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The hemodynamic effects of heparin and their relation to ionized calcium levels

Heparin complexes calcium in vitro and possesses vasodilating properties when given as an intravenous bolus. To investigate the possibility that these hemodynamic effects could be related to the ability of heparin to induce hypocalcemia in vivo, we studied the response to a bolus dose of heparin, 300 IU/kg, in 20 patients undergoing cardiopulmonary bypass for cardiac operations. Ionized calcium decreased significantly after heparin administration, as did mean arterial pressure and systemic vascular resistance. In a further nine patients, 125 mg of calcium chloride was given immediately before the heparin bolus. It induced a small rise in calcium levels and maintained the mean arterial pressure at unchanged values. Our data confirm the vasodilating effect of an intravenous bolus of heparin and show that it is related to an acute lowering of ionized calcium levels. When calcium levels are not allowed to drop, the blood pressure is maintained at stable values. We advise slow injection of the heparin bolus and special attention to the ionized calcium levels before cardiopulmonary bypass.

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There is good evidence that heparin given as an intravenous bolus injection possesses a transient vasodilating effect,[1-3] but to our knowledge no satisfactory mechanism has been found to account for it. Furthermore, although there are conflicting reports concerning the action of heparin in vivo,[4,5] it is well established that heparin is capable of complexing ionized calcium ([Ca^{++}]) in vitro and that such an effect is dose dependent.[6,7]

A number of recent studies have stressed the relationship between both intracellular and extracellular calcium concentrations and blood pressure levels.[8-10] Previous work had shown that the hypocalcemia and hypotension induced in the experimental animal by the infusion of citrate were associated with peripheral vasodilation.[11-13]

We therefore chose to investigate the possibility that the hemodynamic response to heparin could be mediated by a transient hypocalcemia.

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Patients and methods

We examined the response of hemodynamic parameters, [Ca^{++}], total calcium, and pH to a bolus dose of heparin in 23 adult patients undergoing cardiopulmonary bypass for cardiac operations. Two patients who had received vasoactive drugs and one patient who had required defibrillation just before the study period were excluded. The mean age of the remaining 20 patients (15 men and five women) was 60 ± 8 years. Indications for operation were coronary heart disease (10 patients), valvular heart disease (five patients), a combination of these factors (three patients), atrial myxoma (one patient), and atrial septal defect (one patient).

Current medical treatment was continued until the morning of the operation: Three patients were receiving beta blockers, three were being treated with nifedipine, and seven were receiving a combination of both treatments. Premedication consisted of morphine and scopolamine. After induction with thiopenthal, anesthesia was maintained with fentanyl, flunitrazepam, pancuronium, and enflurane. Ventilation was adjusted to maintain a normal carbon dioxide tension, no positive end-expiratory pressure was used, and the inspired oxygen concentration was always 0.5 or higher. None of the patients received calcium or blood transfusion before or during the study period.

All patients had continuous monitoring, with a printout, of the electrocardiogram, radial arterial pressure, central venous pressure, and left atrial pressure. A

Table I

	No.	*Before heparin*	*After heparin*	*p Value**
Ca^{++} (mmol/L)	20	1.14 ± 0.10	1.04 ± 0.14	<0.01
CaT (mmol/L)	20	2.09 ± 0.13	2.09 ± 0.09	NS
pH	20	7.36 ± 0.04	7.36 ± 0.05	NS
Heart rate (beats/min)	20	73 ± 12	75 ± 11	NS
MAP (mm Hg)	20	78.4 ± 13	68 ± 14.9	<0.001
CI (L/min/m^2)	11	2.41 ± 0.38	2.42 ± 0.41	NS
PVR (dynes · sec · cm^{-5})	11	162 ± 112	175 ± 131	NS
SVR (dynes · sec · cm^{-5})	11	1,402 ± 432	1,187 ± 344	<0.05

Legend: Ca^{++}, Ionized calcium. CaT, Total calcium. MAP, Mean arterial pressure. CI, Cardiac index. PVR, Pulmonary vascular resistance. SVR, Systemic vascular resistance.

*Student's paired t test.

Table II

	No.	*Before heparin and $CaCl_2$*	*After heparin and $CaCl_2$*	*p Value*
Ca^{++} (mmol/L)	9	1.19 ± 0.06	1.31 ± 0.06	<0.005
MAP (mm Hg)	9	76.6 ± 7.6	76.3 ± 8.9	NS

Legend: Ca^{++}, Ionized calcium. MAP, Mean arterial pressure

thermodilution catheter was placed in the pulmonary artery of 11 patients for whom it was believed to be clinically indicated; for these 11, mean pulmonary artery pressure (PAP) and cardiac output (CO) were also measured. Systemic and pulmonary vascular resistances (SVR, PVR) were calculated according to the following formulas:

$$SVR = (MAP - CVP/CO) \times 80$$
$$PVR = (PAP - LAP/CO) \times 80$$

in which MAP is mean arterial pressure and LAP is left atrial pressure.

For $[Ca^{++}]$ analysis of the pre-heparin and post-heparin blood levels, venous blood samples were collected in 2 ml disposable plastic syringes, the dead space of which was filled with S-4500 heparin (Radiometer AS, Copenhagen, Denmark) as previously described.[7] Measurements were made in triplicate on whole blood samples with a Nova-2 calcium analyzer (Nova Biomedical, Newton, Mass.).

Levels of total calcium were determined with a cresolphtalein-complexon colorimetric method (SMA-C, Technicon Instruments Corp., Tarrytown, N. Y.), and pH levels were measured with an AVL 940 automated blood gas analyzer.

Protocol. Just before cannulation of the aorta, the surgeon was asked to refrain from manipulating the heart and a set of baseline measurements was obtained (hemodynamics, $[Ca^{++}]$, total calcium, and pH values). Heparin, 300 IU/kg of body weight (Liquemine, Hoffmann-La Roche, Basel, Switzerland), was injected as an intravenous bolus and the same set of measurements was then repeated at the time of maximum decrease in blood pressure or after 3 minutes if no change in blood pressure had occurred.

For nine other patients, also undergoing cardiopulmonary bypass for cardiac operations under similar conditions, the same set of measurements was made but 125 mg of calcium chloride was given immediately before the heparin.

Statistical analysis was performed by the two-tailed paired Student's t test to compare values before and after heparin or heparin plus calcium chloride. A p value less than 0.05 was considered significant.

Institutional approval for the study was obtained.

Results

Heparin. In 17 of the 20 patients studied, the intravenous bolus administration of heparin 300 IU/kg induced a fall in MAP and the mean time to maximum decrease in blood pressure was 76 ± 29 seconds. The MAP remained unchanged in two patients and rose slightly in one. The mean values for MAP were 78.4 ± 13 mm Hg before and 68 ± 14.9 mm Hg after heparin ($p < 0.001$). Heart rate remained essentially unchanged.

For the 11 patients with a thermodilution catheter, there was a significant drop in the SVR from 1,402 ± 432 to 1,187 ± 344 dynes · sec · cm^{-5} ($p < 0.05$), with no significant change in PVR or cardiac output.

Mean $[Ca^{++}]$ decreased by approximately 9% after heparin administration from 1.14 ± 0.10 to 1.04 ± 0.14 mmol/L ($p < 0.01$), whereas both total calcium and pH remained constant (Table I).

Heparin plus calcium chloride. When 125 mg of calcium chloride was injected immediately before heparin administration, the MAP remained essentially

unchanged; 76.8 ± 7.6 before and 76.3 ± 8.9 mm Hg after the double injection. The [Ca^{++}] levels rose significantly from 1.19 ± 0.06 to 1.31 ± 0.06 mmol/L ($p < 0.005$) (Table II).

Discussion

Our data confirm the vasodilating effect of an intravenous bolus of heparin and show that it is related to an acute lowering of blood [Ca^{++}]. The unchanged values of total calcium and the stable pH after heparin injection support the hypothesis that this effect is due to complexing of Ca^{++} by heparin in the circulation.

The observed hemodynamic effects of heparin closely resemble those obtained in the experimental animal submitted to a citrate infusion to induce hypocalcemia, with a decrease in SVR as the central event.[11-13]

The failure of the cardiac index to rise in response to the lowered peripheral resistance most probably represents the added depressant effect of hypocalcemia on myocardial contractility.[14] The absence of the reflex tachycardia that would be expected after vasodilation can be explained either by a direct negative chronotropic effect of hypocalcemia or by preexisting beta blockade, since half the patients studied were receiving such treatment.

When heparin administration was immediately preceded by an injection of 125 mg of calcium chloride, the [Ca^{++}] levels rose significantly and the fall in MAP was prevented.

The hypotensive effect of heparin is marked and the magnitude of the changes we observed for MAP and SVR agree well with the values previously reported.[1-3] To our knowledge, however, no definite mechanism has yet been proposed to account for the action of heparin, and only a "direct" effect on the vascular wall or a histamine-like activity have been evoked.[2] Marin-Neto and associates[15] failed to demonstrate any hemodynamic consequences of heparin administration, but the measurements were obtained 10 minutes after the bolus injection: In our experience, both the hypocalcemia and the lowering of the blood pressure are short-lived and could thus have been overlooked.

Heparin is known to activate lipoprotein lipase, with liberation of free fatty acids and secondary displacement of certain drugs from their albumin-binding sites.[16,17] Such an effect could contribute to the heparin-induced hypotension by displacing beta blockers or benzodiazepines, for example, from plasma proteins.

Surprisingly, although the ability of heparin to induce hypocalcemia in vitro is well established, its effects on [Ca^{++}] levels in vivo have received little attention and their evaluation has led to conflicting results: Jones and associates[5] found no effect of heparin on [Ca^{++}] levels in the dog, and the reasons for this apparent contradiction with our findings is not clear; possibly such factors as the rate of heparin administration, the type of anticoagulation used in the samples,[7] or better calcium homeostasis in the dog may have played a role. Catinella and colleagues[4] obtained results similar to our own with a significant drop in [Ca^{++}] from 1.04 ± 0.02 to 0.968 ± 0.03 mmol/L after heparin administration to eight patients before cardiopulmonary bypass, but hemodynamic data were not reported.

In practical terms, we believe that the present observations warrant slow administration of the bolus dose of heparin to all patients undergoing cardiopulmonary bypass. In case of unstable hemodynamics, the added monitoring of [Ca^{++}] values during the operation should help detect hypocalcemia and prevent marked reactions to further lowering of [Ca^{++}] after heparin.

Similar precautions may well be justified in other clinical settings when heparin is given to patients likely to have a low [Ca^{++}], such as those having massive pulmonary embolism or undergoing hemodialysis for acute renal failure.

For selected patients, the cautious use of small doses of calcium chloride just before heparin administration to maintain MAP at stable levels may be the answer.

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