Interaction between verapamil and contrast media in coronary arteriography: comparison of standard ionic and new nonionic media

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ABSTRACT Coronary arteriography is frequently performed in patients receiving verapamil therapy. Since verapamil and contrast media both cause depression in electrophysiologic and contractile function of the heart and since both may exert these effects by actions on ionic calcium, the interaction of verapamil and intracoronary contrast media was assessed in 16 anesthetized dogs. Before verapamil, ionic contrast medium (Renografin 76, 3 ml) caused significant (p < .01) decreases in left ventricular peak systolic pressure, left ventricular dP/dt, extent of segment length shortening, and rate of change of segment length (dL/dt). The hemodynamic effects of verapamil and Renografin were additive, but the severity of the hemodynamic changes in response to Renografin in the presence of verapamil were not significantly different from those produced before verapamil. On the other hand, PR interval prolongation by Renografin 76 was significantly greater in the presence of verapamil (p < .001); most of the animals developed second-degree heart block in response to Renografin 76 in the presence of verapamil. Both before and in the presence of verapamil, Renografin 76 induced a similar decline in Na+ and Ca++ levels and an increase in Na+/Ca++ of coronary sinus blood. Nonionic contrast medium (iohexol) caused small but significant increases in peak dP/dt and dL/dt both before and in the presence of verapamil. This contrast medium caused no significant changes in the PR interval before or in the presence of verapamil. The changes in Na+, Ca++, and Na+/Ca++ were significantly (p < .01) less marked than those caused by Renografin 76 and were not significantly different before or in the presence of verapamil. The major finding of this study is that the effect of ionic contrast media on atrioventricular conduction is markedly enhanced in the presence of verapamil. On the other hand, nonionic media cause no deleterious inotropic or dromotropic effects, either in the presence or absence of verapamil.


VERAPAMIL and other calcium antagonists were initially used in the treatment of coronary arterial spasm and have subsequently been effective in the management of other forms of ischemic heart disease.1,2 Consequently, many patients are now undergoing coronary arteriography while being treated with calcium antagonists. In addition to a potent vasodilatory action, some antagonists have important cardiac effects. Verapamil, in particular, has actions on the heart.3,4 The cardiac effects and cellular mechanism involved in these actions are similar to those invoked by angiographic contrast media. Verapamil and contrast media cause direct inhibition of the conducting system5,6,7 and depression of myocardial contractile state.4,8 Both also induce hypotension by a direct vasodilating action on vascular smooth muscle.5,8 The effective myocardial cellular actions are also similar, since contrast media bind Ca++ while verapamil blocks the influx of Ca++ into the myocardial cell.6

Consequently, it is appropriate to consider the possible interaction or additive effects of verapamil and contrast media. The current study was intended to assess the effects of contrast media on atrioventricular conduction and left ventricular contractile state before and in the presence of verapamil. Since nonionic contrast media have been found to cause less significant alterations in electrophysiologic and contractile parameters,7,8,10 a new nonionic medium, iohexol, was

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evaluated as well as the standard ionic medium, meglumine sodium diatrizoate (Renografin 76).

Methods
The study was conducted in 16 adult mongrel dogs premedicated with morphine sulfate, 1.5 mg/kg sc, and pentobarbital, 25 mg/kg iv. The effects of contrast media on left ventricular dynamics and PR interval were studied in 10 dogs, and the effects on constituents of coronary sinus blood were studied in a separate group of six dogs.

Experimental model 1. In 10 dogs the experimental protocol was designed to study the effects of the contrast media on left ventricular contractile function and atrioventricular conduction before and in the presence of verapamil. A solid-state pressure gauge (P20; Konigsberg Instruments) was positioned in the outflow tract of the left ventricle through a small apical stab wound.11 A stable position in the left ventricular outflow tract was confirmed fluoroscopically to avoid catheter entrapment in the left ventricular apex. The pressure gauge was calibrated against a fluid-filled catheter connected to a Statham P23 strain gauge manometer. The left ventricular pressure signal was electronically differentiated to yield left ventricular dP/dt. A modified Judkins catheter was introduced into the femoral artery and advanced into the circumflex coronary artery under fluoroscopic guidance. A pair of ultrasonic dimension crystals were positioned through small myocardial stab wounds in a subendocardial position in the lateral wall of the left ventricle. We implanted the crystals along the expected longitudinal axis of subendocardial fibers11 at 90 degrees to the direction of longitudinal orientation of the epicardial fibers, which were visible on the surface of the heart. At postmortem examination the subendocardial position of the crystals (within the inner 30% of the myocardial wall) was verified. The ultrasonic dimension system, previously described,12 continuously measures transit time between the piezoelectric crystals and thereby monitors instantaneous myocardial segment length. Segment length was also electronically differentiated to provide a measure of the velocity of contraction of the myocardial segment (dL/dt). End-diastolic segment length (EDL) was measured at the beginning of the QRS complex of the electrocardiogram (ECG) and end-systolic segment length (ESL) at the point of peak dP/dt.13 Extent of segment length contraction (SL) was computed as the difference between EDL and ESL. Left ventricular pressure, left ventricular dP/dt, segment length, dL/dt, and lead II of the ECG were recorded on a multichannel recorder during the control period before each injection of contrast material and then continuously for 30 sec after intracoronary injection of the contrast media. At each time interval the value for each variable was determined as the average of 5 consecutive beats obtained in the middle of that time interval.

The order of injection of contrast media was alternated among the dogs. At least 5 min elapsed between injections to ensure that all parameters had returned to control levels.

Each contrast medium was administered before and after the administration of 1 mg/kg verapamil dissolved in 50 mL saline and administered over 30 min. In each sequence the first contrast medium was administered within 5 min after the administration of 1 mg/kg verapamil. After 15 min a supplementary dose of verapamil (0.25 mg/kg) was administered over 10 min. After cessation of this supplementary dose, the second contrast medium was injected.

The PR and PP intervals were recorded at 50 mm/sec paper speed and measured in the standard fashion except when heart block occurred. Ten beats in the control period and at each intervention point were analyzed to determine the maximum PR and PP intervals. In the presence of second-degree heart block the maximum PR interval was measured as the duration between the P wave and the next QRS complex. Consequently, in second-degree heart block a second P wave was included within this interval. Measurement of the PR interval in this fashion allowed the occurrence of heart block to be accounted in the quantitation of the changes in PR interval. The maximum values for the PR and PP intervals were determined in the control state and at each interval during the response to contrast media.

Experimental model 2. In six animals a polyethylene catheter with a flared tip was inserted through a small incision into the coronary sinus and held in place with a purse-string suture. The incision in the coronary sinus was located approximately 2 cm proximal to its ostium. The position of the catheter tip in the coronary sinus was confirmed by a small injection of contrast material under fluoroscopic observation. A modified Judkins left coronary artery catheter was introduced into the right femoral artery and advanced into the left coronary artery under fluoroscopic guidance.

After injection of 3 mL of contrast medium, fluoroscopic visualization was used to time the peak opacification and clearance of contrast material from the coronary sinus after coronary arterial injection. The time of peak opacification (Tp) averaged 5.8 sec, and the time of clearance of contrast from the sinus (Tc) averaged 12.7 sec after the start of each injection. The duration of each injection was 2 sec. The order of administration of the two contrast media was randomized among the animals.

After the injection of 3 mL of contrast media, blood samples were withdrawn from the coronary sinus for the determination of ionized calcium (Ca++) and sodium (Na+) and calculation of the Na+/Ca++ ratio. These samples were obtained at Tp, Tc, and 10 sec after clearance. This sequence was conducted before and after the intravenous administration of 1 mg/kg verapamil and it required approximately 3 sec to withdraw the requisite 8 mL of blood from the coronary sinus. When a suitable clot had formed in the blood specimen tubes, the samples were centrifuged and the serum was decanted. Concentrations of ionized sodium and calcium were determined on the fresh serum samples by means of ion selective electrodes (Orion Bio-Med Space-Stat Model 30 and Model 20).14 Commercially available reagent standards were used to calibrate the instrument before analysis of each set of serum samples. The laboratory technician who performed the serum analysis was blinded with respect to which sample corresponded to which contrast agent injection.

Statistical analysis. The method for statistical analysis of the response to a particular intervention was a repeated-measures mixed model univariate analysis of variance.15 Statistical comparison of specific treatment means was done with Tukey's test. The data were analyzed to determine the overall differences between effects of the two contrast media in both experimental states and for the same contrast medium before and in the presence of verapamil. The data were also analyzed to compare each data point (including the control value) before and in the presence of verapamil. Specifically, the following conditions were compared:

1. Renografin 76 vs iohexol in both the preverapamil and verapamil states
2. The magnitude of the absolute change induced by each contrast medium in the preverapamil and verapamil states
3. The value for each variable in the control state and at each sampling point after contrast media in the preverapamil vs the value for each variable in the control state and at each sampling point after contrast media in the verapamil state
4. The value for each variable at each sampling point during the response to a contrast medium.

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Results

Comparison of effects of Renografin 76 before and in the presence of verapamil

Left ventricular dimensions and contractile state (figures 1 and 2). Before verapamil, Renografin 76 caused a bi-phasic response characterized initially (0 to 10 sec) by significant decreases in left ventricular peak systolic pressure (LVP) \( (p < .01) \), peak \( \frac{dP}{dt} \) \( (p < .01) \), \( \Delta L \) \( (p < .01) \), and \( \frac{dL}{dt} \) \( (p < .01) \) and increases in ESL \( (p < .01) \) and EDL \( (p < .01) \). After 10 sec most of these changes were reversed, consisting of significant increases in \( \frac{dP}{dt} \) \( (p < .01) \), \( \frac{dL}{dt} \) \( (p < .01) \), and \( \Delta L \) \( (p < .01) \) and decreases in EDL \( (p < .05) \) and ESL \( (p < .01) \).

The patterns of the responses to intracoronary injection of this contrast medium were similar before and in the presence of verapamil. The magnitude of the changes in each variable in response to Renografin 76 were not significantly different before verapamil compared with those in the presence of verapamil.

Verapamil did cause significant decreases in the basal value for \( \frac{dP}{dt} \) \( (p < .01) \) and \( \frac{dL}{dt} \) \( (p < .01) \). Consequently, at each time interval during the response to Renografin 76 in the presence of verapamil, \( \frac{dP}{dt} \) and \( \frac{dL}{dt} \) were significantly lower \( (p < .01) \) than during the response before verapamil.

Impulse generation (PP interval) and atrioventricular conduction (PR interval) (figure 3). Before verapamil, Renografin 76 caused no significant changes in the PP or PR intervals. Verapamil did not cause a significant increase in the PP or PR intervals. However, the PP and PR intervals were substantially longer \( (p < .01) \) at each time interval after the injection of Renografin 76 in the presence of verapamil compared with those before verapamil.

The PR interval varied from 110 ± 10 msec (SD) to a maximum value of 120 ± 20 msec (NS) in response to Renografin 76 before verapamil. In the presence of verapamil, the PR interval increased from 180 ± 30 msec \( (p < .01) \) to a maximum value of 580 ± 60 msec \( (p < .01) \) in response to Renografin 76. Seven of 10 animals developed second-degree heart block (Mobitz type I) after the injection of Renografin 76 in the presence of verapamil. Heart block persisted for a minimum of 40 sec to a maximum of 8 min. Both the values for the PR interval and the absolute change in PR interval at each time interval during the response to Renografin 76 were significantly greater in the presence of verapamil \( (p < .001) \).

Cation concentrations in coronary sinus blood (figure 4). Renografin 76 induced significant decreases \( (p < .01) \) in Na\(^+\) for up to 20 sec after injection. Verapamil caused no significant change in the baseline value of Na\(^+\). The decreases in Na\(^+\) induced by Renografin 76 were not significantly different before and in the presence of verapamil.

Renografin 76 caused significant decreases \( (p < .01) \) in Ca\(^++\) for up to 20 sec after injection. Verapamil caused a significant decrease \( (p < .01) \) in the baseline value for Ca\(^++\). At each of the sampling intervals up to 30 sec after injection of Renografin 76, Ca\(^++\) was significantly lower in the presence of verapamil \( (p < .01) \) compared with the response before verapamil. However, the magnitude of the fall in Ca\(^++\) in response to Renografin 76 at each time interval was similar before and in the presence of verapamil.

Renografin 76 caused significant increases in Na\(^+\)/Ca\(^++\) only at the sampling interval in the first 10 sec after injection. Verapamil caused no significant change in the baseline value of Na\(^+\)/Ca\(^++\). The
changes in Na⁺/Ca²⁺ in response to Renografin 76 were similar before and in the presence of verapamil.

Comparison of the effects of iohexol before and in the presence of verapamil

Left ventricular dimensions and contractile state (figures 5 and 6). Before verapamil, iohexol caused no significant changes in LVP but did cause significant increases in left ventricular dP/dt (p < .01) and dL/dt (p < .01) at all time intervals after injection. Iohexol caused no significant change in EDL, ESL, or ∆L within the first 10 sec after injection. However, at sampling intervals after 10 sec there were significant decreases in EDL (p < .01) and ESL (p < .01) and an increase in ∆L (p < .05).

The pattern of the response to iohexol was similar before and in the presence of verapamil. The absolute changes in each variable in response to iohexol were not significantly different before verapamil compared with those in the presence of verapamil.

Verapamil did cause significant decreases in the basal values for dP/dt (p < .01) and dL/dt (p < .01). Consequently, at each time interval during the response to iohexol in the presence of verapamil, dP/dt and dL/dt were significantly lower (p < .01) than during the response before verapamil.

Impulse generation (PP interval) and atrioventricular conduction (PR interval) (figure 7). Iohexol caused no signifi-

FIGURE 2. Mean values and standard deviations are displayed for EDL, ESL, ∆L, and dL/dt at control and for 10 sec intervals during the response to Renografin 76 before and in the presence of verapamil.

FIGURE 3. Mean values and standard deviations are displayed for PR and PP intervals at control and for 10 sec intervals during the response to Renografin 76 before and in the presence of verapamil.
significant change in the PP or PR interval before verapamil and no significant change in the PP interval in the presence of verapamil. Within the initial 10 sec after injection of iohexol in the presence of verapamil, the PR interval increased significantly (p < .01). It was only at this time that the PR interval was significantly greater (p < .01) compared with the same sampling period before verapamil. No animal developed heart block in response to the administration of iohexol in the presence of verapamil.

Cation concentration in coronary sinus blood (figure 8). Iohexol produced significant decreases (p < .01) in Na+ and Ca++ for the first 20 sec after injection both before and in the presence of verapamil. Verapamil alone induced no significant change in Na+ but did cause a slight decrease (p < .05) in Ca++. The magnitude of the changes in Na+ and Ca++ in response to iohexol were similar before and in the presence of verapamil.

Comparison of the effects of Renografin 76 and iohexol

Left ventricular dimensions and contractile state. Before and in the presence of verapamil, Renografin 76 caused significantly greater decrease in LVP (p < .01), dP/dt (p < .01), ΔL (p < .01), and dL/dt (p < .01) during the first 10 sec after injection. Renografin 76 also caused significantly greater increases (p < .01) in EDL and ESL. In fact, at this time interval the two contrast media had diastolic effects on some parameters, since iohexol caused significant increases in dP/dt (p < .01) and dL/dt (p < .01) before verapamil, an increase in dP/dt (p < .01), and no significant change in dL/dt at this time interval in the presence of verapamil.

Impulse generation (PP interval) and atrioventricular conduction (PR interval). The effect of Renografin 76 and iohexol on the PP and PR intervals were not significantly different before verapamil. However, in the presence of verapamil, Renografin 76 caused a significantly greater increase in PR interval at all time intervals after injection (30 sec) compared with the response to iohexol.

Cation concentration in coronary sinus blood. Renografin 76 caused significantly greater decreases in Na+ (p < .01) and Ca++ (p < .01) compared with iohexol both before and in the presence of verapamil. Likewise, under both conditions, Renografin 76 caused signifi-
cantly greater increases in the Na\(^+\)/Ca\(^++\) ratios (p < .01).

Discussion

Verapamil has been previously shown to depress myocardial contractility in experimental preparations\(^4\) and left ventricular performance in some but not all studies in man.\(^{16-18}\) It also has been shown to cause prolongation of atrioventricular conduction.\(^5\) The current study also shows that intravenous administration of verapamil causes depression in several parameters of global left ventricular performance and myocardial contractile state in spite of an increase in end-diastolic myocardial segment length. Intracoronary injection of ionic contrast media in this study and in previous studies\(^7, 8, 10\) has also been shown to cause a distinct transient depression in global performance and myocardial contractility as well as prolongation of atrioventricular conduction. When ionic contrast media are injected into the coronary artery, parameters of segmental contraction (dL/dt) and parameters of global left ventricular performance (peak dP/dt) are depressed in spite of an associated increase in end-diastolic segment length and decrease in arterial pressure. These changes in loading factors would tend to offset the direct myocardial depression induced by ionic contrast media. Thus the effect of ionic media on left ventricular performance is a complex resultant of the direct negative action on myocardial contractile state and changes in left ventricular loading factors. The changes in the left ventricular loading factors in response to contrast media were in a direction where an improvement in left ventricular performance would be expected if only preload and afterload changed. Since dL/dt and dP/dt actually declined, ionic contrast media must exert a considerable inhibitory effect on myocardial contractile state. In the current study the deleterious hemodynamic effect of intravenous administration of verapamil and the intracoronary injection of ionic contrast media on left ventricular performance were additive. Consequently, the important parameters of left ventricular contractile state were depressed to a level significantly below that produced by either agent when administered alone.

Before verapamil neither the ionic nor the nonionic medium induced significant increases in the PR interval. However, both caused significant increases in PR interval in the presence of verapamil. The combination of Renografin 76 and verapamil caused a profound effect; PR interval was markedly prolonged in all animals and most experienced periods of second-degree heart block. The increase in PR interval with combination of verapamil and nonionic contrast media was considerably milder and no animals had second-degree heart block.

Iohexol caused no depression in parameters of left ventricular contractile function either before or in the presence of verapamil. In fact, in both states this nonionic medium caused only a small positive inotropic effect. Recent studies have also shown that iohexol as well as other nonionic media cause either no effect or a small positive inotropic effect.\(^10\)

The mechanism of cardiac actions of both verapamil and ionic contrast media involve an action on Ca\(^++\) within the myocardium. Ca\(^++\) is an important com-
mon mediator for myocardial contraction, generation of action potentials, and impulse conduction; 6, 9, 20 myocardial cells are dependent on influx of Ca\(^{++}\) through slow membrane channels for these essential processes. 6, 9, 20, 21 Calcium blockers or antagonists act predominantly by inhibiting calcium influx at slow channels. 5 Contrast media also affect myocardial Ca\(^{++}\) levels. 9, 21 After intracoronary injection, Ca\(^{++}\) concentrations in coronary sinus blood are depressed disproportionately to the reduction in total calcium levels, 21 suggesting that they bind Ca\(^{++}\). Both electrophysiologic 22 and contractile disturbances 9, 21 have been linked to a reduction in Ca\(^{++}\) and an imbalance in the ratio of Na\(^{+}\) to Ca\(^{++}\) by the contrast medium molecule itself. 9, 23 In vitro binding of Ca\(^{++}\) varies among contrast media but is virtually absent with nonionic media. 9

The dose of verapamil used in the current study is similar to those used in animal studies exploring the influence of verapamil on infarct size 24 but greater than that employed clinically. 16-18 Although verapamil has been shown to produce a distinct negative inotropic effect at relatively high doses in the isolated heart 20 and the intact heart of experimental animals, 9, 25 doses similar to those used clinically cause no negative inotropic effects but do produce dromotropic effects. 16-18 In fact, studies in patients have revealed either no change or enhanced left ventricular performance in the presence of the reduced afterload caused by the verapamil-induced vasodilatation. 16-18

The interaction of verapamil and other drugs is not unique. Verapamil in combination with \(\beta\)-adrenergic antagonists has been shown to cause additive or synergistic inhibition of myocardial contractility and prolongation of atrioventricular conduction in animals. 9, 26, 27 Moreover, this combination in man has been reported to cause idiosyncratic responses consisting of severe hypotensive episodes or asystole in certain patients. 26, 29 More extensive evaluation of this combination in one series of patients showed that the negative chronotropic and inotropic effects of verapamil were enhanced in the presence of \(\beta\)-adrenergic antagonists, 30 while a second study showed little or no important additive effect. 31

The current study shows interaction of verapamil and contrast media in producing negative inotropic and dromotropic influences on the heart. Since the actions of both these compounds on the heart involve changes in availability of Ca\(^{++}\) within the myocardium, it must be considered that this interaction will be observed with other calcium antagonists. In this regard, verapamil might be expected to cause the greatest interaction in depressing atrioventricular conduction and left ventricular contractile state because it causes a greater degree of inhibition of heart rate, atrioventricular conduction, and myocardial performance compared with other calcium antagonists. 25, 32

Direct extrapolation of these results to clinical coro-

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nary arteriographic studies must be made with reservation related to differences in species susceptibility, drug dosages, and pathologic status of the coronary circulation. However, this study does indicate the potential for a deleterious interaction between verapamil and contrast media during coronary arteriography. Since this interaction is minimal for iohexol compared with Renografin 76, the use of a nonionic media might be preferable for coronary arteriography in patients on verapamil therapy.

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