Prevention of Blood Donation-related Vasovagal Response by Applied Muscle Tension: a Meta-analysis

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Abstract
Objective: Vasovagal reaction (VVR) is an adverse reaction to blood donation. Applied muscle tension (AMT) has been reported to reduce the probability of VVR during blood donation; however, the results have been controversial. We therefore conducted a meta-analysis to systematically evaluate the effect of AMT in reducing VVR.

Methods: We searched six major databases using “applied muscle tension” and “blood donation-related vasovagal response” as keywords. Relevant articles published in English or Chinese between 1 January 2000 and 30 June 2021 were included in the analysis. The quality of the included articles was evaluated and publication bias was assessed by forest and funnel plots and by Egger’s test.

Results: Fifty-one articles were identified, of which six were included according to the pre-defined inclusion and exclusion criteria. A fixed-effects model was adopted for effect size combination and revealed a relative risk of 0.52 (95% confidence interval 0.40 to 0.67). The AMT group was superior to the control in terms of VVR prevention. A funnel plot and Egger’s test suggested that the findings were accurate and reliable with low publication bias.

Conclusion: AMT could effectively reduce VVR during blood donation. Further multicenter studies with large sample sizes are needed to confirm these results.

Keywords
Applied muscle tension, blood donation, vasovagal response, meta-analysis, volunteer, adverse reaction

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Introduction

About 118.4 million blood donations were collected worldwide in 2020 and the number of blood donors is increasing year after year; however, many countries and regions, especially among developing countries, still face transient or seasonal blood shortages. Over 800 million units of blood are collected worldwide each year, but only 38% of these are collected in developing countries.1–7

Recruiting more blood donors is thus crucial to ensuring a clinical blood supply. However, many first-time donors, especially younger donors, often lack knowledge about blood donation and experience discomfort during the process, including dizziness, sweating, and pallor, which are collectively referred to as the vasovagal response (VVR).8–13

VVR is caused by hypotension due to vasodilation. During the process, the blood donor usually goes through four phases: (1) early stabilization, (2) circulatory instability, (3) terminal hypotension, and (4) recovery.14–17 It is therefore crucial to reduce the hypotensive state in the blood donor, especially during the second phase of circulatory instability. One study also noted that although most adults showed a decrease in cardiac output, only younger individuals showed a gradual decrease in vascular tone.17 Stopping donors from entering the second phase may thus minimize the probability of VVR during blood donation.

The National Health and Family Planning Commission of the People’s Republic of China issued their Guidelines on the Classification of Blood Donation Adverse Reaction (WS/T551-2017) in 2017, which specified the classification, severity assessment, and relevance of adverse reactions during blood donation. The manifestations of VVR are defined as general malaise, weakness, pallor, sweating, anxiety, dizziness, and nausea, while a few donors may experience more severe symptoms such as transient loss of consciousness (syncope), convulsions, or incontinence.18 Fainting and falling can lead to accidental injury. The main contributors to the development of VVR in blood donors include psychological factors and reduced blood volume.19 China has begun to consider the importance of donor responses to adverse reactions during blood donation. The occurrence of VVR during blood donation has also been reported to lead to termination of the donation procedure and to reduce the donor’s willingness to donate again following a bad blood-donation experience.

Recent studies have indicated that practicing applied muscle tension (AMT) during blood donation could substantially alleviate the occurrence of adverse blood-donation reactions.11 To practice AMT during blood donation, donors adopt a lying or sitting position with their legs crossed and tense the muscles in the legs, buttocks, and trunk 20 to 30 times for 5 to 10 s each time, before relaxing for 5 to 10 s each time.11 Practicing AMT throughout the whole blood-donation process can effectively increase venous return and sympathetic excitation. In addition, the donors are distracted and their nervousness can effectively be relieved, thus reducing the occurrence of VVR. However, some studies found similar probabilities of VVR in AMT and control groups, i.e., the effect of AMT was not significant.6 We therefore conducted a meta-analysis to systematically evaluate the effect of AMT in reducing blood donation-related VVR.

Methods

Literature search strategy

We performed a literature search of PubMed, Web of Science, MEDLINE, the
Cochrane Library, China National Knowledge Infrastructure database, VIP database, and China Biomedical Database for articles reporting randomized controlled trials (RCTs) on the effect of AMT in reducing VVR during blood donation. The search strategies used were: (MeSH “vasovagal reaction” OR MeSH “Vasovagal response” OR MeSH “Syncopes, Vasovagal” OR Mesh “VVR”) AND (MeSH “applied muscle tension” OR MeSH “Contraction, Muscle” OR MeSH “AMT”). Relevant articles published in English or Chinese between 1 January 2000 and 30 June 2021 were included in the analysis. The references of the included articles were also screened to identify further relevant studies.

Literature selection

The inclusion criteria for this meta-analysis were as follows: (1) studies based on RCTs investigating the use of AMT during blood donation; (2) studies based on whole-blood donations (articles on other subjects such as plateletpheresis were excluded to ensure comparability); and (3) articles reporting a clear outcome in terms of donor VVR during blood donation.

The exclusion criteria are as follows: (1) studies not examining the use of AMT to reduce VVR during blood donation; (2) articles for which full data extraction was not possible; (3) animal studies; (4) all grey literature, e.g., conference papers, letters, and case reports; (5) and systematic evaluations and meta-analyses.

After removing duplicate data using Endnote X9, the titles and abstracts were screened independently by two authors (Li Chen & Yan Zhang) to remove articles that did not meet the inclusion criteria. The remaining articles were then read in their entirety and the final articles were included based on the pre-determined criteria.

Data extraction

Two authors (Wenwen Shi & Yuanyuan Ma) simultaneously and independently extracted the following relevant information from the included literature, using a pre-designed extraction form: (1) first author’s name, (2) year of publication, (3) country of study, (4) age range of blood donors, (5) sex of blood donors, (6) total number of blood donors, (7) site of blood donation, (8) grouping, and (9) type of scale. Disagreements over data extraction were resolved through discussion or by consultation with a third person. Authors of articles with missing data or not-extractable data were contacted by email, and the articles were excluded if the full data were still not available.

Literature quality assessment

Literature quality was assessed independently by two authors (Cong Wang & Can Cao) using the Cochrane risk bias assessment tool, with the primary focus of evaluating bias in the included literature. This tool consists of seven domains: (1) random sequence generation; (2) allocation concealment; (3) participants and personnel blinding; (4) outcome assessment blinding; (5) incomplete outcome data; (6) selective reporting; and (7) other sources of bias. Each of these domains is further divided into three levels: low, unclear, and high risk of bias. Disagreements were resolved through discussion or by consultation with a third person.

Statistical analysis

The outcome indicator in this study was a two-category variable and we therefore calculated the relative risk (RR) and 95% confidence interval (95% CI). The primary outcome indicator was donor VVR during blood donation. A fixed-effects or random-effects model was selected based on the P-value and I², with a fixed-effects
model for $I^2 < 50\%$ and $P > 0.1$, otherwise, a random-effects model was selected. If the heterogeneity was excessive (e.g., $I^2 > 75\%$), the source of the heterogeneity was explored. Publication bias was evaluated by examining the left-right symmetry of the funnel plot and the results of Egger’s test using Stata ($P > 0.05$ indicated no publication bias). Subgroup analyses were conducted if sufficient studies and sample sizes were available. All statistical analyses were performed using RevMan 5.3 and Stata 14.0.

**Results**

**Literature selection**

Fifty-one articles were identified from the seven databases, according to the pre-defined search strategy. Thirty-one papers were retained after removing duplicates, and 12 relevant papers were left after screening the titles and abstracts. Six papers, five in English and one in Chinese, finally remained after screening the entire article according to the inclusion and exclusion criteria. The study flow is shown in Figure 1.

**Research features**

The six papers included in this study reported on a total of 4226 unpaid voluntary blood donors, of whom 2236 were randomly assigned to AMT groups and 1990 were randomly assigned to control groups. Most of the included studies were conducted in European and American populations, with only one trial from China.
Five of the included studies were based on studies conducted at fixed blood-donation sites, and one study was based on mobile blood-donation sites. All the included studies adopted the Blood Donation Reactions Inventory (BDRI) scale. The basic characteristics of the included studies are shown in Table 1.

**Literature quality evaluation**

The overall literature quality evaluation showed that the six included papers had high-quality ratings. The quality-evaluation chart for each study showed that none of the included studies mentioned whether blinding was used (for subjects, investigators, or evaluators). In addition, the 2003 and 2007 studies by Ditto et al. also failed to mention whether the allocation was based on randomized numbers, and only the use of RCTs was mentioned. All other items were mentioned in each of the included articles. The risk of bias assessment results included in the RCT are shown in Figure 2.

**Overall meta-analysis results**

The heterogeneity test of the six included papers showed $I^2 = 0$, $P = 0.75$, suggesting that the heterogeneity among the included articles was not statistically significant, and a fixed-effects model was therefore selected for the meta-analysis. The combined RR of the six studies was 0.52 (95% CI 0.40 to 0.67), which was statistically significant ($Z = 5.10$, $P < 0.001$), suggesting that blood donation-related VVR was lower in patients with AMT (Figure 3).

**Sensitivity analysis**

The sources of heterogeneity in each study were investigated using RevMan 5.3 software, and no significant differences were found, proving the high stability of this study.

**Publication bias**

Funnel plots for the six included studies were basically left-right symmetrical, indicating no significant publication bias (Figure 4). Egger’s test using Stata 14.0 also showed no publication bias in this meta-analysis.

**Discussion**

This meta-analysis focused on the effectiveness of AMT for preventing VVR in blood donors. To the best of our knowledge, this is the first independent meta-analysis to examine the use of AMT as a primary intervention to reduce the occurrence of VVR. The six included articles were all high-quality RCTs, comprising a total of 4226 blood donors. The combined RR of the six studies was 0.52 (95% CI 0.40 to 0.67; $Z = 5.10$, $P < 0.001$), suggesting that AMT significantly reduced the risk of blood donation-related VVR compared with the control group.

The literature search also identified four large cohort studies, based on a total of 450,000 observations, which were excluded because the meta-analysis was limited to RCTs. However, a review of the abstracts of those excluded articles supported the findings of this study, i.e., the risk of VVR was significantly reduced by AMT.

We also identified one article, the abstract of which suggested similar risks of VVR in the AMT and control groups (both 0). Twelve randomly selected blood donors practiced AMT during blood donation while 12 other donors with matching conditions received no intervention, and the risk of VVR was observed in both groups. None of the 24 blood donors experienced VVR, and the authors thus concluded that AMT did not reduce the risk of VVR in blood donors. However, the probability of VVR during blood
| Study                 | Year | Country | Site | Number of participants | Age (years) | Percentage males | Group                                      | Evaluation scale                                                                 |
|----------------------|------|---------|------|------------------------|-------------|------------------|--------------------------------------------|--------------------------------------------------------------------------------|
| Thijsen et al.       | 2018 | Australia | F    | 734                    | 33.3 ± 12.6 | 39.2             | AMT/placebo/time points                    | BDRI                                                                            |
| Holly et al.         | 2012 | Canada   | M    | 282                    | 12.6        | 53.5             | 1: AMT pre-donation and during donation; 2: AMT pre-donation only; 3: AMT during donation only; 4: no-treatment control | BDRI/SSAI                                                                        |
| France et al.        | 2010 | USA      | M    | 414                    | 20.2        | 48.1             | 1: Standard donation; 2: placebo; 3: pre-donation water; 4: pre-donation water and leg exercise during donation | STAI-Y/BDRI/BDSS/MSS/FS                                                        |
| Ditto et al.         | 2007 | Canada   | M    | 1209                   | 21.9 ± 3.4  | 50               | 1: No-treatment control group; 2: full-AT group; 3: lower-body-tension group; 4: upper-body-tension group; 5: upper-body tension with distraction group; 6: expectation-placebo group | BDRI                                                                            |
| Ditto et al.         | 2003 | Canada   | M    | 605                    | n           | n                | 1: No-treatment control group; 2: placebo control; 3: AMT | BDRI                                                                            |
| Jia et al.           | 2020 | China    | M    | 1784                   | 18–23       | 49.9             | 1: AMT; 2: placebo                          | STAI/BDRI                                                                       |

AMT, applied muscle tension; F, fixed site; M, mobile site; BDRI, Blood Donation Reactions Inventory; SSAI, Spielberger State Anxiety Inventory; STAI, State Anxiety Inventory; BDSS, Blood Donation Satisfaction Survey; MSS, Muscle Soreness Scale; FS, Fatigue Scale; n, not described.
donation has been reported to be low (1.4% to 7%), and the conclusions may thus be biased if the sample size is too small, resulting in less-credible results. Although VVR is mostly mild, a poor blood-donation experience may still affect the donor’s willingness to give blood again. Studies have pointed out two reasons for the low incidence of VVR: subjectively, the on-site staff may not consider that the donor’s discomfort meet the criteria for VVR and therefore do not record it, and objectively, the donor may have mild symptoms but may be unwilling to show physical discomfort and thus suppresses them.

It has been increasingly reported that the occurrence of VVR can decrease the number of blood donors. Notably, the motivation of first-time donors to donate blood again can be drastically reduced by an unpleasant blood-donation experience. This leads to a vicious cycle in that more effort must be directed to recruiting new donors to replace discouraged blood donors, but these replacements may lose motivation due to VVR.
This study had some limitations. First, the number of included articles was small, with only six papers meeting the inclusion criteria. Second, the literature search was limited to articles published in English or Chinese, and articles in other languages were excluded, which could limit further research. Finally, no subgroup analyses were performed due to the small number of included articles.

**Conclusion**

The current meta-analysis indicated that AMT may effectively reduce the occurrence of VVR during blood donation. In the future, 5G network technology and one-on-one on-site education could potentially open up new avenues for reducing the incidence of VVR. However, the current sample size was insufficient due to the small number of included articles, and further large-scale multicenter RCTs should be designed and conducted in the future to confirm the effectiveness of AMT in reducing VVR during blood donation.

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The authors have no conflicts of interest to declare.

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References
1. Wiersum-Osselton J, Prinsze F, Van den Brekel E, et al. An intervention study for the prevention of vasovagal reactions and evaluating donors’ experience: Analysis of donors’ return for subsequent donation. *Vox Sang* 2021; 117: 313–320.
2. Thijsen A, Davison TE, Speedy J, et al. Offering new and returned donors the option to give plasma: implications for donor retention and donor adverse events. *Vox Sang* 2021; 116: 273–280.
3. France CR, France JL, Himawan LK, et al. Donation related fears predict vasovagal reactions and donor attrition among high school donors. *Transfusion* 2021; 61: 102–107.
4. Thijsen A, Masser B and Davison TE. Reduced risk of vasovagal reactions in Australian whole blood donors after national implementation of applied muscle tension and water loading. *Transfusion* 2020; 60: 918–921.
5. Lei LY, Raj SR and Sheldon RS. Pharmacological norepinephrine transporter inhibition for the prevention of vasovagal syncope in young and adult subjects: A systematic review and meta-analysis. *Heart Rhythm* 2020; 17: 1151–1158.
6. Cheung CHY, Khaw ML, Leung WS, et al. Effects of performing applied muscle tension during recovery after phlebotomy in young, first-time donors: a pilot study. *Int J Environ Res Public Health* 2021; 18: 10541.
7. Jia Z, Hui C, Liqin Y, et al. Predonation applied muscle tension to prevent vasovagal reactions to blood donation. *Chin J Blood Transfusion* 2020; 33: 1029–1032.
8. France CR, France JL, Conatser R, et al. Predonation fears identify young donors at risk for vasovagal reactions. *Transfusion* 2019; 59: 2870–2875.
9. Thijsen A and Masser B. Vasovagal reactions in blood donors: risks, prevention and management. *Transfus Med* 2019; 29: 13–22.
10. Mennitto S, Harrison J, Ritz T, et al. Respiration and applied tension strategies to reduce vasovagal reactions to blood donation: A randomized controlled trial. *Transfusion* 2019; 59: 566–573.
11. Thijsen A, Gemelli CN, Davison TE, et al. Does using applied muscle tension at strategic time points during donation reduce phlebotomist- and donor-reported vasovagal reaction rates? A three-armed randomized controlled trial. *Transfusion* 2018; 58: 2352–2359.
12. Wong HK, Chu CCY, Lau CW, et al. Vasovagal reaction in blood donors: prediction and its impact on donor return. *ISBT Science Series* 2018; 13: 421–428.
13. Thijsen A, Masser B, Gemelli CN, et al. Trends in return behavior after an adverse event in Australian whole blood and plasma donors. *Transfusion* 2019; 59: 3157–3163.
14. Fisher SA, Allen D, Doree C, et al. Interventions to reduce vasovagal reactions in blood donors: a systematic review and meta-analysis. *Transfus Med* 2016; 26: 15–33.
15. Thijsen A, Fisher J, Gemelli CN, et al. Facilitating donor compliance with strategies to prevent vasovagal reactions: comparison of web-based and in-center approaches. *Transfusion* 2017; 57: 2449–2457.
16. Wiersum-Osselton J, Romeijn B, Van den Brekel E, et al. Can we prevent vasovagal reactions in young inexperienced whole blood donors? A placebo controlled study comparing effects of a 330 vs 500 mL water drink prior to donation. *Transfusion* 2019; 59: 555–565.
17. Goldman M, Uzicanin S, Marquis-Boyle L, et al. Implementation of measures to reduce vasovagal reactions: Donor participation and results. *Transfusion* 2021; 61: 1764–1771.
18. WS/T 551-2017, Guidelines on the classification of blood donation adverse reaction. [S] National Health and Family Planning Commission, 2017.

19. Ditto B, Gilchrist PT, Holly CD, et al. The effects of leg crossing and applied tension on blood donor return. *Vox Sang* 2013; 105: 299–304.

20. Ditto B, Wilkins JA, France CR, et al. On-site training in applied muscle tension to reduce vasovagal reactions to blood donation. *J Behav Med* 2003; 26: 53–65.

21. Ditto B, France CR, Albert M, et al. Dismantling applied tension: mechanisms of a treatment to reduce blood donation-related symptoms. *Transfusion* 2007; 47: 2217–2222.

22. Ditto B and France CR. Vasovagal symptoms mediate the relationship between predonation anxiety and subsequent blood donation in female volunteers. *Transfusion* 2006; 46: 1006–1010.

23. Kowalsky JM, France JL, Wissel ME, et al. Effect of applied muscle tension on cerebral oxygenation in female blood donors. *Transfusion* 2011; 51: 1802–1808.

24. Holly CD, Torbit L and Ditto B. Applied tension and coping with blood donation: a randomized trial. *Ann Behav Med* 2012; 43: 173–180.

25. Ditto B and France CR. The effects of applied tension on symptoms in French-speaking blood donors: a randomized trial. *Health Psychol* 2006; 25: 433–437.

26. Ditto B, France CR, Lavoie P, et al. Reducing reactions to blood donation with applied muscle tension: a randomized controlled trial. *Transfusion* 2003; 43: 1269–1275.

27. Ditto B, Byrne N and Holly C. Physiological correlates of applied tension may contribute to reduced fainting during medical procedures. *Ann Behav Med* 2009; 37: 306–314.

28. Ditto B, France CR and Holly C. Applied tension may help retain donors who are ambivalent about needles. *Vox Sang* 2010; 98: e225–e230.

29. France CR, Ditto B, Wissel ME, et al. Predonation hydration and applied muscle tension combine to reduce presyncopal reactions to blood donation. *Transfusion* 2010; 50: 1257–1264.

30. Tomasulo P, Kamel H, Bravo M, et al. Interventions to reduce the vasovagal reaction rate in young whole blood donors. *Transfusion* 2011; 51: 1511–1521.