Diploma Thesis

Cardiac Surgery with Cardiopulmonary Bypass in Patients with Autoimmunological Disease

Incidence and specifics regarding the therapy

submitted by

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Graz, 29.08.2025 Katharina Mayer m.p.

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Zusammenfassung

Hintergrund: Menschen mit Autoimmunerkrankungen (AID) machen nur einen kleinen Teil der Patientinnen und Patienten aus, die sich einer kardiopulmonalen Bypass-Operation unterziehen. Autoimmunerkrankungen sind in der Gesamtbevölkerung auf dem Vormarsch und variieren in ihrer Schwere und Symptomatik. Die diagnostischen und therapeutischen Möglichkeiten für diese Patientengruppe werden immer besser, doch auch die individuelle Therapie und mögliche Komplikationen müssen berücksichtigt werden.

Methoden: Monozentrische, retrospektive Kohortenstudie mit Fokus auf die AID von Patientinnen und Patienten sowie die Komplikationen von AID- und Nicht-AID-Patientinnen und -Patienten an der Universitätsklinik für Herzchirurgie Graz zwischen Jänner 2005 und Oktober 2019.

Ergebnisse: Ein Vergleich hinsichtlich der Komplikationen zeigt eine Komplikationsrate von 18.40% in der Gruppe der nicht-autoimmun erkrankten Patientinnen und Patienten (n = 10 318). Die Gruppe der Patientinnen und Patienten mit zumindest einer diagnostizierten Autoimmunerkrankung (n = 547) weisen eine Komplikationsrate von 23.77% auf, was ein um mehr als 5% höheres Risiko für Komplikationen nach einer CPB-Operation birgt.

Conclusio: Patientinnen und Patienten mit AID sind statistisch gesehen stärker gefährdet, eine Komplikation nach einer Operation mit Herz-Lungen-Maschine zu erleiden als solche ohne AID. Es ist ebenso sichtbar, dass zu wenig Literatur und diagnostische Möglichkeiten zur Verfügung stehen, um alle potenziellen AID-Patientinnen und -Patienten zu identifizieren. Eine Intensivierung der Forschung scheint für die Zukunft wünschenswert, insbesondere bei den selteneren AID, um die Statistiken über AID-Patientinnen und -Patienten zu erweitern und die bestmögliche Behandlung zu gewährleisten.

Abstract

Background: Patients with autoimmunological diseases (AIDs) make up a small proportion of the total number of individuals undergoing cardiopulmonary bypass surgery. Autoimmunological diseases are on the rise in the general population and vary in their severity and symptoms. Diagnostic and therapeutic options are improving for this patient group, but attention must be paid to possible complications.

Methods: Monocentric, retrospective cohort study focusing on the AIDs of patients and the complications of AID and non-AID patients at the Cardiac Surgery Department of the University Hospital of Graz between January 2005 and October 2019.

Results: In the group of non-autoimmunological patients (n = 10 318) the complication rate was 18.40%. In comparison, the autoimmunological disease group (n = 547) had a complication rate of 23.77%, showing a more than 5% higher complication risk after CPB surgery.

Conclusion: Patients with AIDs are statistically slightly more at risk for postoperative complications than patients without AIDs. Furthermore, only few literature and diagnostic options are available to identify potential AID patients. It is therefore important to intensify research, especially for the rarer AIDs, to expand data on AID patients and to provide the best possible treatment.

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List of Abbreviations

A	Arteria
ACT	Activated Clotting Time
ALI	Acute Lung Injury
AID	Autoimmunological Disease
AIDs	Autoimmunological Diseases
AKD	Acute Kidney Disorder and Disease
AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
AVB	Atrioventricular Block
BSA	Body Surface Area
CA	Cold Agglutinin(s)
CABG	Coronary Artery Bypass Grafting
CAD	Cold Agglutinin Disease
CPB	Cardiopulmonary Bypass
CKD	Chronic Kidney Disease
CREST	Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasia
CT	Computed Tomography
CTSL	Cathepsin L
DAMP	Damage-associated Molecular Patterns
DSWI	Deep Sternal Wound Infection
ECMO	Extracorporeal Membrane Oxygenation
HCT	Hematocrit
HIT	Heparin induced Thrombocytopenia
ICU	Intensive Care Unit
mmHg	Millimeter Mercury
MRI	Magnetic Resonance Imaging
NO	Nitric Oxide
NPC2	Niemann-Pick Disease Type C2
NPF	Non-Pulsatile Flow
OPCAB	Off-Pump Coronary Artery Bypass

P	Prevalence
PCC	Prothrombin Complex Concentrates
PF	Pulsatile Flow
PF4	Platelet Factor 4
pH	Pondus Hydrogenii
PM	Pacemaker
PVC	Polyvinyl Chloride
PPC	Postoperative Pulmonary Complications
RI	Respiratory Insufficiency
S	Seconds
SLE	Systemic Lupus Erythematosus
SIRS	Systemic Inflammatory Response Syndrome
SVR	Systemic Vascular Resistance
TAVI	Transcatheter Aortic Valve Implantation
TCV	Total Circulating Volume
TEE	Transesophageal Echocardiography
TIVA	Total Intravenous Anesthesia
TNFα	Tumor necrosis factor α
TXNDC5	Thioredoxin Domain Containing 5

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1 Introduction

At the Department of Cardiac Surgery at the University Hospital of Graz (Styria, Austria), archive files showed that 547 patients with at least one autoimmune disease (AID) underwent cardiovascular surgery requiring cardiopulmonary bypass (CPB) between January 1, 2005, and October 19, 2019.

Although patients with AIDs are a comparatively small group of patients treated at the University Hospital, this diploma thesis examines the effects of cardiopulmonary bypass on the postoperative outcome and the special features regarding therapy. First, the function and the procedures performed on the heart-lung machine are summarized and explained. Thereafter, the most common autoimmunological diseases are listed and described. Finally, these two factors are compared with each other, and possible complications and future approaches are described.

This retrospective study examines in particular cases of autoimmunological disease patients, the type of procedures using the cardiopulmonary bypass, the complications that occurred and further explores and describes the postoperative treatment management. It should be emphasized that only data from known autoimmunological diseases are available, but later onset at a later age, undetected diseases and false-negative tests can also distort the statistics. In comparison, there is also less literature on operations of patients with autoimmunological diseases, not least because many entities and etiologies are still unclear or have not yet been sufficiently investigated in studies.

Interdisciplinary collaboration and a special focus on postoperative complications and their treatment are important in order to provide the best possible care for patients with autoimmunological disease in the future.

2 Procedure: Cardiopulmonary Bypass (CPB)

This diploma thesis examines cases of patients in a retrospective study, all of whom underwent surgery with the use of a cardiopulmonary bypass machine. After a brief historical overview, this chapter mainly describes the use and function of the CPB. Possible general risks and complications that can occur in an operation of this procedure are mentioned.

2.1 Introduction

In the 19th century, the idea of a cardiopulmonary bypass machine first evolved, particularly in Europe and North America. Physiological necessities such as the maintenance of organ and nerve functions during surgery, oxygenation and application systems for blood and the conversion of venous to arterial blood were developed for this purpose (Passaroni, Silva and Yoshida, 2015).

Other essential medical discoveries such as the classification of blood groups by Landsteiner in 1900 or the accidental discovery of heparin through studying on animal liver extracts in 1916 by Howell and McLean (the latter a medical student) also shaped the progress of the cardiopulmonary bypass. John Gibbon, who had spent most of his career researching extracorporeal circulation, was the first to successfully operate on a patient with an atrial septal defect using a cardiopulmonary bypass on May 6, 1953 (Passaroni, Silva and Yoshida, 2015).

At this time, the center of research on CPB was the state of Minnesota, where concepts such as cross-circulation, hypothermic circulatory arrest and the bubble oxygenator were first studied. The new possibilities for cardiac surgery through the support of an extracorporeal circuit further advanced research and medical possibilities in the treatment of many heart diseases. Since Gibbon's first operation, research into CPB has steadily increased and improved the outcome of patients (Passaroni, Silva and Yoshida, 2015). Every year, over two million operations are performed with a CPB worldwide (Yang *et al.*, 2024).

2.1.1 CPB at the University Department of Surgery Graz

On November 19, 1962, the first open heart operation with a cardiopulmonary bypass machine was performed by Spath (Chief of Surgery 1947-1970) and Kraft-Kinz (Chief of Surgery 1970-1996) at the University Hospital of Graz. A tetralogy of Fallot, a cyanotic congenital heart defect, was successfully corrected in a 22-year-old female patient. At that time, no satisfactory treatments for anomalies were available and many children with heart defects did not reach adulthood. Since then, as of 2022, almost 36,500 operations for various conditions ranging from heart defects to degenerative diseases have been performed on CPB at the University Hospital in Graz. Every year, around 800 operations are now carried out with CPB, and it has become established and further developed in surgical practice (Pfandl-Pichler, 2022).

2.2 Function: Technical Fundamentals

Conventional cardiopulmonary bypass machines consist of a reservoir, a pump, a heat exchanger, and an oxygenator (Haas and Kleideiter, 2011), as shown in Figure 1. Additionally, modern CPB machines contain systems for monitoring vital signs such as pressure values, oxygen saturation, temperature, blood gases, hemoglobin, and electrolyte values as well as safety features for monitoring machine characteristics (Sarkar and Prabhu, 2017).

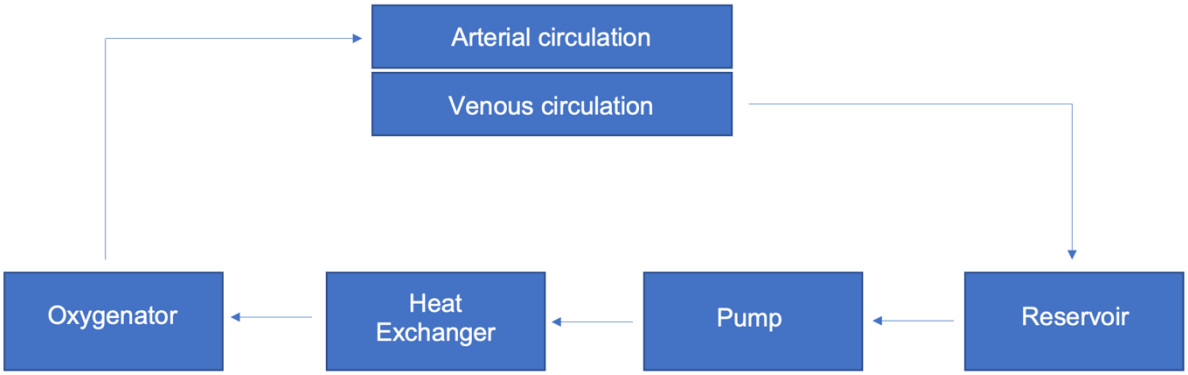


***Figure 1**: Principle of a cardiopulmonary bypass.*

Source: adapted from Sarkar and Prabhu (Sarkar and Prabhu, 2017)

2.2.1 Access

To access the heart, an incision is made via a median longitudinal sternotomy. Alternatively, an anterolateral (4th intercostal space on the right) or posterolateral (3rd intercostal space on the left) thoracotomy can be performed. The type and size of incision differs depending on the indication. For example, the anterolateral thoracotomy is used for minimally invasive closure of an atrial defect and mitral valve reconstruction or replacement. Posterolateral thoracotomy, on the other hand, is preferred for operations on the descending aorta or ductus arteriosus (Schiergens, 2019). Another option is the access via an upper hemisternotomy (UHS). In comparison, for example when performing aortic valve replacement, there is a minimal advantage for the UHS than for the conventional median sternotomy (Klop *et al.*, 2024). UHS is also performed for total arch replacement (TAR), mainly after an aortic dissection (Xia *et al.*, 2023).

2.2.2 Cannulas

The patient is connected to the extracorporeal circuit using modified polyvinyl chloride (PVC) cannulas and a wire reinforcement to prevent kinking. The venous cannulas are either single-stage or dual-stage, depending on the requirements and type of operation. Single-stage cannulas are mainly used in open heart surgery and therefore in CABG surgery. In closed heart surgery (such as replacement of mitral or tricuspid valves), dual-stage cannulas are preferred, with only one cannula being inserted into the right atrium. Alternatively, one-stage cannulas consisting of two cannulas inserted into the superior and inferior vena cava, connected by a Y-piece, can be used. The required drainage is performed by gravity and directs the venous blood into the reservoir equipped with vacuum. In aortic procedures, ECMO or redo operations, arterial and venous cannulas can also be inserted via the femoral vessels. Transesophageal echocardiography (TEE) can help to identify and adjust the correct position using ultrasound technology. Venting is further required to deflate the left side of the heart to allow blood to drain via the bronchial and Thebesian veins. The arterial cannula is mostly inserted into the ascending aorta, alternatively into the femoral or axillary artery or brachiocephalic trunk (Sarkar and Prabhu, 2017).

2.2.3 Roller and Centrifugal Pumps

The comparison between roller and centrifugal pumps shows many advantages and disadvantages. The centrifugal pump is afterload independent and does not require a flowmeter. No backflows can occur here. In comparison, the centrifugal pump is cheaper, limited to a short period of use and has a higher risk of air embolisms and faster tubing debris. The centrifugal pump, however, is afterload-dependent and therefore requires a flowmeter. If the pump comes to a standstill, a potential retrograde blood flow is possible. Centrifugal pumps are more expensive to manufacture, but have a longer service life and are described as having a lower risk of air embolism compared to centrifugal pumps (Sarkar and Prabhu, 2017).

2.2.4 Surfaces

The inner surface of the tubing is made of PVC, which has a long durability and low hemolysis rate. To improve the flexibility of the material, plasticizers such as di(2-ethylhexyl) phthalate are added. However, these chemical ingredients are potentially toxic, as they have also been shown to enter the bloodstream. Dioctyl adipate is a modern alternative that still needs to be sufficiently researched, as it has been proven to be less leaching (Sarkar and Prabhu, 2017).

2.2.5 Flow

The pumps described above generate a non-pulsatile flow (NPF) in their standard setting. During a CPB, however, a pulsatile flow (PF) that imitates the arterial pulse can also be used via several routes within the circuit. There are integrable pulsator devices, the modification of the arterial pump itself or the use of an intra-aortic balloon pump. For pulsatile flow, there is evidence both for and against a reduction in systemic inflammatory response syndrome (SIRS), the systemic inflammatory response and extended protection of the lungs and kidneys. On the other hand, PF is also suspected of increasing the likelihood of hemolysis (Tan, Newey and Falter, 2022).

2.2.6 Reservoir

The mechanical system ensures that venous blood is drained directly from the right atrium via a cannula or from the superior and inferior vena cava via two cannulas into a reservoir. The blood collected in the reservoir is hence fed into an oxygenator via a roller or centrifugal pump. This is where the blood is enriched with oxygen by diffusion and carbon dioxide is removed (Haas and Kleideiter, 2011).

A distinction is made between open and closed reservoir systems. Open reservoirs are used more frequently in CPB. They passively remove venous air and support drainage with vacuum assistance. In addition, reservoirs of this type have a cardiotomy and defoaming circuit that processes the suctioned blood. Closed reservoirs have a comparatively limited volume capacity, but therefore a significantly smaller area where the blood is in contact with an artificial surface. For this reason, systems of this type improve sterility, are less prone to SIRS and reduce the need for post-operative transfusions. However, they require their own separate circuit to process the suctioned blood (Sarkar and Prabhu, 2017).

2.2.7 Heat Exchanger

In addition, the heat exchanger cools or warms the extracorporeally circulating blood as required and allows the body temperature to be manipulated as required. During CPB, the body is cooled to 33 degrees Celsius (for standard procedures at LKH Graz) or even more to 25-28 degrees Celsius to reduce oxygen demand of the entire organism and increase the ischemia tolerance time of the myocardium. To prevent embolisms, the blood is passed through a particle filter before being pumped back into the circulation via the aortic cannula. In addition, patients on the CPB must also be heparinized, as the blood is constantly in contact with foreign surfaces. Anticoagulation can be antagonized with protamine at the end of the operation (Haas and Kleideiter, 2011).

2.2.8 Cardioplegia

Proximal to the aortic cannula, the aorta is clamped, causing the heart to become ischemic. Cardioplegia is then induced to protect the myocardium during the operation. This involves perfusing the heart with a solution that leads to electromechanical arrest and reduces oxygen consumption. The cannula for cardioplegia is inserted proximal to the aortic clamp or directly into the coronary ostia. The cardioplegia solution can be pumped antegrade into the aortic root, alternatively retrograde into the coronary sinus or via a combination of both variants. TEE can identify the position of the retrograde cannula (Sarkar and Prabhu, 2017).

The methodology of cardioplegia can differ in terms of indication, patient age (children or adults) and the specific guidelines in different countries and hospitals. There is no clear, universal, and worldwide consensus on the "one" cardioplegia solution. Cardioplegia solutions differ in their method of administration, composition, additives, and temperature. What they all have in common, however, is that they contain potassium chloride to induce cardiac arrest and are enriched with electrolytes such as magnesium, calcium, chloride, and sodium. Bicarbonate is added just before the cardioplegia solution enters the systemic circulation to adjust the pH if necessary (Carvajal, Goyal and Tadi, 2024).

The form of cardioplegia can be crystalloid (cold) or based on blood (cold or warm) and can be applied either continuously or intermittently. As mentioned previously, potassium-based cardioplegia is most commonly used. Blood-based cardioplegia consists of oxygenated blood mixed with a crystalloid solution in a ratio of 1:1 to 8:1. Mannitol, bicarbonate, calcium, magnesium, adenosine, procaine, glucose, and glutamate can be added (Sarkar and Prabhu, 2017). The solution used, the so-called ice water, has a temperature of 4 degrees Celsius. At the same time, the surface of the heart is cooled with ice water to bring the myocardium to a temperature of approximately 14 degrees Celsius (Schiergens, 2019).

Working with the CPB machine requires a high level of expertise and an interdisciplinary team consisting of specialists from the fields of anesthesiology, cardiology, cardiac surgery and, if necessary, pediatric cardiology. Throughout

Europe, there is a certified training to become a clinical perfusionist to work on the CPB machine; only in Austria is the profession of “cardiotechnician” a state-protected profession (Bauer *et al.*, 2021).

2.3 Induction of CPB

The following subchapter describes the various steps involved in preparing for and following up on a heart-lung machine operation. These include processes such as priming, anticoagulation, anesthesia and perioperative monitoring management, temperature and acid-base management, ultrafiltration, and weaning.

2.3.1 Priming

The priming of a CPB circuit is carried out using priming solutions. These consist of a mixture of colloids and crystalloids, which subsequently cause hemodilution (Sarkar and Prabhu, 2017). Hemodilution lowers hematocrit and whole blood viscosity. For this purpose, all blood components are diluted, including the erythrocytes and the plasma. One form of hemodilution, acute normovolemic hemodilution, is used against intraoperative blood loss to reduce allogeneic transfusion. Although the blood now has a reduced oxygen transport capacity, hemodilution improves the oxygen supply to the organs. This occurs through compensatory reactions such as the induced vasodilation, the increase in cardiac output and the improved blood flow in the organs and myocardium (Lee *et al.*, 2022)

An amount of heparin of 3-4 units/mL are added to the priming solution. The preoperative hemoglobin value determines whether additional blood is added to maintain the target hematocrit value during the operation (for adults approximately 21-24%, for children 28-30%). Certain equations are required for the calculation (Sarkar and Prabhu, 2017) as shown in Table 1.

Total circulating volume (TCV)	Patient's blood volume (PBV) + priming volume
Target hematocrit (Hct) on CPB	Patient's blood volume (PBV) x Hct / TCV
Blood required on prime	(Target Hct x TCV) – (Patient Hct x PBV) / Hct of donor blood
Pump Flow Rate	Body Surface Area (BSA) x Cardiac Index

***Table 1**: Equations for Priming in CPB.*

Source: adapted from Sarkar and Prabhu (Sarkar and Prabhu, 2017).

The Pump Flow Rate equals the Body Surface Area (BSA) multiplied with the Cardiac Index (Sarkar and Prabhu, 2017). The Cardiac index is the cardiac output in relation to the body surface area (Speckmann, Hescheler and Köhling, 2019). A temperature decrease of one degree reduces the required cardiac output by seven percent and therefore also the pump flow (Sarkar and Prabhu, 2017).

2.3.2 Anticoagulation

Coagulation under ongoing CPB surgery is life-threatening. Prior to arterial cannulation, heparin 300 U/kg is administered intravenously (Sarkar and Prabhu, 2017). The most recent guidelines from the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA) 2018 provide recommendations on heparin dosing and monitoring for CPB and suggest a dosage of 300 to 400 U/kg. It is also emphasized that the individual response to heparin can be varied (Cartwright and Mundell, 2023). To assess the effectiveness of the heparin, the activated clotting time (ACT) value is measured, which is normally between 80 and 120 seconds. In CPB surgery, an ACT of more than 480 S (measured after 3 minutes) is targeted. Furthermore, heparin levels must be checked every 30 to 40 minutes during the operation (Sarkar and Prabhu, 2017). Unfractionated heparin is most commonly used to anticoagulate a patient for CPB surgery (Rosin and Holt, 2013).

To minimize the risk of aortic dissection, a systolic pressure around 90 to 100 mmHg should be targeted. The reason why the aortic cannulation is performed first is to allow volume resuscitation to take place in the event of hypotension. As soon as the

aortic cannula is attached to the tube, the pressure of the line is checked to rule out any dissection. Finally, after venous cannulation, the venous clamp is released gradually to start a complete functional CPB, and ventilation is stopped (Sarkar and Prabhu, 2017).

Heparin does not lead to the desired ACT value in all patients. In some patients, additional doses can lead to the appropriate ACT being achieved; from a high heparin dose of 800-1000 U/kg and no failure to respond, this is referred to as heparin resistance (Sarkar and Prabhu, 2017). Other sources indicate that despite increased heparin doses of up to 1200 U/kg, adequate ACT could not be achieved, and high heparin administration can lead to platelet effects and heparin rebound associated with bleeding after CPB. There are various causes of heparin resistance, including a lack of antithrombin, other independent mechanisms unrelated to antithrombin and pseudo resistance (Cartwright and Mundell, 2023).

Other causes of heparin resistance are advanced age, recent use of heparin or nitroglycerin, thrombocytosis or antithrombin deficiency. This changes the treatment of anticoagulation during CPB, in which antithrombin III concentrates or fresh frozen plasma (2 to 4 units) are administered. Patients who have already been affected by heparin-induced thrombocytopenia should not be exposed to heparin again. Instead, alternative anticoagulants such as Bivalirudin, Argatroban, Lepirudin and Danaparoid are used (Sarkar and Prabhu, 2017).

2.3.3 Perioperative Anesthesia Management

In the management of the patient's anesthetic care to maintain the best possible physiological conditions, attention must be paid to values such as perfusion pressure, cerebral blood flow, oxygen saturation, central venous pressure CVP, blood glucose level and others (Sarkar and Prabhu, 2017).

The reference value for organ perfusion is the perfusion pressure, which should remain between 50 and 70 mmHg. Patients with hypertension or an increased risk of stroke require higher perfusion pressures to maintain sufficient organ perfusion.

Monitoring elements such as cerebral oximetry, transcranial Doppler and evoked potentials are used to assess cerebral blood flow. Mixed venous oximetry does not give a clear and reliable indication of perfusion of all tissue layers but should be maintained at 70% or more. High central venous pressure represents a poor venous return; therefore, it should be kept low. Glucose should be targeted around 120 and 180 mg / dL (Sarkar and Prabhu, 2017).

Anesthesia for CPB surgery can be provided by inhalation anesthetics (volatile anesthetics) or total intravenous anesthesia (TIVA). Inhalation anesthetics have a cardioprotective effect, which can be explained by preconditioning. Nitrous oxide cannot be used for this type of surgery to minimize the risk of air embolism. Hypothermia reduces the need for anesthetics (Sarkar and Prabhu, 2017).

A meta-analysis from 2017 compared whether volatile anesthetics or TIVA offer better postoperative effects, especially on cerebral protection. The protein S100B, which is mainly produced in astrocytes, was used as a reference value. S100B is elevated in the blood after ischemic stroke, brain trauma, cardiac surgery with neurological injury and serves as an early marker for brain damage. The meta-analysis shows that 24 hours postoperatively, blood S100B levels were lower in the volatile anesthetic group than in the TIVA group. It can therefore be concluded that volatile anesthetics are better for neurological protection during CPB (Chen *et al.*, 2017).

2.3.4 Temperature Management

It is assumed that perioperative hypothermia will possibly have an organ-protective effect. Cooling increases blood viscosity and enables a higher perfusion pressure to be achieved despite the presence of hemodilution. Core temperature is monitored at the urinary bladder, rectum, oesophagus, and pulmonary artery. The nasopharyngeal temperature is used as an estimate for the brain temperature. However, hypothermia also reversibly inhibits coagulation factors and platelets (Sarkar and Prabhu, 2017). A review shows no significant advantage of hypothermia over normothermia regarding the occurrence of defined clinical events. There is still

insufficient data available and more research needed in this field to draw conclusions about the choice of temperature during CPB surgery and its effects such as neurological deficits (Rees *et al.*, 2001).

2.3.5 Acid-Base Management

Management related to acid-base balance during CPB is essential in hypothermia. The decrease in temperature causes a decrease in partial pressure, which makes carbon dioxide more soluble in the blood and induces alkalosis (Sarkar and Prabhu, 2017).

In this context, the term alpha-stat or pH-stat is used, whereby the alpha refers to the alpha-imidazole ring of histidine. Histidine is considered an important intracellular buffer and the ring's constant charge plays an important role in pH regulation. In the case of alpha-stat, the altered pH is not corrected, and the partial pressure of carbon dioxide might decrease. On the other hand, alpha-stat limits the occurrence of micro embolisms by maintaining cerebral autoregulation. The disadvantage of alpha-stat is the inhomogeneous cerebral cooling (Sarkar and Prabhu, 2017).

As the name suggests, the pH-stat ensures a constant pH value and carbon dioxide partial pressure during hypothermia. For this purpose, carbon dioxide is supplied to the oxygenator to increase cerebral blood flow and support cooling. The pH-stat can lead to severe acidosis during prolonged operations, which is why it is necessary to switch to the conventional alpha-stat during rewarming (Sarkar and Prabhu, 2017).

The choice between alpha-stat and pH-stat is usually based on the patient's age. In adult patients with moderate hypothermia, an alpha stat is advantageous. Infants, on the other hand, usually suffer brain damage during CPB due to hypoperfusion, which is why a pH-stat is sought. In intense hypothermia, a so-called cross-over strategy can be used, in which pH-stat is used in the initial cooling phase and then switched to alpha-stat. This results in maximum cooling of the brain and avoids acidosis due to prolonged pH-stat (Sarkar and Prabhu, 2017).

A Lebanese journal article from 2007 shows that the pH-stat strategy leads to higher oxygen saturation. This may be higher than necessary, which is described in the paper as "luxurious perfusion". The alpha-stat strategy avoids excessive perfusion and ensures a balanced ratio between oxygen supply and oxygen demand (Nauphal *et al.*, 2007).

2.3.6 Ultrafiltration

The principle of ultrafiltration, which is carried out during and after CPB, removes inflammatory mediators, excess fluid and leads to a hemoconcentration. A distinction Is made here between conventional and modified ultrafiltration. Conventional ultrafiltration uses a hemofilter that is introduced into the CPB system. Modified ultrafiltration, however, is only used after the surgical work has been completed and before protamine is administered. For this, blood is taken from the arterial line and returned to the venous line after passing through the hemofilter. If these two forms of ultrafiltration are compared, modified ultrafiltration is more advantageous in terms of lower blood loss and therefore especially in pediatric surgery (Sarkar and Prabhu, 2017).

2.3.7 Weaning

Several steps are necessary in the weaning process to ensure that the circulation is taken over by the heart again in the final phase of the operation. After hypothermia, the body needs sufficient time to rewarm. If this process is carried out too quickly, cerebral damage and hyperthermia can occur. Therefore, a nasopharyngeal temperature of between 35.5 and 36.5 degrees Celsius is the optimum limit and should under no circumstances be higher than 37 degrees Celsius (Sarkar and Prabhu, 2017).

To warm the body evenly, vasodilators can help by increasing venous capacity during transfusion of circulating blood. Normal vital parameters for acid-base

balance, oxygen and carbon dioxide partial pressures, sugar, electrolytes, and hematocrit are aimed for. A serum potassium level of around 4.5-5 mmol/L counteracts cardiac arrhythmias (Sarkar and Prabhu, 2017).

For sinus bradycardia, beta-adrenergic agonists can be administered with or without atropine. If an atrioventricular block persists, epicardial stimulation is used. Ventricular fibrillation can be triggered when the aortic clamp is removed, especially if the patient already suffers from severe aortic stenosis or left ventricular hypertrophy (Sarkar and Prabhu, 2017).
In addition to adequate warming, venting after open heart surgery is important. Again, transesophageal echocardiography can be used to assess the quality of ventilation. A potential complication can be an air embolism, which usually affects the A. coronaria dextra due to its anterior location and can also lead to ST elevation and other cardiac arrhythmias up to myocardial dysfunction. Increasing the perfusion pressure and maintaining pulsatile perfusion can reduce this complication (Sarkar and Prabhu, 2017).

Defibrillation is performed with an energy of 5 to 20 joules, which is delivered via internal paddles. If arrhythmia persists, antiarrhythmic drugs such as lidocaine, magnesium or amiodarone are administered. Mechanical ventilation is then initiated, the venous return is occluded and fills the heart, while the pump flow is gradually reduced (Sarkar and Prabhu, 2017).

The use of inotropic agents should be determined by visual assessment of contractility and TEE. Factors that also influence the choice of inotropic agents are patient history of diseases such as severe pulmonary hypertension or left ventricular dysfunction or inadequate myocardial protection and prolonged cross-clamp time during CPB (Sarkar and Prabhu, 2017).

As a bail-out procedure, if the patient cannot be weaned, mechanical support systems are used. These include an intra-aortic balloon pump, ventricular support system or ECMO (extracorporeal membrane oxygenation) (Sarkar and Prabhu, 2017).

After separation from the CPB system, the heparin is antagonized with protamine at a ratio of approximately 1:1 to 1:3 over 15 minutes. The adverse effects of protamine can be divided into 3 types, with type I triggering hypotension due to too rapid infusion, type II describing anaphylaxis and type III triggering a pulmonary hypertensive crisis. After the administration of protamine, the ACT is checked again. Finally, arterial decannulation is performed (Sarkar and Prabhu, 2017).

2.4 Pathophysiology and Complications

Over the past 70 years, the technology surrounding extracorporeal circulation in CPB has evolved rapidly. Nevertheless, the effects on the organism should not be underestimated as they alter physiological and vital reactions. The pathophysiology includes changes in coagulation, hemodynamics, fibrinolysis, electrolytes and secretion, acid-base balance, the entire metabolism and finally the immune system (Kawahito *et al.*, 2020). In other sources, complications are also divided into mechanical and systemic complications (Sarkar and Prabhu, 2017).

2.4.1 Mechanical Complications

In the process of arterial cannulation, the cannula may be misplaced, which can lead to selective cerebral perfusion, plaque dislocation or dissection. Bleeding can also occur under these circumstances. A dissection is indicated by a reduced arterial pressure and a high arterial pressure above 300 mmHg, the venous return decreases sharply and the vessel turns bluish in color. A dissection can also be diagnosed with a TEE (Sarkar and Prabhu, 2017).

Venous cannulation can also lead to bleeding and malpositioning, which causes air congestion and thus insufficient return flow. This leads to congestion in the cerebral and splanchnic areas. Massive air embolism occurs when pumping from an empty reservoir (Sarkar and Prabhu, 2017).

In the CPB system, oxygenator failure, pump malfunction, clot formation in the circuit, tube rupture and loss of power and gas supply can also occur (Sarkar and Prabhu, 2017). Oxygen delivery can also fail during CPB surgery, with insufficient oxygen delivery occurring in only 0.02% to 0.04% of operations (Hickerson and Acero, 2020).

2.4.2 Systemic Complications

Systemic damage that may occur during or after CPB includes coagulation complications, cerebral damage, acute kidney injury, systemic inflammatory response, myocardial injury, acute respiratory distress syndrome, vasoplegia and others (Sarkar and Prabhu, 2017).

2.4.2.1 Coagulation Complications

Induction of CPB using hemodilution reduces the concentration of coagulation-promoting substances. This intrinsically activates inflammatory, complement, coagulation and fibrinolytic signaling pathways. The probability of a bleeding tendency increases with a long operation, preoperative use of anticoagulants and repeated operations on the CPB (Sarkar and Prabhu, 2017). The occurrence of coagulopathy after CPB surgery is multifactorial and common in incidence and can lead to excessive bleeding, need for transfusion and poorer outcomes (Bartoszko and Karkouti, 2021).

Several papers suggest that a lower heparin dose during CPB is associated with a lower incidence of post-operative bleeding and need for transfusions. However, the results of the prospective observational study from 2013 show that even heparin-resistant patients who have received more heparin do not bleed more postoperatively than heparin-sensitive patients (Rosin and Holt, 2013).

2.4.2.2 Acute Kidney Injury (AKI)

The most common causes of AKI are septic shock and surgery on the CPB. Studies show that the probability of developing AKI after CPB is between 18 and 30% and is therefore a significant marker for postoperative mortality and morbidity (Liu *et al.*, 2021). Even slightly elevated serum creatinine (which is a poor indicator or a renal dysfunction) levels are associated with a poorer prognosis and an increased mortality rate (Yang *et al.*, 2024). Inflammatory reactions and hypotension due to CPB can lead to AKI. Risk factors for this are pre-existing diabetes, sepsis, and a prolonged operation time (Sarkar and Prabhu, 2017). Furthermore, female gender, older age, high creatinine, genetic polymorphisms, lowered hemoglobin, hemodilution and reduced oxygen transport capacity are also associated with an increased risk of AKI after CPB surgery. AKI is associated with a poor outcome and even shows an 8.2-fold increase in hospital mortality. Strokes can also occur (Liu *et al.*, 2021).

Other contemporary sources from 2024 divide the kidney-specific complications into AKI, AKD (acute kidney disease and disorder) and CKD (chronic kidney disease). Of these, AKD and CKD are described as longer-term functional disorders and require intervention over a longer period. CPB is associated with many pathophysiological phenomena due to extracorporeal circulation and the takeover of the cardiovascular system. These complications also interact or overlap with each other. Inflammation, hemodynamic instability, ischemia and reperfusion damage, oxidative stress as well as neurohormonal activation and embolic phenomena can occur. Retrograde autologous priming can be kidney-sparing. Low MAP (below 50-55 mmHg) and active rewarming should be avoided. Rather, passive warming and a higher flow rate should be used (Milne *et al.*, 2024).

2.4.2.3 Neurological Complications

In the case of complications affecting the brain and the central nervous system, the spectrum of cerebral damage ranges from cognitive dysfunction to a cerebral stroke

(Sarkar and Prabhu, 2017). The incidence of neurological complications following CPB surgery are comparatively high. Strokes with an overall risk of 1.6% within 48 hours are clinically recognizable and treatable. On the other hand, postoperative delirium (POD) is probably too rarely recognized and is said to have an incidence of 50%. Seizures can occur in 1%, some sources also speak of 8%. Visual disturbances, peripheral nerve lesions and even comatose states can also occur (Gilbey *et al.*, 2023).

Neurological complications can also be divided into Type-I and Type-II complications depending on the source. If the damage to the brain is caused by an embolically triggered stroke (ischemic stroke) or an intracerebral hemorrhage (hemorrhagic stroke) and symptoms such as paralysis, stupor or even coma develop, this is referred to as a Type-I complication. Type II complications are probably higher in incidence and are characterized by seizures or reduced intellectual function (up to 53% immediately postoperative up to six months, 24% permanent) (Haider *et al.*, 2018).

2.4.2.4 Systemic Inflammatory Response

During cannulation, the vessels meet artificial surfaces. This, as well as reperfusion damage after ischemia, endotoxemia and surgical trauma, leads to a systemic inflammatory reaction. In this process of acute phase reaction, complement factors, endotoxins, cytokines, and nitric oxide (NO) are released, which increases capillary permeability. After hypothermia, rewarming is also a stress for the body, which also releases inflammatory mediators (Sarkar and Prabhu, 2017).

The clinical differentiation of SIRS (Systemic Inflammatory Response Syndrome) from sepsis is still controversial. SIRS is a life-threatening organ dysfunction characterized by a dysregulated response of the organism to damage-associated molecular patterns (DAMPs). The 2022 literature review concludes that the identification of cytokine hubs associated with SIRS-related complications will improve understanding the systematic pathophysiology and provide new opportunities for intervention. (Squiccimarro *et al.*, 2022).

2.4.2.5 Acute Respiratory Distress Syndrome (ARDS)

Pulmonary complications arise due to altered lung mechanics after CPB, impaired gas exchange, hemi diaphragmatic paresis, pain from the sternal wound and surgical drainage. Hypoxemia, pneumonia, acute lung injury (ALI) and ARDS can still occur. Factors such as inflammation, ischemia and reperfusion of the lung are associated with ALI and ARDS. Atelectasis often occurs with general anesthesia and exacerbates hypoxemia, which in turn increases the risk of pneumonia (Huffmyer and Groves, 2015).

Anesthesia causes temporary atelectasis and reduced mucociliary clearance during CPB surgery. This leads to lung damage, which is why pleural effusions or an acute respiratory distress syndrome can occur more frequently (Sarkar and Prabhu, 2017). ARDS has a wide-ranging incidence of 0.4 to 20% and is associated with a high mortality rate of up to 80%. There is no specific therapy, hence the focus is on early detection and the definition of clinical predictors as well as indicative biomarkers. Clinical predictors include increased age and CPB-associated factors such as prolonged duration of surgery and anesthesia, high ultrafiltration and cardioprotective fluid volume. The early increase in the plasma proteomics biomarkers TXNDC5 and CTSL is related to vascular and endothelial injury, and together with intracellular cholesterol transporter 2 (NPC2) are predictive biomarkers for ARDS (Wang *et al.*, 2023).

2.4.2.6 Myocardial Damage

Clamping the aorta can cause myocardial injury despite the cardioplegia, which arrests the heart. The stunning disrupts the function of the myocardium. Important factors in this process are metabolic acidosis, preoperative ventricular function, damage caused by reperfusion and the presence of inflammatory mediators (Sarkar and Prabhu, 2017).

Several studies, including meta-analyses, have shown that the prophylactic administration of corticosteroids reduces inflammation, oxidative stress, and tissue

damage. As a result, the contractility of the heart is restricted less and the incidence of atrial fibrillation decreases. The need for circulatory support measures and shorter intensive care and hospital stays is also reduced. Nevertheless, there are also studies that show no difference (Hatami, Hefler and Freed, 2022).

2.4.2.7 Vasoplegia

If vasoplegia occurs, it is characterized by strong and severe vasopressor-resistant vasodilation. This is based on an activation of nitric oxide (NO) synthase, as well as sensitized ATP (adenosine triphosphate) potassium channels of the vascular smooth muscle and a relative vasopressin deficiency (Sarkar and Prabhu, 2017)

Vasoplegia is characterized by normal to increased cardiac output together with a low SVR, leading to organ hypoperfusion. Vasoplegia is defined as shock occurring 24 hours after CPB with a cardiac index value of more than 2.2 L/kg/m^2 and a low SVR of less than 800 dynsec/cm^5. Vasoplegia can occur in up to 50% of all patients after cardiac surgery. There are predisposing risk factors such as preoperative use of antihypertensive drugs, many comorbidities and CPB-related risk factors such as prolonged operation time and increased temperature. NO and the high use of catecholamines during surgery also play a major role (Busse, Barker and Petersen, 2020).

2.5 CPB Procedures at the Department of Cardiac Surgery Graz

There are various indications for the use of a cardiopulmonary bypass machine. Initially, these include operations in which the heart must be deflated for any intracardiac repairs. A cardiopulmonary bypass machine is also used when mechanical cardiac arrest or moderate to deep hypothermia is required (Carrel, 2023).

In the course of this diploma thesis, the various operations between January 1^{sts} 2005 and October 7th 2019 that were performed in the Department of Cardiac Surgery at the University Hospital of Graz with the support of a cardiopulmonary bypass are examined. The patient collective exclusively comprises autoimmunological patients. It should be emphasized that autoimmunological diseases are not always diagnosed, so that a higher number of unreported cases can be assumed.

CABG surgery (acute or elective) is one of the most frequently performed operations at the hospital using CPB. The procedure may also be combined with valve replacement surgery. High-grade coronary artery disease with severe vascular occlusion has been shown to improve with CABG surgery.

Aortic valve replacement operations, such as in cases of severe aortic stenosis due to, for example, primary congenital bicuspid aortic valve or rheumatic degeneration, are also supported by CPB. Acute and non-acute mitral valve insufficiency with prolapse of the posterior leaflet and tricuspid valve insufficiency are also treated by valve replacement at the CPB.

Aneurysms such as those in the ascending aorta can be corrected using the Hemiarch or Bentall technique by replacing the ascending aorta. Acute dissections such as in the area of the brachiocephalic trunk can also be saved by emergency surgery and supracoronary ascending aorta replacement.

Congenital heart defects, such as large atrial septal defects, can be corrected with Goretex patches in CPB. Corrected heart defects also include Bentall-de Bono operations for an open ductus Botalli or pulmonary vein defect on the right in the superior vena cava, which are transferred to the left atrium using a biopericardial patch.

The operations performed also include revisions, with the purpose of repeating the operation in order to achieve the desired result. In exceptional cases, special indications such as status post emergency caesarean section with subsequent embolectomy and thrombectomy of the thoracic arteries according to Trendelenburg for central PAE were also performed. Myxomas, i.e. benign tumors of the (usually) left atrium, can also be completely removed by surgery with CPB support. Cardiac trauma can also be treated in this way.

3 Autoimmunological Diseases

This retrospective study of cardiopulmonary bypass surgery focuses on patients with an autoimmunological disease (AID). For this purpose, the general criteria of an AIDs are explained, followed by a list of the most common AIDs in Europe. The consequences of AIDs on the cardiovascular system and the vascular system are examined in more detail and risks and complications during cardiovascular operations are listed. Due to the high variability of autoimmunological diseases, the AIDs with the highest prevalence are discussed in more detail. Finally, possible errors and biases are also described, such as the fact that certain AIDs only occur later in life or that laboratory results for tests can be false-negative.

3.1 Introduction and Ranking of AIDs in Europe

The term autoimmunity describes the presence of immunological components that are directed against structures of the patient's own body. However, the definition of an autoimmunological disease presupposes that there is also a circumscribed pathology. There are still no generally valid criteria for diseases of this type, nor a universal consensus on which diseases are considered autoimmunological diseases. Similarly, the various etiologies of individual entities are not fully understood, although it is known that many diseases are based on a gene-environment interaction. Rapid technological progress in the identification of individual genomes has made it possible to investigate the genetic causes, but comparatively limited progress has been made so far in deciphering the even more profound effects of environmental influences. Recent research findings also show that the incidence of autoimmunological diseases has increased considerably in recent decades (Miller, 2023).

A British population-based study, which examined the incidence and prevalence of the 19 most common autoimmunological diseases between 2000-2019, published its results in 2023. The trends of the 22 million individuals studied were also assessed by gender, age, socioeconomic status, and ethnicity (Conrad *et al.*, 2023).

The mean age of the individuals is 54 years with a standard deviation of 21. Of this large population, around 979,000 people received a new diagnosis between 2000 and 2019 and thus had at least one autoimmunological disease as presented in Table 2. The majority (64%) of patients are female. The sharpest increases were recorded for coeliac disease, Graves' disease and Sjogren's syndrome. Approximately 10% of the UK population has an autoimmunological disease. AIDs are also often associated together, such as Systematic lupus erythematosus, Sjogren's Syndrome and Systemic Sclerosis (Conrad *et al.*, 2023).

Autoimmunological Disease	Incidence
Hashimoto's Thyroiditis	**284 755**
Psoriasis	**236 027**
Rheumatoid Arthritis	**107 559**
Polymyalgia Rheumatica	**90 853**
Grave's Disease	**75 524**
Inflammatory Bowel Disease	**66 173**
Pernicious anemia	**62 582**
Vasculitis	**58 919**
Coeliac Disease	**31 447**
Vitiligo	**27 638**
Multiple Sclerosis	**15 634**
Systemic lupus erythematosus	**14 164**
Ankylosing spondylitis	**12 663**
Sjögren's Syndrome	**12 292**
Type 1 Diabetes	**9 022**
Primary biliary cholangitis	**5 683**
Systemic sclerosis	**4 880**
Addison's Disease	**4 319**
Myasthenia gravis	**3 655**
All Autoimmunological Disease 2000-2019	**978 872**

***Table 2**: Incidence of Autoimmunological Disorders 2000-2019 in the UK.*

(Conrad *et al.*, 2023).

To date, there is no globally standardized list of criteria for autoimmunological diseases. Consequently, it is very difficult to delineate autoimmunological diseases or to find several comparable papers on which the same ones can be found.

3.2 Literature: Status quo

A search of bibliographic literature databases such as PubMed for the keywords "autoimmunological" and "cardiopulmonary bypass", obtains around 60 results over the last 20 years (2004-2024) and is listed in Table 3. Compared to the most common autoimmunological diseases, it is clear at first glance that most of the available literature does not cover all autoimmunological diseases. It should be noted that there is no complete access to every paper (50%). To provide an overview of the research, the following table lists the most common autoimmunological diseases found in connection with CPB.

Autoimmunological Disease	Results
Cold Agglutinin Disease (CAD)	19
Autoimmunologic Heparin-induced Thrombocytopenia	6
Antiphospholipid Syndrome	5
Autoimmunological Hemolytic Anemia	2
Cryoglobulinemia	2
Wegener Granulomatosis	2
Factor V Deficiency	1
Guillain-Barré Syndrome	1
Idiopathic Inflammatory Syndrome	1
Miller-Fisher Syndrome	1
Systemic lupus erythematosus	1
Takayasu Arteritis	1
Ulcerative Colitis	1

***Table 3**: Results of the literature search for the combination of "autoimmunological" and "CPB" / “Cardiopulmonary bypass”.*

3.3 Risks and Complications during cardiovascular surgery

The following subchapter focuses on the descriptions of the most common autoimmunological diseases in connection with potential risks that can occur in an operation with CPB. As already described above, it was not possible to find suitable literature for every single AID observed in Graz.

3.3.1 Cold agglutinins

Cold agglutinins (CA) play a significant role in the development of autoimmunological hemolytic anemia. In addition to the known blood group antigens that differentiate the blood groups between people (AB0 system), I/i and Pr antigens are also formed here. From a temperature of 4-18 degrees, the erythrocytes clump together. Apart from the anemia that occurs, CA can also cause symptoms such as acrocyanosis, livedo reticularis or Reynold's phenomenon. Some patients are both asymptomatic and symptom-free until they are exposed to low temperatures. For example, in CPB operations that take place at hypothermia and thus 28 degrees Celsius, the blood can clot despite a suitable activated clotting time (Sayed *et al.*, 2023).

If no cold agglutinins are known, this can be determined during the operation by taking an intraoperative blood sample. As shown in a case report, patients are helped by switching to a warm cardioplegia solution (aiming for 34 degrees) and the operation can be continued. In addition, mannitol and frusemide are administered and the coronary arteries are flushed with warm blood in the antegrade and retrograde direction (hot shot) before the cross-clamp is removed (Sayed *et al.*, 2023).

Preoperatively, plasmapheresis, steroid and immunoglobulin treatments can reduce the titer; the drugs used in addition to cortisone are fludarabine, rituximab and eculizumab. The mild hypothermia caused by warm blood also protects the myocardium (Sayed *et al.*, 2023).

3.3.2 Systemic Lupus Erythematosus

SLE describes a chronic autoimmunological disease that affects most tissues of the body in a variety of ways and has a 6-fold increased cardiovascular risk. SLE is associated with serious complications, from infections to renal and cardiovascular disease and mortality. The incidence of valvular heart disease (mostly mitral valve stenosis), coronary heart disease and aortic disease (aortic stenosis, aortic regurgitation) increases with the duration of treatment. About 40% of all SLE patients have antiphospholipid antibodies and about 10 to 20% develop antiphospholipid antibody syndrome (APS). Less than 40% develop thrombosis as a result (Yamamoto *et al.*, 2023).

According to a retrospective observational study from Japan from 2023, there were no significant increases in deaths or serious hemorrhagic or thromboembolic complications in cardiac surgery. However, perioperative management is much more difficult due to blood clotting disorders. For example, SLE patients have an increased incidence of fibrin degradation products, especially if an aortic aneurysm is also present (Yamamoto *et al.*, 2023).

Postoperatively, patients with SLE recover more slowly and have difficulties with platelet counts and coagulation disorders. Postoperative re-hospitalization due to cardiovascular events such as thrombosis or infections is also more frequent. For this reason, an OPCAB (off-pump coronary artery bypass) technique is also attempted if possible (Yamamoto *et al.*, 2023).

The APS severity classification can help to assess the risk of a thromboembolic event or bleeding. Preoperative blood sampling also helps to detect antiphospholipid antibodies in the serum: enzyme-linked anti-beta-2-glycoprotein-I-test, anticardiolipin immunosorbent assay and LAC test (Yamamoto *et al.*, 2023).

To maintain adequate clotting after CPB surgery, it is assumed that the minimum amount of clotting factor activity is approximately 20 to 30% of the normal circulating plasma volume. For this reason, 20 to 30% was replaced with fresh frozen plasma in SLE patients. Methylprednisolone should also be given on the day of surgery and

one day postoperatively. High-risk patients should continue to be blood thinned with low-dose acetylsalicylic acid after surgery, and anticoagulants such as warfarin have also been researched and recommended in this context (Yamamoto *et al.*, 2023).

3.3.3 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an acquired AID with antiphospholipid antibodies in the blood with an estimated prevalence of 50 in 10,000. These include anticardiolipin antibodies, lupus anticoagulants and anti-β2-glycoprotein-I antibodies. Patients with APS tend to have an increased risk of thrombosis, as the antibodies disrupt the formation of the prothrombinase complex on phospholipids. This subsequently leads to an increase in the activated clotting time and the activated partial thromboplastin time. The increased expression of adhesion molecules and increased cytokine secretion also lead to hypercoagulability. Counteracting mechanisms, such as the activity of protein C and S or the tissue factor pathway inhibitor, are suppressed (Ural and Edelson, 2021).

Thrombin is formed during surgery on the CPB, although this process is even more pronounced in APS patients. In general, ACT must be checked intraoperatively during CPB as a safety measure. This can be done accurately using the Hepcon Hemostatis Management System Plus device. The device also provides precise information on the calculation of the protamine dose to compensate for heparinization. However, there are no clear recommendations for APS patients at CPB (Ural and Edelson, 2021).

3.3.4 Heparin-induced Thrombocytopenia

HIT (heparin-induced thrombocytopenia) is the most common antibody-mediated and drug-induced cause of thrombocytopenia and thrombosis in the clinical context (Cines *et al.*, 2007). Due to the prolonged exposure to heparin during

cardiopulmonary bypass surgery, the incidence of HIT varies from 0.1% to 3% (Tugulan, Chang and Bates, 2021).

The cascade that triggers HIT begins with IgG antibodies that bind to the epitopes of platelet factor 4 (PF4). PF4 is released from activated platelets as soon as it forms complexes with heparin. Antibody formation against PF4 occurs in over 50% of patients undergoing CPB surgery (Cines *et al.*, 2007). Complications of HIT include acute renal failure, stroke and amputations following thromboembolic events. Thrombotic complications are mostly arterial in origin and occur 8.5 times more frequently compared to venous thrombosis (Tugulan, Chang and Bates, 2021). With an incidence of 0.1% to 4%, HIT is a dreaded postoperative complication with a mortality rate of up to 20%, although the causal factors and the individual risk are difficult to classify to date (Seigerman *et al.*, 2014).

3.3.5 Vasculitis

Vasculitides comprise a group of diseases that occur rarely overall and are characterized by inflammation of the blood vessels. Patients are at risk of stenosis, thrombotic occlusion, aneurysm formation and even dissection or complete rupture. Vasculitis can be divided into several subtypes (De Gaspari *et al.*, 2024). This subchapter describes Takayasu's arteritis and granulomatous polyangiitis, also known as Wegener's granulomatosis.

3.3.5.1 Takayasu‘s Arteritis

Takayasu’s arteritis is one of the autoimmunological inflammatory vasculitides. The inflammation affects the large arteries and is therefore particularly relevant in cases of inflammation and wall injuries of the aorta. A case report from 2021 shows a pseudoaneurysm in one such patient following cardiac surgery. In general, pseudoaneurysms can occur, albeit very rarely, as a result of postoperative mediastinitis or pericarditis, repeated operations on the pericardium, progressive aortic migration disease such as Marfan syndrome or Takayasu or infections of the aortic graft. The mortality rate is just under 7%, with over 8% requiring re-exploration

due to bleeding. Approximately 3% suffered a postoperative stroke. Pseudoaneurysms can occur both as an early complication and later after 20 years (Alsatli, AlHalees and Kholaif, 2021).

In order to minimize the complication rate, postoperative management is required for patients with a history of this type of disease. This includes performing a CT thorax, an MRI, imaging of the aorta as in aortography and a transesophageal echocardiogram (Alsatli, AlHalees and Kholaif, 2021).

3.3.5.2 Wegener's Granulomatosis

Another form of vasculitis, Wegener's granulomatosis (WG), is an autoimmunological systemic vasculitis that attacks the small and medium-sized vessels of the body. As it progresses, it leads to necrotizing granulomas, and often also to pulmonary granulomas and aortic root dilatation (etiologically not precisely explainable), which is why WG patients also require cardiac surgery after a certain age. In most cases, cardiac involvement in WG patients (around 40%) leads to pericarditis, heart block and supraventricular arrhythmias. The etiology of WG has not been completely researched, but it is assumed to be a T-cell-mediated damage with increased production of tumor necrosis factor TNFα. Macrophages and cytokines are subsequently activated and the cascade to inflammation is driven forward rapidly. During CPB, there is a significant increase in the immune response, which is probably due to systemic endotoxemia (Edmondson, Attaran and Rosendahl, 2016).

Intraoperative dissection can also occur in patients with WG undergoing surgery with CPB if there is damage to the aortic root. In the case report from 2016, after this complication, the dissection is repaired directly in hypothermic circulatory arrest below 22 degrees Celsius and complete healing and postoperative recovery are achieved. Therapeutically, WG is counteracted with anti-inflammatory drugs such as cyclophosphamide, accompanied by steroids or, in resistant cases, with monoclonal antibodies that trigger a blockade of TNFα (Edmondson, Attaran and

Rosendahl, 2016). In other sources, Wegener's granulomatosis is also known as granulomatosis with polyangiitis (De Gaspari *et al.*, 2024).

3.3.6 Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) presents with neuromuscular paralysis of the peripheral nervous system. This entity occurs rarely and is based on a post-infectious, immune-mediated cascade that triggers neuropathy. Symptoms include paresthesia, weakness, and dysesthesia, which can progress to paralysis (Nguyen and Taylor, 2024).

A variant of Guillain-Barré syndrome, Miller-Fisher syndrome, is an acute inflammatory neurological disease that manifests itself symptomatically through the triad of areflexia, ophthalmoplegia and ataxia. MFS can be triggered by viral infections (Campylobacter jejuni, cytomegalovirus, Epstein-Barr, Influenza), pregnancy, vaccinations, or major surgery. The pathophysiological mechanism between CPB and the development of MFS is unknown and difficult to describe due to the limited data available and a general incidence of MFS of 2 per 100,000 (Aldag *et al.*, 2017).

If postoperative symptoms of MFS or GBS occur, differential diagnoses should be ruled out, a neurological consultant consulted, and early treatment initiated. This includes plasmapheresis, intravenous immunoglobulins, inotropic medication, and intubation if severe dyspnea occurs (Aldag *et al.*, 2017).

3.4 AIDs ranking in study, statistics 2005-2019

The German Autoimmunological Foundation lists over 48 autoimmunological diseases that were used for the classification of our patient collective. Here different figures can be seen when compared with the figures from the British autoimmunological study. The German Autoimmunological Foundation does not list by incidence, but by prevalence (P), which is why the figures appear higher in Table 4 (Huber, 2024).

Nr	Autoimmunological Disease	P per 100.000
1.	Type 1 diabetes	946
2.	Myositis	823
3.	Hyperthyroidism	629
4.	Rheumatoid arthritis	381
5.	Ulcerative colitis	378
6.	Crohn’s disease	225
7.	Psoriasis	197
8.	Multiple sclerosis	182
9.	Uveitis	149
10.	Polymyalgia rheumatica	112
11.	Idiopathic thrombocytopenia	72
11.	Guillain-Barré syndrome	72
13.	Autoimmunological thyroiditis	62
14.	Pernicious anemia	54
15.	Celiac disease	50
16.	Sjögren’s syndrome	48
17.	Autoimmunological hepatitis	45
18.	Systemic lupus erythematosus	32
19.	Vitiligo	29
20.	Scleroderma	23
21.	Alopecia	21
22.	Myasthenia gravis	18
22.	Addison's disease	18
24.	Autoimmunological hemolytic anemia	17
24.	Dermatopolymyositis	17
26.	Pemphigus vulgaris	16
27.	Primary biliary cholangitis	12
28.	Wegener's granulomatosis	10

***Table 4**: Table of the most common AIDs (Huber, 2024).*

4 Autoimmunological Diseases in CPB Surgery

After the previous chapters explained the surgical procedure with the cardiopulmonary bypass and the patient collective, these two components are brought together and compared now. The results of the retrospective study from the Department of Cardiac Surgery, University Hospital of Graz, are presented and compared with existing literature.

4.1 Patients and Methods

This retrospective, monocentric cohort study, which was conducted at the Department of Cardiac Surgery at the University Hospital of Graz contains data from all patients treated at the CPB from January 1, 2005, to October 7, 2019. A total of 547 patients with at least one AID and 10.301 patients without any diagnosed AID were included into the study, if they had a procedure done on the CPB.

4.2 Inclusion and Exclusion Criteria

The empirical part of this thesis, the retrospective study, used an Excel list containing anonymized data records with over 24,000 pieces of data. All cardiac surgery procedures from January 1, 2005, to October 7, 2019 performed at the University Hospital of Graz were listed. The categories into which the data was categorized include first and foremost patients on the heart-lung machine together with complications, if any.

All patients who underwent pacemaker (PM) treatment (including implantation, battery replacement, inflammation, and other complications) were excluded. If a patient required a PM directly after a CPB operation, this counts as a complication of CPB and was therefore included. Patients who were treated using the OPCAB technique (off-pump coronary artery bypass) and TAVI (transcatheter aortic valve implantation) patients were excluded from the study. Port-a-cath implantations, mostly for oncological treatments, were also immediately excluded.

The primary list with other 24,455 patient records were reduced to 547 patients with operations on CPB and at least one diagnosed AID which were finally included for this retrospective study. For this purpose, an archivist was commissioned to assign this AID to all patients. However, all diabetes types were grouped together, so that a more precise selection into type 1 and type 2 diabetes had to be made. Likewise, atherosclerosis and polyneuropathy could not be included because, although these diseases have autoimmunological components, their pathogenesis is not fully understood and is more likely to be a degenerative disease.

4.3 Process

All duplicates were first removed from a large file with a total of 24,455 entries in order to determine the absolute number of patients from 2005-2019. This resulted in a total file size of 16,801 patients. Patients previously labeled with an autoimmunological disease and treated at CPB in the course of an operation resulted in 776 patients. However, type 1 and type 2 diabetics were grouped together under “diabetes”. The autoimmunological form of diabetes mellitus, even if the pathophysiology is not yet fully explained, is type 1. The patient data was sorted again for this purpose. After a second check, these were 547 patients that fulfilled the criteria. Figure 2 shows the tree diagram of patients selected for the retrospective study.

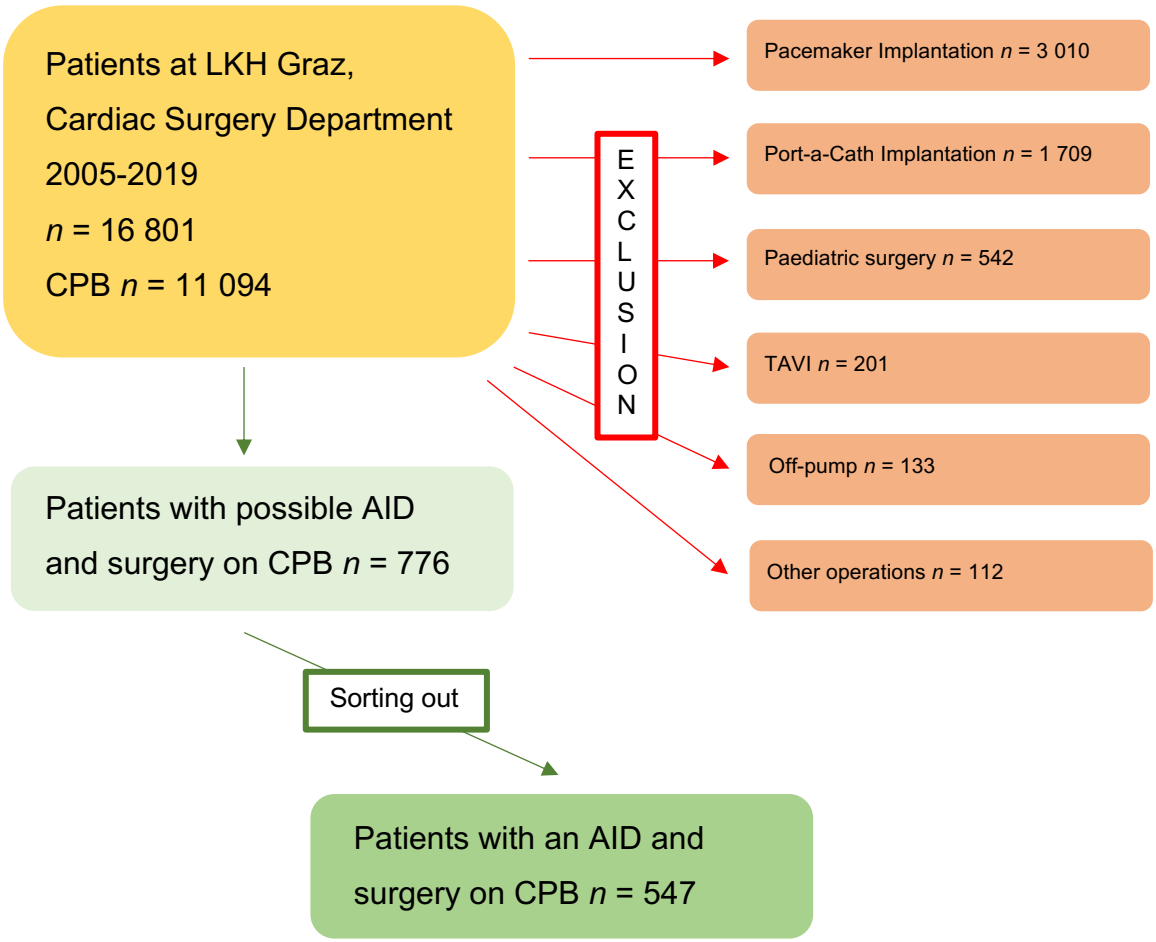


***Figure 2**: Tree diagram to visualize the inclusion and exclusion criteria.*

The anonymized original file contained the consecutive patient number, the number of cases, the date of the operation, the diagnosis, the operation, and the autoimmunological disease (also with the code if several AIDs are present in one patient). All AIDs were shown in the following table (Table 5) with the absolute and relative number of patients in order to supply a ranking of the most common autoimmunological diseases in our Department for Cardiac Surgery.

n		Single	Multiple	Total		
1	DM1	94	7	**101**	16,42	%
2	Hashimoto's disease	53	13	**66**	10,73	%
3	Rheumatoid arthritis	53	13	**66**	10,73	%
4	Psoriasis	41	5	**46**	7,48	%
5	Autoimmune Gastritis	33	4	**37**	6,02	%
6	Sjögren's disease	20	10	**30**	4,88	%
7	SLE	15	6	**21**	3,41	%
8	Ankylosing spondylitis	16	4	**20**	3,25	%
9	Temporal arteritis	19	1	**20**	3,25	%
9	Graves' disease	16	4	**20**	3,25	%
11	Ulcerative colitis	16	2	**18**	2,93	%
11	Juvenile rheumatoid arthritis	13	5	**18**	2,93	%
11	Sarcoidosis	15	3	**18**	2,93	%
14	Polymyalgia rheumatica	12	3	**15**	2,44	%
15	Antiphospholipid syndrome	10	3	**13**	2,11	%
16	Crohn's disease	9	2	**11**	1,79	%
16	Werlhof's disease	11	6	**17**	2,76	%
18	Goodpasture Syndrome	2	6	**8**	1,30	%
18	Morbus Wegener	6	2	**8**	1,30	%
20	Fibromyalgia	4	2	**6**	0,98	%
20	Celiac disease	4	2	**6**	0,98	%
22	Guillan Barre Syndrome	4	1	**5**	0,81	%
22	Multiple sclerosis	4	1	**5**	0,81	%
24	CREST syndrome	2	2	**4**	0,65	%
24	Mixed collagenosis	1	3	**4**	0,65	%
24	Myasthenia gravis	4	0	**4**	0,65	%
24	Pemphigus vulgaris	4	0	**4**	0,65	%
28	Pernicious anemia	1	2	**3**	0,49	%
28	Lichen ruber	3	0	**3**	0,49	%
28	Rheumatic fever	3	0	**3**	0,49	%
28	Vitiligo	0	3	**3**	0,49	%
32	Cold agglutinin disease	2	1	**3**	0,49	%
32	Addison's disease	2	0	**2**	0,33	%
32	Scleroderma	1	1	**2**	0,33	%
35	Polyendocrine autoimmune insufficiency	1	0	**1**	0,16	%
35	Dermatomyositis	0	1	**1**	0,16	%
35	Autoimmune hepatitis	0	1	**1**	0,16	%
35	Polymyositis	1	0	**1**	0,16	%
35	Reiter's syndrome	1	0	**1**	0,16	%
				615	**n**	

***Table 5**: Ranking of all AIDs in the retrospective study in absolute (which occurred alone, and which occurred with other AIDs) and relative numbers.*

4.3.1 Complications in AID patients

Documented complications were listed in each additional row of the Excel table. These were described with the date, type of complication and treatment. As many different doctors and nursing staff have documented these complications over the past fifteen years, some complications are listed twice or named with different synonyms. For this reason, an ordinal list was also drawn up here, which, for the purpose of evaluation, divides the complications into numbers from 1 to 31, each of which was assigned to a complication. Table 6 shows a ranking of the most common complications.

Nr	Type of complication	Absolute	Relative
1	Postoperative AV block	32	18.61%
2	Postoperative hemorrhage or hematoma	31	18.02%
3	Wound healing disorder	26	15.12%
4	Pleural effusion	20	11.63%
5	Respiratory insufficiency	15	8.72%
6	Infected suture dehiscence	7	4.07%
7	Circulatory failure requiring ECMO connection	6	3.49%
	Cerclage irritation	6	3.49%
9	Postoperative low cardiac output syndrome	4	2.32%
	(Tension) Pneumothorax	4	2.32%
	Burst thorax	4	2.32%
12	Pericardial effusion	3	1.74%
13	Unstable sternum	2	1.16%
	Granuloma	2	1.16%
	Heart failure	2	1.16%
	Upper thoracic aperture skin emphysema	2	1.16%
17	Sternal fistula	1	0.58%
	Postoperative mediastinitis	1	0.58%
	Pericardial fistula	1	0.58%
	Seroma following inguinal cannulation	1	0.58%
	Cardiac arrest	1	0.58%

	Pneumonia	1	0.58%
	Total	**172**	**100%**

***Table 6**: Complications among patients with AID.*

4.3.2 Complications in non-AID patients

In comparison, the group of non-AID patients who were also treated on a CPB between January 2005 and October 2019 was considered with regard to complications that occurred.

The group consists of 10,318 patients. Here, 1,899 patients and therefore 18.40% had a complication after surgery at the CPB. 1,446 patients (76.14%) had 1 complication, 330 patients (17.37%) had 2 complications, 91 patients (3.63%) had 3 complications, 26 patients (1.37%) had 4 complications, 4 patients (0.21%) had 5 complications and 1 person (0.05%) had 7 complications.

A total of 2,506 documented complications (as shown in Table 7) occurred, which indicates that one patient had approximately 1.32 complications. An average age was not available for the 10,318 patients, but it can be assumed that this is similar to that of the AID. Even though more men were operated, significantly more men (1,248 patients, 65,72%) suffered from complications than women (651 patients, 34.28%). The risk ratio (risk of men divided by risk of women) was 0.878, with men without AID therefore having a lower risk of complications than women (approximately 88% of the risk of women). Similarly, the odds risk was lower than for women (OR = 0.852). Thus, although more men were operated on in the group of non-AID patients overall and men had more complications in absolute terms, the individual risk was lower than that for women.

Nr	Type of complication	Absolute	Relative
1	Postoperative hemorrhage or hematoma	529	21.10%
2	Pleural effusion	528	21.07%
3	Postoperative AV block	338	13.49%
4	Wound healing disorder	260	10.38%
5	Respiratory insufficiency	200	7.98%
6	Pericardial effusion	162	6.46%
7	(Tension) pneumothorax	88	3.51%
8	Cerclage irritation	71	2.83%
9	Infected suture dehiscence	58	2.31%
10	Postoperative low cardiac output syndrome	43	1.72%
11	Unstable sternum	42	1.68%
12	Circulatory failure requiring ECMO connection	41	1.64%
13	Resuscitation	36	1.47%
14	Burst thorax	30	1.20%
15	Heart failure	18	0.72%
16	Sternal fistula	13	0.52%
17	Upper thoracic aperture skin emphysema	8	0.32%
18	Corpus alienum	7	0.28%
19	Postoperative mediastinitis	6	0.24%
	Sepsis	6	0.24%
21	Compartment syndrome	5	0.20%
22	Hernia cicatricea	4	0.16%
	Myocardial infarction	4	0.16%
24	Granuloma	3	0.12%
	Cerebral infarction	3	0.12%
26	Dermatosis	1	0.04%
	Kidney failure	1	0.04%
	Pneumonia	1	0.04%
		2,506	**100%**

***Table 7**: Complications among patients without AID.*

In Figure 3 the total number of complications and the proportion of AID and non-AID patients are shown.

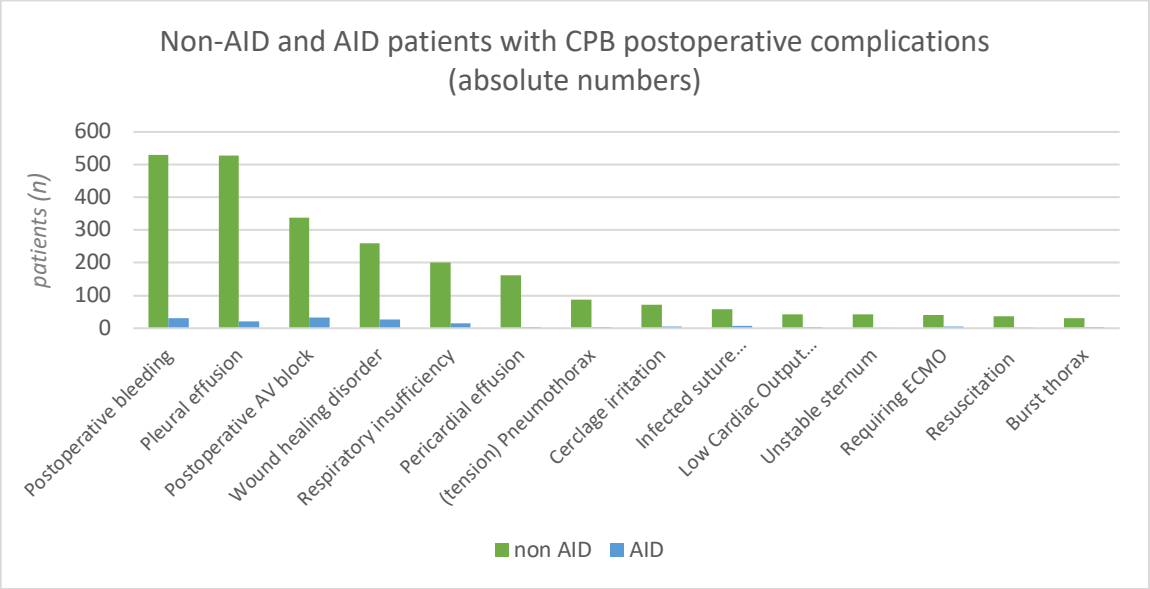


***Figure 3**: Total numbers of complications of non-AID and AID patients (n=10.848).*

In addition, Figure 4 shows the percentage distributions of complications in non-AID and AID patients.

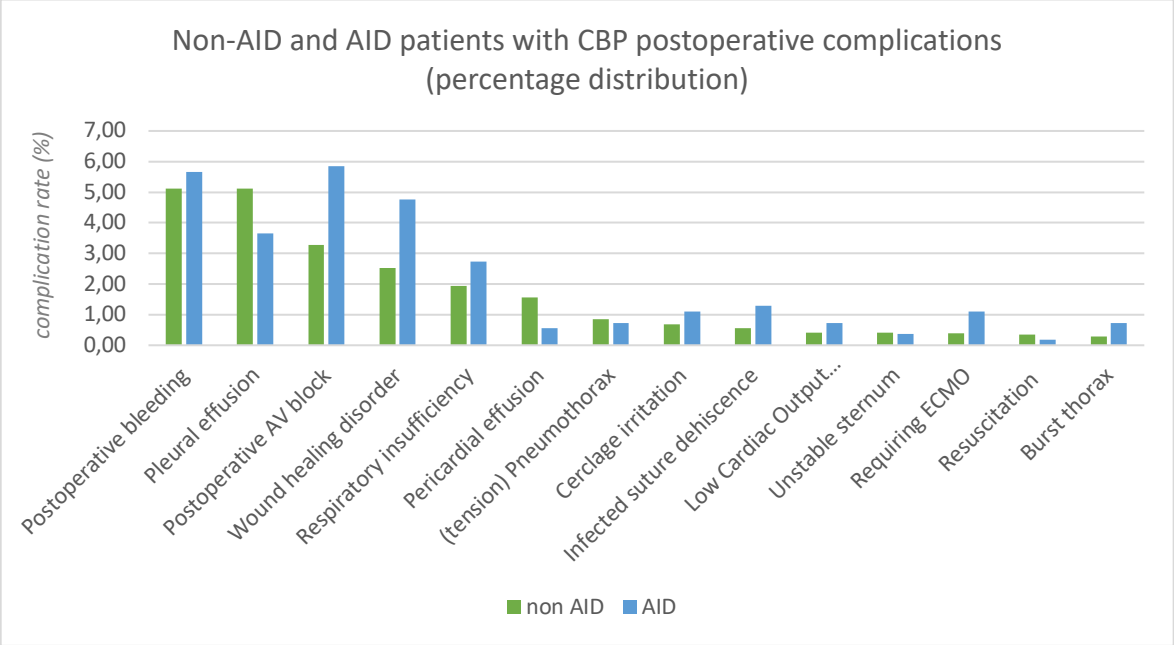


***Figure 4**: Percentage distribution of complications of non-AID and AID patients (n=10.848).*

It is also important to emphasize which complications occurred in which autoimmunological patients. The three most common complications in the most common 17 AIDs (alphabetical order) are shown in Table 8.

AID	N	øyr|	Med	♂ n	♂ %	♂ øyr	♂ Med	♀ n	♀ %	♀ øyr	♀ Med	C ♂	C ♀	Top 3 Complications
Ankylosing spondylitis	22	66.6	67	19	86.36	67.4	67.3	3	13.64	61.9	62.3	21.1%	0%	1) AV block requiring PM (1) Pleural effusion (1) Postoperative bleeding (1) Respiratory insufficiency (1)
Antiphospholipid syndrome	13	67.2	68.8	10	76.92	64.9	66.3	3	23.08	74.9	75.1	0%	66%	1) Wound healing disorder (2) 2) Postoperative mediastinitis (1) Wound infection (1)
Autoimmune gastritis	37	74.2	75.9	23	62.16	71.6	74	14	37.84	78.4	77.3	21.7%	28.6%	1) Postoperative bleeding (3) 2) AV block requiring PM (2) Wound healing disorder (2)
Diabetes mellitus Type 1	101	70.1	71.2	53	52.48	67.8	69.3	48	47.52	72.6	74.1	18.9%	29.2%	1) Postoperative bleeding (8) 2) AV block requiring PM (7) Pleural effusion (7)
Grave's disease	20	65.8	68.9	7	35	60.9	60.1	13	65	68.5	69.5	14.3%	30.8%	1) AV block requiring PM (3) 2) Low Cardiac Output Syndrome (1) Postoperative bleeding (1) PPC requiring ECMO (1)
Hashimoto's disease	66	65.4	65.8	23	34.85	66.7	67.9	43	65.15	64.6	64	30.4%	32.6%	1) Wound healing disorder (6) 2) Respiratory insufficiency (3) 3) AV block requiring PM (2) Cerclage irritation (2) Pneumothorax (2) PPC requiring ECMO (2)
Juvenile rheumatoid arthritis	18	70.7	71.8	10	55.55	69.3	69.6	8	44.45	72.5	74.1	20%	12.5%	1) Pericardial effusion (1) Pneumothorax (1) Respiratory insufficiency (1) Subcutaneous emphysema (1) Wound healing disorder (1)
Polymyalgia rheumatica	15	74.5	76.1	6	40	71	72.2	9	60	76.9	76.2	0%	22.2%	1) Postoperative bleeding (1) Wound healing disorder (1)
Psoriasis	46	63.8	62	33	71.74	61.8	60.6	13	28.26	68.7	67.7	18.2%	23.1%	1) AV block requiring PM (3) 2) Pleural effusion (2) Wound healing disorder (2)
Rheumatoid arthritis	66	72	73.3	32	48.48	71.3	71.9	34	51.52	72.6	73.9	21.9%	39.4%	1) AV block requiring PM (6) 2) Wound healing disorder (5) 3) Pleural effusion (4)
Sarcoidosis	18	64.4	66.0	10	55.55	62.8	63.3	8	44.45	66.8	71.9	10%	62.5%	1) Wound healing disorder (2) 2) Burst pneumothorax (1) Cerclage irritation (1) Granuloma (1) Pericardial effusion (1) Postoperative bleeding (1)

Sjögren's disease	30	69.8	70.6	19	63.33	70	70.9	11	36.64	69.6	69.7	15.8%	18.2%	1) 2)	AV block requiring PM (2) Cerclage irritation (1) Postoperative bleeding (1) Postoperative mediastinitis (1) Wound healing disorder (1)
Systemic Lupus Erythematosus	21	61.6	62.6	11	52.39	63.9	63.1	10	47.61	59	61.7	9.1%	20%	1) 2) 3)	Wound infection (1) Wound healing disorder (2) Cerclage irritation (1) Postoperative bleeding (1)
Temporal arteritis	20	69.6	75.8	10	50.00	63	67.6	10	50,00	76.1	79.8	20%	30%	1) 2)	Wound infection (1) Postoperative bleeding (3) Low Cardiac Output Syndrome (1) Pleural effusion (1) Respiratory insufficiency (1)
Ulcerative colitis	18	66.7	66.4	15	83.33	66.1	66.1	3	16.67	69.4	71.6	33%	0%	1)	AV block requiring PM (2) Postoperative bleeding (2) Wound healing disorder (2)
Werlhof's disease	17	66.7	68.7	12	70.58	65.4	66.8	5	29.42	69.8	72.4	41.7%	0%	1) 2)	AV block requiring PM (3) Pleural effusion (1) Wound healing disorder (1)

MED = Median
C = Complications

***Table 8**: List of the top 16 AIDs in the retrospective study with gender distribution, average age and median age, complication rate in male and female and the three most common complications.*

4.4 Result Overview

A total of 547 patients suffered from at least one AID and underwent CBP surgery between January 2005 and October 2019.

Among these 547 patients, 612 AIDs were found. Specifically, 497 patients (90.86%) suffered from one known AID, 39 patients (7.13%) from two different AIDs, eight patients (1.46%) from three AIDs, two patients (0.37%) from four AIDs and one patient (0.18%) from five different AIDs. With 612 AIDs in 547 patients, this results in a number of 1.16 AID (known and diagnosed) per patient. A representation of these numbers is shown in Figure 7.

The patients who met the criteria for this study were born between 1919 and 2000 (the study includes data from 2005-2019) and were all adults at the time of surgery. The mean age at surgery of 68.3 years (as shown in Figure 5), (18 to 94 years, range 76 years, median 69.7 years, mode 62 years, standard deviation 11.3 years, variance 126.6). These relatively large values indicate that there is a considerable spread in the data.

In the study, 308 of the patients were males and 239 females. Contrary to literature research, which has often shown a higher prevalence of AIDs in women, 56.31% of the participants in this retrospective study are male. The need for cardiac surgery and a generally higher cardiovascular risk makes this group larger in this context than in the general population (El Khoudary *et al.*, 2020).

The average age of women in this retrospective study is 70.1 years (median: 72.4), the average age of men is 67.7 years (median: 66.7). Women included in this study were 21 to 94 years old (therefore a range of 73 years), men were 18 to 85 years old (a range of 67 years) as shown in Figure 6.

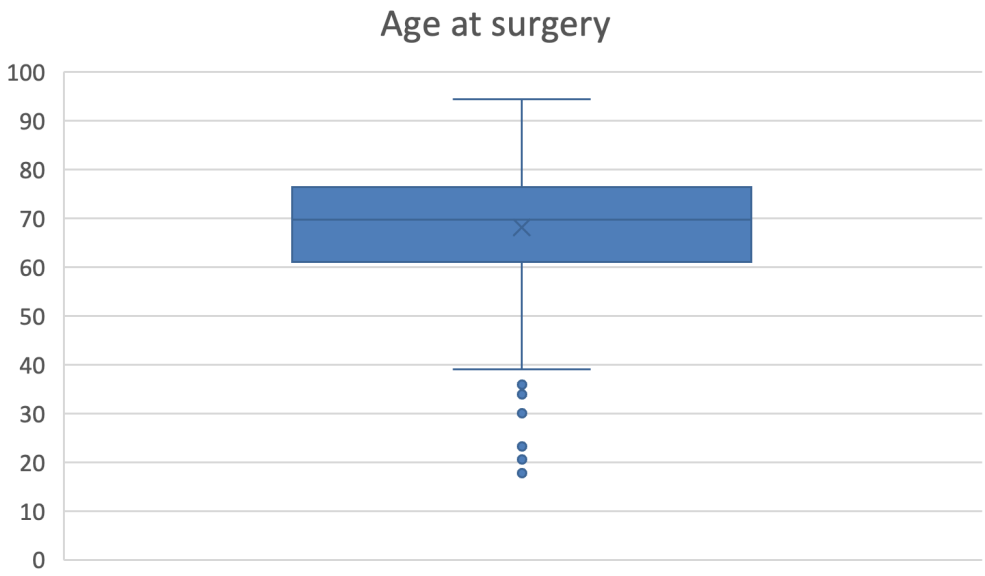


***Figure 5**: Age at surgery box plot diagram, both sexes (n=308).*

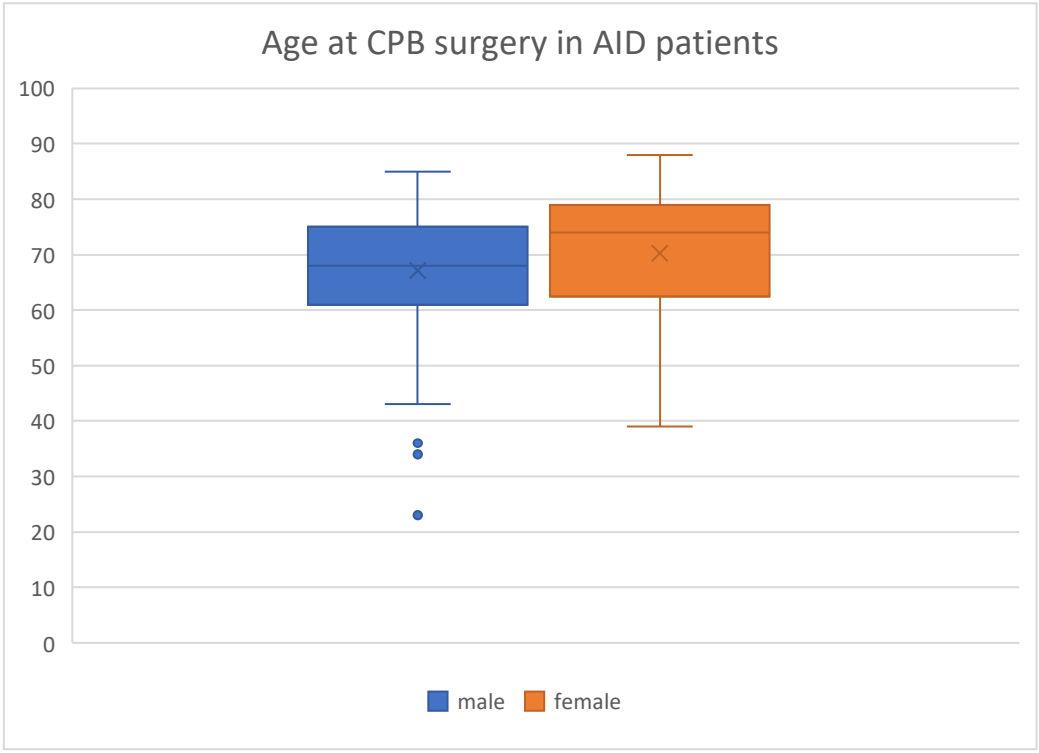


***Figure 6**: Age at surgery box plot diagram, gender distribution (n=547).*

We examined which AID could be found in patients who underwent surgery at the CPB. The majority of patients had only one (diagnosed) AID, but in addition to the absolute number, this statistic also visualizes how often the disease occurs alone (blue) or in combination with other AIDs (orange), depicted in Figure 7.

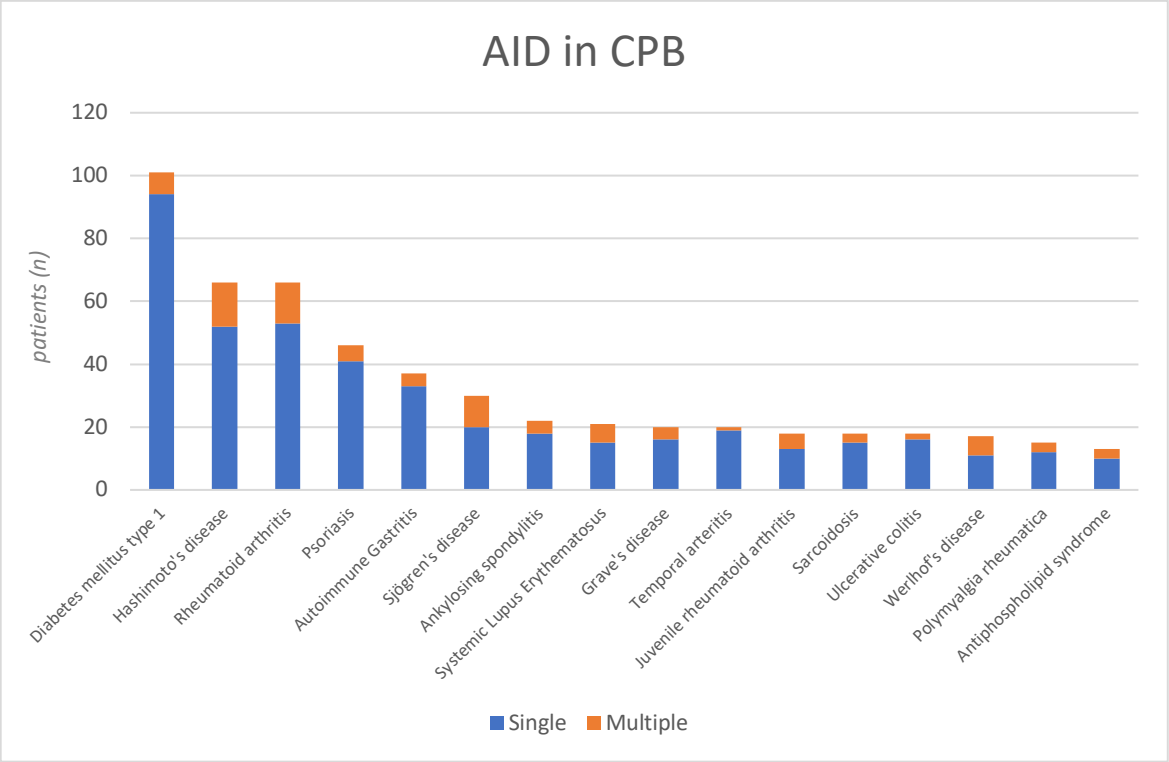


***Figure 7**: Bar chart AID distribution into single and multiple diseases.*

This bar chart (Figure 7) shows which autoimmunological diseases occurred most frequently in the evaluation. The most common 16 out of 39 AID were selected. The remaining 23 autoimmunological diseases occur very rarely: Crohn's disease (n = 11, 1.80% of AID in the study), Wegener's disease (n = 8, 1.31%), celiac disease (n = 6, 0.98%), fibromyalgia (n = 6, 0.98%), Guillain Barré syndrome (n = 5, 0.82%), multiple sclerosis (n = 5, 0.82%), CREST syndrome (n = 4, 0.65%), Goodpasture syndrome (n = 4, 0.65%), mixed collagenosis (n = 4, 0.65%), myasthenia gravis (n = 4, 0.65%), pemphigus vulgaris (n = 4, 0.65%), lichen ruber (n = 3, 0.49%), pernicious anemia (n = 3, 0.49%), rheumatic fever (n = 3, 0.49%), vitiligo (n = 3, 0.49%), Addison's disease (n = 2, 0.33%), cold agglutinin disease (n = 2, 0.33%), scleroderma (n = 2, 0.33%), autoimmunological hepatitis (n = 1, 0.16%), dermatomyositis (n = 1, 0.16%), polyendocrine autoimmunological insufficiency (n = 1, 0.16%), polymyositis (n = 1, 0.16%) and Reiter's syndrome (n = 1, 0.16%).

In the case of AIDs such as Hashimoto's disease, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, juvenile rheumatoid arthritis and Werlhof's disease, according to these statistics in the study, it is common for this AID not to occur alone but together with other AIDs.

4.4.1 Interpretation of the AID ranking

When reviewing the data list of the most common AIDs (Figure 7), it is noticeable that the first five diseases in particular, including diabetes mellitus, Hashimoto's disease, rheumatoid arthritis, psoriasis, and autoimmunological gastritis, have very distinct and usually recognizable symptoms. To list a few, specific parameters as in Hashimoto's disease, joint pain as in rheumatoid arthritis, visible skin changes in psoriasis, persistent abdominal pain as in autoimmunological gastritis and severe hypoglycemia in diabetics lead to a high recognition and clearer diagnosis rate. Over the past years, diagnostic methods and treatment options improved and therefore reduced the risk of undiagnosed and untreated patients.

AIDs further down the list, such as polyendocrine autoimmunological insufficiency, is a symptom complex that does not manifest itself as frequently and clearly. The list only includes diagnosed diseases.

An exact diagnosis usually also leads to treatment. If an AID is so rare that there are hardly any sufficient therapies, it can also be assumed that the disease is present in a more severe form and could therefore lead to far more complications.

5 Discussion

In this chapter, the general statistical results of the retrospective study are presented and explained. A correlation is established between the statistical results and the clinical relevance. These results give rise to considerations that should improve the treatment of autoimmunological patients in the future.

5.1 Complications and Treatments

No complications needing surgical revision and further treatment occurred in 417 patients (76.23%) out of a total of 547 patients. This means that at least one complication occurred in around a quarter of the patients. One complication occurred in 98 patients, two complications in 20 patients, three complications in 6 patients and four complications in 4 patients. In 130 patients (23.77%), at least one complication was found after the surgery (represented in Figure 8).

244 of the 308 men had no complications (79.22%). 49 male patients had one complication (15.90%), 10 men showed two complications (3.24%), 3 men suffered from three complications (0.97%) and only two men showed four different complications (0.64%).

173 of the 239 female patients had no complications (72.38%). 48 women had one complication (20.08%), 13 women had two complications (5.54%), 3 women had three complications (1.25%) and only two women had four different complications (0.84%). This shows that the complication rate is slightly higher among women.

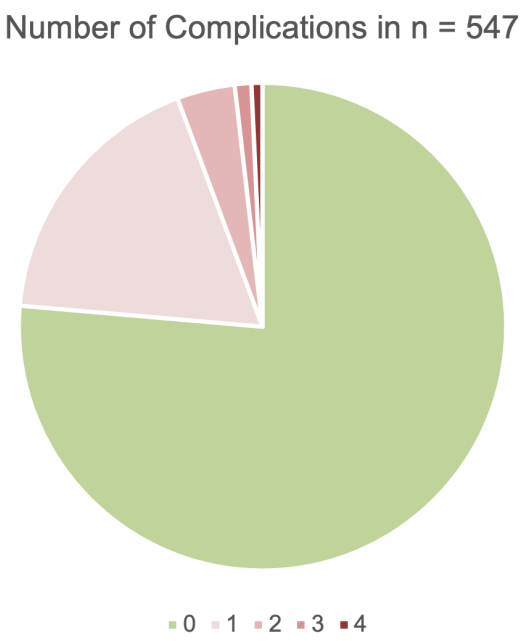
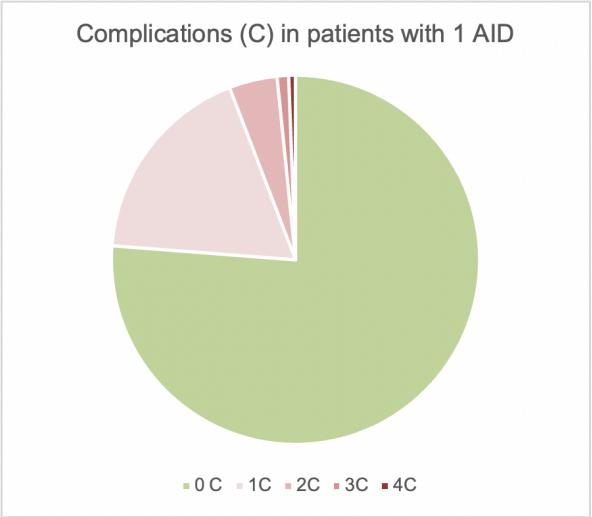
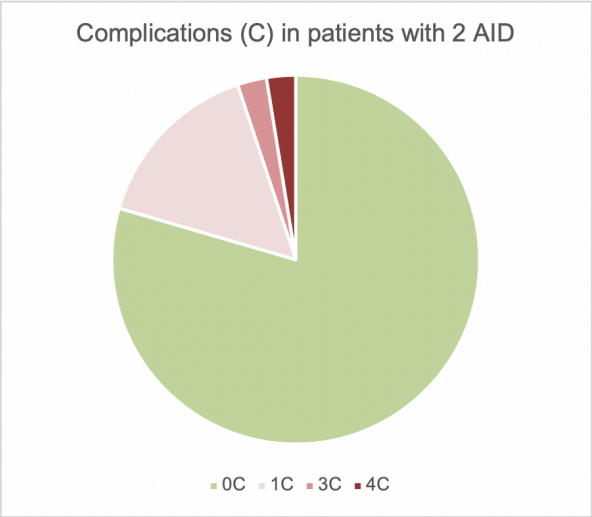


***Figure 8**: Total number of complications (1 to 4 complications) per patient among 547 patients with AID and CPB surgery.*

Subsequently, the question arises as to whether an increased incidence of AIDs (more than 1 AID per patient) leads to multiple complications. Therefore, the number of complications in patients with one and two AIDs was compared in Figure 9. As only a few patients had three, four or five AIDs, these eleven patients were not included in the statistic.





AID	0 C	1C	2C	3C	4C
1	76,20%	17,94%	4,23%	1,01%	0,60%
2	79,49%	15,38%	0%	2,56%	2,56%

***Figure 9**: Patients with one (n=497) or two (n=39) AID and their complications.*

Contrary to the expectation that more AIDs would lead to more complications overall, it was found that patients with two AIDs suffered 3.29% more complications at all. However, there were more serious cases with three or four complications in the group of patients with 2 AIDs.

In the course of the retrospective study, there were 22 different linkable complications in the 15 years of ongoing heart operations in patients with at least one diagnosed autoimmunological disease. Those complications are described in more detail in the following chapter including the following therapy.

5.1.1 Postoperative Atrioventricular Block

The most common arrhythmias that can occur postoperatively after cardiovascular surgery include bradyarrhythmia, onset of sinus node dysfunction and atrioventricular block (AVB). Trauma caused during surgery, local edema, ischemia, or inflammation can be involved in the development of an AVB. The risk is increased by age, duration of clamping of the aorta or pre-existing arrhythmias. According to the meta-analysis from 2023, many AVBs heal spontaneously, but if they persist for

more than 7 days postoperatively, pacemaker implantation should be considered (Yaghoobian *et al.*, 2023). In Graz, implantation was usually performed after a week or two, as described in the literature. In individual cases, however, a pacemaker was implanted on the 2nd postoperative day if an AV block was symptomatic, high grade or unlikely to resolve.

AVBs subsequently lead to an increased risk of heart failure, ventricular tachycardia, syncope, asystole, and even sudden cardiac death. Any complication caused by the AVB can increase the length of stay in hospital. However, the implantation itself can also cause infection, heart injury, a pneumothorax, hematoma, electrode failure or thrombosis (Yaghoobian *et al.*, 2023).

A total of 32 patients (5.85%) with AID required pacemaker implantation after their CPB surgery. Documented indications were most frequently postoperative AV block, but also persistent bradycardia (also with atrial fibrillation) or sick sinus syndrome. The average age of the mixed group was 71.2 years. Around 60% of these patients were male and the average age of those men who received a PM was 70.95 years. 40% of the patients who received a PM are female and the average age here is 71.62 years. This means that the age of women is again higher, but this is also reflected in the overall average age. The most frequent AIDs of the 32 patients with pacemaker implantation were diabetes (7), rheumatism (6) and immune thrombocytopenia, also known as Werlhof's disease (3).

5.1.2 Postoperative Bleeding

Postoperative bleeding after treatment with a CPB is, as already previously described, multifactorial and can be related to the blood exposure of the bypass components. This may lead to complications such as a reduction in the number or dysfunction of platelets, hyperfibrinolysis and hypofibrogenemia and increased consumption and dilution of coagulation factors. Coagulopathies and the resulting bleeding are the most common reasons for transfusion of blood products after CPB surgery. Plasma transfusions in particular can lead to lung injuries, circulatory overload, and infectious and allergic complications (Smith *et al.*, 2022)

In order to counteract this, the use of prothrombin complex concentrates (PCC) has increased in recent years, particularly in the case of perioperative bleeding. PCCs have the great advantage that they are compatible with all blood groups, have a higher factor concentration with a lower infusate volume and can be stored at room temperature (Smith *et al.*, 2022).

However, it must also be emphasized that the administration of protamine to neutralize heparin can lead to side effects such as antibody formation and protamine-induced thrombocytopenia, complement activation, vasoplegia and pulmonary hypertension (Boer *et al.*, 2018). In the case of hematomas or pericardial effusions up to tamponades, these were cleared out, the suture was revised and, if necessary, the aortic cannulation suture was improved with a (revised) tobacco-pouch suture.

A total of 31 patients (5,67%) with AID suffered a postoperative hemorrhage or hematoma after their CPB surgery needing surgical revision. The average age of the mixed group was 67,4 years and therefore presents in a younger age than e.g., an AV block with following PM implantation. The gender distribution of the group is very balanced, with 16 out of 31 patients being female and therefore slightly in the majority. The average age of women who have suffered this complication is 67.06 years, that of men 67.67. Even if there is not a whole year's difference on average, the result stands out, as otherwise the women were also older on average overall. The most frequent AIDs of the 31 patients with postoperative hemorrhage and hematomas were diabetes (8), and chronic atrophic gastritis (3) and temporal arteritis (3). It can therefore be said that chronic inflammation, particularly of the vessels (temporal arteritis), can cause a more complicated postoperative outcome.

5.1.3 Postoperative Complications requiring ECMO

Veno-venous ECMO is used for severe forms of ARDS, (aspiration) pneumonia, asthma, chest trauma, air-leak syndrome, as a bridge before and after lung

transplantation, whereas veno-arterial ECMO is used postoperatively after surgery on the CPB. This is mainly used in cases of refractory cardiogenic shock, combined cardiorespiratory failure, unstable arrhythmias, massive pulmonary embolism, or failure of CPB weaning (Kanchi *et al.*, 2022).

In order to emphasize the difference in functioning of CPB and ECMO, important keywords such as duration, anticoagulation and its neutralization, hemodilution, hypothermia and air-blood interface were clearly presented in a table (Millar *et al.*, 2016), as shown below Table 9.

	CPB	**ECMO**
Duration	Minutes to hours	Days to weeks
Anticoagulation	High-dose heparin	Low-dose heparin
Neutralization	Protamine	Not used
Hemodilution	Yes	Yes (but less than CPB)
Hypothermia	Yes	No
Air-Blood-Interface	Yes	No – closed circuit

***Table 9**: Differences between CPB and ECMO*
Source: adapted from Millar et al. *(Millar* et al*., 2016)*

Complications of the lungs and respiratory system are summarized in descriptive studies and papers under Postoperative Pulmonary Complications (PPC) (Fischer *et al.*, 2022). The data from the University Hospital of Graz include pneumothoraxes, respiratory insufficiency, postoperative mediastinitis or pneumonia, as well as pleural effusions and burst thoraces. In the case of tension pneumothorax, a suction-irrigation drainage was inserted into the pleural cavity. Tracheostomies were also inserted postoperatively after the 10th postoperative day for long-term mechanical ventilation. The other pulmonary complications, which did not require ECMO, were assessed and evaluated separately.

A total of 6 patients (around 1%) with AID suffered postoperative complications requiring ECMO therapy right away. The average of the mixed group was 60.3 years, and therefore is younger than other complications. The gender distribution

was completely balanced, but due to the very small number of patients and outliers, it is difficult to discuss the age average numbers (men 61.3, women 59 years). It is also difficult to make a specific statement about the most frequent AIDs in these patients, as it turns out that one third, i.e. two patients, had a known diagnosis of Hashimoto's thyroiditis.

5.1.4 Postoperative Heart Failure

In postoperative heart failure, a clinical distinction is made between forward and reverse failure with different symptoms. Acute forward failure of the right ventricle is characterized by secondary left heart failure with reduced cardiac output. This leads to microvascular dysfunction, hypoperfusion of multiple organs and thus to centralization. This is clinically manifested by altered consciousness, cold extremities, oligo- to anuria and hypoxemia. Both forward and reverse failure lead to gastrointestinal and liver failure. Acute reverse failure also leads to hepatojugular reflux, distension of the jugular vein, tricuspid regurgitation, and a paradoxical pulse. Over time, ascites, anasarca, and peripheral edema develop if not treated in time or unsuccessfully (Ende *et al.*, 2022).

As a measure for mechanical circulatory support, an intra-aortic balloon pump (IABP) is used to prevent or treat low cardiac output syndrome. In addition, the IABP can be used postoperatively after heart surgery, but also in cases of ischemic heart disease, heart failure and acute coronary syndrome. If IABP is used during surgery, studies show that cardiac output can improve by 10 to 30%, especially if patients have a low left ventricular ejection fraction and therefore a low cardiac output. By reducing afterload and increasing diastolic pressure, IABP reduces the oxygen demand of the myocardium and at the same time improves oxygen supply (Samanidis *et al.*, 2020).

A total of 6 patients suffered either postoperative heart failure (2) or diagnosed postoperative low cardiac output syndrome (4) and therefore presents in approximately 1% or patients with an AID after their CPB surgery. The average age

of the mixed group was 71,8 years, the distribution between male and female was 2:4. Given the small numbers and the outliers, it was difficult to compare the average age figures, which for both sexes was 72 years. All 6 patients had a different AID, so no statement can be made here as to which AID might have been most frequently involved in this complication.

5.1.5 Postoperative Wound Healing Disorders and Infections

As described in chapter 2.2.1, the most common surgical approach for cardiac surgery, especially with CPB, is the median sternotomy. If a wound healing disorder occurs postoperatively and this scar becomes infected, a deep sternal wound infection (DSWI) develops. This shows an infection or spontaneous dehiscence, positive evidence of cultures of the mediastinal fluid, sternal wound swaps and/or in the blood culture, a body temperature of over 38 degrees Celsius and / or pain in the chest with sternal instability. At least one of the criteria must apply. Patients at risk of DSWI include older, obese, and diabetic patients, as well as long-term smokers and patients with impaired immune function (Song and Liu, 2020). Additionally, more than a quarter of patients show hypertrophic scarring after a median sternotomy following CPB surgery, which is usually caused by an increased inflammatory load, especially after cardiac surgery (Chello *et al.*, 2021).

Extended wound management is required to counteract DSWI. This includes surgical debridement, antibiotics, and wound closure treatment. Covering the skin defect with a pedicled omental flap or vertical or transverse flaps of the rectus abdominis muscle have not been considered successful, so a pectoralis major muscle transfer flap is currently considered the best method. However, this method damages the pectoral muscle and restricts its blood supply and therefore the function of the upper limbs (Song and Liu, 2020). According to a study from Pakistan, an increased body mass index is not significantly ($p>0.05$) associated with prolonged wound healing. However, according to the study, a low albumin level and poor blood glucose control were significant preoperatively. This shows that a

nutritional intervention can have a better outcome with regard to complications (Zaffar *et al.*, 2022).

Wound revision, wound debridement and necrectomy, secondary suturing and repetitive VAC changes were usually performed at the University hospital of Graz. VAC changes were performed under laryngeal mask anesthesia or sedoanalgesia. In the documented complications, the (delayed) wound healing is not only associated with the median sternotomy scar, but also with the saphenectomy to harvest the graft during CABG surgery. Methods used to close the incision wound are standard wire, wire closure z, Robicsek method and metal plates.

In the category of wound healing disorder, a distinction was made as to whether there was prolonged wound healing or a disorder, or whether the wound had also become infected. A total of 26 patients with an AID and therefore 4,75% and therefore 4.75% had severely prolonged or impaired wound healing. The average age in the mixed group is 67.7 years. Approximately 70 percent of wound healing disorders occurred in women with AID, showing a definite difference in this complication between the two sexes. Women with impaired wound healing after CPB surgery were on average 66.83 years old, men 69.25 years old. However, no sufficient data were available to examine this difference; the standard deviation was 9.69 years for men and 11.67 years for women. The largest group was Hashimoto's thyroiditis (6), followed by diabetes (5) and rheumatism (4). It was also worth noting that around a quarter (5) of these patients with wound healing disorders had multiple AIDs.

Of the 26 patients with a wound healing disorder, 6 patients later had an infected wound. The average age in this smaller group, which was significantly more balanced from a gender perspective (4 women, 3 men), was 64,9 years with a strong outlier of a 39-year-old woman. Once again, it was shown that two out of seven patients had multiple AIDs as mentioned one paragraph earlier, with no single AID standing out in particular.

5.1.6 Postoperative Pneumothorax

A pneumothorax is the presence of air in the pleural cavity. It can occur not only as a postoperative complication, but also as a result of traumatic, malignant, inflammatory, hormonal, or infectious etiologies. The degree of severity varies from asymptomatic to life-threatening (Huan, Sidhu and Thomas, 2021). A multicenter prospective observational study from the United States compared the different postoperative pulmonary complications (PPC) within the first 7 days after surgery and claimed that, out of several complications, pneumothorax was a rarer one. Nevertheless, PPC may lead to prolonged ICU or hospitalization (Fernandez-Bustamante *et al.*, 2017).

Postoperative pneumothorax occurred in 4 out of 547 patients with AID, i.e., a proportion of 0.73%. The average age was 70.3 years. These 4 patients included two women (average age 68.5 years) and two men (average age 72 years). Again, it was difficult to make a statement about the frequency of AIDs because the data set was very small. However, 2 of these 4 patients suffered from Hashimoto's thyroiditis.

5.1.7 Respiratory insufficiency (RI)

Respiratory insufficiency (RI) describes the inadequate gas exchange between the inhaled air and the body's own organs. Pathophysiological mechanisms that lead to RI are often found in the lung tissue itself or in alveolar hypoventilation. RI is subsequently divided into hypoxic and hypercapnic RI. If non-invasive therapy in the form of oxygen administration is not sufficient, invasive methods must be used (Fritsch and Bickenbach, 2018).

At the Cardiac Surgery Department in the University Hospital of Graz, respiratory insufficiency was categorized as such and listed as a complication if it also required invasive treatment. Longer intubation times or slow weaning after CPB surgery are not uncommon, which is why only tracheotomies that are helpful against severe respiratory insufficiency were included.

A total of 15 patients (2.74%) with AID suffered respiratory insufficiency after their CPB surgery. The average of the mixed group was 68.5 years. The gender distribution was strongly male-dominated and showed a percentage of 80 per cent (12 of the 15 patients). The male was on average 69.5 years old and was therefore approximately 5 years older than the female group, which only had three patients with an average age of 64.6 years. The consideration of AID was difficult because there were many different diseases that also suffered from postoperative respiratory insufficiency. Therefore, the largest group included 3 cases with Hashimoto, followed by 2 patients each with diabetes and rheumatism.

5.1.8 Pleural effusion

In a healthy body, the production and absorption of pleural fluid is intact and amounts to approximately 0.2 mL/kg/hour. The volume of this fluid is determined by the balance of oncotic and hydrostatic pressure differences. If this balance is disturbed by heart failure, malignant diseases, bacterial pneumonia or pulmonary embolism, the new pressure differences lead to an increase in pleural fluid and thus to pleural effusion (Jany and Welte, 2019). The treatment for the pleural effusions included punctures of the pleural cavity (performed under local anesthesia), drainage and sternal refixation.

Of 547 patients, 20 patients, i.e., 3.66%, developed a pleural effusion postoperatively. The average age of these patients is 70.3 years, the group is exactly balanced in terms of gender. The 10 men have an average age of 65.7 years (standard deviation 13.62), that of the 10 women is 74.8 years (standard deviation 10.27). It is therefore very clear that younger men unfortunately suffer from pleural effusions more often than women, although both groups suffer equally from AID and were operated on with CPB. Among these 20 patients, 7 patients had diabetes and 4 patients had a rheumatic disease.

5.2 Errors and Bias

5.2.1 Publication bias

As described in Chapter 3.2 Literature: Status quo, publications with regard to the individual autoimmunological diseases is very sparse. Unfortunately, not all publications are available directly or in the common literature libraries (in this thesis, PubMed was mainly used). This means that research results are not available for all diseases associated with CPB and therefore this information cannot be processed adequately. Similar to the time period of the operations, the literature was selected from the last twenty years, mostly from the last five years. Similarly, papers are more likely to be published that indicate a significant difference in their results, which leads to other studies being underrepresented. And just as there are only a few autoimmunological diseases in the patient group of the retrospective study, it can be assumed that too little information and data is available for individual autoimmunological diseases to date to process them in a study.

5.2.2 Information bias

This bias can occur when information such as a diagnosis is not available or was not available almost 20 years ago when the first data for the retrospective study were collected. It is not known whether all patients who have an autoimmunological disease have already been tested and diagnosed. This leads to an incorrect estimate of the number of patients with an autoimmunological disease. Not every autoimmunological disease manifests itself at the same age, which is why there may also be an inequality here. Under these circumstances, it can be assumed that the number of unreported cases is higher. The documents are also not always accessible because they are subject to paywalls, and it was not always possible to pay for them in the case of over 50 papers. It is also possible that AIDs are known, but not noted in the patient file. It can therefore be assumed that the actual percentage and thus the number of unreported cases of patients with AIDs is higher.

5.2.3 Observer bias

Observational bias arises when people deliberately look for papers on specific topics that confirm or contradict their own hypothesis or expectations. Other studies can be neglected or even ignored, and the bias can thus influence the result. When evaluating almost 11,000 patients, it is also possible to be influenced by the data above or below the datasets and categorize similarly too quickly.

5.3 Approaches: Preoperative screening for AIDs

Following the evaluation and consideration of the data on AID patients, including the potential complications following surgery at CPB, the question arises as to how future patients should be treated.

5.3.1 Preoperative Screening for AIDs

One of the biggest problems continues to be that many AIDs remain undetected and underdiagnosed. The most striking manifestation of AIDs is the production of autoantibodies, which, depending on the state of research of the disease in question, are potentially detectable in laboratory parameters (Pisetsky, 2023).

Ultimately, a blood test or other laboratory analysis still requires a medical history interview in which questions about potential AIDs are asked. However, the fact that CPB examinations often have to be carried out urgently means that there is no time for a detailed interview. In addition, the symptoms of AIDs are extremely varied. They can trigger organ-specific, but also organ-spanning symptoms, but can also be clinically (still) asymptomatic. Possible anamnestic questions would include family-related genetic history in addition to symptoms that have already occurred. The time of manifestation of AIDs is also too different to be able to set age limits that could be used as a guide. Therefore, the medical history interview with laboratory diagnostics prior to surgery at the CPB remains a suggestion, but not a guarantee for the definitive diagnosis of autoimmunological diseases.

5.3.2 Specialist consultation

Since it must be assumed that not all AID patients will be discovered in a preliminary consultation prior to CPB surgery, it is necessary to focus on known diagnoses in the patient history in order to best address individual needs. An AID diagnosis can also be compared with the table in Chapter 4.2, for example. This provides

informative results for the 16 most common AIDs from 15 years (2005-2019) regarding possible complications that can occur due to CPB.

If the patient is known to have a very rare or complication-prone AID, a rheumatology, neurology, or dermatology consultation can be convened to review the requirements for CPB surgery and clarify them with the cardiac surgeon, the CPB team and the anesthesiologist. In this way, possible complications can also be potentially prevented by changing e.g., the heparinization, adjusting the hypothermia temperature or pre-, intra-, or postoperative medication and individually adjust the conditions to the patient. As patients with AIDs tend to increase in the population (statistically also due to better diagnostic options) and will therefore always remain part of operations, it would also be advantageous to continue updating data lists in order to stay up to date, identify changes and acquire new data and findings.

6 Conclusio

After the completion of this retrospective study and with regard to the incidence of AID patients in the overall collective of patients requiring cardiac surgery at the Department for Cardiac Surgery at the University Hospital of Graz, the clinical relevance of this patient group became apparent.

When evaluating the data, the question always arises as to whether autoimmunological diseases should be considered in relation to gender or age. In addition, AIDs occur in men and women in varying degrees of severity, manifest themselves at different times and can be continuous or progressive, mild to negligible or severe. The classification into the different categories and the search for the one “right” category, the equally decisive effects of other (non-AID-related) diseases on the body and the still uncertain and insufficient data on AIDs make it difficult to find clear answers. More research is definitely needed, ultimately also with regard to the definitions of individual AIDs and far-reaching pathogenesis. Such findings could help to understand further pathogenetic mechanisms in relation to cardiopulmonary bypass and reduce complications.

It is clear in this retrospective study that the complication rate in AID patients is around 5% higher than in patients without AID. This shows a need for action and far-reaching, interdisciplinary cooperation for the best possible patient care in the future.

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