Vasovagal reactions in apheresis donors

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BACKGROUND: The incidence rate of vasovagal reactions (VVRs) in apheresis is known to be higher in women than in men donors. VVRs in women apheresis donors were therefore analyzed to find out possible factors for their high incidence.

STUDY DESIGN AND METHODS: VVR incidence was compared between whole blood (WB) and apheresis donation in relation mainly to age and circulatory blood volume (CBV). In addition, blood pressure and pulse rate were measured during apheresis.

RESULTS: In WB donors, the VVR incidence was 0.83 and 1.25 percent, while in apheresis donors it was 0.99 and 4.17 percent in men and women, respectively. The VVR incidence decreased with age in WB donors, but age dependence was very weak in apheresis donors. In elderly women, the incidence increased with repeating cycle of apheresis. There were three different patterns of pulse fluctuation during apheresis, that is, stable (type A), increased rate during blood withdrawal (type B), and irregular pattern (type C). Elderly women donors and donors who suffered from VVRs mostly showed type B fluctuation. There was no particular fluctuation in blood pressure in relation to apheresis cycles.

CONCLUSION: The VVR incidence rate was particularly high in women apheresis donors over 45 years old and increased with repeating cycles of apheresis. Smaller CBV, high sensitivity of low-pressure baroreceptors, and citrate effects on cardiovascular reflex might be major factors involved in the high incidence of VVRs.

ABBREVIATIONS: CBV = circulatory blood volume; VVR(s) = vasovagal reaction(s); WB = whole blood.

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Blood donors occasionally have adverse reactions such as weakness, pallor, nausea, sweating, and fainting during or after blood withdrawal.[1,2] These symptoms are generally called vasovagal reactions (VVRs). The rate of incidence of VVRs has been analyzed mainly on the whole blood (WB) donors and reported to be higher in younger donors and at the first time of donation.[2-4] The contribution of other factors such as body weight and blood pressure is less clear. It has been reported for Japanese donors that there is no clear sex difference of VVR incidence in WB donors (1.70% in men, 1.85% in women), but that the rate of VVRs in apheresis is significantly higher in women (4.04%) than men donors (1.24%).[4] Failure of proper circulatory compensation by the autonomic nervous system may be an important factor responsible for the VVRs, but the mechanisms underlying these reactions are still mostly unclear. In the present study, therefore, the VVR incidence was demographically analyzed mainly on the apheresis donors in our blood center. In addition to this, blood pressure and pulse rate were measured to determine if characteristic alterations occurred during apheresis.

MATERIALS AND METHODS

The data accumulated from the voluntary blood donors were analyzed for the incidence of VVRs in the population of WB donors (a total of 20,025 men and 8,164 women during a 1-year period in 2000; including 200 and 400 mL phlebotomy) and in apheresis donors (14,523 men and 6,722 women; combined plasma [68.1%] and platelet collection [21.9%]), during the 3-year period 1999 to 2001. The equipment used for apheresis was either a multicomponent system (MCS 3P) or a component collecting system (Haemonetics, Tokyo, Japan). There was little functional difference between these machines. VVRs were judged from donor's symptoms described in the introduction by experienced nurses. VVRs were mostly relatively minor and syncopal episodes only occurred in a few percent of VVR donors. The VVR incidence rate was calculated for each age or for the circulatory blood volume (CBV) at a 100-mL step and averaged at each range indicated in the figures. Numerical values are expressed

as means ± SD. The data approximated most closely to normal distributions when examined with the Kolmogorov-Simirnov test. Significance of the difference was tested by with two-tailed, unpaired t-tests and the level of significance was set at $p < 0.05$.

The CBV (in mL) was estimated by following equations proposed by Ogawa et al.[5] for Japanese people:

$$CBV = 168H^3 + 50W + 444 \text{ for men}$$

$$CBV = 250H^3 + 63W - 662 \text{ for women}$$

where H is height (m) and W is weight (kg).

Blood pressure and pulse rate were measured automatically every 1 minute during apheresis in 42 men (19-67 years old) and 72 women (18-69 years old) with a automatic blood pressure monitor (Paramatec, PS-230). The reliability of the pulse rate measurement was confirmed by the simultaneous electrocardiograph measurements in three donors. All procedures were fully explained beforehand and carried out on donors who agreed to participate in the study.

RESULTS

In Fig. 1, the incidence of VVRs that occurred in WB and apheresis donation was compared between men and women donors of different ages. The incidence rate of VVRs associated with WB donation decreased with advancing age both in men and in women. In contrast, there was no such a clear tendency in VVRs in apheresis and the VVR incidence rate in apheresis was much higher in women than men, particularly in elderly donors. The mean incidence of VVRs of WB donors was 0.83 percent in men and 1.25 percent in women, while that of apheresis donors was 0.99 percent in men and 4.17 percent in women. These incidence rates were similar to those previously reported.[4]

The relationship between the VVR incidence and age in apheresis donors differed depending on the apheresis cycle (Fig. 2). In men donors, the incidence of VVRs that occurred during the first and second cycles decreased with age and was similar to the WB donation shown in Fig. 1, but it was independent of age at the third-fourth cycles. In women donors, the incidence also decreased with age at the first cycle, but it was independent of age at the second cycle and increased slightly with advancing age at the third to fourth cycles. There was a clear tendency for VVRs to occur at a later stage of apheresis with advancing age.

VVRs are known to occur more frequently in first-time donors than in repeated donors.[2-4,6] However, in women apheresis donors, there was no significant difference in the number of previous donations between healthy and VVR donors. Nearly all of the women apheresis donors over 45 years old who suffered from VVRs donated repeatedly (mean, 24.8 times) and VVRs were detected in only one first-time donor (1 of 45).

The high rate of VVRs in women donors in apheresis could partly be related to the fact that the CBV is significantly less (approx., 20%) in women than in men donors (Table 1). The mean CBV of the donors who suffered from VVRs was also slightly less (approx., 4%) than that of the control donors and the differences were significant ($p < 0.01$) both for men and for women donors.

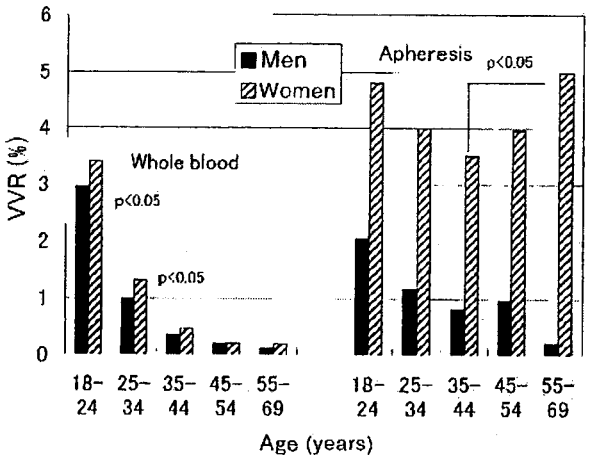

Fig. 1. VVR incidence rate in relation to age in WB and apheresis donors. Note that in men donors the incidence decreased with advancing ages both in WB and in apheresis donation, but that in women donors there was a large difference between WB and apheresis donation. The difference was significant ($p < 0.05$) between the younger three ranges of WB donors and men apheresis donors and also between 35- and 44- and 55- to 69-year-old women apheresis donors.

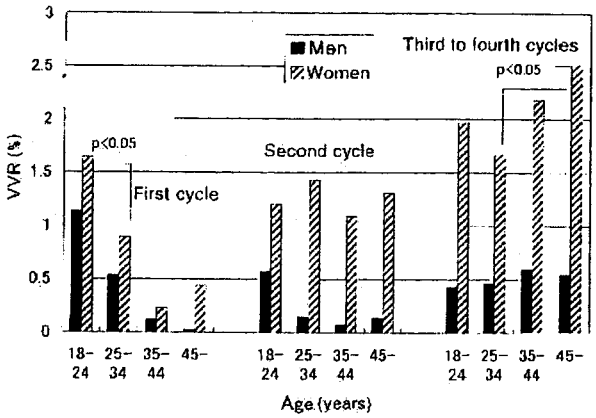

Fig. 2. The relationship between VVR incidence and age at different stages of apheresis. In younger donors, VVRs incidence did not differ much at different cycles of apheresis. In contrast, older donors tended to experience VVRs at a later stage of apheresis. A significant difference was indicated by the p value of less than 0.05. The difference between 18- and 24- and 25- to 34-year-old men donors at the second cycle was also significant ($p < 0.05$).

TABLE 1. CBV (mL) in WB and apheresis donors*

	Control	VVR donors
WB		
Men	4617.5 ± 536.4 (n = 1582)	4417.7 ± 496.8 (n = 168)
Women	3681.3 ± 520.2 (n = 668)	3475.5 ± 447.6 (n = 102)
Apheresis		
Men	4587.8 ± 505.0 (n = 1592)	4431.9 ± 431.5 (n = 144)
Women	3719.1 ± 546.7 (n = 734)	3584.7 ± 425.7 (n = 280)

* The values of control WB and apheresis donors were based on the data for 1- and 4-month periods, respectively. The differences of blood volume between control and VVR donors were statistically significant ($p < 0.01$) for WB and apheresis donors of both sexes.

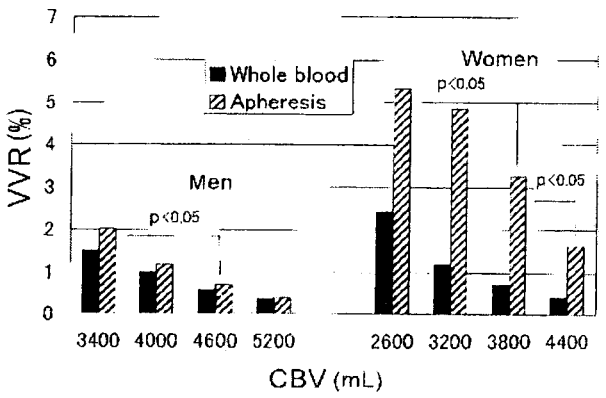

Fig. 3. VVR incidence in relation to CBV in WB and apheresis donation. The CBV was calculated by the equations described in the method. The significance of the difference is indicated by $p < 0.05$.

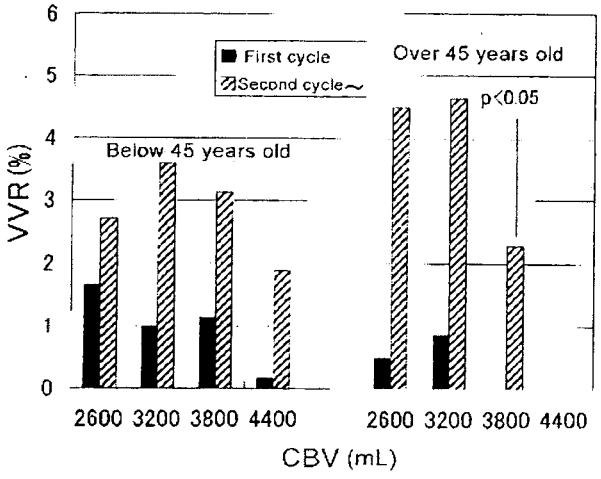

Fig. 4. VVR incidence in relation to CBV before (first cycle) and after the end of first cycle of apheresis (second cycle) in women donors below and over 45 years old. Note the higher incidence with smaller CBV and also after the first cycle of apheresis.

The relationship between the CBV and VVR incidence was compared in WB and apheresis donation (Fig. 3). In men, there was a tendency for the incidence of VVRs to decrease with larger CBV both in WB and in apheresis donors. In women apheresis donors, the CBV dependency was weaker in apheresis compared with WB donors.

CBV dependency of the VVR incidence was greater in older than young women donors. The incidence rate of women donors over 45 years old was 4.8, 2.8, and 0 percent with CBV of 2600 to 3700, 3800 to 4300, and greater than 4400 mL, respectively. In contrast, in the donors below 45 years old, it was 5.1, 3.6, and 1.9 percent, respectively. In men donors, such a clear difference was not detected.

The relationship between CBV and VVR incidence during the first and the second to fourth cycles of apheresis differed between women donors younger and older than 45 years old, as shown in Fig. 4. Below 45 years of age, approximately 25 percent of VVRs occurred at the first cycle relatively independent of the CBV, whereas over 45 years of age, only 10 percent of VVRs were observed at the first cycle. In women over 45 years old, the VVR incidence was much less in the donors having CBVs greater than 3800 mL.

VVR incidence during apheresis in women donors over 45 years old was relatively high (see Fig. 1), particularly at the later stage of apheresis (see Figs. 2 and 4). To investigate the possible mechanisms underlying these factors, blood pressure and pulse rate were measured during apheresis in 72 women (19-36 years old, n = 53; 40-69 years old, n = 19) and 42 men donors (19-27 years old, n = 27; 44-67 years old, n = 15).

Typical examples of blood pressure and pulse rate recorded during apheresis are shown in Figs. 5A and 5B, by averaging values obtained from five donors. Systolic blood pressure gradually decreased by about 15 mmHg in 10 to 15 minutes after starting apheresis and then became more or less steady. Diastolic pressure also decreased with time at the beginning but its degree was less than systolic pressure. Irregular fluctuations were often observed in diastolic pressure. No clear change was observed in relation to blood withdrawal and return both in systolic and in diastolic pressure. A particular pattern of blood pressure could not be used for prediction of VVR occurrence.

In contrast to blood pressure, blood withdrawal affected the pulse rate. Three different patterns of changed pulse rate were found during apheresis. One pattern was a reasonably stable rate throughout apheresis (type A), as shown in Fig. 5A. The second showed an increase in pulse rate during withdrawal and its recovery during return of

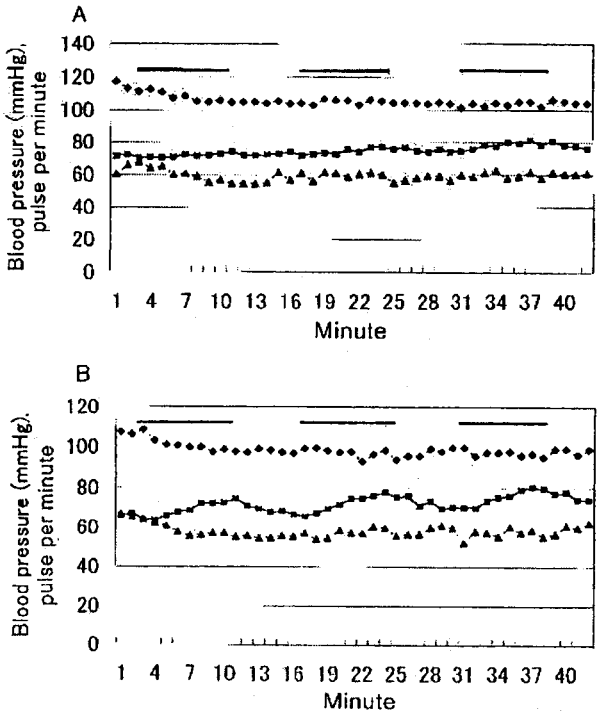

Fig. 5. Blood pressure and pulse rate measured every 1 minute during apheresis, averaging from five women donors whose pulse rate was stable (A) and increased (B) during blood withdrawal. (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

TABLE 2. CBV (mL) in donors showing stable pulse (type A) and fluctuating pulse rate (type B) during apheresis and in VVR donors*

Men	
Type A	4657.3 ± 284.3 (n = 20)
Type B	4347.1 ± 391.7 (n = 19)
VVR	4160.8 ± 458.6 (n = 2)
Women	
Type A	3819.1 ± 387.0 (n = 21)
Type B	3550.9 ± 341.1 (n = 41)
VVR	3535.6 ± 248.6 (n = 6)

* The differences of blood volume between type A and type B donors were statistically significant ($p < 0.05$) for both men and women donors. There was no difference in blood volume between VVR donors and type B donors.

blood (type B), as shown in Fig. 5B. The third was an irregular fluctuation without any clear relationship to blood withdrawal (type C, not shown). Types A, B, and C were shown in 31, 60, and 9 percent of women donors and 49, 46, and 5 percent of men donors, respectively. Women donors over 40 years old mostly (15 of 19) showed the type B fluctuating pattern, and there were only two each of donors showing types A and C, respectively. In contrast, in men donors over 40 years old, 40 percent were type B (6 of 15) and 60 percent were type A.

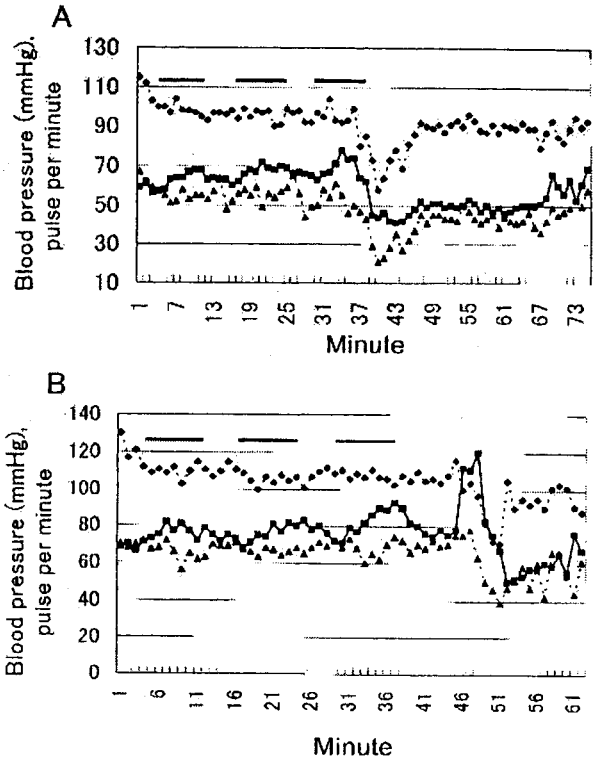

Fig. 6. (A) Blood pressure and pulse rate in a women donor (43 years old) who suffered from VVRs during the third cycle of blood withdrawal. VVRs were accompanied by tachycardia and lowered blood pressure, and then tachycardia was followed by prolonged bradycardia. The donor was laid down flat until recovery. (B) Another example of VVRs (a 20-year-old woman donor). VVRs occurred when she started to leave the bed and were accompanied by bradycardia and hypotension following transient tachycardia. Both donors showed an increase in pulse rate during blood withdrawal (indicated by horizontal bars). (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

The mean CBV of the donors showing pulse rate fluctuations (type B) was less (about 7%) than those showing stable pulse rate (type A) both for men and for women donors (Table 2), and their differences were significant ($p < 0.05$).

The pulse rate data on VVRs were obtained from six women (20-43 years old) and two men donors (23 and 44 years old). They all showed the pulse rate fluctuations of the type B before the appearance of VVRs, as shown in two examples illustrated in Figs. 6A and 6B. The donors shown in Fig. 6 were kept in bed horizontally until they recovered, without medication. Typical VVRs were accompanied by marked bradycardia and periods of hypotension of various durations. The mean CBV of donors

who suffered from VVRs was similar to that of donors showing pulse fluctuations of type B both for men and for women (see Table 2).

DISCUSSION

The incidence of VVRs decreased with advancing age in the population of WB donors, both men and women donors, as previously reported.[2-4,6] A similar relationship was observed in men apheresis donors. However, no such a tendency was found in women apheresis donors. The VVR incidence of women apheresis donors was rather independent of age or even higher over 45 years old (see Fig. 1). This was not due to a high proportion of first-time donors in older women, because most donors over 45 years old were repeated donors.

The CBV was significantly (approx., 20%) less in women and it was also about 4 percent less ($p < 0.05$) in VVR donors than in healthy control donors. The VVR incidence tended to be higher with smaller CBV (see Figs. 3 and 4). It is possible in old donors that the actual CBV is less than that estimated solely from the height and weight determinations[7] and that the peripheral blood pool is small.[8] This may explain the larger effects of blood withdrawal in older donors. If stronger hypovolemia was a major factor in VVR incidence, it seems difficult to explain the difference in VVR incidence between WB and apheresis donors (see Figs. 1 and 3). Some other factors such as autonomic malfunction and hypocalcemia are more likely to be involved in higher VVR incidence in women, particularly older, apheresis donors.

A tachycardia was often observed during blood withdrawal without an associated change in arterial pressure. The ratio of the donors who showed such pulse rate fluctuations (type B) was higher in women than men and this difference was larger over 40 years of age. Furthermore, the VVR donors all showed type B fluctuations. Donors having smaller CBV have a tendency to produce tachycardia during apheresis (see Table 2). The increase in pulse rate usually became more marked with increasing cycles of blood withdrawal. This may have been due to an increased hypovolemia, because the extracorporeal blood volume increases with number of apheresis cycles. Tachycardia, without any significant changes in arterial blood pressure, has also been reported in response to a decreased venous return caused by lower-body negative pressure in humans[9,10] or by hemorrhage of up to 10 mL per kg blood in conscious dogs.[11] These responses are likely to be mediated by cardiopulmonary (low-pressure) baroreceptors, the sensitivity of which to hemorrhage is shown to be higher than those of carotid sinus (high-pressure) baroreceptors in dogs.[12] The mechanism causing the tachycardia during blood withdrawal is likely to be involved in triggering the patterns of VVRs by the circulatory control center.

In the apheresis, it is possible that the sensitivity of baroreceptor-mediated reflex is increased by a decrease in plasma Ca^{2+} concentration that is known to be caused by the supply of citrate during blood return.[12,13] This is probably one of the factors involved in the high VVR incidence in older women apheresis donors, whose VVR incidence is increased by repeating blood withdrawal and return. Not only the effects of blood withdrawal, but also the effects of citrate on the reflex mediated by cardiopulmonary baroreceptors would be stronger in the smaller CBV of old women donors. These factors may explain a high VVR incidence of elderly women donors and at later stage of apheresis.

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