Giving blood: Donor stress and hemostasis
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General introduction

Ms. R., a healthy young woman, is not an experienced blood donor and, until now, has made only one donation. During that donation, however, she fainted. When receiving the second invitation card to donate blood, Ms. R. feels her heart beating. Again?

After a few days of thinking about it, she decides to go. Together with a close friend she plans a visit, even though they both have a lot of work. Unfortunately, it’s rather busy at the collection center, so that the hostess has little time for her. On the donor health questionnaire, Ms. R. indicated that she had fainted during the previous donation. Despite her nervousness, during the health screening she has a good talk about this with a pleasant donor physician.

Whilst waiting a few minutes in the donation area until a bed is available, she is anxious and looks curiously at the other donations being performed. A friendly nurse then performs a routine venipuncture, and remarks on the excellent accessibility of her veins.

After what feels like an eternity - but is in fact only a few minutes - needle removal takes place. On the previous occasion, this was the moment when she fainted. Again, she feels her heart beating and tension in her legs and shoulders. However, this time nothing happens and, after a successful donation, she is directed to the donor canteen. She grabs a pink biscuit and a cup of tea, and with a sigh of relief, sits down at a table.

Every day, people donate blood at blood collection sites around the world. At Sanquin (the Netherlands) each year about 343,000 blood donors voluntarily provide this blood bank with approximately 435,000 units of whole-blood and 285,000 units of plasma or platelets [1]. Blood units and their derived products are essential for modern healthcare as they are widely used in hospitals (e.g. during operations) and for the processing of drugs (e.g. against hemolytic disorders) [2, 3].
In recent decades there has been a slight increase in donor-related studies that have investigated, for example, the incidence and management of negative donation experiences, the recruitment and retention of donors, or the effect of negative experiences on donor return rates [4–7]. However, very few studies have explored donation-induced stress responses [8, 9]. Until now, the effects of these donation-induced stress responses on the donor’s hemostasis, as assessed in general stress literature [10], have largely been overlooked.

An introduction to stress

Before introducing stress in a donation-related setting, a brief overview of stress is presented and stress as a concept is defined. During the past century, researchers have developed different conceptual models to describe and understand the human stress response and its consequences [11–13]. The acute stress response was originally proposed as being a response to a stressor, such as confrontation with a dangerous entity, such as a large snake.

When exposed to such a (potential) stressor, an accumulation of different responses takes place, interacting with each other and, overall, increasing the total level of arousal or awareness. This cascade can be divided into three pathways: psychological stress, hormonal stress, and physiological stress. Psychological stress responses include increased levels of anxiety, fear or tension [14–16]. Hormonal stress responses include increased adrenaline and cortisol excretion [15, 17]. Physiological stress responses include increased heart rate, increases in systolic/diastolic blood pressure [18–20], and differential changes in heart rate variability parameters [20, 21]. In addition, changes in hemostasis can take place, leading to increased coagulation [22, 23].

These common stress responses are affected by several factors. One important factor known to add to a stress response is unfamiliarity with a situation [16]. Other factors influencing psychological and hormonal stress reactions are gender and levels of non-acute stress. However, depending on the type of challenge and stress reaction assessed, inconsistent and conflicting effects are reported for gender [24–26]. Non-acute stress (i.e. the wide range of daily hassles or minor daily pressures) is reported to enhance acute stress levels [27].

The cognitive activation theory of stress

The cognitive activation theory of stress (CATS) was proposed by Ursin and Eriksen in 2004, and their concepts are used in this thesis [15]. Briefly, their theory states that a stress response occurs when there is a discrepancy between what is expected or regarded as being the ‘normal’ situation, and what is happening in reality or is expected to happen. It is important to realize that, in contrast to previous stress
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Theories, in the CATS a stress response may be triggered by both negative and positive situations, and is regarded as a general alarm, producing general and unspecific neurophysiological activation to face and deal with the new situation. The stress response implies non-specific changes as part of a general preparation to face any form of challenge or danger, by changing the behavior. Subsequently, the stress responses are reduced or eliminated when positive results of the actions are expected. When these expectancies are positive there is no health risk in a healthy organism. However, negative effects may arise when there is a lack of ability to deal with the situation. This has been defined as 'helplessness', i.e. the expectancy that there is no relation between response and reinforcement, and 'hopelessness', i.e. the expectancy that most or all responses lead to a negative result. When the behavior remains unchanged, both helplessness and hopelessness may eventually lead to disease.

Stress and hemostasis

As part of the stress cascade, physical activity and acute psychological stress are associated with a number of immediate effects in hemostatic parameters [10, 22, 23]. Studies on stress and hemostasis have described stress-induced increases in a number of clotting factors, e.g. factor VII, factor VIII and fibrinogen, as well as increases in von Willebrand Factor (vWF).

Figure 1 Schematic overview of the coagulation cascade.
Chapter 1. General introduction

Although often used interchangeably, hemostasis is defined as the process which causes bleeding to stop, and involves coagulation (or the clotting of blood) as the process by which blood changes from a liquid to a blood clot to end blood loss from a damaged vessel [28, 29]. This response might be due to a trauma damaging the vessel wall (e.g. an injury); however, as this process is part of the stress response, also physical activity or acute psychological stress can initiate onset of the cascade [10], starting within minutes after the onset of stress [22]. Although a detailed description of the entire mechanism is beyond the scope of this thesis, exploring some of the main processes seems relevant. In primary hemostasis, after injury of the vessel wall, circulating platelets in the blood adhere to the vessel wall with the help of vWF, and become activated so that they can aggregate and form an initial thrombus. Simultaneously, secondary hemostasis starts by activation of the coagulation cascade. The coagulation cascade comprises multiple components and a number of subsequent steps, amplifying the response. A schematic overview of the coagulation cascade is provided in Figure 1. As indicated by the dotted grey lines, the two pathways are separated, eventually joining together in a common pathway. The solid grey squares indicate the onset of the different pathways, whereas the solid black squares indicate the various factors involved. The black arrows indicate the activation routes of the pathways. In the extrinsic pathway, the exposure of sub-endothelial tissue factor initiates the cascade. Via a number of steps, this leads to the formation of factor Xa. In the intrinsic pathway, contact with negatively charged surfaces leads to activation of XII, which initiates a number of reactions eventually resulting in the formation of factor Xa. At this point, the intrinsic pathway joins the extrinsic pathway, leading to the formation of thrombin (factor IIa). Importantly, it is also thrombin that initially amplifies the whole cascade by activation of (among others) factor VIII. This causes amplifying feedback loops necessary to allow effective clotting. After its formation, thrombin initiates the formation of fibrin out of fibrinogen, which finally leads to the formation of a blood clot, e.g. on the site of injury.

Stress in blood donation

Since evidence suggests that acute stress might affect hemostasis, the potential of a donation-induced stress response is an interesting phenomenon. This stress response is influenced by the type of stressor, the specific situation, and the subject under stress. When transposed to a blood donation setting, the donation itself, or each step in a donation procedure, might elicit a stress response; however, the magnitude of this response is likely to be donor dependent. Thus, it is important to establish what is in fact known about this donation-induced stress response and its effects on blood products.
Donating blood

The first donor, Ms. R., has already been introduced. Now donor Mr. B. is presented, who serves to illustrate a different response pattern to a routine donation procedure.

Mr. B. is a healthy, middle-aged man, having made over 25 donations. Due to travelling, however, his last donation was some time ago.

After receiving an invitation card for a donation, Mr. B. decides to go immediately to the donation center, as, fortunately, he has that day o. After entering the center he is warmly welcomed by the hostess. There are no surprises on the donor health questionnaire, and also none during the health screening.

Because it’s not busy, during the preparation of the phlebotomy he has a pleasant conversation with the donor nurse. Insertion of the needle, withdrawal of the blood, and removal of the needle all go according to his previous experience. However, when he stands up he feels as though he is slightly faint. Luckily, this quickly passes, and he walks to the donor canteen to enjoy a cup of coffee and a waffle, and read a magazine.

In the Netherlands, a routine donation comprises a fixed order of steps: invitation letter, registration, health questionnaire, health and eligibility screening, phlebotomy, and refreshment area [30]. The stories of the two donors illustrate the variety in responses that might be shown to essentially the same procedure. Familiarity with the situation, indicated by donation experience (i.e. the number of previous donations) and previous experiences (e.g. adverse events), might influence the perception of experiencing the donation as being a stressful event or not, thereby shaping the subsequent stress response. Although a few studies have examined anxiety during a blood donation [8, 31], a systematic overview is still lacking, i.e. assessing the factors (e.g. donation experience) and associating them with psychological, hormonal and physiological stress reactions in blood donors in a blood donation setting.

Anticipatory stress response

Apart from a few studies reporting positive donation effects, such as a feeling of satisfaction after having performed this voluntarily activity [8], most of the literature in the field of blood donation describes negative donation experiences. These studies include the occurrence of a vasovagal reaction or bruise, the effects of negative donation experiences on donor return rates, and the interaction between the two [4–7]. For
instance, the presence of an adverse event has been shown to reduce return rates [4]. This effect differs between donors as, for example, men report less negative donation events than women, but are more likely to refrain from donating after experiencing one [5]. Because anticipatory stress is also known to cause (physiological) arousal [32, 33], donors who had a negative experience might show an increased stress response at the subsequent visit. As illustrated by Ms. R., feeling her heart beating, this increased anticipatory stress might be indicated by an increased pre-donation blood pressure. However, no studies have assessed this anticipatory stress response following a negative experience.

In addition, after having had a negative experience, the donor’s general anxiety and attitude to a future donation might influence the anticipatory stress response. Attitude is a measure of how the donor rates giving blood in terms of importance and pleasantness, and predicts the intention to donate in the future [34]. The influence of general, non-acute donation anxiety (i.e. how the donor rates the donation in advance in terms of fear) on donation intention is still unclear: some studies show no difference in intention [35] whereas others present evidence for a negative influence [36]. Although the effects of both factors on the intention to donate are under investigation, no studies have evaluated the effects of general anxiety and attitude to donating blood on the anticipatory stress response following a negative experience.

**Immediate donation-induced stress**

The donation procedure itself might also be perceived as a potential stressor, and donation-induced stress responses have been described in a limited number of studies. Although overall results indicate an increased pre-donation psychological stress response, mostly only pre- and/or post-donation anxiety levels were assessed [8, 9]. In addition, potential differences in the donation-induced stress response throughout the donation procedure have not been considered. Studies evaluating hormonal and physiological stress responses are scarce and, thus far, provide inconclusive evidence [37]. Differences in donation-induced stress responses between gender and donation experience, or between levels of non-acute stress, have not yet been systematically investigated, whereas such factors can potentially influence the general stress response [16, 24–27]. Thus, in summary, there is a need for more detailed knowledge on donation-induced stress responses, comprising multiple stress measures at several key moments during a donation, and discriminating between the various groups of donors.

**Donation-induced effects in hemostasis**

The main purpose of a blood donation is the provision of blood related products for clinical patients in need [2, 3]. This means that the quality of the derived blood products is of utmost importance and must meet quality criteria to assure patient
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As described above, acute mental stress is capable of inducing changes in hemostasis. Therefore, the question arises whether blood donation-induced stress responses are capable of inducing changes in hemostatic parameters, i.e. influencing the coagulation cascade, causing a higher clotting potential and possibly leading to undesired changes in the blood product. Although such an effect should be of interest in a blood donation setting, no research to date has investigated the potential effect of this donation-induced stress response on hemostatic parameters.

Donation-induced stress responses and their effects

To illustrate graphically the topic of thesis, a model was constructed encompassing the various elements related to blood donation-induced stress responses investigated in this thesis. This model is presented in Figure 2. As indicated by the thick arrows, central in this model is the concept that a blood donation procedure induces a stress response, which then has a number of potential effects. The stress response comprises psychological, hormonal and/or physiological stress reactions, which are thought to be influenced by a blood donation. Subsequently, these donation-induced stress responses might affect the immediate changes in hemostatic parameters. Donor characteristics play an important role, as stress responses might be influenced by characteristics such as gender, donation experience, levels of non-acute stress and the donor’s general anxiety and attitude to donating blood.

![Figure 2 Conceptual model of the effects of donation-induced stress responses.](image-url)
Chapter 1. General introduction

Aim, objectives and research questions

A routine whole-blood donation might be seen as a potential stressor and, thus, capable of inducing psychological, hormonal or physiological stress responses. The overall aim of this thesis is to provide detailed insight into the course of donation-induced stress responses and their effects on the donor’s hemostasis. This leads to the following objectives:

I Examination of the donation-induced psychological, hormonal and physiological stress response patterns during a blood donation procedure;

II Investigation of the effects of the donation-induced stress response on immediate changes in hemostatic parameters.

These objectives lead to the following research questions:

i What factors are associated with stress reactions in blood donors in a blood donation setting?

ii Do donors with and without a negative experience show different blood pressure levels at the pre-donation screening of the subsequent visit, and is this association influenced by the donor’s general anxiety and attitude related to donating blood?

iii Does a blood donation induce psychological, hormonal and physiological stress in whole-blood donors, and are there differences between men and women, first-time and experienced donors, and donors high or low on non-acute stress?

iv Does donation-induced stress have an immediate effect on hemostatic parameters in whole-blood donors?

Outline of the thesis

The remainder of Part I of this thesis is dedicated to the first objective, i.e. the evaluation of donation-induced stress responses. Chapter 2 presents a systematic literature review performed to explore research question i, to identify which factors (e.g. donation experience) are associated with psychological, hormonal and physiological stress reactions in blood donors in a blood donation setting.

In Part II, research question ii is investigated by examining whether donors with and without a negative experience show anticipatory stress at the subsequent visit (Chapter 3). This effect is evaluated by blood pressure levels at the pre-donation screening of a visit following a negative experience. In Chapter 4, this effect is further considered by assessing the role of general anxiety and attitude to donating blood among new donors.
In **Part III**, blood donation-induced psychological, hormonal stress, and physiological stress response patterns in whole-blood donors are explored in **Chapters 5 and 6**, to investigate research question iii. Differences between men and women, first-time and experienced donors, and donors with high or low non-acute stress are investigated and evaluated.

The second objective is studied in **Part IV** of this thesis. In **Chapter 7**, the effect of a donation-induced stress response on hemostatic parameters is assessed to answer research question iv.

To conclude the thesis, **Part V** provides a general discussion, in which the main findings are summarized and interpreted (**Chapter 8**). Various methodological and theoretical considerations are discussed, and implications and recommendations for future research and blood bank practices are presented.