PROTAMINE-INDUCED HYPOTENSION IN HEART OPERATIONS: APPLICATION OF THE CONCEPT OF VENTRICULAR-ARTERIAL COUPLING

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Protamine sulfate often causes hypotension during heparin neutralization. The concept of ventricular-arterial coupling was applied to determine whether a negative inotropic effect or a vasodilating effect of protamine was the major contributing factor to this hypotension. Thirty-five patients who underwent cardiac operations were studied during operation by measuring instantaneous left ventricular pressure and aortic flow to examine the end-systolic pressure-volume relationship. We obtained end-systolic elastance and effective arterial elastance values in a beat-to-beat fashion with a single-beat estimation method. In 28 of the 35 patients (80%), mean arterial pressure decreased more than 10 mm Hg with protamine infusion. Parameters were compared at the following three points: before a decrease in mean arterial pressure (control), at maximally decreased mean arterial pressure (maximum), and at a middle point between control and maximum values (midpoint). At both midpoint and maximum, mean arterial pressure decreased significantly (control 79.6 ± 12.6 mm Hg, midpoint 66.5 ± 10.8 mm Hg, maximum 52.7 ± 9.9 mm Hg; $p < 0.01$). Similar changes were observed in effective arterial elastance (control 2.00 ± 0.75 mm Hg/ml, midpoint 1.60 ± 0.53 mm Hg/ml, maximum 1.31 ± 0.46 mm Hg/ml; $p < 0.01$). Although the decrease in end-systolic elastance at midpoint (control 3.08 ± 1.61 mm Hg/ml, midpoint 2.92 ± 1.68 mm Hg/ml) did not reach statistical significance, end-systolic elastance significantly decreased at maximum (2.63 ± 1.46 mm Hg/ml; $p < 0.01$). Continuous measurements showed that the decreases in mean arterial pressure and effective arterial elastance always preceded the depression of end-systolic elastance and that afterload reduction by vasodilating effect of protamine was the mechanism most likely to have initiated the hypotension. Delayed decrease in contractility may be ascribed to reduced coronary perfusion pressure caused by vasodilation or to a direct effect of protamine. (*J Thorac Cardiovasc Surg* 1996;112:462-71)

Protamine sulfate has been used after cardiopulmonary bypass (CPB) to neutralize anticoagulation induced by heparin. Adverse cardiovascular effects of protamine, including hypotension, anaphy-

lactoid reactions, and catastrophic pulmonary vasoconstriction, have been reported.¹ Among these responses, hypotension is frequently observed. Such hypotension during the critical postoperative period may cause detrimental hemodynamic changes if an appropriate intervention is not given. It has been suggested that this hypotension may result either from a vasodilating effect or from a negative inotropic effect of protamine. Despite the large number of studies,²⁻¹³ it has not been clear which of the two, vasodilation or reduced contractility, contributes quantitatively more manner to hypotension.

Ventricular-arterial coupling is a concept built on the framework of the ventricular pressure-volume relationship.¹⁴ This concept enables one to evaluate the specific contribution of the end-systolic proper-

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ties of the ventricle and parameters of the arterial system to stroke volume (SV) and end-systolic pressure (P_{es}). Arterial and left ventricular P_{es} can be predicted from a simple equation consisting of three parameters representing preload (end-diastolic volume, V_{ed}), afterload (effective arterial elastance, E_a), and systolic function (slope of the end-systolic pressure-volume relationship, ESPVR). Continuous assessment of the ESPVR has not been possible, however, because simultaneous measurements of both pressure and volume in various loading ventricular contractions are usually required to obtain ESPVR. To measure ESPVR continuously in the operating room, we used a method of estimating ESPVR from a single ejecting beat without measuring ventricular volume in a beat-to-beat fashion.^{15, 16} The purpose of this clinical study was to investigate whether a negative inotropic effect or a vasodilating effect of protamine was the major contributing factor to the hypotension. We attempted to quantify the contribution of each parameter to protamine-induced hypotension.

Methods

Patients. Thirty-five patients who underwent elective cardiac operations were studied (Table I). The study protocol was approved by the Human Subjects Committee of our institution. Informed consent was obtained from all patients.

Instrumentation. A radial arterial line and a central venous line were inserted. Before CPB was begun, each patient received intravenous heparin (3 mg/kg). Multidose cold (4° C) oxygenated crystalloid potassium cardioplegic solution was used for myocardial protection, as described elsewhere.¹⁷ In addition, topical cooling with iced lactated Ringer's solution and moderate systemic hypothermia (28.4° ± 2.5° C) was employed. At the end of CPB, a micromanometer (model MPC-500; Millar Instruments, Inc., Houston, Texas) was inserted into the left ventricle through the roof of the left atrium or the ascending aorta. The time derivative of the left ventricular pressure signal (dP/dt) was calculated by a differentiator (model 1323; Nihon Koden, Tokyo, Japan). An appropriately sized electromagnetic flow probe (model FR series; Nihon Koden) was placed around the ascending aorta, proximal to the arterial cannulation site. The venous drainage cannula was then removed, and major bleeding from the heart and great vessels was surgically corrected. From 5 to 35 minutes (14.8 ± 9.5 minutes) after the end of CPB, when the patient was in hemodynamically stable condition, protamine sulfate (3 mg/kg) was infused from the central venous line over 3 minutes at a constant rate.

Data analysis. The electrocardiogram, arterial pressure, central venous pressure (CVP), left ventricular pressure, aortic flow, and dP/dt were displayed on an eight-channel chart recorder (Polygraph 360 system; NEC San-ei, Tokyo, Japan) and were stored on a tape (MR-30;

Table I. Patient profile

	Hypotension (n = 28)	No hypotension (n = 7)
Sex (M/F)	15/13	2/5
Age (yr)	40.3 ± 13.3	53.7 ± 8.8*
NYHA	1.8 ± 0.7	2.0 ± 0.6
CTR (%)	53.5 ± 7.0	61.4 ± 4.2†
EF (%)	59.4 ± 13.7	50.0 ± 11.7
Operation		
ASD	9	2
OMC	6	1
MVR	4	1
AVR	6	3
Other	3	0
AXT (min)	61.6 ± 29.9	70.1 ± 32.3
CPBT (min)	101.1 ± 40.2	116.7 ± 44.6

NYHA, New York Heart Association functional class; CTR, cardiothoracic ratio; EF, ejection fraction; ASD, direct or patch closure of atrial septal defect; OMC, open mitral commissurotomy; MVR, mitral valve replacement; AVR, aortic valve replacement; Other, extirpation of left atrial myxoma, left ventricular myectomy, anbd membranectomy of right ventricular outflow tract; AXT, aortic crossclamp time; CPBT, cardiopulmonary bypass time. Values are mean ± standard deviation.

* $p < 0.05$ by unpaired t test.

† $p < 0.01$ by unpaired t test.

TEAC, Tokyo, Japan). All recorded signals were appropriately calibrated and digitized off line at a sampling interval of 5 msec. The stored signals were analyzed by a program developed in our laboratory with a signal-processing computer system (7T17; NEC San-ei).

We used a method of estimating ESPVR from a single ejecting beat^{15, 16} to follow the serial hemodynamic changes. As shown in Fig. 1, if we obtain left ventricular peak isovolumic pressure (P_{max}) from a given ejecting beat, a tangential line can be drawn from the P_{max} point to the left upper corner of the left ventricular pressure-volume loop, which yields ESPVR. The slope of this line represents end-systolic elastance (E_{es}).^{18, 19} We estimated P_{max} from a pressure curve during isovolumic contraction period. By means of the Gauss-Newton nonlinear least-square method, the pressure curve was fitted to the following equation²⁰:

$$HMP(t) = \frac{1}{2} \cdot DP_{max} \cdot (1 - \cos \omega t) + P_{ed} \quad (1)$$

where HMP is hydromotive pressure, which reflects the pressure wave of nonejecting beat, DP_{max} is maximum developed pressure, P_{ed} is left ventricular end-diastolic pressure, ω is $2\pi/T$ (in which T is the duration of contraction), and t is time. Originally, data from both isovolumic contraction and the relaxation phase of the ejecting beat were used.²⁰ We made the estimate with only the data of isovolumic contraction phase, however, because of the afterload dependency of pressure curve during the relaxation phase.²¹ Once P_{max} was estimated, the ESPVR line was drawn from the point of P_{max} at arbitrarily set V_{ed} to the left upper corner of the pressure-volume loop of the ejecting beat. The pressure of this left upper corner represented left ventricular P_{es} . The trajec-

Fig. 1. Principle used to assess E_{es} and E_a from a single ejecting beat. *Left panel:* Estimation of P_{max} . The solid line shows a measured ejecting beat. The left ventricle was assumed as a linear time varying hydromotive pressure source, $HMP(t)$. By fitting the isovolumic contraction portion of the measured left ventricular pressure (LVP) to the function described at the bottom of the figure (equation 1), estimated isovolumic LVP (dashed line) and P_{max} were obtained. *Right panel:* Estimation of E_{es} and E_a . The line connecting the estimated P_{max} point to the left upper corner (P_{es}) of the pressure-ejected volume loop that was obtained by integration of aortic flow yields the slope of ESPVR (E_{es}) and V_e ($V_{ed} - V_0$). E_a is the slope of the P_{es} -SV relationship.

tory of the pressure-volume loop was obtained by plotting left ventricular pressure and the time integral of the ejected flow subtracted from V_{ed} : $V_{ed} - \int_0^t \text{flow}(t)dt$. Because V_{ed} was an arbitrarily set number, we did not know the absolute value of the volume axis intercept of ESPVR line (V_0). The difference between V_{ed} and V_0 , however, which we term "effective end-diastolic volume," or V_e ($V_{ed} - V_0$), was available. E_a was calculated as P_{es}/SV .¹⁴

Other hemodynamic parameters such as heart rate (HR; 60/cycle lengths), mean arterial pressure (MAP), P_{ed} , cardiac index (CI; $SV \cdot \text{HR}/\text{body surface area}$), and systemic vascular resistance (SVR; $[\text{MAP} - \text{CVP}] \cdot 80/\text{cardiac output}$) were also determined in a beat-to-beat fashion. When we thought arterial pressure had reached a nadir, we slowly infused volume while being careful to avoid overinfusion. Comparisons of hemodynamic parameters were conducted at the following three points; just before MAP started to decrease after the infusion of protamine (control), when MAP was maximally decreased before volume loading (maximum), and at the middle between control and maximum (midpoint). At each point, the hemodynamic values of 5.4 ± 2.6 consecutive beats were averaged.

Evaluation of the effect of each parameter on hypotension. First, we analyzed relationships between percentage changes from each control value in MAP and changes in each parameter during hypotension.

Second, from the concept of ventricular-arterial coupling, the following equations were obtained (Fig. 1):

$$P_{es} = E_{es} \cdot (V_{es} - V_0) \quad (2)$$

$$P_{es} = E_a \cdot SV \quad (3)$$

$$SV = V_{ed} - V_{es} \quad (4)$$

$$V_e = V_{ed} - V_0 \quad (5)$$

where V_{es} is end-systolic volume. From these equations, the following equation is obtained:

$$P_{es} = \frac{E_{es} \cdot E_a}{(E_{es} + E_a)} \cdot (V_{ed} - V_0) = \frac{E_{es} \cdot E_a}{(E_{es} + E_a)} \cdot V_e \quad (6)$$

With this equation, we evaluated the effect of parameters including contractility (E_{es}), afterload (E_a), and preload (V_e) on the degree of hypotension. The values of one parameter at midpoint and maximum were substituted in this equation, leaving the other parameters set to the control value. For example, the effect of E_{es} at midpoint on P_{es} was calculated as follows:

$$\begin{aligned} \Delta P_{es}(E_{es, \text{Mid}}) &= (P_{es} \text{ at } E_{es, \text{Mid}}) - P_{es, \text{Cont}} \\ &= \frac{E_{es, \text{Mid}} \cdot E_{a, \text{Cont}}}{(E_{es, \text{Mid}} + E_{a, \text{Cont}})} \cdot V_{e, \text{Cont}} - P_{es, \text{Cont}} \quad (7) \end{aligned}$$

where $E_{es, \text{Mid}}$ is a value of E_{es} at midpoint and $E_{a, \text{Cont}}$, $V_{e, \text{Cont}}$, and $P_{es, \text{Cont}}$ are the control values of those param-

eters. The difference between P_{es} at $E_{es, Mid}$ and $P_{es, Cont}$ was obtained to quantify the effect of that parameter on P_{es} .

Compression of the femoral arteries. The results of this study in the first several patients suggested that the protamine-induced hypotension in these patients was caused mainly by the decreased afterload. We therefore presumed that protamine-induced hypotension could be reversed by increasing afterload. To increase afterload, we compressed the bilateral femoral arteries with the fists during the hypotensive period in seven patients rather than performing volume loading. Data obtained before and after compression of the femoral arteries were compared.

Statistical methods. Measured values were expressed by mean and standard deviation. A repeated-measures analysis of variance was used to examine the differences among the parameters at the three points. A p value less than 0.05 was considered to be statistically significant. If an overall difference was present, Bonferroni's adjustment was performed.²² Comparisons of the data before and after compression of the femoral arteries were conducted by paired t test. Multiple linear regression (least squares) was used to correlate the changes of MAP with those of other parameters.

Results

Clinical profiles of the patients studied. Table I summarizes preoperative and operative profiles of the studied patients. Of 35 patients studied, 28 patients (80%) showed a decrease in MAP greater than 10 mm Hg during protamine administration. More advanced age and larger hearts were noticed in the patients without protamine-induced hypotension. In seven of 28 hypotensive patients, flow signals were not available because of electrical noise. Consequently, we analyzed a total of 21 patients who showed protamine-induced hypotension. Their body weights and body surface areas averaged 55.2 ± 8.7 kg and 1.56 ± 0.17 m², respectively.

Representative tracing of hemodynamic parameters. In each case, there was no change in hemodynamic parameters during the protamine infusion before MAP started to decrease. Representative changes of hemodynamic parameters during protamine-induced hypotension in a beat-to-beat fashion are shown in Fig. 2. In this case, initial decrease in MAP was observed at 50 seconds after protamine administration, and MAP was maximally decreased within next 20 seconds. Marked decreases in SVR and E_a were observed in association with the decrease in MAP. On the other hand, CI increased slightly. The other hemodynamic parameters were relatively unchanged.

Fig. 2. Representative changes of hemodynamic parameters during protamine-induced hypotension in a beat-to-beat fashion.

Changes in hemodynamic parameters during protamine-induced hypotension. The changes in hemodynamic parameters during protamine-induced hypotension are shown in Fig. 3. MAP started to decrease 81 ± 32 seconds after protamine administration was begun, and the maximum decrease in MAP occurred at 115 ± 38 seconds. A repeated-measures analysis of variance revealed significant decreases ($p < 0.01$) in MAP, SVR, E_a , and E_{es} . At both midpoint and maximum, MAP decreased significantly (control 79.6 ± 12.6 mm Hg vs midpoint 66.5 ± 10.8 mm Hg, $p < 0.01$; control vs maximum 52.7 ± 9.9 mm Hg, $p < 0.01$; and midpoint vs maximum, $p < 0.01$). Similar trends were observed in changes of SVR (control 1359 ± 433 dynes $\cdot$ sec $\cdot$ cm⁻⁵ vs midpoint 1050 ± 330 dynes $\cdot$ sec $\cdot$ cm⁻⁵, $p < 0.01$; control vs maximum 826 ± 320 dynes $\cdot$ sec $\cdot$ cm⁻⁵, $p < 0.01$; and midpoint vs maximum, $p < 0.01$) and E_a (control 2.00 ± 0.75 mm Hg/ml vs midpoint 1.60 ± 0.53 mm Hg/ml, $p < 0.01$; control vs maximum 1.31 ± 0.46 mm Hg/ml, $p < 0.01$; and midpoint vs maximum, $p < 0.01$). Although the

Fig. 3. Changes of hemodynamic parameters during protamine-induced hypotension. Results are shown for each point with averaged raw data for each of the 21 patients.

slight decrease in E_{es} at midpoint (control 3.08 ± 1.61 mm Hg/ml vs midpoint 2.92 ± 1.68 mm Hg/ml) did not reach statistical significance, E_{es} decreased significantly from control ($p < 0.01$) and from midpoint ($p < 0.01$) at the maximum point (2.63 ± 1.46 mm Hg/ml). HR, CI, P_{ed} , and V_e did not change significantly. The data regarding percentage change, P_{es} , dP/dt , and E_a/E_{es} are summarized in Table II.

Effects of each parameter on hypotension. The percentage changes from the each control value in MAP during hypotension correlated well with changes in SVR and E_a (Fig. 4). On the other hand, there were no correlations between the percentage changes in MAP and changes in E_{es} and V_e .

Because P_{es} , as determined by single-beat estimation, was close to MAP ($P_{es} = 0.97 \text{ MAP} + 24.3$, $r = 0.80$, $p < 0.001$, standard error of estimate 2.7 mm Hg), we evaluated the effect of each parameter on P_{es} as a substitute for MAP.¹⁴ This is summarized in Fig. 5. There were negative effects on P_{es} in response to decreases in E_{es} and E_a . Potential decreases in E_{es} at midpoint and maximum would reduce P_{es} by 1.8 ± 4.4 mm Hg (not significant) and 4.5 ± 7.1 mm Hg ($p < 0.01$), respectively, provided there were no changes in the other parameters. Greater potential effects of E_a would be observed at both midpoint (10.0 ± 6.6 mm Hg, $p < 0.01$) and maximum (19.3 ± 9.9 mm Hg, $p < 0.01$). Because there was no significant change in V_e during hypotension, the

changes in V_e did not have any significant effect on P_{es} .

Compression of the femoral arteries. Systemic arterial pressure was increased about 10 to 20 mm Hg with compression of the femoral arteries during protamine-induced hypotension. The hemodynamic parameters before and after compression of the femoral arteries in the seven patients treated this way were summarized in Table III. SVR and E_a were increased significantly with compression of the femoral arteries, thereby increasing MAP significantly. HR, CI, P_{ed} , V_e , and E_{es} did not change significantly.

Discussion

In this study, the hemodynamic changes of protamine-induced hypotension in patients who were separated from CPB occurred at 80 to 120 seconds after protamine administration at a constant rate over 180 seconds. During this period, as shown in Figs. 2 and 3, MAP, SVR, and E_a rapidly decreased, whereas the other parameters, including HR, P_{ed} , V_e , and CI, remained relatively unchanged. Although the load-insensitive parameter of contractility, E_{es} , decreased significantly at the end of this period, continuous measurement of these changing parameters showed that the change in E_{es} was always preceded by the changes in MAP, SVR, and E_a . The concept of ventricular-arterial coupling predicts that decreases in both E_a and E_{es} will

Fig. 4. Relationships between percentage changes from each control value in MAP (%MAP) and changes in E_a (% E_a), E_{es} (% E_{es}), SVR (%SVR), or V_e (% V_e) during protamine-induced hypotension. %MAP had significant correlations with %SVR (dashed line; $y = 0.55x + 36.9$, $r = 0.74$, $p < 0.001$, standard error of the estimate 5.7%) and with % E_a (dashed line; $y = 0.47x + 39.9$, $r = 0.60$, $p < 0.001$, standard error of the estimate 7.5%). Neither % E_{es} nor % V_e had any significant correlation with %MAP.

Table II. Summary of hemodynamic parameters during protamine-induced hypotension

	Control	Midpoint	Maximum	<i>p</i>
MAP (mm Hg)	79.6 ± 12.6	66.5 ± 10.8*	52.7 ± 9.9*†	<0.01
SVR (dynes · sec · cm ⁻⁵)	1359 ± 434	1050 ± 330*	826 ± 320*†	<0.01
E_a (mm Hg/ml)	2.00 ± 0.75	1.60 ± 0.53*	1.31 ± 0.46*†	<0.01
% E_a (%)	100	81.8 ± 10.7*	67.2 ± 13.4*†	<0.01
E_{es} (mm Hg/ml)	3.08 ± 1.61	2.92 ± 1.68	2.63 ± 1.46*†	<0.01
% E_{es} (%)	100	94.9 ± 10.5	87.5 ± 14.5*‡	<0.01
dP/dt (mm Hg/sec)	1647 ± 523	1587 ± 509	1484 ± 534*†	<0.01
P_{es} (mm Hg)	103.0 ± 14.7	87.2 ± 14.6*	71.4 ± 13.8*†	<0.01
E_a/E_{es}	0.88 ± 0.66	0.75 ± 0.58	0.65 ± 0.44*	<0.01
HR (beats/min)	83.0 ± 15.3	82.6 ± 14.6	81.4 ± 14.1	NS
P_{ed} (mm Hg)	11.0 ± 2.9	10.5 ± 2.9	10.1 ± 2.9	NS
V_e (ml)	90.4 ± 49.2	88.9 ± 44.3	86.5 ± 36.5	NS
CI (L · min ⁻¹ · m ²)	2.94 ± 0.73	3.08 ± 0.73	3.04 ± 0.69	NS

% E_a , Percentage change of E_a from control value; % E_{es} , percentage change E_{es} from control value; NS, not significant. Values are expressed as mean ± standard deviation; *p* values obtained by repeated-measures analysis of variance with Bonferroni's adjustment.

**p* < 0.01 vs. control.

†*p* < 0.01 vs midpoint.

‡*p* < 0.05 vs midpoint.

decrease arterial pressure. In our studies, there were greater potential effects of E_a than those of E_{es} , and the decrease in MAP correlated well with the decreases in SVR and E_a but not with that in E_{es} (Figs. 4 and 5). These results suggest that the possible mechanism by which protamine induces hypotension is afterload reduction through its vasodilatory effect.

Left ventricular ESPVR is nearly linear across the working range of the heart, and the slope of this relationship (E_{es}) reflects contractile state. E_{es} is therefore considered a load-insensitive parameter of contractility on the basis of studies with isolated heart preparations.²³ Analysis of left ventricular ESPVR in human beings has been hindered, however, by difficulties in simultaneous measurement of

Fig. 5. *Left panel:* Bar graph showing decreased MAP at midpoint and maximum during protamine-induced hypotension. *Right panel:* Bar graph showing effect of each parameter on the change in P_{es} . ΔP_{es} describes the effect of a change in a parameter on the P_{es} provided that the other two parameters remain at their control values.

left ventricular pressure and volume under altered loading conditions. In several studies in human beings,²⁴⁻²⁶ left ventricular volume and pressure were measured by cardiac catheterization, radionuclide angiography, or a conductance catheter. The ESPVR was constructed by altering the loading conditions, under the assumption that the contractile state was not affected by neurohumoral control mechanisms during alterations in loading, which may not actually be the case. In addition, continuous assessment of ESPVR in a beat-to-beat fashion has not been available. Moreover, these volumetric methods, with the exception of the conductance catheter, are not available in the operating room. We therefore applied the method previously used to assess E_{es} of the in situ canine heart^{18, 19} to patients who underwent heart operations. We estimated P_{max} from a given ejecting beat with the curve-fitting technique (Fig. 1).^{15, 16, 20} The validity of the estimate of P_{max} and E_{es} was not tested in human beings. We did, however, examine the relationship between E_{es} calculated by this method and E_{es} measured by actual aortic crossclamping in 17 canine hearts.¹⁵ The estimated and measured P_{max} of 232 beats in various loading conditions were compared, and the correlation coefficient was 0.92. The estimation error of the E_{es} obtained by this method relative to that obtained by actual aortic crossclamping was approximately 10%. Takeuchi and coworkers¹⁶ have validated independently the similar

Table III. Hemodynamic parameters before and after compression of the femoral arteries

	Before	After
MAP (mm Hg)	53.8 ± 7.2	68.0 ± 9.3*
SVR (dynes · sec · cm ⁻⁵)	954 ± 357	1216 ± 358*
E_a (mm Hg/ml)	1.30 ± 0.47	1.67 ± 0.53*
E_{es} (mm Hg/ml)	2.78 ± 1.89	2.79 ± 1.80
HR (beats/min)	78.8 ± 18.6	81.7 ± 18.8
P_{ed} (mm Hg)	9.7 ± 2.9	9.9 ± 3.5
V_e (ml)	85.2 ± 46.4	92.1 ± 55.0
CI (L · min ⁻¹ · m ²)	2.63 ± 0.89	2.62 ± 0.90

Values expressed as mean ± standard deviation.

* $p < 0.01$.

method in patients by measuring ventricular volume with angiography. We therefore considered the estimated P_{max} and E_{es} to be acceptable. Simultaneous measurements of aortic flow and left ventricular pressure, combined with the estimation of P_{max} , enabled us to assess E_{es} in a beat-to-beat fashion under changing hemodynamic conditions.

The concept of ventricular-arterial coupling is based on the framework of ventricular pressure-volume relationship.¹⁴ This coupling was made possible by characterizing the linear functions of both the ventricle and the arterial system in terms of their P_{es} and SV (P_{es} -SV) relationships. This approach yielded P_{es} and SV as the intersection between the ventricular P_{es} -SV relationship and arterial P_{es} -SV relationship. Accordingly, as described in the Methods section, P_{es} can be predicted by a simple equation consisting of three parameters representing preload, afterload, and systolic function. From the equation, the effects of E_{es} and E_a on P_{es} are summarized as follows: (1) If E_{es} is equal to E_a , the changes in E_{es} and E_a have equivalent effect on P_{es} . (2) If E_{es} is greater than E_a , the changes in E_{es} have a smaller effect on P_{es} than do the changes in E_a . (3) If E_{es} is less than E_a , the changes in E_{es} have a larger effect on P_{es} than do the changes in E_a . In this study, the control value of E_a was smaller than E_{es} . In addition, the absolute changes in E_a were larger. The net effect of E_a on P_{es} was therefore larger than the effect of E_{es} , as shown in Fig. 5. Decreases in E_{es} represent depression of myocardial contractility, whereas decreases in E_a reflect more complex physiologic responses. Because E_a can be approximated by the ratio of total arterial resistance to cardiac cycle length,¹⁴ relative changes in these two factors determine E_a . During protamine-induced hypotension, cardiac cycle length did not change signifi-

cantly. The decreases in E_a in this study therefore represented decreases in arterial resistance.

The concept of ventricular-arterial coupling also provides information about ventricular mechanical and metabolic efficiency.²⁷ When the E_a/E_{es} ratio lies between 0.5 and 1.0, both mechanical and metabolic efficiencies are greater than 90% of optimal values in the analytic model. Asanoi, Sasayama, and Kameyama²⁸ suggested that the coupling was normally set toward higher metabolic efficiency (the E_a/E_{es} ratio toward 0.5) in human beings. In our study, despite a relatively large amount of patient-to-patient variability, the mean E_a/E_{es} ratio at control was 0.88 ± 0.66 , and this was comparable to the values (0.90 ± 0.21) reported by Asanoi, Sasayama, and Kameyama²⁸ for patients with mild left ventricular dysfunction.

Adverse cardiovascular responses to protamine have been reported to fall into three distinct types: transient hypotension, anaphylactoid reactions, and catastrophic pulmonary vasoconstriction.¹ There may be complex mechanisms inducing such variable responses. Anaphylactoid reactions were not seen in the 35 patients in our study. Although not all patients had been monitored for pulmonary artery pressure, pulmonary arterial hypertension was not seen in the monitored patients and no respiratory problems were seen in the other patients. Consequently, we decided that we could analyze protamine-induced transient hypotension in our study. Because not all patients had induced hypotension (Table I), variability in patient response to protamine may exist. We included several different types of procedures in the study, which may have influenced the variability. With respect to the composition of the procedures, we could not include coronary artery bypass grafting because the method used for measurement requires an electromagnetic flow probe to be placed around the ascending aorta.

The mechanisms of protamine-induced hypotension have not been clearly defined.¹ Dose-related direct negative inotropic effects of protamine have been reported in both human⁷ and porcine¹³ isolated muscle preparations. In an isolated rabbit heart preparation, protamine had dose- and time-specific adverse effects on cardiac contractility.¹² There may be differences between findings in isolated heart preparations and those in *in vivo* studies, where neurohumoral reflexes can minimize protamine-induced vasodilation; effects of protamine on myocardial function were reported as positive inotropic changes,⁹ negative inotropic changes,¹⁰ or no

changes¹¹ in several *in vivo* animal studies. As reported by Jaques,⁸ marked variations in protamine toxicity were observed among species used for experimentation. In addition, the influence of CPB was not involved in the studies on small animals. Several authors reported that protamine in their clinical studies had certain effects on the myocardial function or the peripheral vascular beds,²⁻⁴ whereas others reported no effects.^{5,6} We observed both depressed myocardial contractility and vasodilation, and we quantitatively showed the greater potential effect of vasodilation than depressed contractility. Shapira and associates³ continuously recorded the hemodynamic parameters in a human study, and their results were generally compatible with ours. Because they observed a decrease in myocardial contractility simultaneous with the decrease in blood pressure, they suggested that the depressed myocardial contractility was a direct effect of protamine. In our study, however, decreased contractility was preceded by decreases in MAP and afterload. Consequently, a delayed decrease in contractility at the end of hypotensive period seems to be ascribable to two possible mechanisms. One possible explanation is exhausted coronary autoregulatory reserve at the end of hypotension, which might be below a level of critical coronary perfusion pressure.²⁹ The other is the direct effect of protamine because the decreased contractility did not increase with the moderate increase in MAP by the femoral artery compression technique (Table III). The isovolumic measurements of myocardial contractile element velocity that Shapira and associates³ used as an index of contractility have been reported to lack sufficient stability during acute changes in loading conditions.³⁰ The difference in used indexes of contractility may have contributed to the difference.

Our conclusion that protamine-induced hypotension was initially caused by decreased afterload was partially verified by use of the femoral artery compression technique. As shown in Table III, MAP, E_a , and SVR were increased by simply compressing the bilateral femoral arteries with the fists, leaving other parameters unchanged. Several interventions against protamine-induced hypotension have been reported. Those include pretreatment with calcium chloride, infusion of inotropics, volume loading, and combinations of these interventions.⁹ Because this hypotension is usually transient, as reported by Shapira and associates,³ such interventions may not be always required. Patients with good cardiac functional reserve may tolerate this hypotensive condi-

tion, but patients with poor cardiac functional reserve may, because reduced coronary perfusion pressure impairs myocardial contractility, show further deterioration if an appropriate intervention is not performed.²⁹ Compression of the femoral arteries provided prompt recovery of MAP and thus would increase coronary perfusion pressure. Recently, we have routinely used this simple and effective method to treat protamine-induced hypotension by maintaining coronary perfusion pressure.

Certain limitations of this study should be mentioned. First, recent studies questioned the load independence and linearity of ESPVR under a variety of conditions.^{31,32} Little and coworkers,³³ however, reported that a consistent nonlinearity present at all inotropic states did not prevent ESPVR from being well approximated by a straight line and that E_{es} provided a sensitive parameter of contractile state. We reported elsewhere that the average variance of the E_{es} measured by actual aortic crossclamping in the canine heart during volume loading within the physiologic range was small enough to be negligible.¹⁹ We therefore consider ESPVR to be acceptable for measuring contractility. Second, under changing hemodynamic conditions with decreasing afterload, ejecting ventricular pressure may be modulated by a changing relationship between ventricle and arterial system. The ventricular pressure curve of relaxation phase was also reported to be dependent on afterload.²¹ We did not use the pressure curve of the isovolumic relaxation phase, however, but instead used that of the isovolumic contraction phase in our single-beat estimation method. Accordingly, the estimated E_{es} would be relatively insensitive to changes in ventricular pressure during ejection and relaxation. Third, E_a was originally defined as a steady-state arterial parameter that incorporates the principal elements of vascular load.¹⁴ Because of the viscoelastic properties of the arterial system, the accuracy of estimating E_a in a beat-to-beat fashion during decreasing arterial pressure is controversial. Because we adopted the measured parameters at maximum, however, when arterial pressure had reached a nadir, at least the points of control and maximum were considered to be at a steady state. Only with these two sets of data could we make the same conclusion regarding the contribution analysis in a quantitative manner (Fig. 5; control vs. maximum). Fourth, we could not analyze the data for seven of 28 hypotensive patients because of electrical noise in the flow signals. Although changing hemodynamic

patterns of acquired pressure data for these seven patients were not different from those in 21 analyzed patients, it is unknown whether exclusion of 25% of the patients might have affected results and conclusions. Finally, because the volume axis intercept of the ESPVR line (V_0) could not be measured by our method, we applied V_e to substitute for V_{ed} . Even if V_0 was changed during the hypotension, the ventricular P_{es} -SV relation and arterial P_{es} -SV relation merely moved parallel along the volume axis, so the change in V_0 would not influence the coupling of these relations.

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