Pulmonary Hypertensive Response to Declamping of the Aorta during Abdominal Aortic Reconstructive Surgery — Role of Metabolic Derangement and Anaphylatoxin in the Reaction

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Metabolic parameters and anaphylatoxin activities in mixed venous blood were measured in 16 patients undergoing abdominal aortic reconstructive surgery to study the mechanism of pulmonary hypertensive response after aortic declamping. This reaction was confirmed by a rise in ratio between mean pulmonary arterial pressure and mean systemic arterial pressure (Pp/Ps). Aortic declamping was followed by a significant increase in lactate level and lactate-pyruvate ratio (L/P ratio) as compared with pre-declamping level ($P < 0.01$). Although anaphylatoxin C3a concentration rose significantly after declamping ($P < 0.01$), C5a showed no change at any stage. When the patients were divided into two groups according to the degree of Pp/Ps change by declamping, significant elevation of L/P ratio and C3a level were observed in the group with higher increase (Post-/Pre-declamp value $\geqq 1.25$) of Pp/Ps compared to the lower (<1.25) group. After declamping, in the higher Pp/Ps group, a positive correlation existed not only between Pp/Ps change and aortic clamp time, but also between L/P ratio and C3a level. The present results suggest that muscular metabolic derangement distal to the aortic clamp may play an important role in the development of post-declamping pulmonary hypertensive response through anaphylatoxin C3a. (Key words: aortic aneurysm, aortic declamping, pulmonary hypertension, anaphylatoxin)

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During vascular surgery in which prolonged occlusion of the abdominal aorta is necessary, release of the aortic clamp is accompanied by hemodynamic instability and impaired cardiac performance particularly in elderly and poor-risk patients[1]. Aortic declamping induces a marked fall in the systemic arterial pressure, and a significant rise in the pulmonary arterial pressure[2,3]. The exact cause of these declamping phenomena remains unknown, though systemic hypotension has been considered due to effects of accumulated metabolites which were washed out from ischemic leg muscles[4–6] as well as abrupt enlargement of vascular bed. A knowledge of pathophysiology of the pulmonary hypertensive response to aortic declamping will be helpful in preventing an occasional disaster following release of the clamp and in choosing vasoactive agents for declamping shock. Recent

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Table 1.

	Pre-clamp	Pre-declamp	Post-declamp				
			1'	5'	10'	15'	25'
mean PAP (mmHg)	15.05 ± 4.55 (8–26)	15.30 ± 4.09 (9–24)	14.05 ± 4.37 (8–24)	18.78* ± 5.16 (12–30)	18.00* ± 5.04 (11–31)	17.86* ± 4.57 (12–27)	16.00 ± 4.40 (8–26)
Pp/Ps	0.173 ± 0.068 (0.10–0.32)	0.169 ± 0.055 (0.10–0.26)	0.188 ± 0.056 (0.10–0.31)	0.211* ± 0.060 (0.09–0.32)	0.199* ± 0.058 (0.10–0.32)	0.197* ± 0.058 (0.09–0.33)	0.179 ± 0.048 (0.10–0.28)

Changes in mean PAP and Pp/Ps before and after aortic declamping in 23 patients. Statistical analysis by ANOVA with Tukey's multiple test. *$P < 0.01$ compared with pre-declamping values. PAP = pulmonary arterial pressure, Pp/Ps = ratio between mean pulmonary arterial pressure and mean systemic arterial pressure. Numbers in parenthesis indicate ranges.

studies have indicated that aortic clamping is often associated with the formation of anaphylatoxins C3a and C5a which cause vasoconstriction[7]. Anaphylatoxins have been also known as a potent mediator of thromboxane and histamine, more powerful pulmonary vasoconstrictors[8,9]. Thus anaphylatoxin formation may be involved in pulmonary hemodynamic response to aortic declamping.

The present study was designed to document relationship between hemodynamic changes, especially pulmonary arterial pressure, and metabolic parameters or anaphylatoxin activities after declamping of the aorta in patients undergoing aortic reconstructive surgery.

Patients and Methods

Prospective study was performed in 23 patients, with a mean age of 68 ± 7 years, who underwent elective repair for abdominal aortic aneurysm by prosthetic Y graft replacement. In three of the patients, coexistence of aorto-iliac occlusive disease was recognized on preoperative aortogram. Anesthesia was induced with diazepam and fentanyl, and maintained by using N_2O-O_2, fentanyl (total dose of 15–30 mcg·kg^{-1}) and pancuronium bromide, supplemented by halothane or enflurane as necessary. Normocapnia was maintained by controlled ventilation with 50% nitrous oxide in oxygen throughout the study. In all cases, temporary infrarenal aortic clamping was performed, which lasted for 100 ± 31 min, ranging from 60 to 183 min. Banked blood or shed blood was transfused before declamping, at the rate enough to keep pulmonary arterial wedge pressure around 10 mmHg, to alleviate marked systemic hypotension after declamping. Systemic arterial pressure, pulmonary arterial pressure (PAP), ratio between mean PAP and mean systemic arterial pressure (Pp/Ps) and mixed venous oxygen saturation ($S\bar{v}_{O_2}$) were continuously measured. Each arterial pressure was digitally recorded every 1 min by microcomputer. $S\bar{v}_{O_2}$ was monitored using a flow-directed pulmonary artery catheter connected to Oximeter (Opticath®, Oximetrix). In 16 patients, lactate, pyruvate and anaphylatoxins C3a and C5a were measured before clamping of the aorta, at the end of clamping period and 3 min after initial restoration of blood flow to one leg. Blood samples for metabolic analysis were taken from the pulmonary artery. Lactate and pyruvate were determined with an enzymatic technique, and anaphylatoxins with a radio immunoassay. No patient received any drug affecting the cascade of arachidonic acid before and during the study. 1 mg·kg^{-1} of heparin used during clamping period was reversed with protamine after completion of the study. During operation, blood and fluid were administered according to clinical condition. Data were analyzed by one-way analysis of variance (ANOVA) with Tukey's

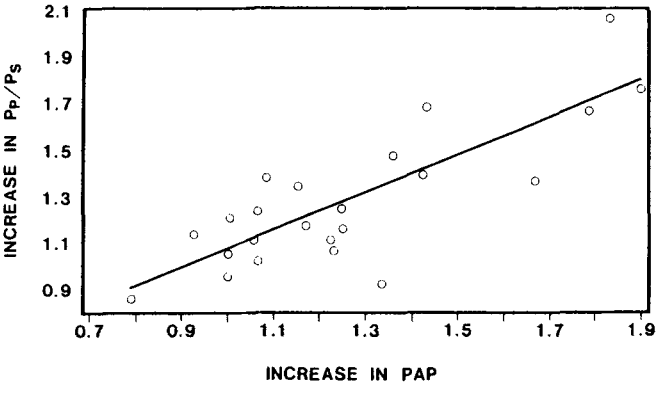

Fig. 1. The correlation between PAP and Pp/Ps after declamping in 23 patients. Both axises show the degree of PAP or Pp/Ps change by declamping, a ratio between value at 5 min after declamping and pre-declamping value. Regression equation for the relationship was: $Y = 0.81X + 0.27$; and the coefficient of correlation 0.82.

Table 2.

	Pre-clamp	Pre-declamp	Post-declamp
Lactate ($mg \cdot dl^{-1}$)	12.9 ± 3.1	16.9 ± 7.1*	25.9 ± 10.1*,#
	(7.1–17.5)	(8.6–37.4)	(10.7–50.7)
Pyruvate ($mg \cdot dl^{-1}$)	0.57 ± 0.25	0.87 ± 0.55*	1.05 ± 0.44*
	(0.25–1.24)	(0.28–2.23)	(0.46–2.19)
L/P Ratio	24.8 ± 5.7	21.8 ± 5.7	25.8 ± 7.6#
	(13.9–38.3)	(12.7–34.0)	(15.7–46.9)
C3a ($\mu g \cdot ml^{-1}$)	239.3 ± 98.4	423.5 ± 328.8	550.4 ± 455.5*
	(138–458)	(117–1326)	(132–1810)
C5a ($\mu g \cdot ml^{-1}$)	< 10	< 10	< 10

Mean metabolite and anaphylatoxin concentration in blood before, during and after clamping of the aorta in 16 patients. Statistical analysis is the same as in table 1. $^*P < 0.01$ compared with pre-clamping values, $^{\#}P < 0.01$ compared with pre-declamping values. Numbers in parenthesis indicate ranges.

test or Student's t-test. Correlation coefficient was calculated as described by Pearson or Spearman. A two-tailed P value less than 0.05 was considered significant. Results are expressed as mean ± SD in all tables.

Results

1. Changes in mean PAP and Pp/Ps

PAP rose significantly at 5, 10 and 15 min after declamping and then returned to basal level at 25 min (table 1). Similar tendency was seen with Pp/Ps. Since maximal response was attained 5 min after declamping, degree of PAP or Pp/Ps change by declamping was evaluated as a ratio between value at 5 min after declamping and pre-declamping value (XD/XC). Figure 1 reveals a correlation between PAP change and Pp/Ps change after declamping. The greater an increase in PAP after declamping, the greater Pp/Ps elevated (r = 0.82).

2. Changes in the levels of metabolites and anaphylatoxins

As shown in table 2, aortic clamping increased serum lactate and pyruvate concentrations. Then blood lactate production was accentuated by declamping, resulting in a rise in lactate-pyruvate ratio (L/P ratio), an indicator of tissue hypoxia. Although C3a level rose significantly from the pre-clamping state by declamping, C5a level showed no change in any case during or after clamping of the aorta.

3. Relationship between hemodynamic changes and metabolic parameters or anaphylatoxin activities

Table 3.

	Higher increase in Pp/Ps (XD/XC) ≧ 1.25 (N=7, 1.54 ± 0.28)	Lower increase in Pp/Ps (XD/XC) < 1.25 (N=9, 1.07 ± 0.12)	
Age (yr)	68.3 ± 5.7	65.4 ± 8.3	NS
Duration of OP. (h)	5.90 ± 2.07	5.21 ± 1.14	NS
Duration of XC (h)	1.86 ± 0.58	1.51 ± 0.32	NS
Blood loss before XD (l)	0.40 ± 0.31	0.25 ± 0.17	NS
Urine output before XD (l)	0.65 ± 0.32	0.40 ± 0.17	NS
L/P (XC)/L/P (C)	0.91 ± 0.21	0.88 ± 0.19	NS
L/P (XD)/L/P (XC)	1.37 ± 0.19	1.07 ± 0.21	$P < 0.02$
C3a (XC)/C3a (C)	1.88 ± 0.78	1.54 ± 1.05	$P < 0.05$
C3a (XD)/C3a (C)	2.25 ± 0.71	1.90 ± 0.94	$P < 0.05$
$S\bar{v}_{O_2}$(C)[a] (%)	78.5 ± 6.7	81.8 ± 4.3	NS
Minimum $S\bar{v}_{O_2}$(XD)[b] (%)	50.4 ± 11.7	64.2 ± 9.0	$P < 0.02$
Range of $S\bar{v}_{O_2}$ fall at XD[c] (%)	21.4 ± 6.8	15.7 ± 6.9	NS
Degree of $S\bar{v}_{O_2}$ fall during and after XC[d] (%)	9.6 ± 10.6	18.0 ± 9.1	$P < 0.02$

Characteristics of patients in two groups divided according to the degree of Pp/Ps change by declamping. The Student's t-test was used for comparison between two groups. NS = not significant. XC = aortic cross-clamping, XD = aortic declamping. (C) = pre-clamping value, (XC) = pre-declamping value, (XD) = post-declamping value. Referring to figure 1, a) = ①, b) = ③, c) = ② - ③ and d) = ① - ③.

One minute after declamping, PAP decreased and Pp/Ps increased (table 1), indicating that post-declamping pulmonary hypertensive response can be detected more easily by an elevation in Pp/Ps than that in PAP itself. When the patients were divided into two groups according to the degree of Pp/Ps change by declamping, significant elevations of L/P ratio and C3a level were present in the group with higher increase (XD/XC ≧ 1.25) of Pp/Ps compared to the lower Pp/Ps (<1.25) group (table 3). In the higher Pp/Ps group, a close correlation was observed after declamping not only between Pp/Ps change and aortic clamp time ($r_s = 0.75$), but also between elevation in L/P ratio and that in C3a level ($r_s = 0.72$) by applying Spearman rank correlation. In three patients with aorto-iliac occlusive disease, however, only minor increase in Pp/Ps (<1.1), if any, occurred by declamping. In one case with Pp/Ps change of 1.21, aortic clamping and declamping were followed by 4.1-fold and 5.9-fold rise in serum thromboxane B_2 (TXB_2) concentrations (breakdown product of TXA_2) as compared with pre-clamping level, respectively.

4. Change in $S\bar{v}_{O_2}$

A marked decline in $S\bar{v}_{O_2}$ was noted immediately after declamping (fig. 2). The minimum level of $S\bar{v}_{O_2}$ was significantly smaller in the higher Pp/Ps group than in the lower one, while the range of $S\bar{v}_{O_2}$ fall was without statistical difference. There was also a significant difference in the degree of $S\bar{v}_{O_2}$ reduction from the pre-clamping to the minimum level of $S\bar{v}_{O_2}$ after declamping (table 3).

Discussion

This study confirmed the occurrence of post-declamping pulmonary hypertensive response because Pp/Ps increased significantly after release of the aortic clamp. Since hemodynamics fluctuates quite rapidly by declamping, cardiac output measurement using a thermodilution technique made it difficult to pursue a detailed change in pul-

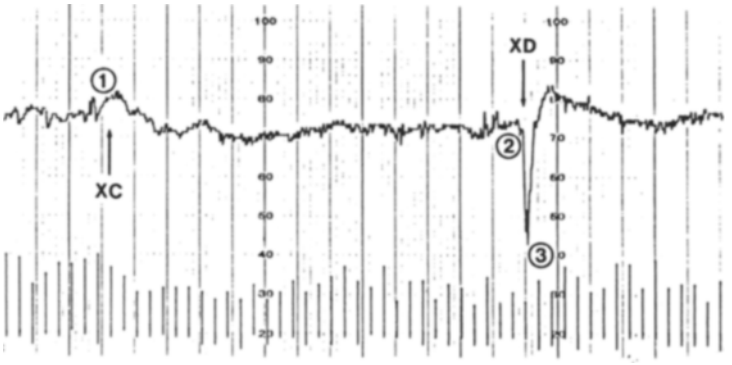

Fig. 2. Representative record showing change in $S\bar{v}_{O_2}$ (%) during and after clamping of the aorta. XC = aortic clamping, XD = aortic declamping. Chart speed was one section/min on the graph paper and aortic clamping lasted for about 63 min in this case. ① and ② are $S\bar{v}_{O_2}$ values at pre-XC and pre-XD. ③ is minimum $S\bar{v}_{O_2}$ immediately after XD.

monary vascular resistance (PVR) and to verify its elevation in real time. High cardiac output noted after declamping partly affects the pulmonary hypertensive response. A good correlation between rise in PAP and increase in Pp/Ps, as shown in figure 1, suggests that an elevated PVR is mainly responsible for this phenomenon.

Increase in PVR could be explained by the biological effect of anaphylatoxins, because they can act as a mediator of powerful vasoconstrictor such as TX or histamine[8,9]. Another explanation might be a hypoxic pulmonary vasoconstriction (HPVC) mediated by a decreased $S\bar{v}_{O_2}$ after declamping[2]. TXA_2 has been reported to play a major role in the development of HPVC[10]. In addition, recent evidences have suggested that HPVC can be enhanced by hypercapnia commonly noted after declamping and also by leukotriene activated through anaphylatoxin[11–13]. Therefore, anaphylatoxin C3a must be at least involved in the formation of an unidentified agent causing a rise in PAP. Complement could have been activated by blood and/or plasma transfusion. However, Paterson et al.[3] has indicated that PAP and TXB_2 level changed independently from transfusion. Transfusion might be unlikely primary cause of complement activation.

In the present study, good correlations were present after declamping not only between Pp/Ps change and aortic clamp time, but also between C3a level and L/P ratio in the higher Pp/Ps group. In the lower group, on the other hand, no correlation existed among these variables and L/P ratio showed only small change by declamping, probably due to minor metabolic alterations in leg muscles. It is thus conceivable that metabolic derangements in leg muscles distal to the clamp may have close relationship with the pulmonary hypertensive response.

Ischemia plays an important role in the formation of anaphylatoxins, with its molecular mechanism being unknown. Reperfusion to the ischemic leg muscles has been also postulated to accentuate metabolic disorder and cause more pronounced change after declamping[14]. According to Johnston et al.[15], periaortic collateral circulation can develop in patients with aortic occlusive disease and lessen hemodynamic stress from aortic clamping. In fact, only minor changes in Pp/Ps could be noted in our patients with aorto-iliac occlusive disease. Post-declamping increase in C3a and C5a was not observed by Bengston et al.[7] in their study during reconstructive surgery for aortic occlusive disease, reflecting good collateral perfusion during the period of aortic clamping. Thus the range of increased Pp/Ps after declamping may reflect the magnitude of metabolic change distal to the clamp, which will depend on the degree of collateral development. Bengston et al. also reported in the same study that anaphylatoxin was released less under epidural anesthesia than under general anesthesia. Epidural anesthesia may be

preferable in some case because it is possible to dilate collateral vessels and to enhance blood supply to the ischemic muscles even during clamping period.

It is concluded that metabolic derangement resulting from muscular cell damage due to aortic clamping and declamping enhances the formation of anaphylatoxins, which may be liberated into the systemic circulation leading to pulmonary hypertensive response.

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