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ORIGINAL ARTICLE

Prediction of heparin induced hypotension during cardiothoracic surgery: A retrospective observational study

Masakazu Kotoda, MD, PhD[1], Tadahiko Ishiyama, MD, PhD[2], Hiroyuki Nakajima, MD, Ph.D[3], Takashi Matsukawa, MD, PhD[1]

[1]Department of Anesthesiology, Faculty of Medicine, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi, 4093898, (Japan), mkotoda@yamanashi.ac.jp
[2]Surgical Center, University of Yamanashi Hospital, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi, 4093898, (Japan), ishiyama@yamanashi.ac.jp
[3]Department of Surgery-II, Faculty of Medicine, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi, 4093898, (Japan), hiroyukin@yamanashi.ac.jp

Correspondence: Masakazu Kotoda Department of Anesthesiology, Faculty of Medicine, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi 4093898, (Japan) Tel: +81-55-273-9690 Email: mkotoda@yamanashi.ac.jp

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ABSTRACT

Background: High-dose heparin occasionally causes severe hypotension during cardiothoracic surgery. Being able to predict the severity of the decrease in blood pressure prior to administration of heparin would improve hemodynamic and anesthetic management. The aim of this study was to investigate the predictors of heparin-induced hypotension and the effects of high-dose heparin on various hemodynamic and physiologic parameters.

Methodology: The records of adult patients who underwent elective cardiothoracic surgery at University of Yamanashi Hospital between January 2016 and December 2017 were retrospectively reviewed. Single and multiple linear regression analyses were conducted to identify the predictors of heparin-induced hypotension.

Results: High baseline systemic vascular resistance index (SVRI) and non-use of preoperative antihypertensive medication were significant predictors of heparin-induced hypotension with a following regression equation: Percent change in mean arterial pressure = 17.273 + 0.00457 × (baseline SVRI) - 14.043 × (antihypertensive medication), where antihypertensive medication is coded as 0 = no antihypertensive drug and 1 = one or more antihypertensive drug(s), F = 7.80, the multiple correlation coefficient is 0.68645, and R adjusted for degrees of freedom is 0.41078.

Conclusion: The baseline SVRI and non-use of preoperative antihypertensive medication are significant predictors of the severity of heparin-induced hypotension.

Abbreviations: MAP - Mean arterial blood pressure; CVP - central venous pressure; PAP - pulmonary arterial pressure; SVRI - systemic vascular resistance index; BMI: body mass index; ASA-PS: American Society of Anesthesiologists physical status classification; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; EDVI: end-diastolic volume index; CI: cardiac index; SvO2: mixed venous oxygen saturation; LVEF: left ventricular ejection fraction; HR: heart rate.

Preregistration: The study was approved by the institutional review board of University of Yamanashi (study H30036, registered May 28, 2018).

Key words: Antihypertensive medication; Cardiothoracic surgery; Heparin; Hypotension; Systemic vascular resistance

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INTRODUCTION

Heparin is the oldest anticoagulant drug in clinical use and has been used extensively for the control of coagulation during surgery performed under cardiopulmonary bypass since 1953.[1] Generally, high-dose heparin (300–450 U/kg) is administered intravenously to achieve anticoagulation levels that are adequate for cardiopulmonary bypass. Heparin exerts its anticoagulant effect by facilitating the inhibitory effects of antithrombin 3 on thrombin and activated factor Xa.[2,3] Given the ease with which it controls coagulation and the availability of a potent reversal drug, protamine, heparin is used first-line as an anticoagulant agent during cardiopulmonary bypass.

However, in addition to its anticoagulant activity, heparin reportedly has vasodilatory effects and can lower blood viscosity, which could reduce blood pressure.[4-10] A previous study reported that heparin-induced hypotension occurred in 86% of patients undergoing cardiothoracic surgery under cardiopulmonary bypass.[4] While protamine-induced hypotension is widely known.[11,12] Heparin-induced hypotension is a less well recognized iatrogenic state. During cardiothoracic surgery, the patient's hemodynamic status tends to become unstable gradually as the surgical procedure reaches the heart or surrounding tissues. Hypotension in response to administration of heparin at this time can be catastrophic, and urgent establishment of cardiopulmonary bypass is sometimes required.[13] Being able to predict the severity of the decrease in blood pressure prior to administration of heparin would improve hemodynamic and anesthetic management during cardiothoracic surgery.

Objective of study

The aim of this study was to identify the predictors of a heparin-induced decrease in blood pressure during cardiothoracic surgery. The primary outcome was the predictive regression equation for a heparin-induced decrease in blood pressure during cardiothoracic surgery. Secondary outcomes were the incidence of heparin-induced hypotension, effects of high-dose heparin on various hemodynamic and physiological parameters, and any correlations between hemodynamic and physiological parameters.

METHODOLOGY

Inclusion criteria and measurements:

The records of adult patients who underwent an elective cardiothoracic surgery in the Department of Surgery at the University of Yamanashi Hospital between January 2016 and December 2017 were retrospectively reviewed. The following preoperative information and data were obtained: age, sex, height, weight, body mass index, American Society of Anesthesiologists physical status classification, use of antihypertensive medication, presence of diabetes mellitus, estimated glomerular filtration rate, total plasma protein, albumin, fibrinogen, and antithrombin 3 levels, and left ventricular ejection fraction on echocardiography. Intraoperative hemodynamic and physiological data, including skin temperature, heart rate, mean arterial blood pressure (MAP), central venous pressure (CVP), pulmonary arterial pressure (PAP), systemic vascular resistance index (SVRI), end-diastolic volume index, cardiac index, and mixed venous oxygen saturation were obtained from the anesthetic charts. Skin temperature was measured using a pad thermometer (Mon-a-therm, Medtronic, Minneapolis, MN, USA), and MAP and CVP were measured using a radial arterial catheter and right jugular vein catheter, respectively. PAP, SVRI, end-diastolic volume index, cardiac index, and mixed venous oxygen saturation were measured using a pulmonary arterial catheter (Edwards Lifesciences Corp, Irvine, CA, USA). The physiological and hemodynamic parameters were updated and recorded at 1 min intervals using an anesthesia information management system (ORSYS TETRA, PHILIPS, Amsterdam, Netherlands). Baseline hemodynamic and physiological values were defined as those recorded immediately before administration of heparin. At our institution, 300 U/kg of heparin is administered as a bolus injection prior to cardiopulmonary bypass. The post-heparin administration values were obtained when the MAP was at its lowest value in the 10 min after administration of heparin.

Hematocrit and serum K^+ and Ca^{2+} levels before administration of heparin, measured via arterial blood gas analysis during surgery, were also obtained from the anesthetic charts. Blood viscosity was estimated using the equation proposed by Simone et alcf with the values expressed in centi-poise (cP) as follows: $0.12 \times$ (hematocrit) $+ 0.17 \times$ (total plasma protein) $- 2.07$.

Exclusion criteria:

The study exclusion criteria were as follows: use and/or change in dose of inotropes, vasoconstrictors, and/or vasodilators within 10 min before and 5 min after administration of heparin; fluctuating hemodynamic state (presence of a change in MAP > 20% in the 10 min before administration of heparin); the presence of surgical procedures that might have affected the patient's hemodynamic condition (customary recorded as a note in the anesthetic chart by the anesthesiologist); and congenital heart disease.

Statistical analysis:

The statistical analysis was performed using Stat

Flex version 6.0 (Artec, Osaka, Japan). Single and multiple linear regression analyses were used to identify parameters that were significantly associated with a decrease in arterial blood pressure. The forward stepwise selection method was used for the multiple linear regression analysis. Correlations between each of the variables were assessed using the Pearson's correlation coefficient. If a correlation larger than 0.3 between two variables was found, one of the variables was removed from the multiple linear regression analysis to avoid multicollinearity. The two-tailed paired t-test was used to compare values at baseline with those obtained after administration of heparin. The data are shown as the mean ± standard deviation. A p-value < 0.05 was considered statistically significant.

RESULTS

One hundred and sixty-seven adult patients underwent elective cardiothoracic surgery during the study period. Ninety-eight patients were excluded because of use and/or a change in dose of inotropes, vasoconstrictors, and/or vasodilators (n = 20), fluctuating hemodynamics (n = 76), and congenital heart disease (n = 2). A further 6 patients were excluded because of missing information concerning administration of heparin (n = 4) or an irregular heparin dose (n = 2). The data from the remaining 63 patients were included in the single and multiple linear regression analyses.

The patient demographics and clinical characteristics are shown in Table 1.

Table 2 shows the values for the hemodynamic and physiologic parameters at baseline and after administration of heparin. After a bolus injection of heparin 300 U/kg, there was a significant decrease in MAP (from 70 ± 8 mmHg to 54 ± 8 mmHg, 22 ± 11% decrease, $p < 0.0001$) and SVRI (from 2050 ± 645 dyne·sec·m^2/cm^5 to 1500 ± 442 dyne·sec·m^2/cm^5, $p < 0.0001$). In 51 patients (81%), the MAP decreased to below 60 mmHg after administration of heparin.

Table 3 shows the results of the single linear regression analysis. There were positive correlations between percent change in MAP and the baseline SVRI ($r = 0.414$, $p = 0.008$) and MAP ($r = 0.342$, $p = 0.006$). Weak negative correlations were found between percent change in MAP and the serum albumin level ($r = -0.272$, $p = 0.031$) and use of antihypertensive drugs ($r = -0.270$, $p = 0.032$). Although there were trends towards a weak positive correlation between percent change in MAP and age ($r = 0.229$) and a weak negative correlation between percent change in MAP

Table 1: Demographic profile and preoperative findings

Demographic characteristics	mean ± SD (range)
Age (years old)	69 ± 11 (43–88)
Sex (male/female)	45/18
Height (cm)	160.1 ± 8.5 (134.8–175.0)
Weight (kg)	60.6 ± 11.1 (41.5–88.7)
BMI (kg/m^2)	23.5 ± 3.1 (18.5–31.9)
ASA-PS (3/4)	10/53
Antihypertensive drug (+/-)	54/9
Smoking (pack-years)	22.2 ± 25.5 (0–100)
DM (+/-)	28/35
Preoperative examination	**mean ± SD (range)**
eGFR (mL/min)	50.9 ± 22.0 (4.0–97.6)
Total protein (g/dL)	7.0 ± 0.6 (3.8–8.0)
Albumin (g/dL)	4.0 ± 0.5 (1.8–4.8)
Fibrinogen (mg/dL)	300 ± 76 (137–543)
Antithrombin 3 (%)	90 ± 16 (61–146)
LVEF (%)	59.2 ± 15.5 (18.0–79.0)
Hematocrit (%)	36.4 ± 4.9 (25.6–46.5)
Ca^{2+} (mmol/L)	1.16 ± 0.06 (1.04–1.39)
K^+ (mmol/L)	4.0 ± 0.6 (3.1–6.0)
Estimated blood viscosity (cP)	3.49 ± 0.60 (2.02–4.67)

Values expressed as mean ± SD (range) except for the Sex, Use of antihypertensive drug(s), and presence of DM.

Table 2: Baseline and post-heparin values of hemodynamic and physiologic parameters

Parameter	baseline	post-heparin administration	P value
HR (beats/min)	73 ± 17 (47–128)	75 ± 17 (49–136)	0.0391
MAP (mmHg)	70 ± 8 (54–93)	54 ± 8 (16–74)	**< 0.0001**
CVP (mmHg)	7 ± 4 (2–21)	7 ± 3 (2–22)	0.5272
mean PAP (mmHg)	20 ± 7 (6–40)	18 ± 6 (7–42)	**0.0004**
SVRI (dyne·sec·m^2/cm^5)	2050 ± 645 (1163–3808)	1500 ± 442 (859–2631)	< 0.0001
EDVI (mL/m^2)	121 ± 28 (66–252)	122 ± 26 (66–222)	0.6391
CI (L/min/m^2)	2.6 ± 0.6 (1.6–3.8)	2.7 ± 0.6 (1.6–3.8)	**0.0016**
SvO_2 (%)	79 ± 6 (63–93)	79 ± 6 (61–87)	0.3090
Skin temperature (°C)	31.5 ± 2.9 (26.0–36.4)	31.5 ± 2.9 (26.0–36.4)	> 0.9999

Values expressed as mean ± SD (range). Heparin administration significantly decreased the MAP and SVRI. HR: heart rate;

Table 3: The results of single-linear regression analysis

Correlations between %MAP change and each independent variable			
No.	**Variable**	**r**	**p**
1	Age	0.229	0.071
2	Sex	-0.040	0.753
3	Height	-0.006	0.962
4	Weight	-0.090	0.483
5	BMI	-0.111	0.386
6	ASA-PS	0.129	0.313
7	Antihypertensive drug	**-0.270***	**0.032**
8	Smoking	-0.023	0.868
9	DM	0.033	0.797
10	eGFR	-0.207	0.109
11	Total protein	-0.138	0.281
12	Albumin	-0.272*	0.031
13	Fibrinogen	-0.199	0.117
14	Antithrombin 3	0.043	0.756
15	LVEF	0.074	0.565
16	Hematocrit	-0.100	0.436
17	Ca^{2+}	0.046	0.720
18	K^{+}	0.052	0.686
19	Viscosity	-0.122	0.342
20	Skin temperature	-0.040	0.778
21	HR	0.041	0.749
22	MAP	**0.342****	**0.006**
23	CVP	-0.075	0.573
24	mean PAP	-0.075	0.567
25	SVRI	**0.414****	**0.008**
26	EDVI	-0.151	0.323
27	CI	0.016	0.913
28	SvO_2	-0.126	0.340

*Correlations between % MAP change and each independent variable were analyzed using single-linear regression analysis. *p < 0.05; **p<0.01*

and estimated glomerular filtration rate (r = 0.207), neither correlation reached statistical significance (p = 0.071 and p = 0.109, respectively).

Before the multiple linear regression analysis, correlations between each independent variable were investigated to remove correlated variables, such as weight and body mass index, to avoid multicollinearity. A correlation (r = 0.561) was found between the baseline MAP and SVRI. The SVRI had a stronger correlation with percent change in MAP than with baseline MAP, so baseline MAP was removed from the multiple regression analysis. Sex, height, body mass index, smoking status, and hematocrit were also removed because of a high correlation with weight (r = 0.673, 0.714, 0.831, 0.422, and 0.409, respectively). Mean PAP was removed because of a correlation with CVP (r = 0.549), total serum protein and viscosity were removed because of their correlation with serum albumin level (r = 0.649 and 0.464 respectively), and estimated glomerular filtration rate was removed because of a correlation with use of antihypertensive medication (r = 0.303).

The multiple linear regression analysis was performed using the forward stepwise selection method. Baseline SVRI and non-use of preoperative antihypertensive medication remained as predictors. The following regression equation was found to predict the percent decrease in MAP based on the baseline SVRI and preoperative use of antihypertensive medication: percent decrease in MAP = 17.273 + 0.00457 × (baseline SVRI) - 14.043 × (antihypertensive drug), where antihypertensive drug is coded as 0 = no antihypertensive drug, and 1 = one or more antihypertensive drug(s) and SVRI is measured in $dyne{\cdot}sec{\cdot}m^2/cm^5$ (F value = 7.80, multiple correlation coefficient (R) = 0.68645, R adjusted for the degrees of freedom = 0.41078).

DISCUSSION

The results of this study confirm that hypotension in response to administration of heparin is a common phenomenon during cardiothoracic surgery.[4] Single and multiple linear regression analyses using the forward stepwise selection method revealed that the baseline SVRI value and non-use of preoperative antihypertensive medication can be used to predict heparin-induced hypotension.

In our study, a heparin-induced decrease in the MAP and SVRI was accompanied by a slightly increased heart rate and cardiac index, indicating that a decrease in systemic vascular resistance (SVR) was the direct cause of hypotension. According to Poiseuille's law, SVR is dependent on blood vessel diameter and blood viscosity, and a decrease in SVR is caused by vasodilation and/or a decrease in blood viscosity. Several possible mechanisms that could explain the heparin-induced vasodilation have been reported. Heparin dilates blood vessels via release of histamine, cGMP, and endothelium-derived nitric oxide, as well as calcium inhibition.[6,15,16] On the other hand, there is some evidence suggesting that heparin reduces blood viscosity.[7-9] However, the effect on blood viscosity was

trivial and not considered clinically significant.[8] In the present study, there was no significant correlation between blood viscosity and percent change in MAP after administration of heparin. Moreover, the major determinants of blood viscosity are hematocrit and total serum protein,[14] which are not likely to be influenced significantly by acute administration of heparin. On balance, it is assumed that the decrease in SVR was attributable to vasodilation rather than decreased blood viscosity.

The results of the multiple regression analysis revealed that non-use of preoperative antihypertensive medication was also an independent predictor of heparin-induced hypotension. Patients who were prescribed preoperative antihypertensive drug developed less severe hypotension, indicating that the vessels of these patients were already dilated or resistant to pharmacologically-induced vasodilation.[17]

The baseline MAP value can be used instead of SVRI as a predictor of heparin-induced hypotension. However, MAP is markedly affected by cardiac function, and the correlation with the percent change in MAP was smaller than that of baseline SVRI. Therefore, baseline MAP should be used as a predictor only when SVRI is not available.

Although a weak correlation was found between the serum albumin level and the percent change in MAP, the correlation coefficient was small ($r = -0.272$). Furthermore, the results of multiple regression analysis did not suggest that the serum albumin level can be used as a predictor of heparin-induced hypotension.

Regarding other independent variables, although heparin exerts its vasodilatory effect via binding to Ca^{2+} [5] the baseline Ca^{2+} concentration was not correlated with the percent change in MAP after administration of heparin. The present results suggest that the influence of serum Ca^{2+} levels on heparin-induced hypotension is negligible. Skin temperature was monitored to evaluate the peripheral vascular circulation and resistance, and no significant correlation was found between the baseline skin temperature values and either SVRI or percent change in MAP. It is likely that the skin temperature values were largely affected by individual differences in skin condition.

Several techniques to prevent heparin-induced hypotension have been proposed. These include slow injection or administration of heparin in a fractionated dose rather than in a bolus dose,[5,10] administration of diphenhydramine 30 minutes before administration of heparin,[6] intravenous administration of calcium chloride immediately before administration of heparin,[5] use of phenylephrine,[18] and preoperative use of H1 receptor blocker[18] or antihypertensive medication.[17]

Heparin occasionally causes severe hypotension and hemodynamic instability.[13] Anesthesiologists should be able to predict and prevent heparin-induced hypotension and hemodynamic instability during cardiothoracic surgery. Hyperkalemia is also associated with administration of heparin during cardiothoracic surgery.[10,13] Heparin should be administered carefully, particularly in patients with a potassium homeostasis defect who frequently develop hyperkalemia in response to heparin-induced hemodynamic instability.[19]

This study has a limitation to be acknowledged in that the surgeons usually manipulate the heart and surrounding tissue at the time of heparinization, and those actions could have affected the hemodynamic status of the patients in some degree. However, at our institution, it is customary for the surgeons to inform the anesthesiologist if their procedure can significantly affect hemodynamic parameters, and the anesthesiologist leaves this information as a note on the anesthetic chart. Although the influence of the surgical procedures on the hemodynamic parameters could not be fully eliminated from this study, it can be considered minimal because the anesthetic charts of the patients included did not contain such notes.

CONCLUSION

Heparin-induced hypotension is common during cardiothoracic surgery performed on cardiopulmonary bypass. The baseline systemic vascular resistance index and non-use of preoperative antihypertensive medication are significant predictors of the severity of heparin-induced hypotension.

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Authors' contributions:

MK: Conceived the study, collected data, performed statistical analysis, and drafted the manuscript.

TI, HN, and TM: Collected data, performed statistical analysis, and revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

REFERENCES

1. Cohn LH. Fifty years of open-heart surgery. Circulation 2003;107(17):2168-70. [PubMed] [Free full text] DOI: 10.1161/01.CIR.0000071746.50876.E2
2. Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: Past, Present, and Future. Pharmaceuticals (Basel, Switzerland), 2016;9(3). [PubMed] [Free full text] DOI: 10.3390/ph9030038
3. Lindahl U, Bäckström G, Höök M, Thunberg L, Fransson LA, Linker A. Structure of the antithrombin-binding site in heparin. Proc Natl Acad Sci U S A. 1979 Jul;76(7):3198-202. [PubMed] [Free full text] DOI: 10.1073/pnas.76.7.3198
4. Seltzer JL, Gerson JI. Decrease in arterial pressure following heparin injection prior to cardiopulmonary bypass. Acta anaesthesiol Scand 1979;23(6):575-78. [PubMed] DOI: 10.1111/j.1399-6576.1979.tb01489.x
5. Urban P, Scheidegger D, Buchmann B, Skarvan K. The hemodynamic effects of heparin and their relation to ionized calcium levels. J Thorac Cardiovasc Surg. 1986;91(2):303-6. [PubMed]
6. Casthely PA, Yoganathan D, Karyanis B, Salem M, Yoganathan T, Komer C, et al. Histamine blockade and cardiovascular changes following heparin administration during cardiac surgery. J Cardiothorac Anesth. 1990;4(6):711-4. [PubMed]
7. Ruggiero HA, Castellanos H, Caprissi LF, Caprissi ES. Heparin effect on blood viscosity. Clin Cardiol, 1982. 5(3): p. 215-8. [PubMed] [Free full text] DOI: 10.1002/clc.4960050303
8. Gousios A, Shearn MA. Effect of intravenous heparin on human blood viscosity. Circulation. 1959;20:1063-6. [PubMed] DOI: 10.1161/01.cir.20.6.1063
9. Hitosugi M, Niwa M, Takatsu A. Changes in blood viscosity by heparin and argatroban. Thromb Res 2001;104(5):371-4. [PubMed]
10. Zavala-Villeda JA, V.E.H.-R., Molina-Méndez FJ, Rojas-Pérez EM, Fernández-Rivera B, Vargas-Trujillo C. Hemodynamic and hydroelectrolitic changes secondary to the heparin administration in patients undergoing coronary revascularization. Revist Mex de Anest, 2008;31(2):84-7.
11. Boer C, Meesters MI, Veerhoek D, Vonk ABA. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. Br J Anaesth 2018;120(5):914-27. [PubMed] [Free full text] DOI: 10.1016/j.bja.2018.01.023
12. Kien ND1, Quam DD, Reitan JA, White DA. Mechanism of hypotension following rapid infusion of protamine sulfate in anesthetized dogs. J Cardiothorac Vasc Anesth. 1992 Apr;6(2):143-7. [PubMed]
13. Jacka MJ, Clark AG. Cardiovascular instability requiring treatment after intravenous heparin for cardiopulmonary bypass. Anesth Analg. 2000 Jan;90(1):42-4. [PubMed] DOI: 10.1097/00000539-200001000-00009
14. de Simone G, Devereux RB, Chien S, Alderman MH, Atlas SA, Laragh JH. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. Circulation. 1990 Jan;81(1):107-17. [PubMed] DOI: 10.1161/01.cir.81.1.107
15. Mandal AK, Lyden TW, Saklayen MG. Heparin lowers blood pressure: biological and clinical perspectives. Kidney Int. 1995 Apr;47(4):1017-22. [PubMed]
16. Li JM, Hajarizadeh H, La Rosa CA, Rohrer MJ, Vander Salm TJ, Cutler BS. Heparin and protamine stimulate the production of nitric oxide. J Cardiovasc Surg 1996;37(5):445-52. [PubMed]
17. Dhawan R, Chaney MA. Preoperative angiotensin system inhibitor use attenuates heparin-induced hypotension in patients undergoing cardiac surgery. J Cardiothorac vasc anesth 2013;27(5):828-33. [PubMed] doi: 10.1053/j.jvca.2012.12.007
18. Slaughter TF, Mark JB. Heparin-mediated hypotension associated with cardiac surgery. Anesth Analg 2000:91(3):766-7. [PubMed] DOI: 10.1097/00000539-200009000-00063
19. Oster JR, Singer I, Fishman LM. Heparin-induced aldosterone suppression and hyperkalemia. Am J Med1995;98(6):575-86. [PubMed]

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