Chapter 2

The relationship between SIC and SAS susceptibility

This chapter gives an introduction into the procedures of sustained centrifugation and then focuses on the question whether susceptibility to SIC is correlated with susceptibility to SAS. Where in previous studies susceptibility to SAS was rated after the flight, based on the astronauts' recollection, in recent research susceptibility to SIC and to SAS was scored using a similar head movement protocol, which enabled a more objective comparison between SIC and SAS. Using this method, it was shown that SIC- and SAS-susceptibility are correlated, but that the head movements are more provocative in flight than after sustained centrifugation.

That long duration centrifugation led to symptoms of SAS (and was thus denoted by Sickness Induced by Centrifugation, SIC) was actually discovered by chance. In order to investigate the possible effect of hypergravity on the human immune system the Dutch astronaut Wubbo Ockels, who flew on the D1-mission in 1985, participated in some pilot experiments where long duration centrifugation was applied. While such long centrifuge runs had not been reported on in literature, special care was taken to monitor the astronaut's health every 30 minutes. After a total exposure of 90 min to an acceleration of 3G, the astronaut showed readaptation problems that were similar the symptoms of the Space

Adaptation Syndrome experienced during his flight. Subsequently, all three European D1-astronauts participated in a 90 min. centrifuge run, and they all perceived the readaptation to Earth's gravity after centrifugation as being similar to adaptation to microgravity (Ockels et al., 1989; 1990).

Ockels and his colleagues experienced that head movements were required to induce the symptoms after centrifugation, just as they were in space. They reported that only the slightest pitch head movement triggered strong visual illusions and nausea. This effect was already present after the first 30 minute exposure, but was significantly increased after the second 30 minute exposure. The last 30 minute exposure (thus adding up to 90 minutes in total) did not increase symptom-severity to large extent. The symptoms lasted for several hours after centrifugation. There was only one difference with their space-experiences: after centrifugation only those head movements that changed the orientation of the head relative to gravity (i.e., pitch and roll when erect) while in space yaw movements were also provocative. This special role of gravity in inducing the symptoms already indicates the involvement of the vestibular system in SIC and SAS. Data of these first experiments showed that a cardiovascular cause for SIC was unlikely (Bles et al., 1989; Bles et al., 1997; Ockels et al., 1990).

Also important was that the individual susceptibilities to SAS were reproduced by SIC suceptibility, suggesting that a similar adaptation process is involved in SIC and SAS. This was an important finding, because up till then it was not possible to assess an astronaut's susceptibility to SAS on Earth before space flight. Although SAS was recognized as a form of motion sickness (Graybiel, 1980) many attempts to predict SAS-susceptibility from susceptibility to other forms of motion sickness failed (e.g., Graybiel 1980; Homick et al., 1987; Oman et al., 1986). Astronauts used to be selected based on their relative insusceptibility to Earthly motion sickness, but nevertheless, about half of them still got sick in space.

Taken together, the research paradigm of sustained centrifugation provided opportunities to investigate vestibular adaptation to gravity transitions on Earth, and to further investigate whether SIC and SAS susceptibility were indeed related. It was therefore the start of a new research program that systematically investigated the after-effects of sustained centrifugation in both astronaut and non-astronaut subjects. The current chapter starts with a description of the centrifuge procedures and then focuses on the relationship between SIC and SAS susceptibility by answering the question whether astronauts suffering from SAS during space flight are also the ones who are susceptible to SIC following sustained centrifugation. An overview of the vestibular research elucidating the mechanism underlying SIC and SAS is provided in the next chapter.

SUSTAINED CENTRIFUGATION

All centrifuge runs performed so far have been carried out at the Center for Man in Aviation[4], Soesterberg, The Netherlands. This centrifuge has a free swinging gondola at a radius of 4 m, so that the direction of the gravito-inertial acceleration (GIA) is always directed perpendicular to the gondola floor[5]. During long duration centrifugation a supine position was chosen, resulting in a G_x stimulation (i.e., GIA directed along the naso-occipetal axis) instead of G_z stimulation (i.e., GIA directed along the longitudinal body-axis), which is generally used in aviation. In this way a reduction of cerebral perfusion and excessive pooling of blood in the lower parts of the body was avoided. To enable a supine body position, a mattress was positioned inside the gondola, inclined over an angle of 10º (see Figure 2.1). Due to the limited size of the gondola, the knees were slightly bent in most subjects (feet pointing in the direction of motion). Ample cushioning was provided for support and comfort. Lying in this

[4] Formally known as the Netherlands Aerospace Medical Centre, or NLRGC.

[5] The acceleration gradient within the gondola in the radial direction is less than 3% and will further be ignored.

position, the GIA was predominantly directed in the *x*-direction, along the naso-occipetal axis. Electrocardiogram was always continuously monitored by a physician during the entire centrifuge run and video and audio contact with the control room was available. The G-load was increased and decreased with a moderate 0.1G/s, in order to minimize nauseogenic tumbling sensations during acceleration and deceleration. To induce a GIA with a magnitude of 3G a centripetal acceleration (a_c) of 2.8G is required and an angular velocity of 151°/s. Astronauts were instructed to refrain from head movements during centrifugation, in order to prevent nausogenic coriolis stimulation.

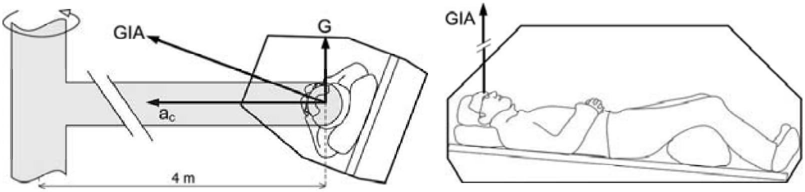

Figure 2.1: The centrifuge gondola swings out during centrifugation, directing the GIA always perpendicular to the gondola floor (see left panel). The subject was lying on a mattress inclined about 10° upwards (see right panel), with the feet pointing in the direction of motion. In this position the GIA was predominantly directed along the naso-occipetal axis.

ARE SIC- AND SAS-SUSCEPTIBILITY CORRELATED?

The relationship between SIC- and SAS-susceptibility has been assessed in a total of 12 astronauts so far. A first group of eight astronauts was tested in the period between 1989 – 1994, as described in Bles et al., 1997. This group included the 3 D1 astronauts who were exposed to a 90 minute centrifuge run at $3G_x$, while the others were exposed to a 60 minute run at $3G_x$. After centrifugation their SIC susceptibility was assessed by means of a head movement protocol: they were to make three head movements about each principal axis (yaw, pitch, roll) and to subsequently rate the experienced level of motion sickness on a 6-point scale (Misery Scale, MISC). In 7 of these eight astronauts their susceptibility to SAS was based on their recollection of symptoms experienced during space flight. In one astronaut a start was made to assess SAS-susceptibility in flight using a similar head movement protocol as used after centrifugation, which enabled a more objective comparison between SIC and SAS. In these eight astronauts a positive correlation between SIC and SAS was demonstrated: *the more they suffered from SAS, the more they suffered from SIC* (Bles et al., 1997).

The second group of four astronauts was tested within the framework of this thesis, in the period between 2003 – 2007. The astronauts participated in different missions (all Russian Soyuz-flights) that were hosted by the European Space Agency (ESA). The experiments were approved by both the TNO and ESA medical ethical boards, and the Russian Space agency. The astronauts gave written informed consent prior to the experiments.

One of the four astronauts already had spaceflight experience, so his susceptibility to SAS was assessed based on his recollection. The other three performed a head movement protocol during flight to assess SAS-susceptibity, and the same protocol was then also used to assess individual susceptibility to SIC after centrifugation. This head movement protocol was part of the Motion Perception questionnaire (MOP, see Figure 2.2), that addressed motion perception (self motion sensations or illusionary motion of the surround) as a consequence of body movements in general, and of head movements in particular. Astronauts were to make 10 self-paced head movements about the yaw, pitch and roll axes ($f \approx 0.25$ Hz, $A \approx \pm 40°$). After each of these stimuli, they described their motion perception and rated any experienced discomfort. The 6-point MISC scale used in the previous astronaut studies was now extended to an 11-point scale, as shown in Table 2.1.

In the ground based part of the experiment, the MOP-questionnaire was filled out just before and after centrifugation (60 min at $3G_x$), and again at two and four hours after the end of centrifugation. All head

Motion Perception Questionnaire

You are kindly requested to fill out this questionnaire *at least once a day at the end of the day, but before dinner*. Please write down in your own words whether you experience(d) illusory self and/or surround motion during the past period. Please make explicit note of the following four elements.

1. Did you experience illusory *self motion*?
2. Did you experience illusory *surround motion*?
3a. What is your maximum MISC score? (0 = OK, 10 = vomiting)?
3b. If so, what kind of discomfort did you experience?
4. Which (head)*motions* were most noticeable in these respects?
5. Did you take any anti-motion sickness medication (encircle): Yes / No

If you feel comfortable, you are kindly asked to make some deliberate head movements.

6. Do you object to this for reasons of anticipated discomfort? Yes / No

If Yes, you may skip the remainder of this query.

Please stand (if possible, sit if necessary) and make up to *10 deliberate head movements* over a total *angle of approximately 80º* at a rate of *one cycle per 4 seconds* in *yaw, pitch, and roll*, with your ***eyes open***. Stop whenever you feel uncomfortable. Please answer the following questions.

Yaw

7. What is your MISC score **before** making the yaw head movements? (0 = OK, 10 = vomiting)
8. What is your MISC score **after** making the yaw head movements?
9. Did you experience additional illusory motion? If yes, what kind?
10. How many cycles could you complete (0-10)?
11. Estimate the number of additional cycles you ***could*** have performed before vomiting (encircle): 0 cycles / 1-5 cycles / 6-10 cycles / > 10 cycles

NOTE:
Questions 7 to 11 are repeated for pitch and roll (Q12 – Q21). The order in which the head movements are requested is randomized.

22. Which head movements were **most** provoking? yaw / pitch / roll / N.A.
23. Which head movements were **least** provoking? yaw / pitch / roll / N.A.

END OF QUESTIONNAIRE

Figure 2.2: Questions addressed in the MOP-Questionnaire. The original questionnaire also provided drawings of the requested head movements and the MISC-scale (see Table 2.1).

movements were performed with eyes closed, once while sitting erect and once while lying in a supine position.

During spaceflight, the astronauts completed the MOP-questionnaire daily (at the end of each day) from 2 days before the launch (denoted by L–2), until at least flight day 7 (denoted by FD7), and subsequently from the day of return (R+0) until six days later (R+6). Because the effects were expected to be largest right after launch and landing, one additional questionnaire was requested as soon as possible on FD1 and on R+0. In order to prevent serious sickness caused by the inflight head movement protocol, astronauts were instructed to stop the experiment as soon as they reached MISC 8: severe nausea. During one mission the maximum amount of head movements per axis was restricted to three (in both the inflight and ground-based testing), whereas during the other missions 10 head movements were requested about each principal axis. Astronauts were considered to suffer from SIC or SAS if they scored 5 or higher on the 11-point MISC.

TABLE 2.1
Misery scale (MISC)

Symptom	Rating
No problems	0
Stuffy or uneasy feeling in the head	1 or 2
Stomach discomfort	3 or 4
Nauseated	5 or 6
Very nauseated	7 or 8
Retching	9
Vomiting	10

Results

The data of this second astronaut group showed that two of the four were not suffering from SAS and not from SIC. The other two developed symptoms, both in space and following sustained centrifugation. The severity of the symptoms was, however, different for SIC and SAS. Figure 2.3 gives an overview of the collected MISC scores, where the astronauts are denoted by *A1 – A4*.

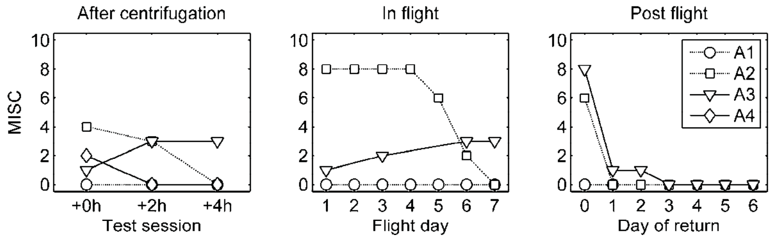

Figure 2.3: MISC scores (maximum from the yaw-, pitch, and roll-score) as elicited by the head movement protocol for the three astronauts, after centrifugation (left panel), in flight (middle panel) and post flight (right panel). No inflight or postflight data was available for astronaut A4. Note that astronaut A3 was not able to perform the head movements on FD2, 4, and 5 due to nausea and that his head movement protocol was restricted to three head movements instead of 10. MISC scores before centrifugation and before flight were 0 in all astronauts.

Whereas astronaut *A1* did not suffer from SAS during his flight, astronaut *A2* was seriously affected by the head movements early in flight. The actual number of performed head movements (maximal 10) was inversely related to the MISC score (Spearman rank correlation= –0.72, $p<.05$), but he was able to perform the protocol at FD6 without serious problems. Astronaut *A3* was requested to make only three head movements, and he started with low MISC scores right after launch. However, he was unable to do the experiment again that day due to severe nausea, which was also the case on FD2. He later reported that, from FD3 on, normal daily activities were not really disturbing, but passive 360º body turns that were part of another scientific experiment were very provocative. This suggested that this astronaut was susceptible to SAS, despite his relatively low MISC scores. During the other flight days (3, 6, 7) astronaut *A3* was able to perform the requested head movements without serious problems.

These latter two astronauts also experienced serious symptoms on the day of return (R+0). Astronaut *A4*, who rated his SAS-susceptibility based on his recollection, mentioned that he did not suffer from any symptoms during his spaceflight, except for one single episode of instantaneous vomiting, without preceeding symptoms of nausea. From these data is is concluded that astronauts *A1* and *A4* were considered unsusceptible to SAS, whereas astronauts *A2* and *A3* were considered susceptible.

Before addressing the data on SIC, it is noted that astronaut *A2* rated all head movements as equally provocative during flight, whereas astronaut *A3* showed minor differences between the effects of head movements. He rated yaw as least provocative, and roll as most provocative. Because this was also the order in which the head movements were performed by this astronaut, this could reflect an order-effect. To account for this, the order of the head movements was randomized in the following missions. Notably, right after landing both astronauts rated all head movements equally provocative.

The two astronauts who developed (mild) symptoms of SAS during space flight also developed symptoms of SIC after centrifugation (see Figure 2.3, left panel). However, after centrifugation the MISC scores remained relatively low: below MISC5, which was, on forehand, defined as the threshold for SIC susceptibility. This indicates that the effects of head movements were less after centrifugation than in space, especially for astronaut *A2*. Despite of this, Figure 2.3 clearly shows that the two astronauts who scored ‘positive’ on the MISC (i.e., the headmovements raised the average MISC score) after centrifugation, also scored positive in flight *and* post flight. Vice versa, the astronaut who scored ‘negative’ on the MISC (i.e., the average MISC score was not raised by the head movements) after centrifugation also scored negative in flight *and* after centrifugation. When the value *1* is assigned to a positive score and the value *0* to a negative score, the chance that this distribution (i.e., three times *1* or three times *0*) appears in three subjects is only 1/64, or p=0.01525. Thus, this distribution indicates a relationship between one’s susceptibility to these gravity transitions.

Next to the MISC scores, there were marked differences between the overall behaviour of the astronauts. The astronauts who were unaffected by centrifugation behaved normally within minutes and recovered very fast (Astronaut *A4* scored MISC 2 right after centrifugation but recovered quickly) Conversely, the affected astronauts reported motion illusions (floor moving, pushing the stairs down instead of themselves up) and visual illusions (oscillopsia) like 'the visual surround being attached to the head by rubber bands, lagging the head movement and resulting in an oscillating image'. These astronauts were also careful in their movements, preventing fast (head) movements and turns. In addition, pitch head movements were disturbing postural balance. These examples illustrate that centrifugation did affect their behaviour, despite the relatively low MISC scores. When this overall behaviour is also taken into account, astronauts *A1* and *A4* were considered unsusceptible to SIC, whereas astronauts *A2* and *A3* were considered susceptible. This is in accordance with their individual SAS susceptibility.

DISCUSSION

With the latter four astronauts added to the database, there are now 12 astronauts who participated in a sustained centrifuge run. The data of this second group of four are in accordance with the data of the first group of eight (Bles et al., 1997): the astronauts who did not experience SAS during their flight also did not suffer from SIC. Furthermore, although the MISC-scores remained below the preset threshold for SIC-susceptibility, the astronauts who scored positive on the MISC after centrifugation, also did so during, and after space flight. When the astronaut's general behaviour was incorporated in assessing SIC susceptibility as well, the astronauts who were rated SIC susceptible appeared to be the ones also susceptible to SAS. This thus unscores the correlation between SIC and SAS (see Table 2.2).

TABLE 2.2
Distribution of SIC and SAS-susceptibility in 12 astronauts

	SAS	non-SAS
SIC	5	0
non-SIC	0	7

However, it is clear that is is easier to conclude that someone is *not* susceptible to SIC (nor to SAS) than it is to decide the opposite. After centrifugation the MISC scores of two astronauts remained relatively low, which might suggest that centrifugation did not induce SIC. Nevertheless, these astronauts behaved quite different from the other two astronauts after centrifugation, indicating that they were by no means *un*affected by the centrifuge run. Here we touch upon a difficulty that is connected to this kind of research: if you ask an observer to rate an astronauts susceptibility, he will definitely rate these two astronauts as SIC-susceptible based on their overall behaviour: they move slowly and carefully, they make the head movements with much more precaution and they have more trouble with vertical movements (e.g., sitting or lying down). It is also important to note that the severity of the symptoms is directly related to the amount of movement. In other words: if you don't move, you don't get sick, even if you are susceptible. It is then the experimenter's job to provoke a similar amount of active behaviour in every astronaut, in order to make a fair comparison. Faster or more head movements would have raised the MISC scores, in line with astronaut reports. Thus, based on these considerations astronauts *A2* and *A3* were considered susceptible to SIC, which correlates with their susceptibility to SAS.

The astronauts' reports nicely illustrate the role of anticipation in developing SIC, which is in line with the 'subjective vertical mismatch theory' on motion sickness, presented in Chapter 1. During the debriefing the astronauts noted that the head movements they performed during the head movement protocol were not as disturbing as movements they made *in between* the tests. During the test they were prepared for the movements and they were aware of the fact that these movements could make them sick. In between the tests, they were more relaxed and did not concentrate on every movement they made. Illustrative is the observation that during lunch, one of the astronauts was called by someone standing behind him and he reflexively looked over his shoulder: this was pretty disturbing! Another astronaut remarked that he was able to control his nausea during the head movement protocol, because of anticipation. The head movements, however, decreased his 'nausea-margin': any other, unanticipated movement would have made him sick, he reported.

The fact that the symptoms of SIC that were evoked by the prescribed head movements were less after centrifugation than in space suggests that it may be not feasible to score SIC and SAS using the *exact* same protocol. The aforementioned examples illustrate that symptoms of SIC are most evident during a task where fast head and body movement are involved, without a strong anticipatory component. A head movement test where subjects are 'provoked' to make head movements in reaction to certain triggers (De Graaf & De Roo, 1993) is expected to decrease this anticipatory component. An adapted version of this latter test will be used in the experiment described in Chapter 4 to provoke symptoms of SIC.

To increase the reliability of the SIC and SAS-assessment it is recommended that head movement characteristics are registered, by means of accelerometers (as was also done by Oman et al., 1986) or by e.g., video-recording. This performance registration is also added in the experiment described in Chapter 4. Of course movement registration during daily activities (in space) or in between the tests (after centrifugation) would also improve the assessment. Alternatively, the MOP-questionnaire could be extended with more questions about experiences during daily activities.

Conclusion

The data showed that a more strenuous head movement protocol is required to elicit symptoms of SIC after centrifugation. Nevertheless, when also the astronauts' behaviour is included in the assessment of SIC and SAS susceptibility, the correlation between the two still holds. With these four astronauts, a positive correlation between SIC and SAS susceptibility has been established in 12 subjects now: five of them were susceptible to SIC and to SAS, whereas seven of them were not. This is comparable to the incidence of SIC as determined in all non-astronaut subjects who participated in any of the centrifuge studies performed so far: 31 out of 67 were considered susceptible to SIC (42%). More importantly, it is comparable to the incidence of SAS (Davis, 1988; Matsnev et al., 1983). Thus, this correlation is in line with the hypothesis that SIC and SAS share a similar underlying mechanism.