Giving blood: Donor stress and hemostasis
Hoogerwerf, M.D.

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This thesis provides insight into the course of donation-induced stress responses, and their effects on the donor’s hemostasis. The first objective was to examine the donation-induced psychological, hormonal and physiological stress response patterns during a blood donation procedure. The second objective was to investigate the effects of the donation-induced stress response on immediate changes in hemostatic parameters. In this chapter, the main findings are presented, methodological considerations are addressed and the results are interpreted. Finally, recommendations are made for clinical practice and future research.

Main findings

Stress reactions during a blood donation and associated factors

The first research question was investigated in Part I by examining stress reactions in blood donors in a blood donation setting, as well as the associated factors (Chapter 2). Literature provided strong evidence for the occurrence of psychological stress responses and less conclusive evidence regarding hormonal and physiological stress responses in whole-blood and plasmapheresis donors. Overall, in response to the first research question, the results suggest a decrease in stress from between the start until towards the end of a routine blood donation.

Stress responses were reported to be mainly influenced by donation experience, whereby an increasing number of previous donations reduced the level of stress. Other factors triggering or enhancing the stress response were: watching high-distraction television during the phlebotomy, habitual anxiety, negative expectations, and extraversion. An avoidant and problem-focused coping style was associated with lower stress reactions, and was more frequently expressed by donors with a greater number of donations. Finally, increased ratings of pain and physical symptoms (e.g. dizziness and lightheadedness) were also associated with more stress.
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Anticipatory stress response following negative experiences

The second research question (Part II) focused on whether donors experience an anticipatory stress response after having had a negative experience during their last donation (Chapters 3 and 4). In addition, the effect of the donor’s general anxiety and attitude to donating blood were examined on the association between a negative event and anticipatory stress at the following donation. Overall, the results indicate that negative experiences induce an anticipatory stress response in experienced whole-blood donors, but general anxiety and attitude to donating blood do not influence this effect among first-time donors (research question ii).

Evidence was found for an anticipatory physiological stress response (evidenced by increased blood pressure) at the subsequent visit in mainly experienced whole-blood donors who were confronted with a negative experience at their prior donation. Among the different negative experiences, fainting and dizziness showed the highest associations with increased blood pressure. Furthermore, non-donor complications (such as problems with the apparatus) were also associated with significant increases in systolic (men and women) and diastolic (women) blood pressure. Plasmapheresis donors did not show any significant changes in blood pressure related to negative donation experiences. Although differences in blood pressure were small, and not of clinical value, they indicate the presence of an anticipatory stress reaction following a negative donation experience.

Among inexperienced donors, no evidence was found that, after a previous negative experience, a donor’s general anxiety or attitude to donating blood influenced the stress response, i.e. pre-donation blood pressure.

Immediate donation-induced stress

Donation-induced psychological, hormonal stress, and physiological stress response patterns in whole-blood donors were evaluated in Part III to answer the third research question (Chapters 5 and 6). Overall, a donation-induced stress response was found to peak at needle insertion and uncoupling and decrease thereafter towards the end of the donation procedure. Differences were found related to gender, donation experience and levels of non-acute stress.

Psychological stress showed a clear donation-induced response in terms of donation-stress and arousal. Donation-stress increased towards needle insertion and declined thereafter. Moreover, higher levels of donation-stress were found in women compared to men, first-time compared to experienced donors, and donors high compared to low on non-acute stress. A high and constant level of arousal was observed, indicating that donors were aroused throughout their visit. With regard to hormonal stress, no cortisol reactivity was observed.

For physiological stress, a clear donation-induced response in blood pressure was found, again with increasing levels towards needle insertion and a decrease thereafter.
Pulse rate showed a U-shaped curve, with lowest values at needle insertion and uncoupling. The drop in parameters of the time and high frequency domains of pulse rate variability during needle uncoupling, suggest a short-term increase in stress at that moment. Also, since an increase in high frequency power is associated with increased breathing, these results suggest a lowered breathing rate during needle uncoupling, i.e. a 'holding of the breath' [101].

Donation-induced effects in hemostasis

For the final research question the effects of a donation-induced stress response on the levels of hemostatic parameters were assessed (Part V, Chapter 7). In general, higher levels of donation-induced hormonal and physiological stress responses were associated with higher levels of various hemostatic parameters, indicating an increased coagulation in higher-stressed donors. These effects were comparable to general stress literature.

Methodological considerations

An important strength of this thesis is the use of a combination of different research methodologies to assess donation-induced stress and its effects on the donor, i.e. a systematic review (Chapter 2), routinely administered register data from the blood bank (Chapter 3) which were combined with data from a survey study (Chapter 4), and an observational field study (Chapters 5 - 7).

Methodology

First, conducting a systematic overview of the literature (Chapter 2) provided a body of knowledge on the existing stress-related literature in the field of blood donation. Although the systematic review was designed to assess stress responses within a single routine donation procedure and, as such, did not explicitly include the concept of an anticipatory stress response after a negative donation experience, one study suggested the presence of an anticipatory stress response in relation to personality. The general concept of anticipatory stress [33] was supported, as donor return rates were decreased after experiencing a negative donation experience, such as a deferral or a vasovagal response [4, 7, 36]. Hence, we studied the possible effects of negative experiences on anticipatory stress responses, i.e. blood pressure (Chapters 3 and 4), based on routinely assessed cohort data from the blood bank as well as a survey study, and including large groups of donors. Results from the systematic review also suggested a non-linear psychological stress response. By including multiple measurement moments around a donation procedure, such an effect was indeed found in the observational field study (Chapters 5 - 7). In this thesis, use of these different
research methodologies made it possible to assess donation-induced stress responses in a systematic and comprehensive manner.

**Assessment of anticipatory stress**

The database of Sanquin contains all donor screening data (e.g. blood pressure, hemoglobin) and donation information (e.g. donation success and adverse events) since 2004. Although the use of this type of data might limit the choice of parameters of interest to variables that are included in the dataset, this registry allowed to study the anticipatory stress response in large groups of donors. As a general rule, by including large numbers of participants, also very small differences between groups are likely to become statistically significant [34]. Results indeed showed several significant, albeit small positive associations between blood pressure and a number of negative experiences. However, the clinical relevance of the significant differences found (up to 3.0 mmHg systolic blood pressure) is limited, i.e. no deferral or immediate health consequences can be based on these values [124]. Nevertheless, the increase in blood pressure was considered to be an indication of anticipatory stress [33] and, thus, indicated an increased anticipatory stress in donors who had had a negative experience.

The effect of the donor’s general anxiety and attitude to donating blood was assessed in a subset of data, which was collected using data from a survey study among new donors investigating return behavior [42, 83]. In this specific group of inexperienced donors, no increased anticipatory stress response following a negative experience was found. The explanation for the disparity between both studies is twofold, including i) differences between new and experienced donors and ii) the different methods used to assess negative experiences, which is also addressed in Chapter 4. With regard to i), the explanation might be that experienced donors are prone to a cumulative effect of stress [27], or are surprised by a negative experience, or that first-time blood donors are already more stressed in the first place [80], or that they take the negative experience more in their stride. With respect to ii), in Chapter 3 regular blood bank data were used, whereas in Chapter 4 a questionnaire was used to explore to what extent donors felt they were affected by a negative experience. However, self-reporting often results in higher prevalence rates than on-site recording [8, 41]. In our study, this might be caused by reports of only the severe negative experiences on-site, whereas also less severe negative experiences might be reported by the donor. Thus, even in the absence of severe visible physical symptoms (as reported by the donor nurse), donors might perceive a negative experience as being severe (using a self-report). Either way, it is remarkable that first-time donors did not show an increased stress response following a negative donation experience, whereas this was shown by the experienced donors, as it might indicate a change in perception throughout the donor career.
Assessment of donation-induced stress

To evaluate the stress experienced during a routine donation in a real-life setting, all measurements were made during an entire routine donation procedure. In other studies, physiological stress measures were assessed in a much narrower setting, i.e. mostly examined immediately before and after phlebotomy [94, 97–99]. However, our assessment method minimized the impact of the study on the donor by limiting the number of visits and needle insertions.

A total of 1,502 invitation letters were sent out. With an overall response rate of 46%, 519 (35%) respondents were willing to participate in the study. Of these, eventually, 399 donors were measured during a whole-blood donation. Group differences were observed: first-time donors showed a response rate of 28% for men and 32% for women, whereas experienced donors showed a response rate of 73% for men and 83% for women. Response rates for new donors are lower than in previous studies at Sanquin [125], probably due to recent changes within the organization in the procedures of donor management and invitation. In addition, with respect to differences between the groups, potentially creating bias, the number of first-time donors that visit the blood bank to donate after having received an invitation card is lower than the number of experienced donors (28% for first-time donors and 59% for experienced donors; unpublished data).

The variety in measurement methods (i.e. psychological, hormonal and physiological stress measures) provided valuable information concerning the different stress responses. The assessment of multiple key moments during the donation procedure (e.g. screening and needle insertion) gave insight into the pattern of these responses. In addition, the continuous measurement of pulse rate and pulse rate variability is likely to be more reliable and less invasive than measuring this multiple times [93, 103, 126]. When comparing the various measures, the advantage of multiple assessment at key moments is evident: if levels of stress are assessed only at pre- and post-donation, the peak during needle insertion or uncoupling will then be missed. In addition, the advantage of measuring several stress measures becomes apparent: comparison between stress measures shows a clear peak in psychological stress during needle insertion (i.e. donation-stress), but also a short-term change in stress response at needle uncoupling in a subset of physiological stress measures (i.e. a drop in the parameters of the time and high-frequency domain of pulse rate variability). However, this latter effect disappears quickly and is not captured by psychological, hormonal or other physiological stress measures at this point.

The repeated measurements of psychological and hormonal stress responses, as well as the apparatus used to measure physiological stress, might have caused study-related stress in itself [16, 46]. The magnitude of this study-induced stress on top of the routine donation-induced stress is difficult to quantify but, assuming that it increases stress more or less equally across groups, might be considered non-relevant when comparing patterns between the several donor groups. Overall, assuming that the study did (to some extent) increase stress, then routine donation-induced stress
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responses are expected to be smaller than found in the study included in Chapters 5 and 6 of this thesis.

Assessment of the donor’s hemostasis

In line with the assessment of the stress measures, hemostatic parameters should (ideally) be assessed multiple times in each donor, so that the changes within an individual as a result of donation-induced stress can be observed [10, 82, 107–109]. However, one challenge was that needle insertion was indicated to be the most severe stressor [58], implying that taking another blood sample would in fact represent an additional stressor. As the main goal was to assess the routine donation-induced stress response, this was not acceptable. Therefore, to overcome this problem, it was decided to assess the differences in hemostatic parameters between high and low stressed donors. However, this necessitated the inclusion of a larger sample of donors.

A second challenge was the choice of hemostatic factors of interest. A selection of potential parameters of interest was based on literature examining both basic coagulation as well as stress [10, 22, 23, 28, 29, 82, 107–109]. Subsequently, a subset of these parameters was chosen based on feasibility; however, the choice of parameters was affected by several factors. Firstly, the choice to perform the evaluation during a routine donation already precluded a number of factors, since the way that routinely obtained blood samples were collected and stored was determined by standard operating procedures. This, for instance, includes the use of a tourniquet, which is known to influence factors related to serum [127]. Secondly, more pragmatic reasons affected the final choice of parameters, including the costs of analyses, and the fact that one collection site would be unable to provide a sufficient number of donors within a reasonable time frame. With respect to this latter issue, donors were included at two sites, i.e. Nijmegen and Utrecht. However, the blood bank laboratories are situated in Amsterdam and the routine blood bank transport (i.e. not an express service) was used for the blood samples obtained. Because some potentially relevant analyses needed to be performed very soon after obtaining a blood sample, the transport system also excluded some parameters which might have been of interest [128].

Interpretation of findings

In the General introduction of this thesis, a model was presented for the studies that focused on whether a donation induces stress responses and how these responses might affect the donor’s hemostasis. Having discussed and reflected on the main findings and methodology, it is now discussed what there is learned from this work, based on an adjusted conceptual model (presented in Figure 1). In this figure, the
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various key elements (e.g. donation procedure, donor characteristics) are divided into specific factors (e.g. gender) and their relationships (as found in this thesis) are indicated by means of arrows. The black boxes/lines indicate the main elements and pathways (as also presented in the General introduction). The grey boxes/lines indicate more specific relationships between these factors. An arrow with a bullet head indicates that no effect was found, whereas arrows with an arrow-head indicate that an effect was found.

![Diagram](image)

**Figure 1** Adjusted conceptual model of the effects of donation-induced stress responses. The black boxes/lines indicate the main elements and pathways studied in this thesis. The grey boxes/lines indicate more specific relationships between a number of factors. An arrow with a bullet head indicates that no effect was found, whereas arrows with an arrow-head indicate that an effect was found.

**Donation-induced stress responses and hemostasis**

As shown throughout this thesis, a donation-induced stress response is apparent in all donor groups, with small differences between the groups. In accordance with literature assessing psychological stress [57, 58, 62], needle insertion was found to induce the most stress, as clearly shown by increases in psychological donation-stress and systolic blood pressure. In addition, results for the time domain and high frequency parameters of pulse rate variability, indicate a short-term (probably
unconscious) change in stress reactivity. This brief change in stress reactivity during needle uncoupling is immediately followed by relief, indicated by the lowered levels of psychological donation-stress at this point. In addition to this overall donation-induced stress response, donor characteristics were also found to affect the stress responses.

In the General introduction to this thesis, two donors were introduced: Ms. R. and Mr. B.. Would it be possible to predict their stress response based on the findings in this thesis, as well as the meaning of their responses? In short: Ms. R. was a healthy young woman, with little experience with donations, who had recently fainted during her previous donation. In contrast, Mr. B. was a healthy middle-aged man, with lots of experience in donating blood; however, due to travelling, his last donation has been some time ago.

Concerning the psychological parameter donation-stress, this differed according to gender, donation experience and levels of non-acute stress. Therefore, based on the evidence emerging from this thesis, compared to Mr. B., Ms. R. is likely to show both a larger stress response for donation-stress, as well as a higher overall stress level. For arousal, results suggest Ms.R. would express lower levels of arousal during the entire procedure compared to Mr. B., but they will both express reasonably high levels and be aroused throughout the donation procedure. These results are in line with earlier studies, indicating a decrease in stress from pre- to post-donation [9, 55–62]. When evaluating hormonal stress, neither Ms. R. nor Mr. B. are likely to show cortisol reactivity as we found no evidence of this response. This was in contrast to studies indicating differences between first-time and experienced donors [58]; however, this might be because the latter authors also assessed serum cortisol (i.e. adding another stressor due to two extra needle insertions).

Concerning physiological stress, results in this thesis indicate potential differences between Ms. R. and Mr. B. for the different measures, whereas this type of stress was not consistently evaluated in other studies [37, 61, 94–101]. However, apart from being somewhat uncertain, the relevance of these latter findings might also be limited since the differences found in this thesis were relatively small in the light of general stress-induced differences with respect to these variables [10, 18, 20, 32].

The next step was evaluation of the effects of this donation-induced stress response on the donor’s hemostasis. As shown in Chapter 8 of this thesis, donation-induced stress caused increased coagulation by raising the level of several hemostatic parameters. The increases found were comparable to laboratory mental stress tests [10, 82, 107–109]. Interestingly, here a discrepancy is revealed between the various stress measures, i.e. whereas an increase in the psychological parameter donation-stress was associated with decreased coagulation, increased hormonal and physiological stress were more robustly associated with pro-hemostatic effects. This implies that donors might state that they are not stressed, whereas our findings indicate that they are physiologically and hormonally stressed, a phenomenon that has also been described in working professionals such as ambulance workers [63].
Taking the consequences of donation-induced stress one step further

When evaluating the donation-induced stress responses and their effects on hemostasis presented in this thesis, the first question that might arise is whether this thesis’ findings require action and from whom. The findings in this thesis might be considered relevant in two ways: for the donor, and for the quality of the obtained blood product. Over-arching is the relevance for the blood bank institute, which is on the one hand dependent on the donor, and obliged to deliver a safe product for a patient on the other hand.

Regarding safety of the blood product, no studies have explored this potential donation-induced effect on blood products; moreover, the potential effects of prolonged clotting times or increases in hemostatic factors on the quality of blood products have not yet been described before. Meanwhile, the pro-hemostatic changes found in this thesis are relatively small, implying that factors such as storage and processing (both of which might reduce or enhance the changes found) are likely to have more influence [119–121].

Concerning relevance for the donor, two main aspects emerged, i.e. the stress responses might give the donor an uncomfortable feeling [8], and might also have potential (undesirable) health effects. With respect to the health effects, the relatively small increases in hemostatic parameters found are similar to results from mental or physical stress tests, which are thought to be indicators for the onset of acute coronary symptoms [10]. From this viewpoint, the repeated exposure to stress as a result of a blood donation (with up to 5 times a year for a whole-blood donor and 27 times a year for a plasma donor in the Netherlands [129]) could be potentially harmful. However, such issues do not seem to be apparent to whole-blood donors, perhaps for the following reasons. First, there is increasing evidence for a ‘healthy donor’ effect, showing that donors are generally healthier compared to the average population [122]. Second, the main mechanism behind a stress-induced increased risk for acute coronary symptoms is vascular damage due to the so-called shear stress induced by flowing blood [10]; increases in hematocrit or decreases in plasma will increase this shear stress [10]. Donors are protected from this mechanism because red blood cell donation lowers the hematocrit [123], making an increase in shear stress due to changes in hematocrit or plasma unlikely. Therefore, the potential negative health consequences of a blood donation are likely to be smaller than the health consequences due to acute mental stress tests.

Thus, the donation-induced stress responses seem to mainly affect the donors themselves, i.e. they experience them as being uncomfortable. However, as a blood donation in the Netherlands is voluntarily, donors can choose to avoid this discomfort by ceasing to donate, as they often do when, for instance, they have had a negative experience [4, 6, 7, 36]; therefore, this item is highly relevant for the blood bank. This thesis provides evidence that not only negative experiences cause anticipatory stress in a subsequent visit among experienced donors, but also that a routine dona-
tion procedure can cause a stress response. Vasovagal reactions are known to cause donors to refrain from donating in the future [4, 5, 7] and donation anxiety is also negatively associated with donor return [36]. As the costs of recruiting and screening new donors are high, and new donors have a higher risk of transmitting infections compared to regular donors [130–132], the retention of donors is an important factor. This thesis provides valuable information and data on: i) stress response patterns, ii) differences between the various donor groups and iii) important moments during a donation process; all these factors are highly relevant when introducing/evaluating interventions to minimize the stress experienced during a donation and, subsequently, to minimize donor loss - both for new and experienced donors.

Returning to the differences in the characteristics of the two donors, Ms. R. and Mr. B., one of the most obvious actions might involve the way both donors are received and handled at the donation site. Whereas Mr. B. is likely to be content with going through the procedure by himself, Ms. R. might require more guidance during this process. Indeed, social support is known to decrease anxiety during a donation [57]; in addition, interventions aimed at reducing vasovagal reactions, such as water loading [77], applied muscle tension [31], the use of coping strategies [133], or the intake of salt [43] have also been investigated. According to the theory of Ursin and Eriksen (the CATS, presented in the General introduction), these measures might lead to a more positive expectation of the outcome, thereby lowering the stress experienced [16].

**Recommendations for practice and research**

The evidence provided in this thesis is useful for researchers in the field of donor studies as well as for the general literature on stress. It also provides detailed information relevant for 'on the job' donor physicians and nurses.

Donor physicians and nurses should be aware of the phenomenon that negative experiences are associated with increased stress levels, and should attempt to comfort the donor during the negative experience, as well as during subsequent visits. This might be achieved by detailed signals in the blood bank information system, as well as by more targeted questions about how the donor experienced the various parts of the donation procedure. The differences found in the anticipatory stress responses between experienced and inexperienced donors might mainly be caused by overall increased anticipatory stress at the first visits, also indicated by increased psychological stress in first-time compared to experienced donors. Therefore, researchers should examine the number of donations it takes until a donor becomes accustomed to donating blood, in other words, when and why this increased anticipatory stress response fades away. In addition, research should focus on whether new and existing interventions aimed at preventing and handling negative experiences are justified/necessary to preserve a pool of relaxed and returning donors.
This thesis defines a number of key moments during a routine donation (e.g. at arrival, medical screening, needle insertion and uncoupling) which are likely to cause an increase in psychological and/or physiological stress. In addition, evidence is provided for an effect of donor characteristics, i.e. gender, donation experience, and levels of non-acute stress. This information is important to help decide when to comfort specific groups of donors at certain stages in a donation procedure. Therefore, future research should focus on the most effective ways to handle the donor's stress at these specific points; in addition, the magnitude of the effect of donation-induced stress on return behavior is needed to be assessed, as increased stress is likely to prevent individuals from donating again.

Since routine donation-induced changes in blood pressure and pulse rate do occur, they may lead to an overestimation of genuine blood pressure or pulse rate during the medical screening. Both donor physicians and blood banks should be aware of these phenomena, and question the use (regarding both reliability and relevance) of discrete blood pressure assessment during the medical screening.

Finally, as this thesis has provided the most detailed exploration of donation-induced stress until now, more research is needed to replicate and extrapolate the present findings; in particular, the different stress measures and their effects on hemostasis. Concerning the stress measures, objective evaluation of these can be achieved by, for instance, assessing the emotional stress of the donor via a smartphone or tablet camera in the near future. The effects on hemostasis might be extended by sampling multiple times during a donation procedure to establish changes within a donor, and by examining factors such as platelet function and circulating inflammatory markers [10, 71]. Although these changes do not appear to compromise donor safety, future studies should further explore the clinical relevance for the donor and combine this with the effects of donation-induced stress on the blood product and possible consequences for the future recipient of this product.