28 patients, and after left ventricular or aortic injections, or both, in 21 patients. The other patients had less prolonged or less systematic observation.

Sodium and methylglucamine diatrizoate (75 per cent or 90 per cent Hypeaque) was the radiopaque material injected into all patients. The dose was 30 to 50 ml., depending upon body weight, heart size, and site of injection. Sodium and methylglucamine diatrizoate (90 per cent) contains 30 per cent sodium salt and 60 per cent methylglucamine salt with edathamil calcium-disodium 1:10,000, and the pH is adjusted to between 6.5 and 7.5. At body temperature, the 90 per cent solution has a viscosity approximately four times that of water and an osmolality 10 times that of blood. The 75 per cent solution is made up of 25 per cent sodium and 50 per cent methylglucamine salts. No qualitative or obvious quantitative difference in reactions to the two concentrations was noted, and hence no distinction was made between the two in the analysis of results.

The Hypeaque was injected by a power syringe at a pressure of 8 to 10 kg/cm.² and delivered...
in 1.5 to 3 seconds. Pressure measurements were made with a p23A Statham strain-gage. Cardiac output was measured with indocyanine green and the indicator-dilution curves were inscribed with a Gilford 103 IR densitometer and a Harvard withdrawal pump. Cardiac output calculations were performed as described by Hamilton.\textsuperscript{16}

### Results

#### Observations in Patients Undergoing Cineangiography

**Left Atrial Pressure**

A typical record of left atrial pressure prior to and after the injection of radiopaque material into the left atrium of a patient with mitral stenosis is shown in figure 1. The left atrial mean pressure often increased by 100 per cent or more. The increase began within 30 seconds after the injection and persisted for as long as 15 minutes. The "v" wave regularly increased more than the "a" wave. Figure 2 shows that there is no evident relationship between the resting left atrial pressure and the increase resulting from the injection. Figure 3 shows the average pressures and time sequence of changes in 28 patients. Similar left atrial pressure changes were recorded after injections into the aortic root as well as in patients with normal mitral valves (although the changes were of lesser magnitude).

### Left Ventricular Diastolic Pressure

Left ventricular end-diastolic pressure was measured in 21 patients before and after injection of Hypaque into the left ventricle or aortic root, and the results are shown in figure 4. In all patients, the left ventricular end-diastolic pressure increased but there was great variability in the magnitude of the in-
Mean values for peripheral artery pressure, heart rate, and left atrial pressure from 28 patients with mitral valve disease who had pre-injection measurements recorded and serial measurements (at 1 or 2 minute intervals) for 12 to 15 minutes after injection of Hypaque into the left atrium.

Left Atrial-Left Ventricular Pressure Gradient

In 21 patients with mitral valve disease, simultaneous left atrial-left ventricular pressures were obtained before and after the injection of Hypaque. An increase in diastolic gradient always resulted. Figure 5a illustrates the pressure tracing from a patient with pure mitral stenosis (on the basis of clinical, cineangiographic, and operative findings). Figure 5b was obtained from a patient who has primarily mitral regurgitation (on the basis of clinical and cineangiographic findings). The left atrial pulse contour is similar in the two patients following the injection although the pre-injection pulse contours are very different and the mitral valve lesions are dissimilar.

Cardiac Output

In six patients, cardiac output was meas-

Figure 3

maximal LVEDP rise after Hypaque in 21 patients

Figure 4

Left ventricular end-diastolic pressure (LVEDP) before and at designated times after injection of Hypaque into left ventricle or aortic root in 21 patients. 0 on time scale indicates instant of injection.
Figure 5

Simultaneous left atrial and left ventricular pressures immediately before and after injection of Hypaque into the left atrium. A., upper. Tracings from a patient with pure mitral stenosis. There is elevation of left ventricular end-diastolic pressure, increase in gradient, and marked increase in “v” waves. The heart rate is not changed. Postinjection tracing was obtained 3 minutes after 40 ml. of Hypaque into the left atrium. B., lower. Tracings obtained before and 5 minutes after the injection of 40 ml. of Hypaque into left atrium of a patient who had primarily mitral regurgitation. “V” wave again has markedly increased with slightly increased gradient. Heart rate has slowed.

Peripheral Artery Pressure

The changes in arterial pressure are illustrated in figure 3. During the first minute after injection of Hypaque into the left heart, a drop in peripheral artery pressure of 20 to 30 per cent occurred. This hypotension was accompanied by a transient increase in heart rate of 10 to 15 per cent. Both arterial pressure and heart rate returned to control values within 3 or 4 minutes after the injection.

ured with indocyanine green before and within 10 minutes after injections of Hypaque into the left heart. Cardiac output increased in each case; the average increase was 21 per cent. It was appreciated that indocyanine green may not be measured accurately in the presence of radiopaque material, but any error introduced by optical interference of the material would result in an underestimate of the cardiac output.17

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Hematocrit Determinations

In 11 patients, serial hematocrit determinations were made. The initial blood sample was taken within the first minute after injection of Hypaque and serial measurements were continued for a period of 10 to 15 minutes. All samples were obtained from the free flow of an indwelling arterial needle. A marked and sudden fall in hematocrit level occurred immediately after the injection, with return to control values in 10 to 15 minutes (fig. 6). No gross hemolysis was detected in the plasma, and spectrophotometric analysis with correction for the interfering effects of radiopaque material indicated that hemolysis was absent or present only to a minimal degree.

Supplementary Observations in Dogs and in Vitro Studies

To supplement the observations made during cineangiography 24 mongrel dogs were studied with a variety of preparations. Observations were made with use of hypertonic solutions of sodium chloride and glucose, but in general Hypaque was used, since the primary objective was a better understanding of conditions that prevailed in patients undergoing cineangiography. The systematic study of the effects of solutions of varying hypertonicity was not attempted here. As hematocrit and spectrophotometric changes in the blood occur with the injections of hypertonic solution, and these alterations can influence the flow measurements, it is important to emphasize that similar flow changes were recorded whether dye-dilution, rotameter, or electromagnetic flow meter was utilized for the cardiac output determination.

Hematocrit Value

In 14 dogs, serial hematocrit determinations after injection of 50 per cent glucose showed changes similar to those resulting from injections of Hypaque. Hematocrit changes occurring after a regional injection of the material were also studied. The femoral artery was most frequently used as the site of injection and samples were withdrawn from the accompanying vein. The drop in hematocrit level in the first minute after injection was extreme, usually more than 50 per cent, sometimes as much as 70 to 80 per cent of the control value.

The effect of hypertonic solutions on the hematocrit level was studied in vitro by adding solutions to blood in a beaker. The addition of a volume of Hypaque equal to 2 per cent of the volume of blood in the beaker resulted in a 10 per cent reduction in the hematocrit level. Therefore, the drop observed in vivo was at least in part the result of shrinkage of red blood cells due to the loss of red cell water (fig. 7). Shrinkage and deformation of red cells could be observed by light microscopy after the addition of radiopaque material.

Observations on the Effects of Hypaque on the Coronary Circulation

In five dogs, left coronary blood flow, left ventricular diastolic (or left atrial) and peripheral artery pressures, myocardial contractile force, and multiple electrocardiographic leads were recorded during the intracoronary injection of ½ to 2 ml. of radiopaque or other hypertonic media. The changes are illustrated in figure 8. There was an initial marked drop in coronary blood flow, which may be attributed to the high viscosity of Hypaque.
An in vitro study demonstrating that the early fall in hematocrit must be due to loss of red cell water. A quantity of whole blood in a beaker had its volume increased by the addition of radiopaque material in the amounts indicated and serial hematocrit values were determined, e.g., when 4 ml. of 90 per cent Hypaque were added to 100 ml. whole blood the hematocrit of the solution was only 85 per cent of the control value (40 and 34, respectively).

or may be due to the agglutination of red blood cells and transient mechanical blockage of the coronary vascular bed, and subsequent-

ly a marked prolonged increase in coronary blood flow. Myocardial contractile force and peripheral artery blood pressure fell transiently, while there was a minimal elevation of left ventricular end-diastolic or left atrial pressures. Striking changes in the electrocardiogram have been observed following the injection of Hypaque into the coronary arteries. These may be summarized by stating that the T-wave vector moves away from the mass of myocardium being perfused by the hypertonic medium. Isotonic solution also causes T-wave changes when injected into the coronary arteries, but these are less marked and more transient. In two animals in which the left coronary artery was cannulated and supplied with blood from a perfusion bottle, the changes resulting from left heart injections of radiopaque material were not significantly altered. Hence, injection of Hypaque into the coronary arteries does not produce changes similar to those occurring with injections into the left heart chambers and, excluding the coronary circulation, does not modify the effects of left heart injections.

Figure 7

An in vitro study demonstrating that the early fall in hematocrit must be due to loss of red cell water. A quantity of whole blood in a beaker had its volume increased by the addition of radiopaque material in the amounts indicated and serial hematocrit values were determined, e.g., when 4 ml. of 90 per cent Hypaque were added to 100 ml. whole blood the hematocrit of the solution was only 85 per cent of the control value (40 and 34, respectively).

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Figure 8

Tracing obtained when 1 ml. of 90 per cent Hypaque was injected into the left coronary artery of a dog whose artery had been cannulated with a Gregg cannula and flow measured with a rotameter. Myocardial contractile force (top), femoral artery pressure (middle), and left atrial pressure (bottom) in addition to left coronary artery flow are shown. Simultaneous electrocardiographic monitoring (not shown) showed profound T-wave changes that persisted for 2 or 3 minutes after the injection.
"Artificial" Mitral Stenosis

By the technique of Davila,18 an umbilical tape was passed around the AV ring and a left ventricular-left atrial diastolic gradient was produced to simulate mitral stenosis in four dogs. These animals showed the same pressure and flow changes as seen in patients. In addition, contractile force was measured with a strain-gauge arch placed on the ventricle. Although contractile force was decreased by the injection of Hypaque, the decrease was small (less than 25 per cent) and transient (usually not longer than 10 to 12 seconds). An example of the pressure changes produced in these dogs is illustrated in figure 9.

Comparison of Right- and Left-Sided Injections

In animals, sequential injections of Hypaque and other hypertonic media into the right and left side of the circulation were possible. In six animals, it was demonstrated that 1 ml./Kg. of Hypaque into the right side of the circulation usually produced output increases and pressure alterations similar to changes described with left-side injections of the same quantity of the material. However, injections of larger quantities into the right side of the circulation (up to 3 ml./Kg.) produced very different results. Again, peripheral artery pressure fell but pulmonary artery pressure rose sharply, cardiac output fell markedly and cardiac arrhythmias frequently occurred. After several injections of these volumes of Hypaque, tachyphylaxis developed, which likely was due to the hypervolemia created.19 Hence, a number of studies were performed with use of hypertonic saline (18 per cent) which produced identical effects as the Hypaque but with lesser volumes of injectate required. Figure 10 is a record from an animal

![Figure 9](image)

Serial excerpts from a continuous tracing from a dog with "mitral stenosis" created acutely by passing umbilical tape about AV ring. Time designations are seconds after injection. Peripheral artery pressure, left ventricular diastolic and left atrial pressure are shown. Cardiac output was 1.6 L./min. at time of control pressure tracing and was 2.2 L./min. 1 minute after injection. Note large "a" wave prior to injection and elevation of all aspects of left atrial pressure pulse injections. There is a marked drop in femoral artery pressure with beginning recovery at 50 seconds after injection, when left ventricular-left atrial diastolic pressure gradient is much increased over control. Note that the left ventricular end-diastolic pressure did not significantly elevate in this instance and heart rate is relatively constant throughout. (The left ventricular-left atrial and femoral artery pressures are on different amplification, and separate calibration scales are shown at left margin of figure.)

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in which sequential injections of hypertonic saline were made into the right and left heart. A control injection of isotonic saline is also shown. With larger volumes of hypertonic saline (1 ml./Kg.) injected directly into the pulmonary artery, peripheral artery pressure and flow sometimes fell to zero and the animal died. The immediate drop in peripheral artery pressure (and rise in pulmonary artery pressure) with right-sided injections must be due to mechanical blockage of the pulmonary vascular bed by clumping of red cells as postulated by Read and noted by Wolcott's group.

Discussion

It was the recognition of the change in left atrial pressure (most pronounced in patients with mitral stenosis) after injection of radiopaque material that stimulated this investigation. An increase in cardiac output is chiefly responsible for the changes, but a rise in left ventricular end-diastolic pressure also contributes, and the elastic properties of the left atrium must play a role.

It is important to note that there is no evidence to indicate that an increase in the severity of mitral regurgitation or the development of this lesion is responsible for the changes in pulse contour. Many of the patients with “pure mitral stenosis” showing the increase in the “v” wave have been operated upon and no mitral insufficiency has been found; in others, mitral regurgitation has not been seen during left ventricular angiograms. Studies in dogs with surgically produced “mitral stenosis” confirm the fact that increases in stroke output account for the increase in the “v” wave, since mitral insufficiency cannot occur in this preparation. Hence, it is clear that the “v”-wave increase is due to increased atrial filling as a result of the increase in cardiac output.

The simultaneous left atrial and left ventricular pressures obtained in patients after injection of Hypaque into the left atrium, which show that the left ventricular end-diastolic pressure rises, “v” wave increases, and mitral diastolic gradient becomes greater,
emphasize the potential inaccuracy of methods that attempt to evaluate the functional status of the mitral valve by analysis of left atrial pulse contour alone. This point has been emphasized by Nixon.24

The decrease in peripheral artery pressure after left-sided injection is the result of peripheral vascular dilatation, and, when considered with the increase in cardiac output, indicates that a marked fall in peripheral vascular resistance has occurred. The increase in cardiac output is achieved by an increase in stroke output, since tachycardia does not occur. This "relative bradycardia" in face of an increased output and decreased peripheral vascular resistance is difficult to explain. The effect of the vagus nerve can probably be excluded as all patients have received atropine prior to the study, and, in dogs, sectioning of the vagi did not alter the heart rate response. In the dog experiments, the vagolytic effect of barbiturate anesthesia may account for the failure of rate to increase after vagotomy.25 It is also possible that some direct effects of radiopaque material on the myocardium or on the neural effector organs within the heart may account for this peculiar rate response.

The profound and sudden drop in hematocrit level must be chiefly due to shrinkage of red cells, but its persistence may be attributed to an increase in plasma volume due to imbibition of extravascular fluid.26 Shrinkage of red cells should be anticipated when they are placed in solutions 3 to 4 times the osmolality of blood.27 and shrinkage was directly demonstrated by the in vitro studies. Hemolysis was not detected in these studies and therefore did not contribute to the decrease in hematocrit level. The absence of hemolysis is important from another point of view in that some of the peripheral effects of Hypaque might be explained by the liberation of potent vasodilatory agents known to be present in red cells. The absence of hemolysis on spectrophotometric examination makes this unlikely, although minute amounts of hemolysis can be responsible for market hemodynamic changes.28-30

It seemed possible that some of the hemo-
dynamic changes could be the result of a high-pressure rapid injection, since the existence of pressor receptors in the left heart chambers31 has been postulated. The failure of injections of isotonic saline in dogs to elicit significant hemodynamic changes rules out the mechanical effect of injections as an important contributor to the reaction.

Our observations on the effects of injection of Hypaque directly into the coronary circulation, which agree with those of others,32,33 and the observation that exclusion of the coronary circulation does not alter the reaction make it evident that entry of the material into the coronary circulation is not necessary for the changes reported here.

The many observations by other investigators,34-39 as well as measurements in this study, indicate that a wide number of hypertonic agents will dilate the peripheral vascular bed. It must be this action of the Hypaque that is primarily responsible for the reactions following left heart injections we have recorded. Pressures and flow changes are readily accounted for as a consequence of this dilatation. Other actions occur and modify the outcome, among them the peculiar heart rate response and direct myocardial and possible neural effects of radiopaque material speculated upon earlier.

The effects of the injection of hypertonic media into the right side of the heart can be different in many important ways from the effects observed after left-sided injection. As previously mentioned, the changes with the right-sided injections are more variable than those resulting from left-sided injections and must be dependent on the amount as well as the hypertonicity of the solutions delivered. After right-sided injections, pressures rise in the pulmonary artery and throughout the right heart, systemic pressure falls, and cardiac output falls; bradycardia and ectopic beats regularly occur. Numerous animal experiments4,20 have led to the suggestion that blockage of the pulmonary vascular bed by aggregated red blood cells can be the explanation for the events that follow right-sided injection. The hematocrit changes dem-
onstrated in the current investigation are in keeping with the hypothesis that sludging and clumping of the red cells are occurring, but indicate that the flow and pressor responses to this phenomenon are quite different in the systemic and pulmonary circulations. In the presence of pulmonary hypertension and increased pulmonary vascular resistance, these differences between right- and left-sided injections may be especially important when considering the "toxic effects" of contrast material.

The changes resulting from the injection of hypertonic radiopaque material into the central circulation in man are widespread and dramatic. Awareness of these factors is important in the interpretations of data obtained after angiography as well as in explaining and avoiding untoward effects of radiopaque material. Contrast media have become safer in recent years, but hypertonicity will almost certainly remain as a property of these agents, and hence the effects described in this report will continue to occur with such agents. The relative safety of the injection of Hypaque into the heart or central circulation is illustrated by the fact that more than 500 patients were studied by cineangiography during the period when the data for this report were accumulating, and no deaths occurred although many patients had two or three injections. Significant reactions were few and chiefly limited to transient periods of mild hypotension or arrhythmia.

Summary

The hemodynamic changes resulting from injection of radiopaque material into the left heart in a series of patients undergoing cineangiographic studies have been reported. The hypertonicity of radiopaque materials appears to be responsible for much of the observed reaction. The mechanism whereby hypertonic solutions produce the observed physiologic changes remains unknown.

Changes observed in patients could be reproduced in experimental animals. The combined experimental and clinical data show that left atrial pressure increases, left atrial pulse contour alters, stroke output increases, heart rate is much unchanged, peripheral artery pressure falls, hematocrit level falls, and myocardial contractile force decreases mildly and transiently.

The difference between the physiologic effects of injecting hypertonic media into the right and left sides of the circulation is discussed.

Because the pressure changes are easy to monitor and parallel the other features of the hemodynamic reaction, it is good to wait until pressures have returned to the pre-angiographic level before proceeding with the injection of more radiopaque material. This usually requires 15 minutes.

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