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FROM THE EDITORIAL BOARD

Dear readers,

The thirteenth edition is already the last edition of the academic year. This year flew by and as the fifth editorial board of RAMS, we can look back on an amazing year. With our five years, we are a relatively young organisation. An organisation that has been existing for a little longer is the Batavierenrace. This year, the 47th Batavierenrace will take place. At this event, over 8,500 students run a relay from Nijmegen to Enschede.

In teams, they run a total distance of 175 kilometres, divided over 25 stages. With all this effort and training in advance, there is no doubt that these students follow the advise of the current guidelines for physical exercise. By doing this, they lower their risk of developing chronic diseases such as diabetes, cardiovascular diseases and even reduce symptoms of depression. The effects of physical exercise are also further explained in one of the articles in this edition, so be sure to read all about this topic!

Besides the article about physical exercise, you can mainly find articles that are intertwined with the topic of this year's Summer School, which focuses on cardiology. Apart from cardiology, we also present articles concerning depression and of course, our *Zebras of Medicine* that focuses on a totally different subject, namely Ambras syndrome. Furthermore, you can read about the importance of innovation in healthcare and the difficulties of implementation.

By the release of this thirteenth edition, this also means that our *lustrum* year has come to an end and that this issue will be the last one of the 2018-2019 board and editorial board. From the bottom of our hearts, we would like to thank you as our readers, and all the people who have made this year for RAMS a great one. Hereby, we also want to wish the future board and editorial board good luck with their upcoming year.

On behalf of the Editorial Board,

Maaike Plug, Scientific Editor-in-Chief
Joyce Krekels, Editorial Editor-in-Chief

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A LITTLE EXERCISE A DAY KEEPS THE DOCTOR AWAY

Mylène Gorissen[1]

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Introduction

Insights

In 1994, a pioneering exercise epidemiologist named Jeremy Morris described physical activity as "the best buy in public health for the West" [1]. Nowadays, medical students are educated with the same knowledge from the first moment they enter university classrooms. Over the past years, the health benefits of physical activity have been proven to reduce the risk of many chronic diseases such as cardiovascular diseases, diabetes, cancer and dementia [2, 3]. In honour of the theme of the current edition of RAMS, this editorial article will focus on the mechanisms of exercise-induced beneficial effects on the heart.

Myocardial infarction and reperfusion injury

In the industrialised world, cardiovascular diseases such as coronary artery disease and myocardial infarction (MI) remain a major cause of death [4]. In 80% of the cases, MI is caused by an atherosclerotic-induced thrombus [5]. The occlusion of a coronary artery leads to oxygen deprivation and ischemia in peripheral cardiac tissue. The magnitude of cardiac injury depends on the location and time of occlusion [5]. The most important therapeutic goal is to restore blood flow to the ischemic region because the extent and reversibility of the tissue damage are directly related to the duration of the ischemia [6]. During reperfusion, however, there are a number of biochemical changes that eventually will result in cell death and necrosis of the myocardium, shown in figure 1 [6]. This process of pathology is called ischemia-reperfusion (IR) injury [4, 6]. It is well established that exercise training provides protection against this type of injury by reducing cardiovascular risk factors (e.g. high blood pressure, smoking and obesity), but most importantly it promotes cardioprotection through a direct effect on the myocardium cells (myocytes) [6].

IR-induced cardiac cell death

During ischemia, oxygen supply to the mitochondria (the key organelles for the viability of human cells) is interrupted [6]. To fulfill the myocardial energy demand, cellular adenosine triphosphate (ATP) is generated via glycolysis, which is accompanied by an increase in intracellular lactate levels [6]. To compensate for the low intracellular pH, caused by the acid lactate, water accumulates in the cell, causing cellular oedema [7]. A decrease in ATP levels inactivate cellular pumps, like Na^+/K^--ATPase and Na^+/Ca^{2+}-ATPase, which are important in homeostasis [6]. In a physiological situation, Na^+/K^+-ATPase removes sodium out of the myocyte, while potassium enters the cell to maintain the resting electric potential [6]. The Na^+/Ca^{2+}-ATPase is important for muscle contraction [6]. Inactivity of these pumps results in an overload of sodium and calcium, which prevents cell repolarisation and causes contractile dysfunction [4].

During reperfusion, the damage caused by ischemia is exacerbated by the release of reactive oxygen species (ROS; a byproduct of the metabolism of oxygen) in the mitochondria [8]. This causes damage to the mitochondria. When the ATP production in the mitochondria of the myocytes is not preserved (because of the aforementioned damage), this can have two consequences: 1) during reperfusion, the outer membrane of the cardiac myocyte becomes permeable, which results in apoptosis or 2) during both ischemia and reperfusion, pores in the outer membrane of the mitochondria can open followed by mitochondrial swelling, rupture and cell death, shown in figure 2 [4].

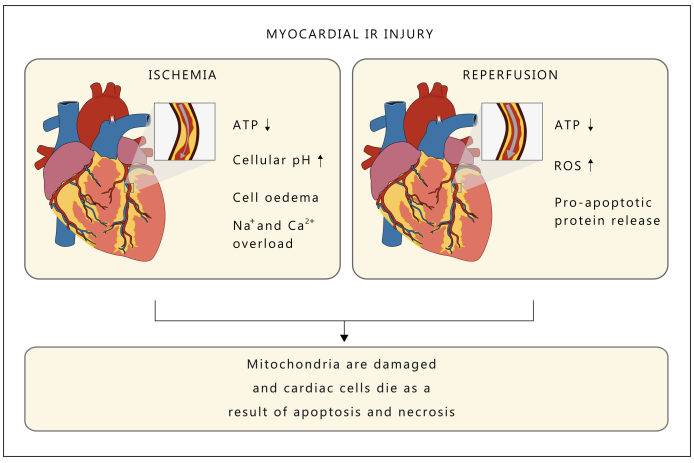

Figure 1: Mechanisms in myocardial ischemia-reperfusion (IR) injury.

Exercise and cardioprotection

Cardioprotection through exercise comprises of two phases, namely short-term and long-term cardioprotection [4]. The first phase starts 30 minutes after exercise and lasts until about three hours [4]. The mechanisms that cause this phase are not well known, but might have something to do with the activation of a specific enzyme in the cardiac myocytes called superoxide dismutase [4]. The second phase of cardioprotection is achieved within 24 hours after five consecutive days of training [9]. This effect persists for nine days [9]. Details about the dose-response impact of exercise will be discussed further on in this editorial.

Changes in coronary circulation

Exercise has the potential to increase coronary flow during reperfusion by structural changes, such as increased diameters of the arteries and arterioles [4]. However, a study performed by Bowles *et al.* on isolated perfused rat hearts showed that short-term exercise provides cardioprotection independent of improvements in coronary flow [10]. Furthermore, a previous review indicated that there is evidence that exercise directly modifies the cardiac myocyte without requiring a change in coronary circulation [4]. Cardiac myocytes isolated from the heart of exercise-trained animals are protected against IR injury [11]. These results suggest that intrinsic factors of cardioprotection may be more important that structural adaptations such as an increased vessel diameter.

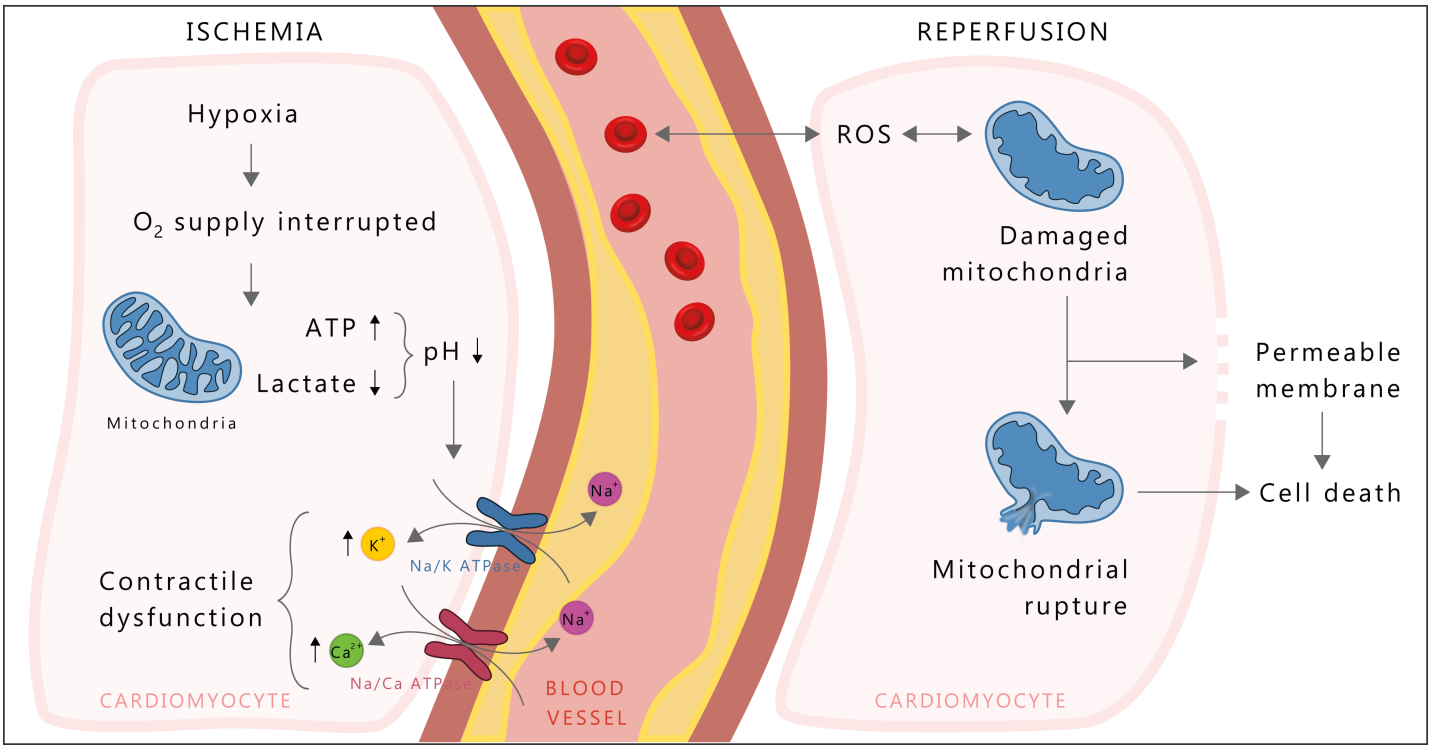

Figure 2: Cellular changes in the myocyte during ischemia and reperfusion.

Changes in mitochondria

There is emerging evidence indicating that exercise induces biochemical changes in mitochondria that are central to cardioprotection [4]. For example, exercise-trained isolated cardiac mitochondria in *in vivo* experiments by, amongst others, Kavazis *et al.* resist stimuli for apoptosis and damage induced by IR injury by not releasing pro-apoptotic proteins when exposed to ROS and/or calcium [4, 12]. Furthermore, research in mitochondrial protein expression suggested that endurance exercise leads to increased expression of beneficial antioxidant proteins and decreased expression of proteins with potentially damaging effects [4]. Taken together, exercise-induced changes in mitochondria could improve the capacity of ATP production during ischemia and may eliminate ROS during the reperfusion phase, leading to an attenuated IR induced damage [4].

Changes in the opioid system

In 1995, Howlett *et al.* discovered that morphine used to treat the pain associated with MI may also reduce the infarcted area and that the levels of beta-endorphins (an endogenous opioid agent) increase in patients with MI [5, 13]. It has been suggested that pharmacological blockade of the opioid receptors might reduce the infarcted area by 50% [13]. Stress conditions, like exercise, are known to increase the levels of opioid agents as well [6]. Immediately after a session of physical activity, the amount of opioid receptors in the heart transiently increases [14]. Although the relationship of opioids with exercise-induced cardioprotection is not studied very extensively, the acute benefits of exercise may be partially mediated by an opioid receptor-dependent mechanism [6].

How much exercise in clinical practice?

The Physical Activity Guidelines for Americans were updated in 2018, as well as the Dutch Guidelines for Exercise in 2017 [3, 15]. These guidelines indicate that adults should perform 150-300 minutes of moderate intensity or 75-150 minutes of high-intensity activity per week to gain most health benefits of an active lifestyle [3]. Most importantly, the greatest health benefits occur when changing from inactive behavior to a lifestyle with small amounts of physical activity [3]. For patients with cardiovascular disease, the American College of Cardiology and the American Heart Association guidelines from 2014 prescribe 30 to 60 minutes of moderate intensity physical exercise for five to seven days a week, apart from their daily lifestyle activities like gardening and household work [2]. The 2018 American guidelines also emphasise that the prior threshold of at least ten minutes of activity is outdated and that even brief amounts of exercise (such as climbing the stairs) are beneficial [3]. Patients thus need to know that they do not need large amounts of time to become healthier. Also, it is possible to perform all activities on one or two days per week because the health benefits from this exercise are similar to those achieved by activity on three or more days per week [16].

Conclusion

Cardiovascular diseases like myocardial ischemia are an important cause of mortality and morbidity in the Western world. One method of providing sustainable cardioprotection is exercise, but the exact underlying mechanisms responsible for this cardioprotection remain a topic of debate and research. Nevertheless, the most convincing evidence indicates that alternations in mitochondria are central in protecting the myocytes against damage from ischemia and reperfusion and that these effects might already occur during little exercise a day. It is important to take this into account, because little exercise is always better than no exercise at all.

Acknowledgements

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EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during your bachelor's!

We challenge you!

Question 1

During a period of abstention from food, fat storage is used. What are the resulting fatty acids mostly used for? For the production of ...

A. Alanine
B. ATP
C. Glucose

(Topic from Q3 MGZ Homeostasis, 2018)

Question 2

An electrocardiogram (ECG) is performed on a 56-year old man during a sport-medical examination. This shows a left bundle branch block. A left bundle branch block can be the result of coronary atherosclerosis. In a left bundle branch block, the ECG is characterised by ...

A. A QRS-width < 0.12 s. with a positive 'notched' QRS in lead V1
B. A QRS-width < 0.12 s. with a positive 'notched' QRS in lead V6
C. A QRS-width > 0.12 s. with a positive 'notched' QRS in lead V6
D. A QRS-width > 0.12 s. with a positive 'notched' QRS in lead V1

(Topic from Q7-Q11 KVS, 2018)

The answers to these questions can be found on page 14 in this journal.

MYTH OR SCIENCE?
POSITIVE PERSPECTIVES ON DEPRESSION

Lia Goltstein[1] and David Bandell[1]

[1] Master Student Medicine, Radboud university medical center, Nijmegen, the Netherlands.

Critical Appraisal

German philosopher Friedrich Nietzsche wrote the famous words: "What does not kill you makes you stronger" [1]. This quote is often used as an ironic expression nowadays, but it can also be used in a positive way; to express determination and optimism in the face of adversity. Some experts have used this expression to describe overcoming depression. Professor Jerome Wakefield from New York University is one of these experts. In his book *The loss of sadness: How Psychiatry transformed normal sorrow into depressive illness*, he states that if we embrace depression, by not just seeing it as a horrible disease, it can motivate us to change our lives for the better [2]. His opinion is often seen as controversial, and has even been described as offensive, as people who have suffered from this disease can tell you how frightening and disabling it can be. Others feel supported by his words, as it offers light at the end of the tunnel [3]. The question remains, is there truth to Wakefield's statement? Are there upsides to feeling down, either on short- or long-term.

Introduction

Everyone has experienced sadness. Most often this sadness is considered to be part of life. Some individuals, however, experience long periods of intense sadness, which is not in proportion to the cause. This pathological sadness is called a depressive symptom [4]. In combination with the other necessary criteria as defined by the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders), this is known as a depressive disorder, hereafter refered to as depression (see table 1) [6]. Depression is a relatively common disorder with a lifetime prevalence of 19%, making it one of the most prevalent diseases in the Netherlands [5]. The prevalence of depression is still increasing amongst all age groups. In children and adolescents, it has almost doubled in the past five years [7]. Half of the individuals who suffered from depression have one or multiple relapses, which increases the prevalence even more [4]. Additionally, depression is both a highly prevalent disorder and a disease with significant consequences. The World Health Organization (WHO) has ranked depression as the leading cause of disability worldwide in 2017, due to the considerable effects on well-being and daily functioning [8]. This means that the disability caused by this disorder is higher than those of cardiovascular disease or cancer, which are also on the top of the WHO disability list. Depression is also the most important risk factor for suicide and suicide attempts [9].

It is clear that depression forms an important problem in our society. Therefore, it is often considered to only have negative consequences for the patients suffering from it. However, there are experts who have a different opinion. These supporters do not only entail scientists, but also individuals who are suffering or have suffered from depression themselves [10]. In this article, we will try to explain parts of the complex aetiology of depression and outline theories and evidence on the benefits of depression to find out if there are upsides to feeling down [2, 11].

The depressed brain

In order to understand the possible benefits of depression, it is important to understand why and how we currently think depression occurs. Studies have shown that both family factors and environmental factors play an important role in the aetiology. The balance between the two is different for each person, but in most cases they are both disrupted [4]. Despite decades of research, the neural basis for depression is still not completely understood. This is mostly because of the complexities in examining the human brain and heterogeneity in the presentation of depression [4]. Many regions in the brain and of the hormonal system have been associated with this disease (figure 1) [12]. An example of a structure that is often linked to depression is the hypothalamus-pituitary-adrenal axis, which plays an important role in the stress response, and the regions that produce the monoamine neurotransmitters noradrenaline, dopamine and serotonin. Certain regions also seem to be more symptom-specific than disease specific. The prefrontal cortex is, for example, associated with anhedonia, which means that the person is no longer able to experience joy, while the locus coeruleus (which produces noradrenaline) is linked to attention and concentration deficiencies [4, 12]. Dr. Pandya, a well-established psychiatrist, mapped all regions that are currently linked to depression and concluded that this disorder seems to lie in many brain regions as well as nowhere in particular (figure 1)[12]. To improve the diagnosis and treatment of depression, a better understanding of the neuro- and pathophysiological basis of this debilitating disease is essential [11]. The fast-paced development of brain imaging studies, such as functional magnetic resonance imaging (fMRI), which measures brain activity by detecting changes in blood flow, will hopefully help achieve this in the future [12]. However, with so much yet unsolved about the pathophysiology of depression and with that many related regions, the question is raised if there are indeed some positive changes related to this disease.

Table 1: DSM-5 criteria for major depressive disorder [5].

DSM-5 criteria for major depressive disorder
At least five of the following symptoms that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
At least one of the symptoms is 1) depressed mood or 2) loss of interest or pleasure
Symptoms must be present almost every day for at least two weeks
Symptoms: 1. Depressed mood most of the day 2. Diminished interest or pleasure in all or most activities 3. Significant unintentional weight loss or gain 4. Insomnia or sleeping too much 5. Agitation or psychomotor retardation noticed by others 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive guilt 8. Diminished ability to think or concentrate, or indecisiveness 9. Recurrent thoughts of death
Diagnosis of recurrent major depressive disorder requires at least two months between two episodes in which criteria are not met

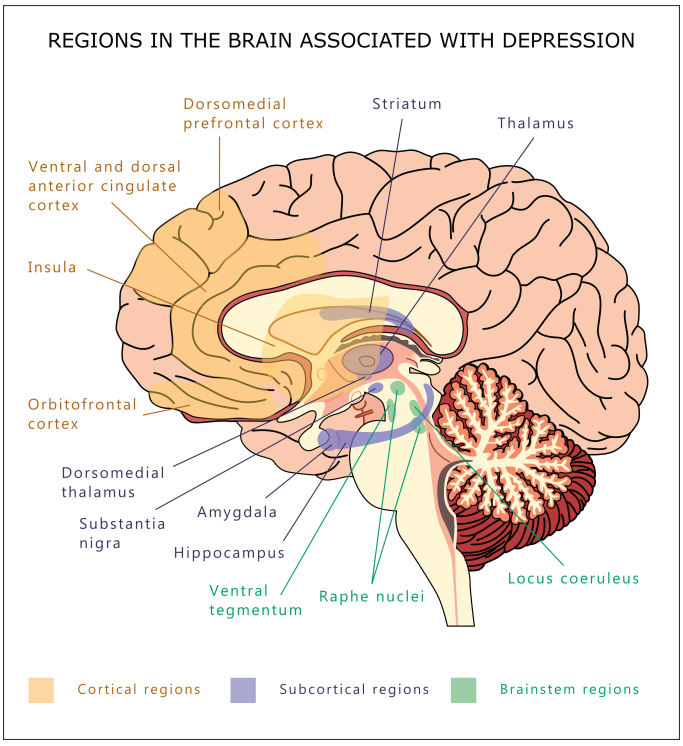

Figure 1: Regions in the brain associated with depression.
Various cordial, subcortical and brainstem regionen of the brain which are previously linked to depression.

Does depression actually exist?

Besides the physiological and molecular mechanisms underlying depression, which are not fully understood, the very existence of depression and where and when it starts is also debatable. Psychiatrist Neel Burton explains that the clinical diagnosis for depression is based on subjective measurements and not on a physical substrate or clinical tests. He, therefore, argues that proving its very existence is a difficult task as the diagnosis is based on a patient's symptoms [13]. The criteria for depression are made to fit to the experienced symptoms of patients and as symptoms would change over time, so would the diagnostic criteria. This will lead to always providing patients with a positive diagnosis and creating an endless cycle of disease [13]. Psychologists Jerome Wakefield and Allan Horwitz also believe that the ongoing rise in the prevalence of depression is at least partially caused by the unclear distinction between pathological sadness, known as depression, and just normal or physiological sadness. They do not question the seriousness of moderate and especially severe depression. However, Wakefield and Horwitz are not sure if the same goes for mild depression. They state that this subtype of depression cannot be unambiguously distinguished from normal sadness, which, as the name implies, is a part of life [2, 3]. Interestingly enough, some linguistic communities, like the Punjabi, an ethnic group associated with the Punjab region in South Asia, do not have a word or even a concept to talk or think about 'depression' [13].

The function of depression

Most hypotheses agree that depression likely evolved as an adaptation to help navigate adverse situations. This is one of the positives about depression and depressive symptoms, as explained by dr. Thomson [14]. He suggests that depression lets your body know that there is a big problem at hand. It hereby forces you to focus on that problem and solve it. Thomson explains: "In that regard, depression is similar to pain which signals your brain that some part of you needs help" [14, 15]. One of the ways that depression might increase your ability to solve problems is by causing an almost obsessive rumination toward particular problems in your life. This causes the mind to adapt itself to focus on a single or possibly a multitude of problems that need to be prioritised first before taking on new challenges. The analytical rumination hypothesis argues that the symptoms of depression, such as anhedonia, results in distraction-resistant and persistent cognitive analysis, which can help individuals resolve difficult challenges in their lives [14, 15]. These in-depth analyses lead to impairment and disengagement from everyday life and are, therefore, commonly considered maladaptive in our rushed society. Nevertheless, they might be quite functional if not taken too far. This point of view is supported by the evidence that indicates that a depressed mood is associated with improved accuracy on complex tasks, increased cognitive processing and enhanced detail-oriented judgement on tasks that require deliberate information processing [16]. Research indeed suggests that those with depression make more informed decisions [17]. This positive function of depression applies in particular to mild forms of the disorder. When the severity of depression increases and/or when someone has experienced multiple depressive episodes, the disease seems to become more autonomous [18].

The fundamental attribution error

People who are being or have been depressed will often tell you that they feel less judgemental about the actions of others. There is scientific evidence that supports this claim. Forgas, a social psychologist, has done multiple studies on the fundamental attribution error (FAE), which is a psychological concept that describes the tendency to judge other individuals that are in an unpleasant situation in a negative way and attribute their behaviour to internal qualities rather than being more understanding and empathetic of their hardships [19]. He performed various experiments to investigate the possible difference in FAE between people in a sad mood and people who felt happy [19]. In all experiments, happy people judged the actions of others more often on salient and readily available information about the actor. In contrast, people in a bad mood would most often become aware of external constraints and modify their first assumptions accordingly. From these experiments, the researchers concluded that a happy mood might increase the FAE, while a sad mood decreased it [19].

Decision-making and risk aversion

Depression is associated with behavioural avoidance. This avoidance is often seen as negative in potentially rewarding situations. It is also thought that depressed individuals respond more to punishment than reward in contrast to their non-depressed counterparts [17]. Depressed individuals are, therefore, more likely to avoid unfavourable risky behaviour and learn faster from trial and error than other individuals [17]. Psychologist Moria Smoski tested this theory by using the Iowa Gambling Test [17]. In this test, there are two card decks an individual can choose from each round. The first deck involves high rewards and similarly high penalties, with an unfavourable reward-to-punishment ratio. The second deck involves low rewards and low penalties, with a favourable reward-to-punishment ratio. In order to succeed the task, the participant should decide, through trial and error, to choose the second deck over the first. Depressive participants had more money in total at the end of the game, because they were initially less likely to choose the first desk. However, they did not seem to learn faster from previous mistakes [17]. It thus appears that depressed individuals are not necessarily faster learners than their non-depressed counterparts, but they do make safer and less impulsive choices. This quality has been important in human evolution, since we have always lived in groups. The group as a whole profits from the majority being cautious, rather than adventurous. Nowadays it is less evident whether being cautious is still an advantage [17].

Depression realism

One important advantage of feeling down is that it has been linked to a better perception of reality in a number of studies. When the average person is asked to judge him- or herself on numerous aspects of life, such as their intelligence or their parenting qualities, they score far above average. This contradiction in itself is proof that people overestimate themselves [20]. They also overestimate their children and their chance to win the lottery [20]. Depressive realism is the effect that those who feel down sometimes have a better perception of reality than others [20]. A better perception of reality can result in people with depressive symptoms making better and more rational decisions, whereas others might make mistakes due to their overestimation of either chances or facts.

Empathy in depression

It is thought that depression changes someone's empathy, but it is not exactly known in what way. Many people who have gone through depression believe that they became more empathetic afterwards. Marjorie Wallace, founder of SANE (a mental health charity) and depression expert through experience, is one of them [11]. It is hypothesised by Thoma *et al*. that depressed individuals could not detach the suffering of others from their own suffering and would, therefore, be less empathetic [21]. In this study of Thoma *et al*. it was concluded that depressed individuals indeed experienced more personal distress. However, they also found that their affective empathy was actually higher than those of controls, meaning that depressed individuals were more capable of recognising emotions of others [21]. A recent study by Tanako *et al*. that used fMRI, found a link between depression and individuals who tend to be more self-sacrificing and willing to promote equity [22].

Discussion

When looking at the positive aspects of depression we stumbled upon a variety of problems. Due to the social stigma on depression, and the controversial view upon the matter, little research has been done on the positive effects of this disorder. When one critically looks at the research that has been done on depression in general, positive and surprising results can often be found. This is, however, rarely reported or not mentioned in the discussion of the article, making it hard to draw conclusions. Moreover, the little research that has been done on this topic has proven itself to be difficult for various reasons. First of all, the diagnosis of depression is largely subjective, making it difficult to experiment on a distinct group of individuals with a depression and a distinct group of individuals without one. Secondly, a good distinction between the severities of depression is often not made. Individuals who suffer from mild depression and those who suffer from severe and crippling depression are often put in the same group. Both of these limitations most likely cause a diminishing in the positive effects of depressive symptoms. Furthermore, it is difficult to objectively measure psychological effects. Most often, researchers are dependent on self-report questionnaires and experiments that do not always correlate well with the real world. The objectivity of these methods are questionable and thus, so are the conclusions of these studies. The development of new medical imaging techniques, such as fMRI, could possibly help solve these hardships. However, since depression does not simply lie in one or a few particular regions in the brain, this is a difficult, if not impossible, task to resolve.

Conclusions

In this article, we have tried to shed a light on a few of the positive aspects of depression. Depression can cause individuals to be less judgemental of others, can lead to safer and less impulsive decisions, can make them more realistic about themselves and more empathetic towards others. These positive aspects are more often linked to mild depression and first episodes of the disorder, rather than severe and recurrent depression. Although the possible benefits of depression may seem small compared to the disadvantages of this disabling disorder, they do exist. However, we urge you to overthink whether or not we should also label depressive symptoms differently. In our hectic daily life, there is not always room for sadness. This emotion is and will always be part of our lives and if it were to be embraced by us, rather than pushed away, it could possibly help us move forward.

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ZEBRAS OF MEDICINE

HIRSUTISM VERSUS SYNDROME OF AMBRAS: A COMPACT COMPARISON

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Abstract

Review

Excessive hair growth has a broad variety in clinical presentations. Its evaluation is subject to personal, social and cultural perceptions. Hirsutism is a frequent form of excessive hair growth in females, with an incidence in 10 percent of the female population [1]. Hirsutism presents itself as limited patterns of excessive terminal hair growth on androgen-dependent areas of the body, such as the upper lip and chest. The syndrome of Ambras shows an extreme form of specific hair growth from birth and is not only present in women. Furthermore, the syndrome of Ambras can show werewolf-like dysmorphic facial features. Treatment of either of these conditions have only one overlapping mechanism, which is removal of excessive hair. This can be done by laser therapy, topical treatment or shaving. Due to the aetiology of hirsutism, some medication can be utilised to reduce the hair growth.

KEYWORDS: Hair growth, androgens, vellus hair, lanugo hair, werewolf syndrome

Introduction

Excessive hair growth has a broad variety in clinical presentation. Its evaluation is subject to personal, social and cultural perceptions. Unwanted hair growth can be a source of embarrassment with negative effects on the quality of life [1]. Hirsutism is a frequent form of excessive hair growth in females, with an incidence of ten percent of the female population [1]. The excessive pattern of hair growth is usually related to androgen-dependent (androgens are steroid hormones that maintain and regulates the development of male characteristics) areas of the body, such as the upper lip and lower abdomen [1]. Hair growth is considered excessive if an individual experiences the pattern of hair growth as 'abnormal' and is thus influenced by cultural and individual perspectives. Although hirsutism is bothersome, other conditions show a more extreme extent of abnormal hair growth. The syndrome of Ambras is an extremely rare condition that shows excessive hair growth from birth, alongside specific werewolf-like dysmorphic facial features [2]. In contrast to hirsutism, that presents itself only in women (mostly of reproductive age), the syndrome of Ambras is not subject to a specific gender or age and has only been described in the literature in ten cases until now [2, 3]. This review sets out to compare hirsutism with the syndrome of Ambras in terms of clinical presentation, diagnosis and treatment.

Clinical presentation

Hirsutism is a condition that mostly appear in women in their reproductive age [1]. It is defined as excessive female terminal hair growth on androgen-dependent areas of the body (figure 1). These areas include the face, chest, upper-lip and thighs [1]. In contrast, the syndrome of Ambras is present from birth and is a condition where the whole body is covered with fine, long vellus hair (figure 1) except for places where hair usually does not grow, such as the palms and soles [2]. Werewolf syndrome is a synonym for the syndrome of Ambras and has arisen due to the werewolf-like features that come with this disorder, such as a broad triangular face with a round nasal top and long spinal hair growth [4]. Furthermore, dental abnormalities are seen in the first and second teeth [4]. The hair growth increases in density and distribution as patients grow older and the hair can get several centimetres long if not shaved [3, 5].

Diagnosis

There are three aetiologies that give rise to hirsutism and are divided in hyperandrogenic, non-hyperandrogenic and idiopathic origins [1]. Hyperandrogenic and non-hyperandrogenic origins mean that it originates from a disturbed androgen balance or not. Androgens are steroids that are involved in the regulation of male characteristics, such hair growth [1]. A well-known androgen is testosterone, a steroid that exhibits functions such as development of muscle strength and male specific hair growth [1]. Hyperandrogenic and non-hyperandrogenic origins have a known aetiology, whereas idiopathic means that the exact cause of the disease remains unknown [1]. Hyperandrogenic origins can be subdivided in polycystic ovary syndrome, androgen-secreting tumours and non-classic adrenal hyperplasia [1]. Medication or Cushing's syndrome can give rise to non-hyperandrogenic hirsutism. Examples of medication that can cause hirsutism include performance-enhancing anabolic steroids, such as danazol and the anti-hypertensive drug minoxidil [1]. Idiopathic hirsutism might be hereditary [1]. The syndrome of Ambras, however, does not originate from any of the pre-mentioned aetiologies, but is caused due to genetic mutations.

Hirsutism can be diagnosed using female history (e.g. onset of hirsutism, symptoms of virilisation, menstrual history, family history and drug history), physical examination (e.g. Ferriman-Gallwey-score, signs of hyperandrogenism, signs of virilisation, signs of Cushing's syndrome and thyroid examination) [1]. The Ferriman-Gallwey-score is the preferred method to evaluate the severity of hirsutism and is based on a four-scaled evaluation of hair growth on nine different body areas (e.g. upper lip, chest and lower abdomen) [1]. Laboratory examinations might be used to determine the origin of hirsutism and is based on concentrations such as total testosterone, sex hormone binding globulin and thyroid stimulating hormone, alongside six other not mentioned tests [1].

Due to the extremely rare frequency of the syndrome of Ambras, no specific diagnostic tools are developed. However, genetic analysis has revealed pericentric- and paracentric inversions or an insertion in chromosome 8 in 80% of the cases [2]. As the patient ages, the fine light coloured primary hair (lanugo hair) that is usually only seen in embryonic development, differentiates to secondary hair (vellus hair) [1]. In a number of body regions, vellus hair further differentiates to fine terminal hair [4]. However, lanugo, vellus and fine terminal hair cannot be distinguished without the

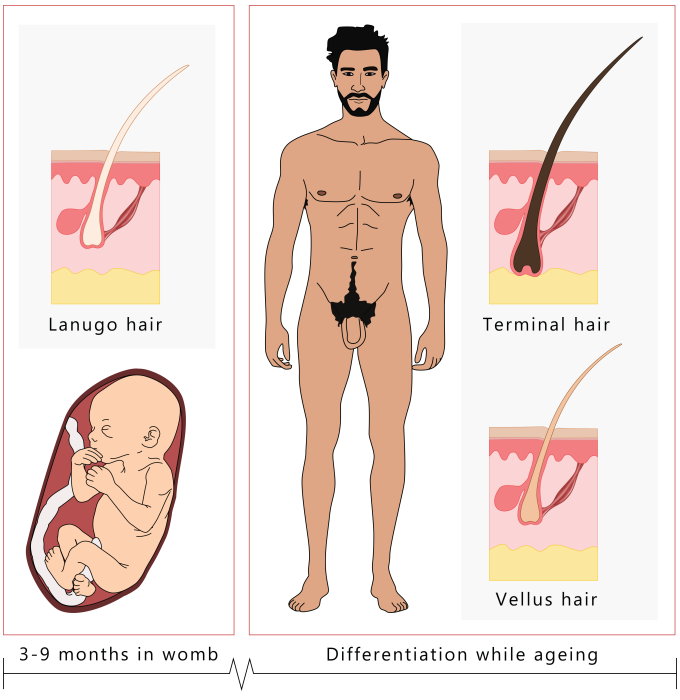

Figure 1: Hair differentiation while ageing.
The unborn develops very thin, often light pigmented hair (lanugo) in the womb. This hair is the first type of hair a person develops, and is therefore called primary hair. Lanugo hair is often shed in the womb or just after being born. The lanugo hair differentiates to vellus hair (secondary hair). In some parts of the body, vellus hair differentiates to terminal hair later in life. Terminal hair is often thicker, and is frequently pigmented. Hirsutism shows a hair growth pattern as seen in males, the typical areas where male hair grows are often androgen dependent. A disturbance in the hair growth cycle in the Ambras syndrome makes vellus hair to remain in the growth phase. This results in vellus hair that can reach considerable length.

use of a microscope [4]. What differentiates the syndrome of Ambras from hirsutism and healthy persons in terms of hair growth, is the characteristic disturbance of hair growth cycles. In healthy persons, hair grows in cycles that consist of a growth (anagen) phase and a resting (telogen) phase [2]. Hair of patients with the syndrome of Ambras remain in the anagen phase [2]. The hair that have differentiated to secondary hair also remain in anagen phase, which results to excessive growth of fine, sometimes pigmented hair, that can reach considerable length if not shaven [4]. Aside from extensive genetic analysis such as DNA-sequencing to find mutations, the syndrome of Ambras is diagnosed using its characteristic clinical presentation, mainly on the growth of consistently growing hair (anagen phase) which remain on the body (either vellus- or terminal hair) [4].

Treatment

The treatments of hirsutism and the syndrome of Ambras overlap. However, due to the underlying aetiology of hirsutism, this condition has several more treatment options. Treatment of hirsutism can be divided into two subgroups, namely medical therapy and physical hair removal [1]. Medical therapy might consist of topical therapy (e.g. eflornithine), contraceptives or anti-androgens (e.g. spironolactone) [1]. Topical therapy, such as eflornithine, is applied locally to the affected skin region and results in slower hair growth and utilises ornithine decarboxylase inhibition in the hair follicle [1]. Ornithine decarboxylase plays a crucial role in hair follicle development and hair growth [1]. Contraceptives reduce the free testosterone levels to slow down hair growth [1]. Furthermore, anti-androgens prevent the activity of androgens at their specific target site, but drug-specific side effects should be monitored [1]. In case of spironolactone, electrolyte imbalance must be checked on a regular interval (every three months), since it can cause diuretic-related side effects [1]. Contraceptives and anti-androgens can be used simultaneously and can have synergistic effects [1].
In contrast to hirsutism, the syndrome of Ambras is not androgen-based [4]. Therefore, only physical hair removal and eflornithine cream are current treatment options [2]. There are several ways to remove excessive hair, such as shaving, bleaching, and chemical depilation [1]. However, each of the available methods has a downside to be considered, especially in children due to their more vulnerable skin [5]. For example, repeated chemical depilatories can lead to skin irritation and might eventually cause contact dermatitis [5]. Waxing is an effective, but painful, treatment option. However, removal of fine vellus hair can result in the transformation to terminal hair, which subsequently leads to the impression of increased hairiness [5]. In the past few years, 5-α-reductase inhibitors are more frequently used off-label for the treatment of hirsutism. However, this is only partially effective in best case, and is negatively advised as off-label prescription [6]. One final discussed therapy is the consideration of laser therapy. This therapy risks scarring after destruction of the deeper parts of the skin, but also other adverse events have been noted such as pigmentary changes [5, 7]. Especially for children, repeated shaving remains the best treatment option, to reduce the risk of permanent damage [5].

Although excessive hair growth does not increase mortality or morbidity, lack of psychosocial acceptance can have an immense impact on individuals [1, 5]. For the syndrome of Ambras, excessive hair removal might be crucial to prevent social isolation [5].

Conclusion

The diagnosis of Ambras syndrome is mainly clinical, whereas hirsutism utilises several measurement tools to evaluate the clinical symptoms [1, 2]. The Ambras syndrome is characterised by excessive hair growth from birth, a familial inheritance pattern and facial dysmorphism, whereas hirsutism has an onset in a later phase in life, has several aetiologies and is only present in women [2]. Treatment of hirsutism and the Ambras syndrome focuses mainly on hair removal, although hirsutism is less limited in treatment options due to the difference in aetiology that gives rise to the condition. Ambras syndrome is limited to therapies that remove hair, such as chemical hair removal, shaving and laser therapy. Hirsutism can optionally be treated with oral medication such as anti-androgens and contraceptives.

Acknowledgements

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CARDIAC ARREST MANAGEMENT REVIVED: AN INVASIVE PRE-HOSPITAL EXTENSION OF CPR

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Perspectives

It is probably among the most frightening sights to witness: somebody suddenly drops to the ground in agony and remains unresponsive. Annually, 6,200 people in the Netherlands are resuscitated with an acute cardiac arrest outside of the hospital, illustrating the magnitude of this problem [1]. Acute cardiac arrest predominantly occurs in men aged between 65 to 68 years [1]. In a best-case scenario, there are plenty of bystanders who are able to start resuscitation, an automatic external defibrillator (AED) is connected and the cardiac rhythm is shockable [1]. Efforts in the Netherlands expand to police and firemen serving as first responders and a call for trained civilians using a text message, resulting in relatively high survival rates [1]. Similarly, on international level attempts are made to improve survival. Lamhaut *et al*. recently took arrest management to the next level in Paris [2]. Additionally to standard resuscitation protocol, they used a device to temporarily support heart and lung function, in an out-of-hospital cardiac arrest setting [2].

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major cause of death in developed countries and affects approximately 360,000 people each year in the United States (US) alone [3]. OHCA is defined as an abrupt dysfunction of the cardiovascular system outside of the hospital caused by e.g. ventricular fibrillation, asystole or sustained ventricular tachycardia [3-4]. This, in turn, may be the result of a coronary syndrome. As a result of this dysfunction, vital organs do not receive sufficient blood supply [4]. The organs in the body cannot handle this insufficient organ perfusion for longer periods of time. Therefore, taking action aimed to quickly restore the circulation is essential in OHCA. Otherwise, the patient's death is inevitable. The current protocol for treating OHCA patients is to perform cardiopulmonary resuscitation (CPR) at the place of occurrence. Around the globe, CPR is widely accepted as the gold standard in regaining circulation in these patients. The current Dutch guideline, composed by the Dutch Resuscitation Council, defines the protocol for CPR as follows: when a person is found lying unresponsive and breathless, emergency services are called and resuscitation is started [5]. A cycle of thirty chest compressions and two artificial ventilations is repeated until there is a reason to stop the CPR [5]. The compressions should have a depth of around 5 to 6 cm and must be executed at a rate of 100 to 120 compressions per minute [5]. The time between the last and first compression (during artificial ventilation) should be as short as possible, with a maximum of ten seconds [5]. The impact of the chest compressions has been studied extensively, but there is less evidence regarding the additional value of the artificial ventilation [6]. Reasons to stop the CPR are return of spontaneous circulation (ROSC), the arrival of emergency medical services (EMS), exhaustion of the first-aid helper making it impossible to continue CPR or when a Do-Not-Resuscitate declaration is found [7]. The additional use of an AED has significantly increased the survival after CPR, although survival is still minimal [5]. Among people with a non-traumatic cardiac arrest treated by EMS, survival was 9.5% in 2010 in the US [8]. In 2018, this number increased to 10.8% [9]. In the Netherlands, survival in OHCA patients is reported notably higher, being 22.8% in 2016 [1].

Still, this shows the remaining potential to improve the survival of patients with OHCA. One upcoming intervention is the pre-hospital use of artificial oxygenation and perfusion support. In this article, we will first describe the technique in a hospital setting, then its novel use in a mobile outreach unit and finally evaluate the feasibility.

Artificial cardiopulmonary life support

As mentioned before, time is everything in case of an OHCA. If spontaneous circulation is restored on the scene, survival rates range between 20 to 50% [10]. This can be achieved by effective bystander CPR and the use of an AED. In case ROSC is not achieved, advanced life support (ALS; a professional extension of CPR) will be initiated by EMS, and continued in the hospital. Despite these efforts, cardiac arrest may persist which is commonly referred to as refractory OHCA if circulation is not restored within ten to thirty minutes [11]. In this dire event, ALS will often be ceased as patients seem to have practically no chance of survival with acceptable clinical outcome [11]. However, techniques have been developed to mechanically maintain an effective circulation until spontaneous circulation is restored.

Extracorporeal (i.e. outside of the body) membrane oxygenation (ECMO) is a cardiopulmonary life support method [12]. A pump drains blood from the vascular system, which is oxygenated outside the body, and then reinfused. ECMO has many clinical indications in which the cardiac or pulmonary system fails. It is mostly used in neonatal and pediatric care but can be deployed for resuscitation purposes (ECPR) [12]. According to the clinical situation, different techniques can be used to support the patient. If only respiratory support is needed, ECMO is connected to two veins and will form a circuit in series with the heart [12]. In case of ECPR, the ECMO will have to support the circulation as well. It will receive oxygen deprived blood from the femoral vein and reinfuses oxygenated blood in the contralateral femoral artery, bypassing the heart and lungs [2, 12, 13]. The femoral vessels are preferred because of their readily accessible location (as shown in figure 1) [12]. While supported by ECMO, patients may receive necessary treatment such as heart catheterisation, a coronary bypass or thrombolysis [11]. After successful therapy, patients can be gradually weaned (i.e. detached) from ECMO after a median duration of two days, which can range between one to five days [13]. Ortega-Deballon *et al.* recently reported the overall survival rate of ECPR in OHCA in a systematic review of international literature. The overall survival rate of ECPR was twenty-two percent of which approximately sixty percent with good neurological recovery, opposed to two percent to elevent percent survival with standard care [11]. ECPR seems a feasible in-hospital strategy in patients who would otherwise have almost no chance of survival. Still, randomised controlled trials are currently performed to confirm these results and further clarify patient selection

Pre-hospital ECMO

Positive outcomes of ECPR seem to be more pronounced if there is a short delay in its initiation [2, 14]. Accordingly, the pre-hospital use of ECMO was proposed to further reduce delay [15]. In 2013, Lamhaut *et al.* published a pilot study showing the feasibility and safety of a pre-hospital ECPR protocol, after which they completed a large observational study in Paris until 2015 [2, 15]. During this period, a pre-hospital ECPR team was dispatched in a mobile intensive care unit if an OHCA patient met inclusion criteria (signs of life and electric heart activity amongst others) and if transportation time to the hospital was estimated to be more than ten to twenty minutes [2]. Patients with lower estimated transportation time and a cardiac arrest during transportation were allocated to in the in-hospital group. An emergency physician or intensivist coordinated the team, further consisting of a nurse anaesthetist and a paramedic. Mechanical CPR was continued until the ECMO was connected [2]. Their efforts shortened the duration in which the patients were in a state of low blood flow (i.e bystander -and mechanical CPR), and lowered the time to ROSC significantly [2]. After optimising their protocol, survival was 38% in a select group of pre-hospital ECPR patients, suggesting good potential for its implementation [2]. However, with propensity score matching (a statistical method to filter out other factors that could have explained the results i.e. reducing confounding) pre-hospital ECPR was not significantly different from in-hospital ECPR [2].

Future Perspectives

There are limitations to the aforementioned studies examining the use of the pre-hospital ECPR. The reduction in low-flow duration was not accompanied by increased survival in the pre-hospital group [2]. This is in conflict with the inverse relationship between survival and low-flow duration described by Chen *et al.* [14]. Lamhaut *et al.* suggests this lack of difference could be due to selection bias towards in-hospital ECPR in their study. Some patients with in-hospital ECPR were excluded after losing their inclusion criteria by losing signs of life or electric heart activity during transportation [2]. Accordingly, less severe arrhythmias seemed to remain included in the in-hospital group, possibly leading to similar survival rates of the pre-hospital group.

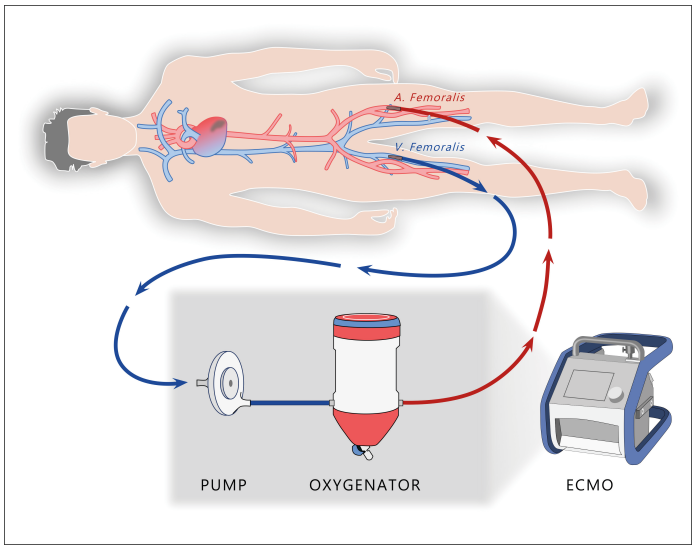

Figure 1: Schematic overview of extracorporeal membrane oxygenation (ECMO)

Oxygen deprived blood is taken from the femoral vein (blue arrow) and is driven through the pump. Next, it is oxygenated inside the device, and subsequently reinfused in the contralateral femoral artery (red arrow) [12]. Hereby, the ECMO bypasses the heart and lungs and supports both hemodynamics and oxygenation.

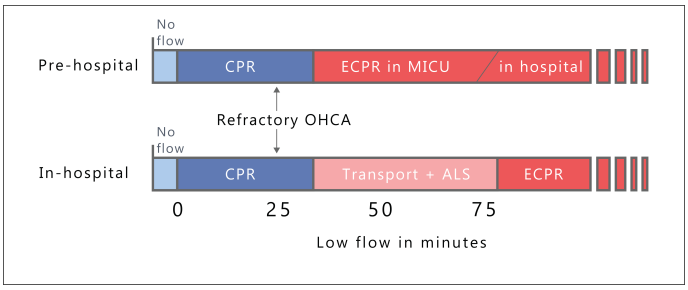

Figure 2: Comparison of the management strategy of low flow for out-of-hospital cardiac arrest (OHCA) between pre-hospital and in-hospital extracorporeal cardiopulmonary resuscitation (EPCR).

In pre-hospital ECPR, patients are connected to ECPR in the mobile intensive care unit (MICU), whereas patients undergo advanced life support (ALS) during transport in the in-hospital ECPR.

Furthermore, the pre-hospital ECMO has only been tested and used in Paris, so it remains to be seen whether it will function in other places as well. In the US for example, the termination of resuscitation (TOR) is in use. TOR states that after at least four two-minute intervals of CPR resuscitation attempts should be terminated if: 1) arrest was not witnessed by EMS, 2) there is no shockable rhythm and 3) no ROSC [16]. The existence of this rule hinders the implementation of pre-hospital ECPR because pre-hospital ECPR is often started without the presence of ROSC and TOR allows transportation only when ROSC is present.

In the Netherlands, little experience with in-hospital ECPR is present, as only a few hospitals have got an ECPR team (including Rotterdam, Nijmegen, The Hague and Leiden). Of these centres, only two are so-called 'centres of excellence' awarded by the Extracorporeal Life Support Organisation (ELSO) [17]. These centres are recognised by the ELSO as centres which have been present for a few years and treated at least five patients a year during at least five years [18]. The other centres do not fulfill these criteria and are thus not experienced enough. Due to this lack of experience, the implementation of pre-hospital ECPR might be a challenge. Generally, the Netherlands is less crowded than Paris, so transportation to a hospital takes less time. According to the Dutch Heart Association this takes approximately eight minutes [1]. As low-flow duration remains fairly short this way, pre-hospital ECPR might not be of additional benefit in the Netherlands. Importantly, costs related to the logistics to be able to perform ECPR, in-hospital and pre-hospital, will be extensive. As survival in the Netherlands is relatively high, limited improvements to survival can be expected. Therefore, the costs might outweigh the benefits of the pre-hospital ECPR. At this moment, a randomised comparative study by Lamhaut *et al.* is running in France. This study aims to answer whether pre-hospital ECPR is more favourable than in-hospital ECPR [19]. Until now, no randomised study has been performed into this topic.

Conclusion

The ultimate goal is to improve survival in patients with refractory OHCA, which requires new techniques and strategies. At this point, survival is low, with only 22.8% in the Netherlands and 10.8% in the US. In Paris, pre-hospital ECPR is used as a novel treatment for refractory OHCA. The effectiveness of this technique is poorly studied, but recent literature hints towards the potential of this strategy to improve survival by significantly reducing the low-flow duration. However, limitations are evident in these studies, so more research is necessary to further determine the feasibility and therapeutic efficacy of this treatment. The first steps are made as, at the moment, a study in Paris investigates whether pre-hospital ECPR is worthwhile or not.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
B. ATP

The breakdown of one mol of C16 fatty acids (palmitate) leads to a gross total yield of 108 mol of ATP. Via oxidation of acetyl-CoA by the citric acid cycle, 80 mol of ATP is synthesised, while 28 mol of ATP is released with the conversion of NADH and FADH2 due to β-oxidation. When it is taken into account that two high-energy phosphates are necessary for the initial activation step, the net gain per mol of palmitate is 106 mol ATP (3233 kJ), which represents 33% of the free energy of combustion of palmitic acid.

For further reading:
Botham, K.M., *et al*. *Oxidation of Fatty Acids: Ketogenesis*. in Harper's Illustrated Biochemistry, Vol. 31e. (McGraw-Hill Education, New York, NY, 2018)

During the exam, 60% of the participants answered this question correctly.

Answer question 2:
C. A QRS-width > 0.12 s. with a positive 'notched' QRS in lead V6

In a left bundle branch block, the left ventricle activation is delayed. This causes the ventricles to contract slower, which results in a positive notched V6. In a left bundle branch block, a deep S wave in lead V1 and a tall late R wave in leads I and V6 can be seen on the ECG. The left bundle branch is also responsible for the initial ventricular activation, which leads also to abnormal Q waves when there is a left bundle branch block.

For further reading:
Bunce, N.H. and Ray, R. *Cardiovascular Disease* - Heart Block in Kumar and Clark's Clinical Medicine, Vol. 9e (Elsevier Ltd, the Netherlands, 2017)

During the exam, 46% of the participants answered this question correctly.

The exam questions can be found back on page 6 in this journal.

Assembly of the clinical issues (KVS) exam

The KVS exam is assembled by the KVS-committee, where many medical specialties are represented. This committee gathers once every two weeks, and during these meetings, new questions (provided by all module coordinators) are evaluated in their appropriateness for the exam. After the exam is made by students, this committee looks extensively to the exam analysis and comments of the students. From this evaluation, it is decided what happens with these questions. Recently, the committee decided that a reaction to the student's commentary will be made available to read for all students. The final grading is then determined based on the Cohen-Schotanus formula, after which the final grades will be checked again and made public within 15 working days after the exam date.

HEALTHCARE DELIVERY INNOVATION AND ITS TROUBLING IMPLEMENTATION

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Abstract

Review

Innovation is an important part of healthcare as it is always changing, which asks for new technologies and new ways to approach the delivery of healthcare. The implementation of innovation into the field of healthcare delivery seems rather difficult for a number of reasons. The most important of these include hindering regulation, passive patients and lack of leadership. In New Zealand, the Health Practitioners Competence Assurance Act (HPCA Act) shows that regulation does not have to be a barrier to innovation. It regulates the safety of the public by ensuring the competence of practitioners via regulations but also leaves room for practitioners to make their own choices and participate in innovation. Since the book *Open Innovation*, this concept is emerging in the field of innovation. This comprises the idea that for successful innovation one should not only rely on internal knowledge but also look beyond the walls of their company. Healthcare could exploit this idea to its advantage, although the rigid structure of healthcare and the inability to make use of patient knowledge seem to be barriers to this type of innovation. The Indiana University Center for Healthcare Innovation and Implementation Science (IU-CHIIS) gives us an example that innovation is possible in the delivery of healthcare. This centre builds an agile and adaptable learning system with which they achieved a lot in the first year of their existence. It remains to be seen what the effects will be on the long term. In conclusion, others need to learn from the IU-CHIIS to develop an adaptable open system in which innovation and regulation can go hand in hand.

Introduction

Innovation is an important aspect of healthcare and it has been throughout the history of medicine and healthcare. New ideas were essential for the development of the first national health insurance system in 1883 in Germany and for all that followed [1]. The life expectancy of people in the Netherlands went from 71.5 years in 1950 to 81.7 years in 2017 [2, 3]. This increase is mainly due to the improved healthcare system in the Netherlands, which in turn is predominantly caused by many innovations during those years. Some innovations led to major breakthroughs in healthcare such as the discovery of antibiotics by Alexander Fleming in 1928 [4]. To this date, innovations still make a difference in healthcare and remain of vital importance to keep improving healthcare. For example, many researchers are working on a possible cure for cancer, a disease with high mortality worldwide. However, innovation is not always easy to implement. Implementing innovation in the field of healthcare delivery (meaning the way healthcare is provided to the patient), for example, appears to be challenging. In this article, we will review current literature on innovation management to identify which factors influence innovation and further elaborate on the difficulties concerning implementing these innovations in the field of healthcare delivery. Lastly, open innovation is discussed and an example of successful innovation implementation is given.

What is innovation?

The definition of innovation is "the development and the successful implementation of new, improved products, services or production and delivery processes" [5-7]. The process of innovation consists of three basic steps that need to be taken : 1) Idea generation, 2) successful development of that idea into an useable concept and 3) successful application of that concept [7]. To successfully accomplish these three steps a few criteria need to be met. An important condition is a climate suitable for innovation; all people in the organisation need to be willing to be innovative [5]. This does not mean that everyone has to be creative, but it requires the ability to let go of conventional practices and ideas. In his article, Cumming *et al.* mentions a few parameters that have to do with the development process [7]. He differentiates into three contributing factors: signal, controls and noise; and two outputs: response and error state [7]. Signal comprises the initial idea for the innovation, the needs of the consumer and the correspondence with the corporate strategy [7]. The controls are the resources that can help to turn the idea into an innovation, such as the correct knowledge, equipment, people and a well-managed plan [7]. Noises are the factors that can disturb the process [7]. These include internal noises, like pressure for success and concerns for the costs and external noises, like changes in the market, financial situation and wishes of the consumer [7]. The outcome of the process can either be the response (a successful application of the idea) or the error state (an unwanted product or a faulty product) [7].

Resistance to change

In his article, Gorman *et al.* showed that healthcare systems are resistant to changes on the macro level (the core operating model) [8]. Despite the drastic change in disease burden, the hospital-based and doctor-led model has not really changed all that much over the last 150 years [8]. According to the article by Gorman, this is due to eight core barriers, which are shortly addressed in table 1 [8]. Wass *et al.* state that regulation seems to hinder innovation [9]. For example, lack of access to patient data is a barrier to innovation in health information services [10].

In the last decade, there have been many changes in the regulation of healthcare, due to the public asking for better regulation [11]. Most governments around the world have acknowledged this [11]. However, seeing barrier five described by Gorman, raises the question whether good regulation and significant innovation team up [8]. As described by Coates, the experience with the Health Practitioners Competence Assurance Act (HPCA Act) in New Zealand shows that they do quite well [11]. The purpose of the HPCA Act is to protect the health of patients by offering mechanisms to ensure the competence of health practitioners during their career [12]. This act obliges practitioners to have a minimum level of competence and to keep up to date with the newest developments in their field [13]. When they do not, regulators can confiscate the ability of them to practise [11].

The HPCA Act seems to have the appropriate balance between regulation and innovation [11]. On the one hand, there is a distinct standard of competence the practitioners have to live up to, ensuring good regulation of the quality of healthcare [11]. On the other hand, the regulators are given enough flexibility with respect to "how they structure the professions they regulate and what they require practitioners to do", leaving enough room for innovation in the healthcare delivery [11].

Table 1: Core barriers for the resistance of healthcare to changes on the macro level.

Core Barriers for Resistance of Healthcare to Changes on the Macro Level			
Models of healthcare are currently centred around the provider and the **consumers are too passive**. Innovation happens only when healthcare becomes 'patient-owned'. That is, patients need to be involved in the process of innovating healthcare delivery. 1	**Insufficient intelligence** in the health system: a lack of required intelligence can make the development of innovations unsuccessful and inefficient. 3	**Regulation leads to restriction**: The regulation of healthcare can be a barrier to innovation. 5	**Territorial behaviour** by potentially disrupted groups and professions: their behaviour is often overstated by the business models and funding schemes, which leads to a negative contribution to innovation. 7
Lack of leadership among clinicians: leadership training does not have a sufficient aim, worsening the training in the process. 2	**Restrictive business models and funding**: the systems of funding and salaries are not always constructed to support innovation, leading to inhibition of innovation and a possible loss of productivity. 4	**Litigation can be a threat to innovation** and can lead to uptake of provider-protective healthcare with low utility. 6	**Flawed health systems**: ministries and departments of health are frequently role conflicted and tactically weak. The ministry is usually not a purchaser, leading to a lack in the stimulation of innovation. 8

However, the Act is not perfect in the sense that it does not explicitly encourages regulators to innovatively change healthcare delivery. For example, if the regulators are encouraged to address health workforce issues, a greater extent of innovation could be achieved [11]. Furthermore, a recent study by Bismarck *et al*. suggests that data, which guides the regulation of practitioners, could be used more often and in a better way [14]. This data could be of vital importance to innovation in the delivery of healthcare.

Open innovation

With the population aging and the ever-growing burden of chronic diseases, healthcare cannot rely on internal knowledge (from within the organisation) only [9]. It must incorporate external knowledge (from outside the organisation) next to internal knowledge to keep their innovation at a steady level [9]. This asks for the so-called 'open innovation' defined by Wass *et al*. as innovation in which an organisation looks beyond the traditional boundaries of their organisation in their innovation process [9].

Since the book *Open innovation* by Chesbrough, the field of open innovation has received enormous amounts of interest [10]. Studies in the context of healthcare are nevertheless lacking, as only 18 articles were published in the period between 2003 and 2014 [9]. Although there is a lack of studies, some things can be carefully concluded. In the first place, open innovation shows some constraining factors in healthcare. The organisation in healthcare is difficult because there are a lot of local variations in the practices in healthcare. In most cases, healthcare also lacks the structure to use the knowledge of the patient and user to improve innovation [9]. In their paper, Dias and Escoval show that hospitals with the classical hierarchical structure have three times less chance of the development of an innovation than hospitals with a dynamic structure [15].

On the other hand, open innovation appears to have some positive outcomes according to Wass *et al*. [9]. This manner of innovation appears to shift the patient from passive to active actor, thus solving the first barrier defined in table 1. Furthermore, it leads to collaboration between several actors [9]. As an example, according to the study by Dias and Escoval mentioned above, hospitals use universities, subcontracted organisations, and healthcare users as external collaborators [15]. Finally, Davey *et al*. display that open innovation can have a positive effect on access to the market [16]. It provides medical innovators with the possibility of the multi-perspective ideas of scientists, engineers, clinicians, and patients [16]. As a result, innovations are more evidence focused and reach the market faster [16].

The Indiana University Center for Healthcare Innovation and Implementation Science (IU-CHIIS)

IU-CHIIS is an example of an organisation that succeeds in improving healthcare delivery by implementing innovations. Launched in September 2013, this organisation aims to offer education and engagement services to aid healthcare delivery systems in meeting the threefold aim proposed by the Institute of Medicine in the United States (US): better care with improved outcomes, at lower costs and with enhanced clinical experiences for patients [17, 18].

They achieved a lot in their first year. They successfully scaled up a dementia and depression care model for older adults from 200 to 2,000 patients, enlarged the Accountable Care Unit from four to fourteen units [19]. The latter led to a 58% reduction in length of stay in the hospital, a 35% reduction in readmissions and a 50% reduction in mortality rate [19]. Furthermore, they created the first program in the US, in which a certificate in innovation and implementation science can be received [19]. This Graduate Certificate Program in Health Innovation & Implementation Science is focused on delivering professionals the skill sets required to become leaders of change in the healthcare system [20]. Lastly, they got funding from National Institutes of Health to investigate the pros

of dementia screening, develop a patient-reported symptom monitor, evaluate side effects of medication and conduct a delirium evaluation in the senior emergency department [19].

This teaches us about the necessity of an agile and adaptable learning system stretching beyond the hospital system [19]. As the paragraph about open innovation suggests, it is crucial for this system to look beyond the traditional boundaries rather than relying on internal knowledge alone. Six components are of vital importance for this to work: effective sensors of the environment; rapid bidirectional information transportation; knowledge storage; critical decision making utilising advanced analytics; efficient, lean and safe execution and last but not least reliable data monitoring [19]. Given the presence of these components, this agile and adaptable learning system can be very effective [19].

From the IU-CHIIS, three sources of variation in the delivery of healthcare emerged: 1) the process of complex decision making, influenced by clinical knowledge and expertise and the implementation of evidence-based practices, 2) the production line, influenced by tools such as quality and process improvement and 3) the complex response of the patient, influenced by personalised medicine, pharmacogenomics and socioeconomic position [19].

Conclusion

In conclusion, there are various reasons as to why implementing innovations in healthcare delivery is proven to be so difficult. The main reason as to why this is the case is the resistance of healthcare to changes on the macro-scale. This is due to various factors including bad innovation models, lack of leadership and passiveness of the patient. The case of open innovation elaborates on these problems, highlighting the local variations in healthcare making innovation challenging. However, it also has some positive effects, such as more active patients, better collaboration and access to more markets. Furthermore, the IU-CHIIS shows that it is possible to create an agile, adaptable learning system in healthcare in which innovation can lead to better healthcare delivery. Then again, this project has just started and the long term results are not really clear, but it seems very promising. In the future, above-mentioned resistances need to be overcome and other projects need to learn from the IU-CHIIS to stimulate innovation to improve the quality of healthcare by enhancing the efficiency and cost-effectiveness of healthcare delivery.

The strategy of the Radboud university medical center is to be personalised and innovative by trying to use innovation in diagnostics, treatment and prevention of diseases. The mission of the Radboud university medical center, which is 'to have a significant impact on healthcare' is a mission that closely resembles the mission of RAMS by wanting to have an impact on the medical scientific formation of (bio) medical students and impact healthcare.

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CEREBRAL PROTECTION STRATEGIES IN AORTIC ARCH SURGERY

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Abstract

Review

Surgery of the aortic arch requires circulatory arrest. During this period, the brain is prone to ischemic and irreversible damage. To protect the brain for longer and more extensive surgery, different cerebral protection strategies have been developed and studied. However, optimal cerebral protection during aortic arch surgery remains technically challenging. Nowadays, three strategies are particularly used for cerebral protection. These three strategies include: deep hypothermic circulatory arrest, retrograde cerebral perfusion and selective antegrade cerebral perfusion. Hypothermic circulatory arrest is essential to operating on the aortic arch. This technique can be adjuncted with either retrograde or selective antegrade cerebral perfusion for longer and more complex surgeries. The mentioned techniques provide cerebral perfusion while the systemic circulation is arrested. Added neuroprotective effects of retrograde cerebral perfusion remain elusive. Selective antegrade cerebral perfusion seems to be a more physiological strategy with better clinical results. In this article, these three most common cerebral protection strategies and their relative advantages and disadvantages are described.

KEYWORDS: Hypothermic circulatory arrest, retrograde cerebral perfusion, selective antegrade cerebral perfusion

> *There is no disease more conducive to clinical humility than aneurysms of the aorta.*
>
> *– Sir William Osler, 1961*

Introduction

An aneurysm, from the Greek word: *ανεύρυσμα*, meaning dilation or to dilate, is an outward bulging of a blood vessel, caused by a localised weak spot of the vessel wall. This might be the result of an acquired disease (e.g. atherosclerosis) or a hereditary condition such as Marfan syndrome. Due to a local increase in blood pressure and a weakened area of the vessel wall, the aneurysm can increase in size and eventually rupture, potentially leading to significant bleeding and subsequent death [1]. Although aneurysms can occur in every blood vessel, they are most often found within the arteries supplying the brain (circle of Willis) and the aorta. Aneurysms of the aorta can be subdivided into thoracic aortic aneurysms (TAA) and abdominal aortic aneurysms (AAA). Figure 1A shows a normal thoracic aorta and figure 1B illustrates a TAA. Small to medium sized TAAs are conservatively treated but are closely monitored for further expansion. Bigger (end diastolic diameter more than 5.5 cm) or symptomatic TAAs require surgical or endovascular treatment [2]. Surgical treatment of ascending and/or arch TAAs is usually performed through open chest surgery (median sternotomy) where the diseased (dilated) part of the aorta is removed and replaced with a synthetic tube graft (figure 1C)[3]. When the disease affects the descending thoracic aorta, a thoracotomy approach is most commonly used where the aneurysm is repaired in the same manner. Surgery of the aortic arch presents a unique risk given the mandatory period of cerebral ischemia, requiring adequate cerebral protection. The brachiocephalic arch vessels must be disconnected to repair these types of aneurysms, thus interrupting the cerebral blood flow. Up to this point, three main cerebral protection strategies have been used in patients undergoing this type of extensive aortic arch surgery. These three strategies include: deep hypothermic circulatory arrest (DHCA), retrograde cerebral perfusion (RCP) and uni- or bi-lateral antegrade cerebral perfusion (ACP). This article aims to provide an overview of the mentioned strategies, discussing their history, clinical technique and relative advantages and disadvantages.

Deep hypothermia with circulatory arrest

The use of deep hypothermia with circulatory arrest (DHCA) was first described in the 1960s and used for the repair of aortic arch arteriovenous fistulas [4]. Griepp and Stinson (1975) reported the first 'actual' case series using DHCA as a cerebral protection technique to repair aortic arch aneurysms. They operated on four patients replacing variable portions of their thoracic aorta with a prosthetic tube graft [5]. Hypothermic circulatory arrest, which was introduced more than 30 years ago, still serves as the basis for surgeries on the aortic arch. This protection technique works by cooling the patient down to dramatically decrease their cerebral metabolism. Studies on canine brains have been done to illustrate the physiologic effects of DHCA [6]. Although the brain takes up only two percent of the human body weight, it uses twenty percent of the total body oxygen consumption and receives fifteen to twenty percent of the circulating blood volume [7]. This is because the brain uses oxygen and glucose at a much higher rate than other organs. Neurons use excessive amounts of adenosine triphosphate (ATP) as their main energy source. This ATP is produced by oxygen-dependent glucose metabolism. Unlike liver cells or muscle cells, the brain cannot store the produced glucose as glycogen. Thus, when the brain does not receive enough glucose or oxygen, neuronal function immediately becomes impaired. The brain does however, have a compensation mechanism by making small changes in the cerebral blood flow, called 'autoregulation' [8]. This homeostatic mechanism is a negative feedback loop that works by vasodilation or vasoconstriction of the small cerebral arterioles to change the total cerebrovascular resistance [9].

To understand by which mechanisms hypothermia protects the brain one must understand two important pathways of ischemic neural injury:

1. When the brain does not receive adequate amounts of oxygen, ATP will be synthesised using anaerobic glycolysis. Anaerobic glycolysis does not produce enough ATP to maintain normal neuronal function [10]. At the same time, anaerobic glycolysis produces lactic acid, lowering the intracellular pH. The combination of energy depletion and accumulation of any produced waste products within the brain will quickly lead to cell damage and necrosis [11].
2. Calcium ions (Ca^{2+}) play a big part in neuronal cell damage. N-methyl-D-aspartate (NMDA) channels get activated by hypoxia through the

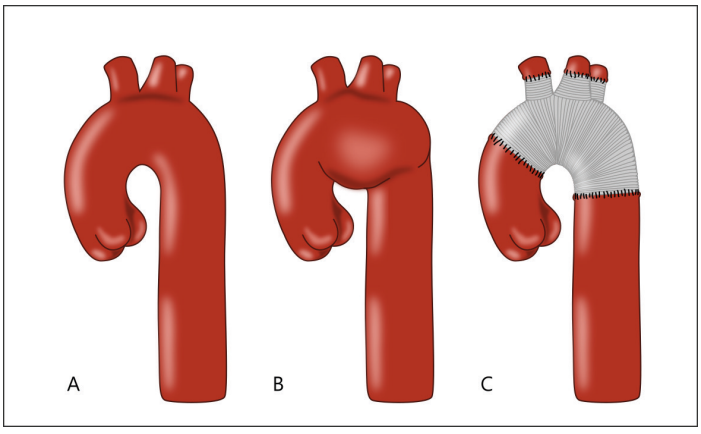

Figure 1: A. *Normal aorta* ***B.*** *Aneurysm of the aortic arch* ***C.*** *Repaired aortic arch.*

release of excitatory neurotransmitters, like glutamate. Activation of the NMDA receptors results in the opening of ion-channels, by which calcium ions can easily enter the cells and accumulate. Imbalance in calcium ions eventually leads to the activation of intracellular proteases and mitochondrial dysfunction resulting in neuronal cell death [11].

Deep hypothermia inhibits both pathways by significantly slowing down the cerebral metabolic rate for glucose and oxygen [10]. Cerebral metabolism slows down by five to seven percent for every single degree Celsius drop in body temperature. At a core temperature of 18 degrees Celsius the metabolic rate of the human body is only 12 to 25% of that at normal temperature, dramatically decreasing the oxygen demand of neurons [12]. Hypothermia also reduces the release of excitatory neurotransmitters resulting in far less NMDA receptors being activated, significantly reducing the amounts of intracellular calcium [11].

Clinical technique

Patients who are to undergo aortic arch surgery with DHCA are placed on cardiopulmonary bypass (CPB) first. The CPB machine completely replaces the function of the heart and lungs allowing surgeons to operate on an empty and arrested heart. To initiate CPB and prepare patients for DHCA, a two-stage cannula is placed in the right atrial appendage for venous return. The ascending aorta is then directly cannulated for arterial perfusion. If this is not possible, femoral artery cannulation is chosen - unless the patient has severe atherosclerotic disease of the descending aorta and/or iliac arteries. In case of severe atherosclerotic disease, right axillary artery cannulation is used. Retrograde flow towards the brain could dislodge debris in the aorta, potentially leading to embolisation in the brain. Figure 2A illustrates the femoral artery cannulation strategy. As soon as the patient is cannulated, CPB is initiated and cooling is started. Cooling is achieved by pumping cold water through a heater-cooler unit located in the CPB oxygenator. Temperature monitoring of the brain is critical during this phase. Most commonly used sites include esophageal, rectal, bladder, nasopharyngeal, tympanum, pulmonary arterial and skin temperature. Most reliable sites seem to be nasopharyngeal, bladder and tympanum [13]. Patients are cooled until establishment of electrocerebral silence, this usually (60% of the cases) occurs at a core temperature of 18 degrees Celsius or after a cooling period of 30 minutes [14]. All patients will reach complete EEG (electroencephalogram) silence at a nasopharyngeal temperature below 12.5 degrees Celsius or after a cooling period of 50 minutes or longer [15]. A two to three degrees Celsius gradient is maintained between the arterial inflow temperature and the venous return temperature to ensure even cooling. As the temperature of blood decreases, Boyles law states that the solubility of gases in blood increases. Arterial blood gas measurements show reduced PaO_2, $PaCO_2$ and an alkalosis when patients are cooled down, requiring the need for accurate pH management. Two strategies: alpha-stat and pH-stat are most commonly used [16]. For pH-stat acid base management, the patient's pH is kept constant and is temperature corrected. In alpha-stat acid-base management, the ionisation state of the amino acid histidine is maintained – this strategy does not correct for any changes in temperature [17]. After sufficient cooling the circulation is arrested, and the aortic arch is repaired [18]. When CPB is resumed after the period of deep hypothermic circulatory arrest, rewarming commences [19]. Rewarming has to happen slow and careful. The perfusion needs to be kept at a gradient of not more than ten degrees Celsius above the measured core temperature to avoid a mismatch between the total body oxygen demand and oxygen delivery [20].

Safety and limitations

Safe duration of DHCA was considered to be 35 to 40 minutes at a core temperature of 20 degrees Celsius [21]. These insights have changed and currently there is no agreement on the safe duration of DHCA. Several studies have shown durations as short as 20 to 25 minutes to be associated with poor neurologic outcomes after surgery [22, 23]. Other authors have reported aortic arch interventions can be safely performed at DHCA times of up to 50 minutes [24]. Complications of DHCA include: cerebral damage (stroke or transient neurologic deficits), post-ischemic hypothermia, impaired autoregulatory mechanisms and blood-brain barrier damage [25]. To increase the duration of the circulatory arrest for more complex aortic repairs and less neurological complications, antegrade selective or retrograde cerebral perfusion have been introduced as additions to DHCA. In this way, the brain is not only protected, but also perfused during surgery.

Retrograde cerebral perfusion

Retrograde cerebral perfusion (RCP) provides retrograde perfusion of the brain using the venous circulation. This protection strategy provides some sort of metabolic support during circulatory arrest and prolongs the safe limits of DHCA. In addition, RCP has the potential added benefit of back-flushing air emboli and debris from the cerebral circulation. These effects are based on the premise that the cerebral venous vasculature is completely free of valves. However, a cadaver study done by de Brux *et al.* has shown valves to be present within the internal jugular veins [26]. RCP was first routinely used by Ueda *et al.* in thoracic aortic surgery to lengthen the safe operating time [27].

Clinical technique

CPB is achieved by cannulating the femoral artery, axillary artery or direct cannulation of the aneurysm. Bi-caval cannulation (both the superior and inferior vena cava are cannulated) is used to allow retrograde flow, while maintaining venous drainage from the inferior vena cava. Figure

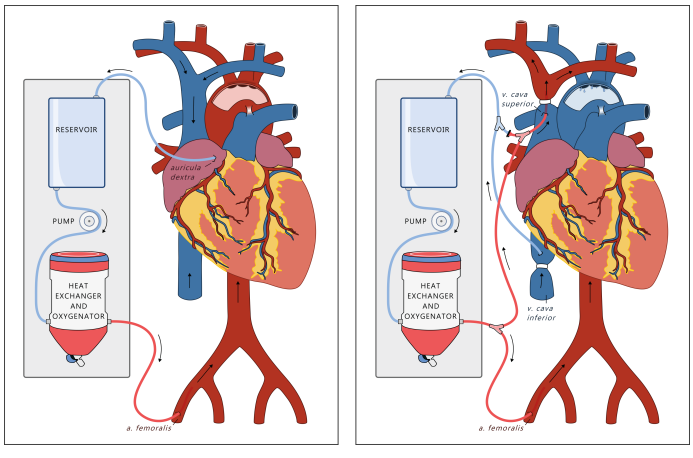

Figure 2: A. *Cannulation for deep hypothermia* ***B.*** *Retrogade cerebral perfusion*

2B illustrates this cannulation strategy. After initiating CPB, cooling of the patient is started. The circulation is arrested after EEG silence is achieved. Nasopharyngeal and rectal temperatures are constantly monitored, pH is controlled using pH-stat or alpha-stat for optimal acid-base management and proper heparinisation is monitored with activated clotting times (ACT). Myocardial protection is achieved in the standard fashion using antegrade and/or retrograde cold diluted blood with added hyperkalemic cardioplegic solution. The bypass circuit allowing RCP includes several Y-connectors: one connected to the cannula in the superior vena cava, splitting the arterial and venous tubes, and one placed in the arterial line (figure 2B). Once the circulation is arrested, arterial blood is routed only through the cannula in the superior vena cava. Flow is adjusted to maintain a proximal venous pressure of around 20 to 25 mmHg, providing a flow rate ranging from 150 to 500 ml/min. Back bleeding from the brachiocephalic vessels confirms retrograde flow, when this obstructs the surgeons vision, RCP flow is briefly reduced. After completing the aortic arch repair, CPB is restarted, RCP is discontinued and rewarming of the patient is started [28].

Safety and limitations

The hypothetical neuroprotective mechanisms of RCP where promising, however, several clinical and laboratory studies have shown that these mechanisms remain controversial. Aforementioned, de Brux *et al.* have shown valves to be present within the internal jugular veins, requiring higher perfusion pressures (up to 40 mmHg) [26]. High perfusion pressures could lead to cerebral edoema, especially when RCP is continued for longer periods of time [29]. The effectiveness in brain preservation of RCP is mainly attributed to the continued cerebral cooling via the venoarterial and venovenous collateral circulations [30]. The technique or mechanism of cerebral protection using RCP remains elusive, requiring the need for an alternative technique [31].

Selective antegrade cerebral perfusion

The most routinely used cerebral protection technique today, was first used in 1957 by DeBakey *et al.* for the resection of an aneurysm of the aortic arch [32]. The patient survived but results of the technique in the following years were very disappointing. ACP was completely abandoned after Griepp *et al.* showed that aortic arch repair is safely possible with DHCA alone [5]. Over time when expertise in aortic surgery increased it became apparent that adjunctive cerebral protection techniques might offer more complete and complex aortic repairs along with better neurological outcomes. Since the effects of RCP remained controversial, selective antegrade perfusion revived.

Clinical technique

The technique of selective antegrade cerebral perfusion (ASCP) is very appealing because it is more comparable with a physiologic flow than the 'no flow' DHCA or the retrograde approaches. The technique is still used as an addition to DHCA, as described before. However, different cooling temperatures are used [33]. There are different cannulation strategies to perform ASCP. The two most commonly used strategies include either direct bi-lateral cannulation of the brachiocephalic vessels using balloon tipped catheters or uni-lateral cannulation of the axillary artery with the use of a side graft sewn to the artery in an end-to-side fashion to allow perfusion of the artery in both directions. A two-stage cannula is placed in the right atrial appendage for venous drainage. Systemic cooling is, as stated before, variable and depends on the anticipated time of the circulatory arrest period. For separate cannulation of the brachiocephalic vessels (figure 3A), the arteries have to be divided and cannulated prior to circulatory arrest [34]. Balloon tipped catheters with individual pressure-monitoring lines need to be used to avoid cerebral hypertension. Optimal protection is achieved by direct perfusion of all three brachiocephalic vessels, not just the innominate artery and left common carotid artery [35]. When cannulating

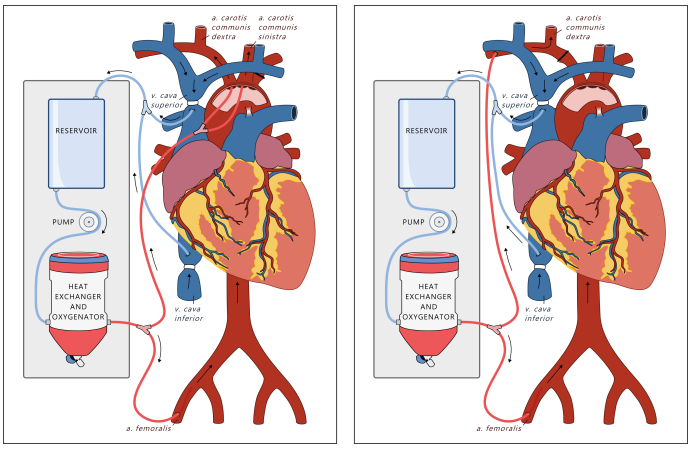

Figure 3: A. *Bi-lateral selective antegrade cerebral perfusion* ***B.*** *Antegrade cerebral perfusion, axillary cannulation*

the axillary artery (figure 3B) - prior to circulatory arrest - the innominate artery is clamped off proximally, selective cerebral perfusion is started and adjusted to maintain a flow rate of 10 ml/kg/min [36].

Safety and limitations

Results using the different cannulation strategies with selective antegrade cerebral perfusion (ASCP) are varied. Dossche *et al.* found hospital mortality to be affected significantly by the choice of cannulation technique used for ASCP. As of today, it remains unclear whether ASCP should be delivered using an uni-laterally or bi-laterally approach. Uni-lateral perfusion using a cannula in the innominate artery resulted in higher mortality rates compared to bi-lateral perfusion [37]. Kazui *et al.* operated on 220 patients using bi-lateral cannulation in the innominate and left common carotid arteries. The left subclavian artery was clamped during ASCP. They found an overall in-hospital mortality of 12.7% and an overall neurologic dysfunction rate of 9.3%, ASCP time did not seem to significantly influence on mortality and neurological outcome [38]. Tanaka *et al.* performed a laboratory study to address important perfusion details such as the optimum perfusion flow rates, pressure and perfusate temperature [39]. From these results, the technique of selective antegrade cerebral perfusion seems to be an extremely useful adjunct to DHCA alone.

Conclusion

Cerebral protection remains a technically challenging asset of aortic arch surgery. Over the years different techniques have been developed and studied to ensure adequate brain protection. Hypothermic circulatory arrest alone is an utmost essential and can be adjuncted with retrograde cerebral perfusion or antegrade cerebral perfusion. The neuroprotective effects of retrograde cerebral perfusion remain elusive. The combination of hypothermic circulatory arrest combined with either uni-lateral or bi-lateral selective antegrade cerebral perfusion is currently considered the optimal protection strategy for aortic arch surgery [40].

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RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Nena Rokx[1]

Summary

With over 3,000 publications per year, scientific research is a cornerstone of the Radboud university medical center [1]. In this section, recent high-impact papers with an impact factor higher than five – published by researchers from the Radboudumc – will be discussed.

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Metallic implants to synthesise antibacterial drugs

To support or replace diseased tissues, in for example trauma surgery, dental, orthodontic and cardiovascular care, metallic biomaterials are very effective. However, bacterial contamination of the surfaces is a major problem and prophylactic treatment with system antibiotics is common. This preventive treatment does not always have the desired effect and can even be harmful. Therefore, it would be useful to develop methodologies for the localised delivery of antibacterial agents to metallic biomaterials. Marja ter Meer, a PhD candidate at the Department of Radiology and Nuclear Medicine of the Radboudumc, made the serendipitous observation that a grooved alloy wire converted fluorogenic substrates into their fluorescent products [2]. After further research, she discovered that frequently used metallic biomaterials also have the enzymatic ability to degrade glycosidic linkages. This study was published in Chemical Communications (impact factor of six). Based on the results of this study, metallic biomaterials would be able to converse a prodrug, containing a sugar group, into active antibacterial agents by degrading glycosidic linkages. This approach is called enzyme-prodrug therapy. Metallic biomaterials themselves do not have enzymatic activity. However, a version with very small grooves in the metal has high enzymatic activity. In these grooves, iron was deposited, which is found responsible for efficient drug conversion through an unknown mechanism. Unfortunately, metallic biomaterials of pure iron are not stable enough and, therefore, an iron coating would be used. This iron coating was shown to be able to effectively convert a prodrug into antibiotics against many types of bacteria. In this way, less systemic antibiotics can be used, which reduces harm for the rest of the body. In the future, this technique may possibly also be implicated for anti-infection, prohealing, anti-cancer and anti-inflammation purposes [2].

Aggregated N=1 trials in rare diseases

About eight percent of the population suffers from a rare disease during their lifetime. However, for rare diseases, it is often impossible to conduct a Randomised Controlled Trial (RCT), which is seen as the gold standard for drug efficacy, due to the small numbers of patients and substantial heterogeneity. This makes it difficult to draw a reliable conclusion about the efficacy and safety of a potential treatment in a rare disease. Bas Stunnenberg from the department of Neurology and Gert Jan van der Wilt from the department of Health Evidence, both at the Radboudumc, investigated whether an aggregated N-of-1 trial design produces efficacy results consistent with those from a RCT [3]. They investigated this for the efficacy of mexiletine (a sodium channel blocker) in 27 patients with the rare chronic disease nondystrophic myotonia, which is caused by mutations in the skeletal muscle channels. Because of these mutations, there is a delayed relaxation of the muscle after voluntary contraction, so-called myotiona, which results in muscle stiffness. The primary outcome measure was the mean daily self-reported stiffness severity score. In an N=1 trial, an individual patient is treated with mexiletine and with a placebo for specific periods until the efficacy in the patient becomes clear. However, credible methods to combine different N=1 trials, to provide information about the overall effect of the drug on the disease, were unavailable. In this study, they found a way to combine the results of the multiple N=1 trials using a Bayesian hierarchical model. In this model, the results from each patient were aggregated into a sample mean and variance. Thereafter, patients' mean effect sizes were modeled with between-patient variance. Using this method, this study found similar results as an international multicenter crossover RCT from 2012; a reduction in mean daily-reported muscle stiffness. These findings support the efficacy of mexiletine in nondystrophic myotonia patients and the potential of N=1 trials for assessing drug efficacy in chronic rare diseases. Moreover, fewer patients are needed compared to RCTs and aggregated N=1 trials can predict the likelihood of the candidate drug having a clinically meaningful effect on individual patients. This study was published in the Journal of the American Medical Association (impact factor of 48) [3].

Little sharing of brain defects in patients with schizophrenia and bipolar disorder

Psychiatry is now the last area of medicine in which diseases are diagnosed solely on the basis of symptoms. An example of a psychiatric disorder is schizophrenia: diagnosed based on the presence of psychoses and specific behavioural symptoms. However, patients with schizophrenia have an extremely variable representation of their symptoms. To better understand the biology behind schizophrenia and bipolar disorder, Thomas Wolfers from the department of Human Genetics and the Donders Centre for Cognitive Neuroimaging at the Radboudumc investigated how much the brains of individual patients differ from the average patient with the diagnosis of schizophrenia or bipolar disorder [4]. The study performed a cross-sectional design using magnetic resonance imaging data from patients with schizophrenia, bipolar disorder and healthy control individuals. To quantify the brain structural heterogeneity, regional brain alterations at the level of individual participants were mapped in reference to normative brain ageing across the adult lifespan. The results of this study were published in the Journal of the American Medical Association Psychiatry (impact factor of 17). On average, patients with schizophrenia had significantly reduced grey matter in frontal regions, cerebellum and temporal cortex and patients with bipolar disorder primarily had deviations in cerebellar regions. However, only in a few regions, an overlap of more than two percent among patients was observed. These findings suggest that there is no average patient in schizophrenia and bipolar disorders and that it is not possible to stratify schizophrenia and bipolar disorder into biologically more homogeneous subtypes. Therefore, the use of brain imaging techniques to diagnose schizophrenia and bipolar disorders is not possible. This study also supports the notion that mental disorders are complex, with little sharing of causal brain structural defects [4].

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RAMS

A Word from the Board of RAMS

Dear reader,

I want to thank you all for reading this edition. This is already the thirteenth and also the last edition of this academic year.
In numerous cultures, the number 13 is associated with bad luck. Triskaidekaphobia is the fear of the number 13. In psychiatry, it is only referred to as a phobia when the social life of a person is severely disrupted.

A quote from the well-known baseball player Matt Kemp goes: "When you think positive, good things happen". Because we have a negative association with the number 13, we tend to link bad things that happen to us to this number. However, if you remain positive, your fear of unpleasant events will be less prominent.

As long as you remain positive, even the number 13 will be a blessing. I can confirm that with this magnificent edition, in which various themes have been reviewed. Did you enjoy reading this and do you want to see more of RAMS? Is surgery and research something you are interested in? If so, do not hesitate and sign up for the upcoming symposium which will be organised in co-operation with VCMS.

On behalf of the board of RAMS,

Rahima Lakanwal
Treasurer of RAMS 2018-2019

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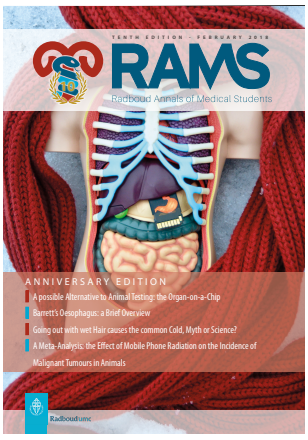

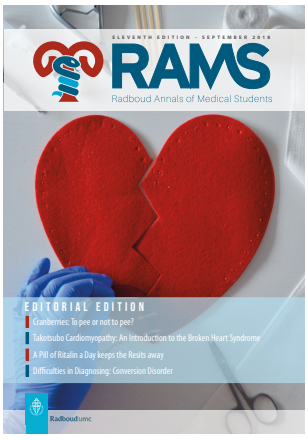

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