Aus dem

CharitéCentrum für Herz-, Kreislauf- und Gefäßmedizin

Klinik für Kardioanästhesiologie und Intensivmedizin

(Direktor: Prof. Dr. Benjamin O'Brien)

Habilitationsschrift

Präklinisches Management von akuten Typ A Aortendissektionen (Stanford-Klassifikation)

zur Erlangung der Lehrbefähigung für das Fach Anästhesiologie

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von

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MEINER FAMILIE

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Verzeichnis der verwendeten Abkürzungen in alphabetischer Reihenfolge

ADDRS – Aortic Dissection Detection Risk Score

AHA – American Heart Association

ATAAD – Akute Typ A Aortendissektion

DHZB – Deutsches Herzzentrum Berlin

HLM – Herz-Lungen-Maschine

HRQoL – Health Related Quality of Life

IRAD – International Registry of Acute Aortic Dissection

LVAD – Left Ventricular Assist Device

LVEF – Linksventrikuläre Ejektionsfraktion

MRT – Magnetresonanztomographie

RVEF – Rechtsventrikuläre Ejektionsfraktion

PCT – Pain Cut Time

PTSD – Posttraumatische Belastungsstörung

PDS – Post-traumatic Diagnostic Scale

PTSS-14 – Post-traumatic Stress Scale-14

RTW – Rettungstransportwagen

SF-12 – Gesundheitsfragebogen in Kurzform

SVAS – Supravalvuläre angeborene Aortenstenose

TEE – Transösophageale Echokardiographie

TTE – Transthorakale Echokardiographie

1 Einleitung

1.1 Historie

Die akute Typ A Aortendissektion nach der Stanford-Klassifikation (ATAAD) gehört auch in der heutigen Zeit zu einer der dramatischsten Erkrankungen der Notfallmedizin. Die erste historische Beschreibung einer ATAAD erfolgte im Jahr 1760 nach dem Tod des damaligen Königs von England, Georg II. Der König kollabierte plötzlich am Morgen des 25. Oktober in seiner Kammer im Kensington-Palast. Man fand ihn regungslos mit einer Platzwunde an der Schläfe am Boden liegend vor. Auf Veranlassung seines damaligen Kämmerers wurde eine Obduktion des Leichnams angeordnet. Der damalige Leibarzt des Königs Frank Nicholls obduzierte den Leichnam am darauffolgenden Tag und beschrieb seine Beobachtungen ausführlich in seinem Bericht. Nicholls (1761) schrieb unter anderem: „[...] *the pericardium was found distended with a quantity of coagulated blood, nearly a pint*" (S. 575). Die Menge des Blutes, ein „*pint*", entspricht ungefähr einem halben Liter. Nachdem er das Blut aus dem Perikard entfernt hatte, zeigte sich im oberen Bereich des rechten Ventrikels ein Loch von der Größe eines kleinen Fingers. Das Blut hat das Herz vollständig komprimiert und damit den Kreislauf zum Erliegen gebracht. Der Leichnam wies somit eine Perikardtamponade als eine der typischen Leitkomplikationen der ATAAD auf. Nach Eröffnung des aufsteigenden Teils der Aorta erkannte der Obduzent neben einer aneurysmatischen Erweiterung der Aorta einen ca. 3,75 cm langen Riss in der inneren Gefäßwand der Aorta. Dieser Einriss fand sich auch in späteren chirurgischen Beschreibungen (siehe Abb. 1) wieder. Nicholls zeigte anhand dessen auch eine der möglichen Ursachen einer ATAAD auf, nämlich eine Erweiterung der Aorta. Diese führte vermutlich auch zu einer Kompression der Pulmonalarterie und damit zu einer Druckbelastung des rechten Ventrikels sowie der letztlichen Ruptur im Rahmen der ATAAD. Des Weiteren ist festzuhalten, dass Nicholls sehr präzise formulierte, dass der Erweiterung der Aorta sicherlich eine längere Entwicklung vorausgegangen war. So hatte der König offenbar bereits viele Jahre vorher über immer wiederkehrende thorakale Beschwerden geklagt.

Als einer der ersten Wissenschaftler beschrieb der Chirurg und Anatom Jean-Pierre Maunoir aus Genf die Dissektion der Aorta bei seinen anatomischen Studien der Arterien (Maunoir, 1802). In weiteren historischen Aufzeichnungen finden sich noch zahlreiche Beschreibungen von Aortendissektionen unterschiedlicher Wissenschaftler im Rahmen von pathologischen Sektionen. Der französische Arzt René Théophile Hyacinthe Laennec beanspruchte als erster den Begriff der

Aortendissektion im Jahre 1819 für sich (Laennec, 1826). Die erste größere pathologische Obduktionsserie und Beschreibung der ATAAD erfolgte durch den englischen Kardiologen und Gründer des London Chest Hospital, Thomas Bevill Peacock. Er stellte in einer Untersuchung von 19 Fällen sehr detailliert die Pathophysiologie der Aorta sowie das Alter und das Geschlechterverhältnis der Betroffenen im Rahmen einer Dissektion dar (Leonard, 1979). Außerdem erkannte Peacock in seinen Beobachtungen als einer der ersten Wissenschaftler, dass es einen Unterschied im zeitlichen Verlauf der Erkrankung bei einer Beteiligung der aufsteigenden oder der absteigenden Aorta bis zum Tode des Patienten gibt. Dies war der erste Hinweis in der Geschichte, dass die Diagnostik, die Behandlung und damit der zeitliche Verlauf der Erkrankung eine entscheidende Rolle bei der Sterblichkeit dieser Patienten spielen könnten. Bis zur ersten erfolgreichen operativen Versorgung eines dissizierten Aortenaneurysmas dauerte es allerdings noch mehr als hundert Jahre. Diese erfolgte am 7. Juli 1954 an einem 58-jährigen Patienten in Houston durch das Team von Michael Ellis DeBakey (Creech, DeBakey and Mahaffey, 1956). Als eine der ersten detaillierten Beschreibungen einer herzchirurgischen Operation an einer dissizierten aneurysmatischen Aorta zählt die Arbeit von DeBakey, Cooley und Creech aus dem Jahr 1956. Die nachfolgende Abbildung 1 aus (DeBakey et al., 1956) zeigt die pathologischen Merkmale eines dissizierten Aortenaneurysmas.

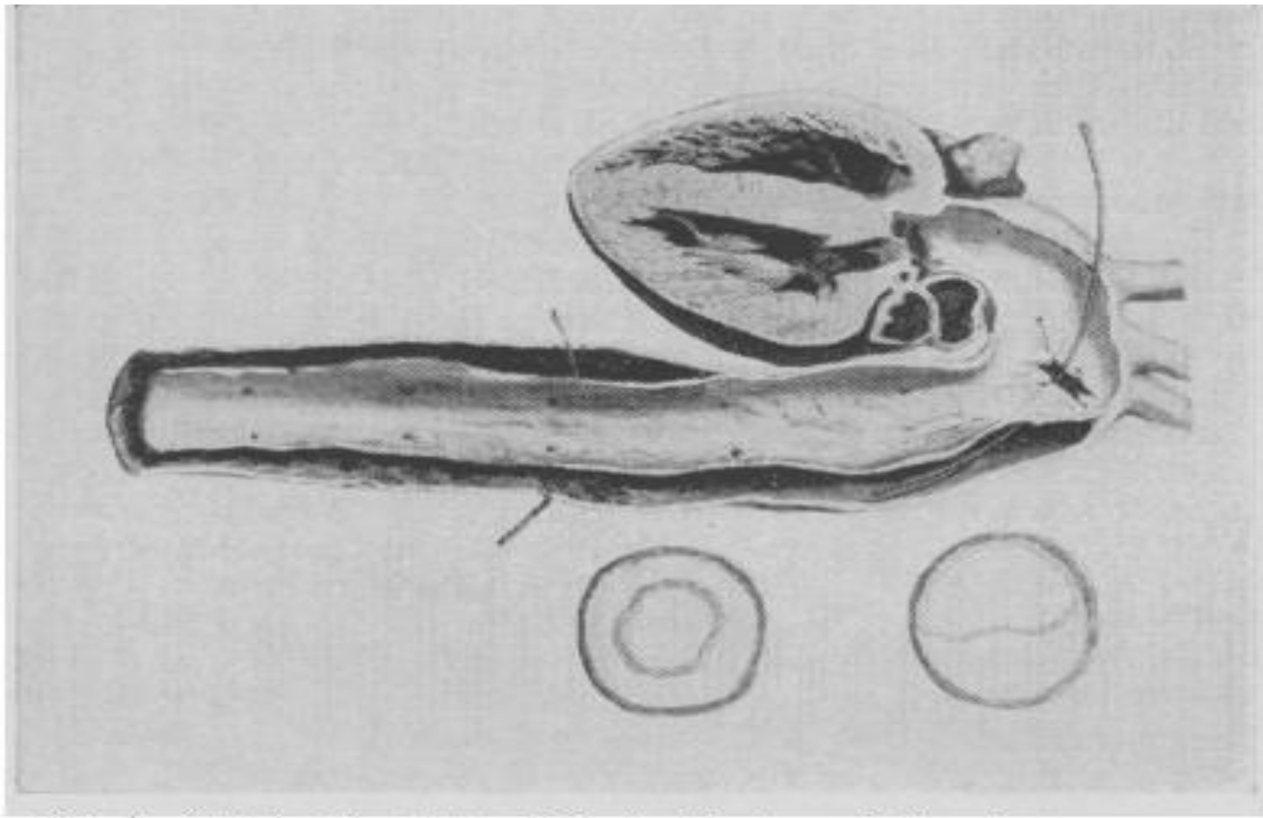

Fig. 1.—Drawing showing pathological features of dissecting aneurysm.

Abbildung 1: Drawing showing pathological features of dissecting aneurysm – SURGICAL TREATMENT OF DISSECTING ANEURYSM (DeBakey et al., 1956)

Die Autoren beschrieben dabei die einzelnen operativen Schritte zur Ausschaltung des Entrys des aufsteigenden Teils der Aorta und auch die damit verbundene perioperative Versorgung eines Patienten in tiefer Hypothermie (DeBakey et al., 1956). Im Gegensatz zur heutigen Operationstechnik war der erste Operationsschritt nach Anschluss an die Herz-Lungen-Maschine die Darstellung der Aorta descendens über eine linksposteriore, laterale Thorakotomie und das Anbringen einer Ligatur. Anschließend erfolgte das Ausklemmen der Aorta, die Entfernung des dissizierten aneurysmatischen Segments und der anschließende Ersatz der Aorta durch einen Homograft. Erst im weiteren Verlauf wurde die Aorta ascendens chirurgisch versorgt. In der nachfolgend dargestellten Abbildung 2 wird der chirurgische Schritt des Ausklemmens der Aorta beschrieben.

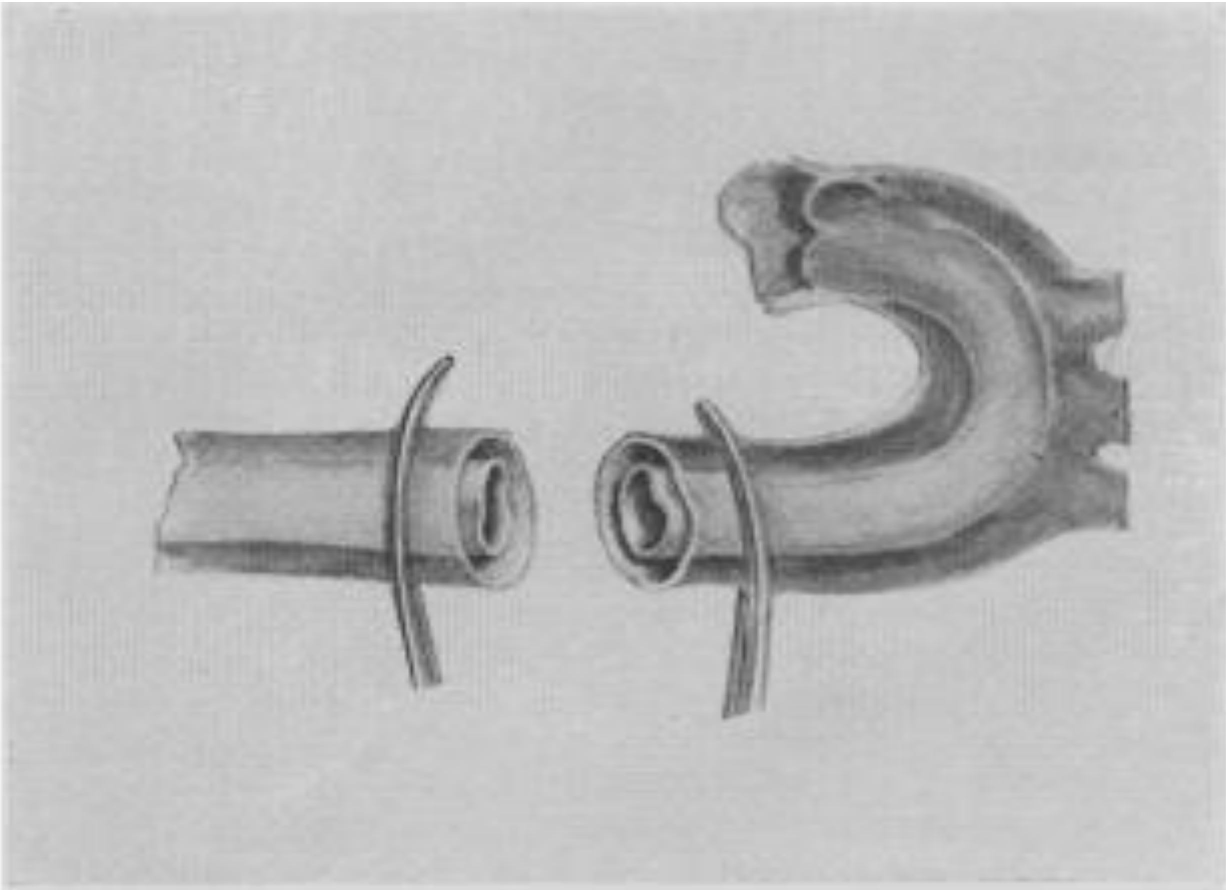

Fig. 4.—Next step in operation, cross clamping aorta and dividing it between clamps. Characteristic "double-barreled" opening representing inner true lumen and outer false lumen may be observed.

Abbildung 2: Next step in operation, cross clamping aorta and dividing it between clamps. Characteristic "double-barreled" opening representing inner true lumen and outer false lumen may be observed – SURGICAL TREATMENT OF DISSECTING ANEURYSM – (DeBakey et al., 1956)

In der heutigen Zeit erfolgt die herzchirurgische Versorgung der akuten Aortendissektion Typ A über eine mediane Thorakotomie und einen Ersatz der Aorta durch ein künstliches Geweberohr (Aortenprothese). Die modernen Aortenprothesen bestehen in der Regel aus Polyethylenterephthalat (PET) oder Polyester. PET-Prothesen werden in der Regel für große Gefäße verwendet (z. B. Aorta), da sie aufgrund ihrer schlauchförmigen Struktur und ihrer gefalteten Oberfläche flexibler sind. Auf diese Weise werden die Eigenschaften echter Gefäße besser nachgeahmt.

1.2 Epidemiologie

Es liegen zahlreiche bevölkerungsbasierte Studien vor, in denen die Inzidenz der akuten Aortendissektion untersucht wurde. Eine der längsten bevölkerungsbasierten Längsschnittstudien aus West-Ungarn ergab nach Untersuchung von 1972 bis 1998 (27 Jahre) eine Inzidenz von 2,9 Fällen pro 100 000 Personen (Mészáros et al., 2000). Eine weitere bevölkerungsbasierte Längsschnittstudie aus Olmsted County, Minnesota, aus dem Jahr 2004 erfasste über einen Zeitraum von 1980 bis 1994 (14 Jahre) alle klinisch diagnostizierten akuten Aortendissektionen. Die Inzidenzberechnung ergab hier 3,5 Fälle pro 100 000 Personen (Clouse et al., 2004). Im Jahr 2006 zeigte eine schwedische bevölkerungsbasierte Längsschnittstudie Studie über einen Beobachtungszeitraum von 1987 bis 2002 (16 Jahre) sogar eine Zunahme der Inzidenz von 10,7 bis 16,3 Fällen bei Männern und 7,1 bis 9,1 Fällen bei Frauen pro 100 000 Personen. Hier ist anzumerken, dass in dieser Studie nicht klar zwischen thorakalen Aortenaneurysmen und Aortendissektionen unterschieden wurde (Olsson et al., 2006). In einer im Jahr 2013 durchgeführten bevölkerungsbasierten regionalen Längsschnittstudie aus Norditalien (Emilia-Romagna) wurde von einer Inzidenz von 4,7 Fällen pro 100 000 Personen im Beobachtungszeitraum von 2000 bis 2008 (8 Jahre) berichtet (Pacini et al., 2013). Eine eigene durchgeführte bevölkerungsbasierte Längsschnittstudie aus der Region Berlin-Brandenburg, unter Einbeziehung von Obduktionsdaten über einen Beobachtungszeitraum von 2010 bis 2014 (5 Jahre), ergab eine Inzidenz von 11,9 Fällen pro 100 000 Personen (Kurz et al., 2017). Alle diese unterschiedlich durchgeführten bevölkerungsbasierten epidemiologischen Studien zeigen jedoch, dass die Erkrankung mit einer Inzidenz von 2,9 bis 16,3 Fällen pro 100 000 Personen zu den seltenen Erkrankungen zählt. Ein weiterer interessanter Aspekt der ATAAD ist die Inzidenz der Erkrankung im Patientengut von zentralen Notaufnahmen. Wundram et al. konnten in ihrer Arbeit aus dem Jahr 2020 zeigen, dass diese Inzidenz zwischen 5,9 und 24,9 pro 100 000 Patienten liegt. Das bedeutet, dass man in einer größeren Notaufnahme mit ca. 50 000 Patienten pro Jahr mit bis zu zwölf Fällen rechnen muss (Wundram et al., 2020).

1.3 Ätiologie

Die Aorta hat eine komplexe Anatomie und Physiologie. Die Wand besteht aus drei Schichten, der Intima (Tunica intima), der Media (Tunica media) und der Adventitia (Tunica externa). Die Tunica intima ist ein stoffwechselintensives, einschichtiges Endothel, das von einer relativ lockeren Gewebeunterschicht getragen wird. Diese Unterschicht ermöglicht die Bewegung der Intima relativ zur Media, wenn sich die Aorta während des Herzzyklus ausdehnt und zusammenzieht. Die Media setzt sich aus ca. fünfzig Lagen gefensterter, lamellarer elastischer Fasern zusammen. Kollagenfasern, glatte Muskelzellen und Elastin sind dazwischen eingelagert und ermöglichen die Dehnbarkeit der Aorta. Elastin (bzw. seine Vorstufe Tropoelastin) ist ein Faser- oder Strukturprotein, das sich in den Blutgefäßen von Wirbeltieren findet. Beide Eigenschaften sind für eine optimale Funktion der menschlichen Aorta notwendig. Mutationen im Elastin-Gen können erbliche Erkrankungen verursachen, wie das Marfan-Syndrom, Dermatochalasis, supravalvuläre angeborene Aortenstenose (SVAS) und das Williams-Beuren-Syndrom. Die kollagenen Fasern der Adventitia sind das genaue Gegenteil des Elastins. Ihre Steifigkeit ist ca. 5000-mal stärker als die von Elastin. Die kollagenen Fasern haben die Aufgabe, die Aortenintegrität zu unterstützen und Scherkräften des Blutflusses zu widerstehen. Die Adventitia besteht aus einer Mischung von Kollagen und Bindegewebe. Die Vasa vasorum innerhalb dieser Adventitialschicht sorgen für die entsprechende Nährstoffzirkulation.

1.4 Pathogenese und Klassifikation

Bei einer akuten Typ A Aortendissektion (ATAAD) kommt es zu einem Einriss in der Intima (Entry) und teilweise der Media mit einer nachfolgenden Aufspaltung (Dissektion) der beiden Wandschichten. Diese Dissektion kann sich auf wenige Zentimeter der Aorta begrenzen, sie kann sich jedoch auch bis auf die gesamte Aorta ausdehnen. Dabei ‚wühlt' sich das Blut zwischen den beiden Schichten entlang und führt im Verlauf der Aorta, je nach Lokalisation der Dissektion, zu einer Unterbrechung der Blutversorgung ganzer Organsysteme. Die nachfolgende Abbildung 3 zeigt die Pathogenese einer akuten Aortendissektion und eines intramuralen Hämatoms der menschlichen Aorta.

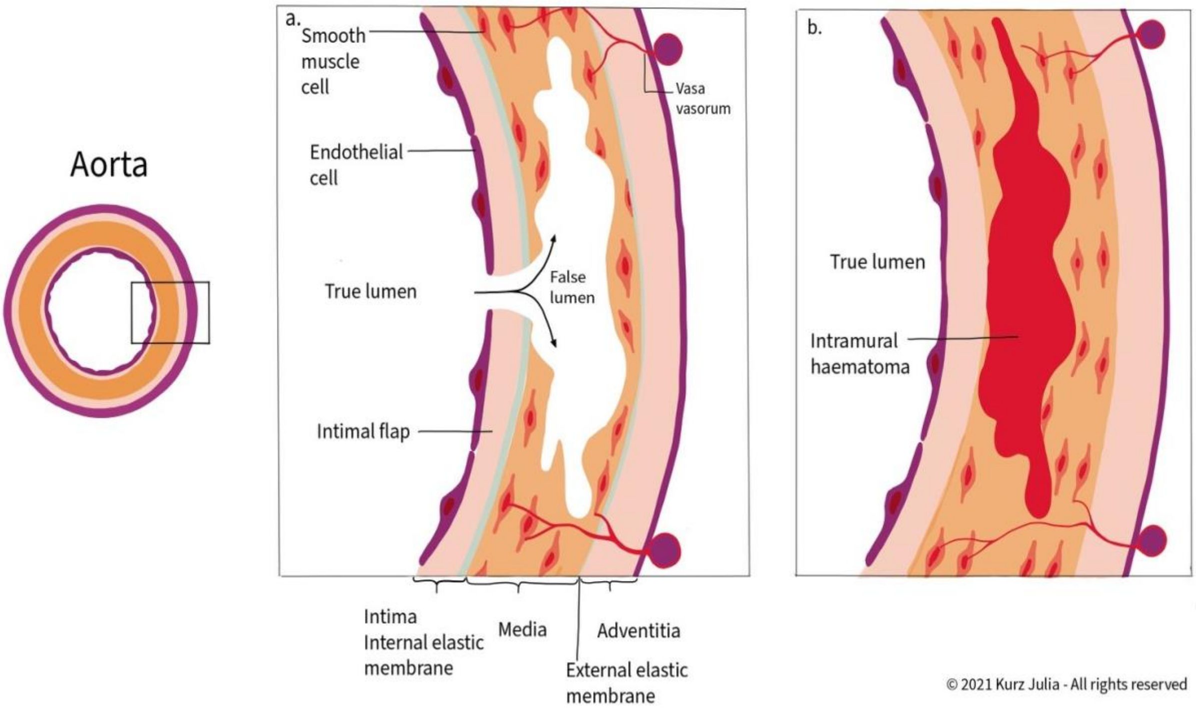

Abbildung 3: Pathogenese einer akuten Aortendissektion und eines intramuralen Hämatoms der menschlichen Aorta (eigene Abbildung)

An der Ausdehnung der Dissektion und am Entry im Bereich der Intima orientiert sich die Strategie der operativen Versorgung. Die erste Klassifikation der ATAAD erfolgte durch DeBakey und sein Team (DeBakey et al., 1965). DeBakey teilte die Erkrankung in drei Kategorien ein. Die erste Kategorie beinhaltet die Fälle, bei denen sich die Ausdehnung der gesamten Dissektion von der Aorta ascendens bis in den peripheren Bereich der Aorta erstreckt. In der zweiten Kategorie beschränkt sich die Dissektion auf den Bereich der Aorta ascendens und in der dritten Kategorie beginnt die Dissektion erst nach dem Abgang der Arteria subclavia. Die international bekannteste Einteilung, die sogenannte Stanford-Klassifikation, erfolgte im Jahr 1970 durch Daily und sein Team von der Universität Stanford (Daily et al., 1970). Ihre Einteilung der Dissektion fasst die beiden ersten Kategorien der DeBakey-Klassifikation unter dem Begriff ‚Typ A‘ und die Kategorie 3 unter dem Begriff ‚Typ B‘ zusammen. Eine zeitliche Einteilung definiert den Krankheitsbeginn innerhalb von 14 Tage als „akutes Ereignis“ und alles älter als 14 Tage als „chronisches Ereignis“ (Hirst, Johns and Kime, 1958). Eine genauere Einteilung war zu diesem Zeitpunkt aufgrund fehlender diagnostischer und chirurgischer Möglichkeiten noch nicht möglich. Eine Empfehlung für eine neuere Einteilung ergab sich aus den Daten des International Registry of Aortic Dissection (IRAD) im Jahr 2013. Die Forscher, die diese Daten analysiert haben, schlagen in ihrer Arbeit vor, den Überlebenszeitraum nach dem Symptombeginn in vier Abschnitte einzuteilen: hyperakut (innerhalb von 24 Stunden), akut (2–7 Tage), subakut (8–30 Tage) und chronisch (> 30 Tage) (Booher et al., 2013). Die Autoren werteten 1815 Patientendaten aus und nutzten zur Kategorisierung Kaplan-Meier-Überlebenskurven. Diese neuere Einteilung wird als robustere und praktikablere Methode in der aktuelleren klinischen Arbeit beschrieben. Die nachfolgenden Abbildung 4 zeigt die offizielle Einteilung nach der Stanford-Klassifikation.

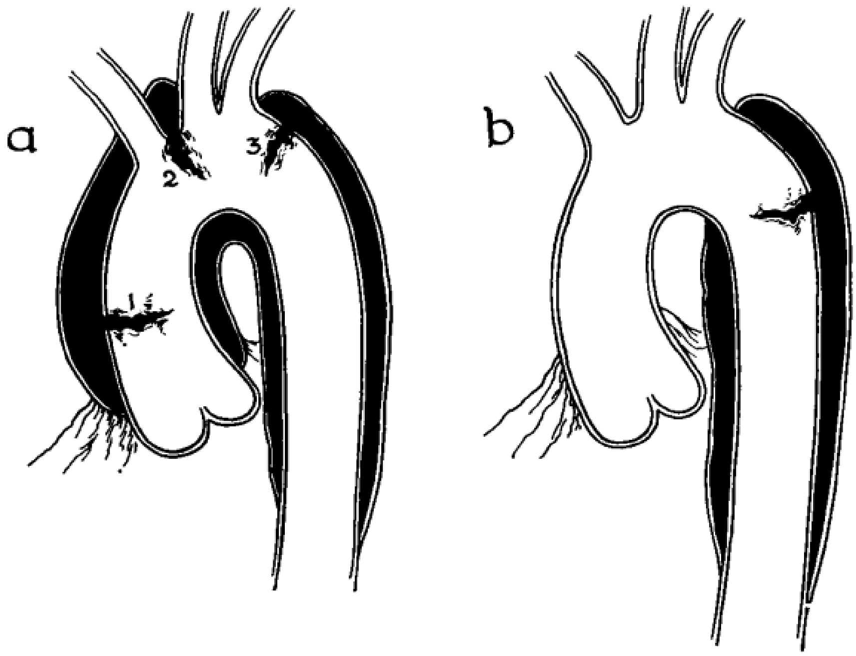

***FIG. 3.* Classification of aortic dissections. *In type A the ascending aorta is dissected* (a). *The intimal tear has always been at position* 1, *but it can occur at positions* 2 *or* 3 *(see text). In type B dissection the dissection is limited to the descending* aorta (b), *and the intimal tear is usually within 2 to 5 cm. of the left subclavian* artery.**

Abbildung 4: Originalabbildung der Stanford-Klassifikation – (Daily et al., 1970)

1.5 Klinisches Bild und Diagnostik

Die ATAAD ist ein lebensbedrohlicher Notfall und ein Überleben ohne herzchirurgische Versorgung ist unwahrscheinlich (Hagan et al., 2000; Golledge and Eagle, 2008; Erbel et al., 2014; Nienaber and Clough, 2015). Die Sterblichkeit der Erkrankung liegt nach 48 Stunden bei 50 % und nach zwei Wochen bei 75 %. In der ersten Phase der Erkrankung beträgt die Sterblichkeit bei 1–2 % pro Stunde (Hirst, Johns and Kime, 1958; Hagan et al., 2000; Lauterbach et al., 2001; Moon, 2009; Erbel et al., 2014). Zu den typischen Risikofaktoren gehören der arterielle Hypertonus, Arteriosklerose und das Aortenaneurysma (Golledge and Eagle, 2008; Nienaber and Clough, 2015). Der plötzlich einsetzende Brust- oder Rückenschmerz mit einer vernichtenden Intensität zählt zu den sogenannten klinischen Leitsymptomen. Im Jahr 2011 veröffentlichte eine Arbeitsgruppe um Rogers et al. ein neues Scoring-System mit dem Namen ‚Aortic Dissection Detection Risk Score' (ADD) zur besseren präklinischen Diagnostik. Dieser Score wurde aus den typischen zwölf klinischen Symptomen und Risikofaktoren zur sogenannten ersten ‚Vortestung' auf ATAAD entwickelt. Zu den typischen Symptomen für ATAAD gehören der plötzlich einsetzende Schmerz, der Vernichtungsschmerz und der wandernde Schmerz. Eine positive Anamnese für Aortenerkrankungen, eine bekannte Herzklappenerkrankung oder ein kürzlich erfolgter herzchirurgischer Eingriff zählen zu den typischen Risikofaktoren. Zu den typischen Risikofaktoren bei der klinischen Untersuchung gehören ein neu aufgetretenes Pulsdefizit, eine Blutdruckdifferenz an den Armen, ein fokales neurologisches Defizit oder eine neu aufgetretene Aorteninsuffizienz. Die beidseitige Blutdruckmessung beim klinischen Symptom Brust- oder Thoraxschmerz ist somit ein einfaches und nicht invasives Verfahren zur Feststellung einer möglichen Blutdruckdifferenz (Rogers et al., 2011). Eine Weiterentwicklung des ADD-Scores erfolgte in einer Arbeit aus dem Jahr 2021; daraus ging ein neuer Score mit dem Namen ‚AORTAs' hervor. Dieser Score verwendet nur sechs der typischen zwölf klinischen Risikofaktoren und ergänzend den Laborwert der D-Dimere. Dadurch konnten die Autoren eine deutlich verbesserte Spezifität erreichen (Suzuki et al., 2009; Nazerian et al., 2018; Morello et al., 2021). Eine der ersten umfassenden Arbeiten zur Validierung von nicht invasiven bildgebenden Verfahren im Vergleich zur Angiographie der Aorta ergab eine fast gleiche Sensitivität für Magnetresonanztomographie (MRT), Transösophageale Echokardiographie (TEE) und CT-Angiographie (CTA) (Nienaber et al., 1993). Die EKG-getriggerte CT-Angiographie zählt jedoch zu den bildgebenden Verfahren mit der höchsten Spezifität und somit zum sogenannten ‚Goldstandard' in der Diagnostik der ATAAD. Sie ist schnell und einfach durchzuführen, weltweit verfügbar und eignet sich beim akuten Brustschmerz auch zur

Eingrenzung differenzialdiagnostischer Überlegungen, um Erkrankungen wie akutes Koronarsyndrom, Lungenembolie, Spannungspneumothorax und Perikardtamponade auszuschließen. Bei einem hämodynamisch instabilen Patienten in der Notaufnahme ist die transthorakale Echokardiographie (TTE) ein wichtiges, vielseitiges und kostengünstiges diagnostisches Tool. Jeder behandelnde Arzt in einer Notaufnahme sollte eine sogenannte ‚fokussierte Sonographie des Herzens (FOCUS)' beherrschen. Im Falle der Verdachtsdiagnose einer ATAAD dient eine fokussierte Sonographie des Herzens u. a. dem Ausschluss einer Perikardtamponade oder eines neu aufgetretenen Klappenvitiums. Unter guten Schallbedingungen lässt sich auch die Aorta ascendens darstellen. Die Darstellung eines Perikardergusses lässt sich in der Regel durch eine subkostale Anlotung diagnostizieren. Die Sensitivität liegt in diesem Fall bei 95–100 % und die Spezifität bei über 85 % (Pepi and Muratori, 2006; Neskovic et al., 2013; Hagendorff et al., 2014).

1.6 Präklinisches Management

Zur besseren Übersicht und Planung von möglichen Interventionen zur Steigerung der Awareness für das versorgte Einzugsgebiet einer herzchirurgischen Einrichtung empfehlen sich eine Gliederung in sechs einzelne Versorgungsabschnitte und die Einrichtung einer ganzjährig sowie Tag und Nacht erreichbaren Hotline (Zschaler, Schmidt and Kurz, 2018b). Im ersten Versorgungsabschnitt hat der Patient in der Regel ein akutes Schmerzereignis und alarmiert den Rettungsdienst. Im zweiten Abschnitt findet in der Regel der erste Kontakt mit dem Rettungsdienst statt. Anschließend erfolgt der Transport des Patienten in das nächstgelegene Krankenhaus. Man spricht hier von dem sogenannten Primärkrankenhaus. Hier beginnt der dritte Versorgungsabschnitt. Die erkrankte Person wird über die Notaufnahme oder Rettungsstelle aufgenommen (die genaue Bezeichnung variiert je nach Region) und es erfolgen die weiteren diagnostischen Schritte. Nach Sicherung der Diagnose beginnt der vierte Versorgungsabschnitt und der Patient wird zur operativen Versorgung in eine herzchirurgische Einrichtung verlegt (Zielklinik). Hierzu wird über die regionale Leitstelle eine notfallmäßige Sekundärverlegung organisiert. Bei der Disposition des Rettungsmittels gilt die gesetzliche Hilfsfrist von 15 Minuten wie bei der Primärrettung (Beispiele: akutes Koronarsyndrom, akuter Schlaganfall). Das bedeutet, dass die regional zuständige Leitstelle ein geeignetes Rettungsmittel innerhalb der vorgegebenen Zeit von 15 Minuten zur Verfügung stellen muss. Die zu behandelnde Person ist so lange ein Notfallpatient, bis sie das geeignete Krankenhaus für die Durchführung der endgültigen Therapie erreicht hat (Kurz et al., 2020). Im fünften Versorgungsabschnitt erreicht die zu behandelnde Person das Zielkrankenhaus. Eine grafische Darstellung der einzelnen Versorgungsabschnitte vom Schmerzereignis bis zur herzchirurgischen Versorgung als Übersicht findet sich in der Abbildung 5.

Abbildung 5: Präklinische Versorgungsabschnitte der akuten TYP A Aortendissektion (eigene Abbildung)

Das initiale Behandlung von Patienten mit einer ATAAD basiert auf den Säulen der Blutdruckkontrolle (Reduktion des Pulsdrucks), der Schmerztherapie und der sofortigen Verlegung in eine geeignete herzchirurgische Zielklinik. Der Blutdruck sollte vor einer Sekundärverlegung in das weiterversorgende herzchirurgische Zielkrankenhaus idealerweise unter 120 mmHg liegen (Mehta et al., 2002; Bossone et al., 2016). Dies dient auch zur Reduktion des sogenannten Scherstresses auf die Aorta (Hall et al., 2000; Kocher et al., 2014). In vielen Fällen ist der Einsatz von mehreren Medikamenten zur Blutdruckkontrolle notwendig. Es empfiehlt sich die Gabe von Betablockern, Alpha-1-Adrenozeptorantagonisten, Glyceroltrinitrat oder Labetalol (Suzuki et al., 2012). Die sofortige Verlegung des Patienten ohne Zeitverzögerung ist für sein Überleben entscheidend. Die Versorgungszeiten vom Schmerzereignis bis zum operativen Eingriff liegen zwischen 5,5 und 8,6 Stunden (Zaschke et al., 2020). Die Verzögerung der Diagnostik hat unterschiedliche Ursachen. Als verlangsamende Variablen wurden Faktoren wie Geschlechtszugehörigkeit (bei Frauen), Hautfarbe, normaler Blutdruck und Fieber identifiziert. Im Gegensatz dazu konnten auch Variablen ausgemacht werden, die die Diagnosefindung beschleunigen. Dazu gehören Hypotonie, Herzbeuteltamponade, Koma oder eine Ischämie der unteren Extremitäten (Rapezzi et al., 2008; Rogers et al., 2011). Auch nach der Diagnose kann es zu einer Verzögerung der Behandlung kommen. Der Median liegt hier zwischen 2,5 und 7,2 Stunden. Patienten im kritischen Zustand wurden schneller verlegt (Froehlich et al., 2018; Zaschke et al., 2020).

1.7 Operative Versorgung und Outcome

Eine ATAAD benötigt in der Regel eine offene operative herzchirurgische Versorgung mithilfe einer Herz-Lungen-Maschine. Es ist nur in wenigen Fällen möglich, eine ATAAD durch eine endovaskuläre Intervention zu versorgen. Je nach Ausdehnung der Dissektion wird entweder nur die Aorta ascendens oder es werden auch weitere Teile der Aorta ersetzt (Teilbogenersatz, Bogenersatz, Frozen-Elephant-Trunk). Die Frozen-Elephant-Trunk- (FET-)Technik ist ein Hybridverfahren aus konventioneller und endovaskulärer Aortenchirurgie, das vor allem bei einer Beteiligung des Aortenbogens und der Aorta descendens eingesetzt wird. Dies gilt insbesondere, wenn das Entry im Bereich des Aortenbogens lokalisiert ist, bei distalen Malperfusionsstörungen und bei jungen Patienten (Di Marco et al., 2017). Die Sterblichkeit der Erkrankung liegt bei 1–2 % pro Stunde (Hagan et al., 2000). 50 % der Patienten sterben innerhalb der ersten 24 Stunden nach dem initialen Ereignis (Howard et al., 2013; Evangelista et al., 2018; Mahase, 2020). Bei der Versorgung von Patienten mit einer ATAAD gibt es aktuell weltweit keine geltenden standardisierten Entscheidungsprozesse. Die Krankenhaussterblichkeit liegt weltweit bei 16–18 %. Die Rate der neurologischen Komplikationen (Schlaganfall) liegt bei 12,7 %, von Nierenversagen bei 14,5 %, von verlängerter Beatmungsdauer bei 50,6 % und die neurologischen Komplikationen inklusive der Krankenhaussterblichkeit werden mit 25,5 % angegeben (Erbel et al., 2014; Conzelmann et al., 2016; Geirsson et al., 2019; O'Hara et al., 2020). Es konnten mittlerweile mehrere Risikofaktoren identifiziert werden, die einen Einfluss auf den Versorgungsprozess und das Outcome der Erkrankung haben. Hierzu zählen das Alter, die linksventrikuläre Pumpfunktion und der präoperative Status (Malperfusionsstörungen, kardiopulmonale Reanimation u. a.) der Patienten sowie die Anzahl der vom Klinikteam durchgeführten Aorteneingriffe pro Jahr (Adam et al., 2018; Reutersberg et al., 2019; Thurau et al., 2019a; Umana-Pizano et al., 2019; O'Hara et al., 2020). Die Versorgung von Patienten mit einer ATAAD ist ein interdisziplinärer Vorgang, der schnelle und komplexe Entscheidungsprozesse erforderlich macht. Es sind detaillierte Kenntnisse der regionalen Versorgungsstruktur, der Inzidenz der Erkrankung, der Patientencharakteristika und die qualitativen Ergebnisse der herzchirurgisch versorgenden Kliniken zwingend notwendig, um die Versorgung und die Entscheidungsprozesse zu verbessern (Benedetto et al., 2021).

2 Eigene Originalarbeiten

2.1 Kurz, S. D., Falk, V., Kempfert, J., Gieb, M., Ruschinski, T. M., Kukucka, M., Tsokos, M., Grubitzsch, H., Herbst, H., Semmler, J. and Buschmann, C. T. (2017). Insight into the incidence of acute aortic dissection in the German region of Berlin and Brandenburg. *International Journal of Cardiology*, 241, 326–329, [online] doi: 10.1016/j.ijcard.2017.05.024.

Diese Originalarbeit zeigt die Häufigkeit von ATAAD in der Region Berlin / Brandenburg und ist damit ein entscheidender Ausgangspunkt zum besseren Verständnis der präklinischen Versorgung von ATAAD. Der nachfolgende Text entspricht dem Abstrakt der Arbeit „Insight into the incidence of acute aortic dissection in the German region of Berlin and Brandenburg" (Kurz et al., 2017, S. 326, doi: 10.1016/j.ijcard.2017.05.024).

„Background: *Stanford acute type A aortic dissection (ATAAD) is a potentially lethal condition. Epidemiology studies show a statistical incidence in Europe of approximately 2–16 cases/100,000 inhabitants/year. In Germany, the estimated incidence (here subsumed under "thoracic aortic dissection" with 4.63 cases/100,000 inhabitants/year) is mainly extracted from medical death certificates by the German Federal Statistical Office. The prehospital incidence of ATAAD deaths is largely unknown. Since patients often die in the pre-hospital setting, the incidence of ATAAD is therefore likely to be higher than current estimates.*

Material and methods: *For the period from 2010 to 2014, we retrospectively analyzed all in-hospital ATAAD data from two of the largest cardiac surgical centers that treat ATAAD in the Berlin-Brandenburg region. In addition, autopsy reports of all forensic medicine institutes and of one large pathological provider in the region were analyzed to identify additional non-hospitalized ATAAD patients. Based on these findings, the regional incidence of ATAAD was calculated.*

Results: *In addition to in-hospital ATAAD patients (n = 405), we identified additional 145 lethal ATAAD cases among 14,201 autopsy reports. The total of 550 ATAAD cases led to an estimated incidence of 11.9 cases/100,000 inhabitants/year for the whole Berlin-Brandenburg region. Arterial hypertension, pre-existing aortic dilatation, and hereditary connective tissue disorder were found in, respectively, 62.7%, 10%, and 1.8% of patients.*

Conclusion: *ATAAD is more frequent than previously reported. Our results show that when patients*

who die outside of cardiac surgery centers are included, the incidence of ATAAD significantly exceeds the rate reported by the Federal Statistical Office".

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Insight into the incidence of acute aortic dissection in the German region of Berlin and Brandenburg

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ABSTRACT

Background: Stanford acute type A aortic dissection (ATAAD) is a potentially lethal condition. Epidemiology studies show a statistical incidence in Europe of approximately 2–16 cases/100,000 inhabitants/year. In Germany, the estimated incidence (here subsumed under "thoracic aortic dissection" with 4.63 cases/100,000 inhabitants/year) is mainly extracted from medical death certificates by the German Federal Statistical Office. The prehospital incidence of ATAAD deaths is largely unknown. Since patients often die in the pre-hospital setting, the incidence of ATAAD is therefore likely to be higher than current estimates.
Material and methods: For the period from 2010 to 2014, we retrospectively analyzed all in-hospital ATAAD data from two of the largest cardiac surgical centers that treat ATAAD in the Berlin-Brandenburg region. In addition, autopsy reports of all forensic medicine institutes and of one large pathological provider in the region were analyzed to identify additional non-hospitalized ATAAD patients. Based on these findings, the regional incidence of ATAAD was calculated.
Results: In addition to in-hospital ATAAD patients ($n = 405$), we identified additional 145 lethal ATAAD cases among 14,201 autopsy reports. The total of 550 ATAAD cases led to an estimated incidence of 11.9 cases/100,000 inhabitants/year for the whole Berlin-Brandenburg region. Arterial hypertension, pre-existing aortic dilatation, and hereditary connective tissue disorder were found in, respectively, 62.7%, 10%, and 1.8% of patients.
Conclusion: ATAAD is more frequent than previously reported. Our results show that when patients who die outside of cardiac surgery centers are included, the incidence of ATAAD significantly exceeds the rate reported by the Federal Statistical Office.

1. Introduction

Acute aortic dissection is defined as a split between the vascular intima and media caused by a lesion in the intima. If this lesion ("entry") is located in the ascending aorta proximal to the branch of the left subclavian artery, it is defined in the Stanford classification as an acute type A aortic dissection (ATAAD). ATAAD is a life-threatening event and survival without surgical treatment is dismal [1,2]. The mortality rate is 50% after 48 h and 75% after 2 weeks; in the early period mortality is 1–2% per hour [3–5]. The most common complication is rupture of the thoracic aorta, which is responsible for 80% of deaths (Fig. 1) [5]. After diagnosis, emergency operation (surgical replacement or repair of the aortic root, ascending aorta and aortic arch) is warranted.

The reported incidence of ATAAD varies greatly in the international literature and, depending on the underlying database, ranges from 2 to 16 cases/100,000 inhabitants/year [9–12]. For the Federal Republic of Germany the official death statistics for 2014 show an incidence of "thoracic aortic dissection" of 4.63 per 100,000 population per year [13]. This statistic probably underestimates the number of cases outside of clinical settings and ATAAD is not recorded separately but is subsumed under "thoracic aortic dissection" (which includes Stanford type B cases). The underestimation of out of hospital ATAAD's combined with the high pre-clinical mortality of the disease render this analysis unreliable. The pre-clinical situation is not only relevant from the

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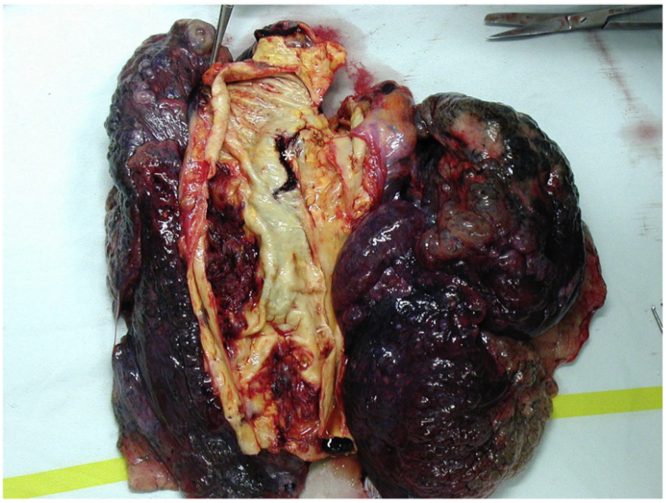

Fig. 1. Autopsy finding ATAAD — intima lesion ("entry") of the ascending aorta.

epidemiological aspect but also has important clinical implications [14–16]. The neglection of non-hospital mortality and the current focus on the clinical incidence of ATAAD suggests that the true incidence of ATAAD is likely to be higher than assumed. A more realistic assessment of the incidence of ATAAD must therefore include both, the data of patients who were hospitalized due to an ATAAD and data on ATAAD deaths that occurred outside the clinical setting. However, cause of death by aortic dissection or more specifically death by ATAAD is frequently not recognized by the doctors filling in the death certificates. The manner of death is, therefore, often recorded as, e.g. sudden cardiac death or as "uncertain". The latter cases may lead to a forensic autopsy if this is ordered by the public prosecutor/the court — which of course does not apply to every uncertain death. Furthermore, differentiation between Stanford type A and Stanford type B dissection is not possible by exterior postmortem examination only.

It is commonly known that postmortem external examinations are inaccurate with regard to the exact cause of death, especially when these postmortem external examinations are performed by inexperienced physicians [17].

Low forensic autopsy rates (e.g. about 7% of all deaths in Berlin; see Table 1) distort the distribution of disease frequencies among the deceased from a particular region, as was shown in the "Görlitzer study" in 1986/87 (almost 100% autopsy rate) with marked disagreement between cause of death given in the death certificates and autopsy findings [17].

Therefore, the analysis of autopsy reports can constitute a suitable method for generating epidemiological data primarily for the pre-clinical stage, when the manner of death was certified as "uncertain" or "non-natural" and a forensic autopsy was ordered by the public prosecutor/the court [14–16]. Autopsy is known to be the gold standard of (emergency) medical quality checks in the case of death.

This study aimed to identify the incidence of ATAAD among all deaths undergoing either forensic or clinical autopsy in our region. From these data the rate of ATAAD among pre-clinical deaths was estimated and combined with known clinical cases to achieve an estimate of total population based ATAAD incidence.

2. Material and methods

The Berlin-Brandenburg region has 6 million inhabitants in a temperate zone in the north-east of the Federal Republic of Germany, where the average age is 42.9 years for Berlin (as of 2014) [18] and 45.7 years for Brandenburg (as of 2010) [19]. For further demographically relevant parameters, we accessed regional data from the Federal Statistical Office (www.destatis.de).

Table 1
Clinical data.

	DHZB/ Charité (B)	Forensic medicine (B)/(BB)	Pathology Vivantes (B)	Total
Basic data				
Number *n* (%)	405 (73.6)	133 (24.2)	12 (2.2)	550 (100)
male *n* (%)	266 (65.9)	85 (63.9)	4 (33.3)	355 (64.5)
Age at event, mean ± SD in a	61.8 (±13.2)	58.3 (±16.4)	77.5 (±9.8)	61.4 (±14.2)
BMI, mean ± SD in kg/m^2	27.6 (±5.1)	28,4 (±6.4)	26.8 (±7.2)	27.8 (±5.5)
Conditions present n (%)				
Arterial hypertension	283 (69.9)	55 (41.4)	7 (58.3)	345 (62.7)
Coronary artery disease	50 (12.3)	9 (6.8)	8 (66.7)	67 (12.2)
Diabetes mellitus type 2	29 (7.2)	4 (3.0)	2 (16.7)	35 (6.4)
Aortic disease (ectasia, aneurysm)	46 (11.4)	7 (5.3)	2 (16.7)	55 (10.0)
Type B dissection	9 (2.2)	0	0	9 (1.6)
Nicotine abuse	115 (28.4)	14 (10.5)	1 (8.3)	130 (23.6)
Alcohol	15 (3.7)	9 (6.8)	0	24 (4.4)
Arteriosclerosis	43 (10.6)	33 (24.8)	0	88 (16.0)
Hereditary connective tissue disorder	7 (1.7)	3 (2.3)	0	10 (1.8)
Hypothyreosis	48 (11.9)	2 (1.5)	0	50 (9.1)
Pregnancy	2 (0.5)	0	0	2 (0.4)
Cocaine abuse	2 (0.5)	0	0	2 (0.4)

ATTAD was diagnosed in clinical cases and autopsy reports according to the Stanford classification, i.e. entry of dissection is located in the ascending aorta, proximal to the branch of the left subclavian arteria (e.g. see Fig. 1).

Data on clinically detected ATAADs in 2010–2014 from the central archives of the German Heart Institute Berlin (DHZB) and the archives of the Department of Cardiovascular Surgery, Charité-Berlin University Medicine at Charité, Campus Mitte (CCM) were reviewed. Both institutions are tertiary care centers with large expertise in the surgical treatment of ATAAD and hence perform the large majority of cases in the greater Berlin/Brandenburg region. Cases from two other regional providers (Brandenburg Heart Center-Immanuel Hospital Bernau and Sana Heart Center Cottbus GmbH) had to be excluded due to lack of feedback.

The term "acute" was used to refer to cases with a period of <2 weeks between the initial event (onset of symptoms) and the time of diagnosis [20,21]. Iatrogenic and traumatic aortic dissection and intramural hematoma were not considered.

In order to assess the incidence of ATAAD among clinically autopsied deaths we analyzed all cases classified as "natural" at the external postmortem examination that were followed by pathological autopsy from the archives of the Pathological Institute of the Vivantes Klinikum in the Neukölln area of Berlin. This institute performs the vast majority of all clinical autopsies in Berlin.

For assessment of ATAAD incidence among forensic autopsies all forensic reports that resulted from legally ordered forensic autopsies for death being judged as "unclear" or of "non-natural causes" in Berlin (Institute of Legal Medicine and Forensic Sciences at the Charité-Berlin University Medicine and the State Institute of Forensic and Social Medicine Berlin) and Brandenburg (Brandenburg Institute of Forensic Medicine in Potsdam) were analyzed. These three institutions are responsible for all forensic autopsies in the region.

The autopsy reports were reviewed for ATAADs based on the keywords ["bleeding to death" OR, "pericardial tamponade" OR "rupture of the aorta" OR "dissection of the main artery" OR "aortic aneurysm"]. The thus identified autopsy reports were manually scanned for the diagnosis of ATAAD. Checks were made to exclude multiple registrations of ATAAD cases. Pre-existing medical conditions in the autopsy cases were extracted from the clinical reports or, if lacking, from the autopsy reports.

2.1. Statistics

Incidences were calculated as number of detected cases per 100,000 autopsies or inhabitants as appropriate and confidence intervals were calculated using the "Wilson" score interval method. Assuming that the rate of ATAAD in the autopsied population is equal to the rate in all deaths, the total number of pre-hospital ATAAD related deaths was estimated by applying the detected rate of ATAAD among autopsies to the total number of deaths in the region.

3. Results

For the observation period, in addition to the clinical ATAAD patients ($n = 405$), we identified 145 further fatal ATAAD cases in autopsies, resulting in a total of 550 cases; of these 345 (64.5%) were men and 195 (35.5%) were women. This distribution was similar in all institutions with the exception of the pathological study group (Berlin-Neukölln Vivantes), where men comprised 33.3%.

The average age was 61.4 ± 14.2 years, the youngest patient being 20 years and the oldest patient 100 years old. The oldest population was found in the pathology study group from Vivantes, at 77.5 ± 9.8 years. The body mass index (BMI) was on average 27.8 ± 5.5 kg/m^2 with a range from 13.8 to 55.6 kg/m^2. In 345 (62.7%) cases we detected pre-existing arterial hypertension. Of 130 (23.6%) patients with known nicotine abuse 88 (16%) suffered from sclerosis of the arterial vascular system and 67 (12.2%) from coronary artery disease. In 35 (6.4%) patients, type 2 diabetes mellitus was present.

Known pre-existing aortic conditions such as aneurysm or ectasia of the thoracic aorta were found in 55 (10%) patients with approximately equal frequency as hypothyroidism with 50 cases (9.1%). In 24 (4.4%) cases, there was alcohol dependency. Hereditary connective tissue disorders (Marfan, Ehlers-Danlos or Turner syndrome) were found in 1.8% and were almost as rare as Stanford type B dissections (1.6%). Only one case each of pregnancy and cocaine abuse were registered (both 0.4%). Details are shown in Table 1.

In the total observation period 405 clinical cases of ATAAD were treated. Among the autopsy reports 145 additional cases were detected. In view of the low documented autopsy rate in the collective of 4.7%, we extrapolated the autopsy numbers to the total number of deceased in the study region (Berlin and Brandenburg) and added the clinical ATAAD cases (DHZB, Charité CCM) which resulted in an estimate of 3506 cases in 5 years. In relation to the total population, this results in an estimated incidence of 11.9 (CI 11.6–12.3) cases/100,000 inhabitants. Further demographic factors in relation to the ATAAD incidence for Berlin and Brandenburg are given in Table 2.

4. Discussion

The main result of the present investigation is that the estimated incidence of ATAAD of 11.9/100,000/year is considerably higher than the number of 4.6 of the German Federal Statistical Office which also includes Stanford type B dissections. The reasons for this discrepancy may be due to several reasons, some of which have already been mentioned in the Introduction. In cases of out of hospital deaths, ATAAD may be misdiagnosed as sudden cardiac death or death due to myocardial infarction by the physician filling in the death certificate. In a comprehensive study in an eastern German region, 45% of initial diagnoses in the death certificate could not be confirmed during autopsy [17]. Even in cases of an ensuing autopsy, only the initial diagnosis will be reported to the statistical office. But also after correct diagnosis and surgical treatment of ATAAD the cause of death reported to the statistical office may represent postoperative complications such as sepsis or multi organ failure.

In a Swedish study Olsson et al. reported an incidence of up to 16.3 cases/100,000 male inhabitants/year and 9.1 cases/100,000 female inhabitants/year for the year 2002 including both pre-clinical and in-hospital aortic dissection. In this study, the incidence was based on the definition of "thoracic aortic syndrome", which does not discriminate between dissection and aneurysm or between Stanford type A and type B dissection. It is likely that the total incidence (12.2 cases/100,000 inhabitants/year), would have been lower if a distinction had been made between aneurysm and dissection (30% or $n = 4425$ of 14,229 cases) and between type A and type B dissection [10].

Pacini et al. showed that in geographically differing regions there is a higher probability of ATAAD in flat than in mountainous areas. These results suggest that the overall incidence of ATAAD in Germany would be reduced by the allegedly decreasing incidence in the mountainous southern part of Germany so that at the overall, federal level "international conditions" might prevail [9].

Our collection of ante- and postmortem clinical and pathological data on the incidence of ATAAD (DHZB, Charité CCM, Vivantes Neukölln pathology) can be regarded as relatively comprehensive since ATAAD patients from the Brandenburg region are mostly transferred for surgical therapy to Berlin and in the case of death are autopsied there.

4.1. Putative sources of bias

For the estimation of the number of pre-clinical deaths due to ATAAD we assumed that the rate of ATAAD among the autopsied population is equal to the rate in all deaths. However, ATAAD might be overrepresented in the autopsied population. Sudden death without known pre-existing conditions as probable cause of death would often result in diagnosis of "unclear" cause of death in the death certificate — which may be followed by a forensic autopsy in some cases.

Especially when younger people with apparently perfectly good health suddenly die of an ATAAD, which is not rare, a "natural" cause of death is lacking in the medical history, and classification of these cases as "unclear" deaths should be comprehensive. The decision in favor of an autopsy in these unresolved deaths is, then, not a medical, but a legal decision by the public prosecutor/the court. In recent work we were able to show, at least for Berlin, that deaths from trauma in younger individuals and the non-hospital deceased were significantly

Table 2
Incidence aortic dissection and baseline characteristics.

	2010	2011	2012	2013	2014	Total
Population, n						
Berlin (B)/Brandenburg (BB) total	5,963,998	5,779,182	5,824,733	5,871,022	5,927,721	29,366,656
Number of deaths, n						
Berlin (B)/Brandenburg (BB) total	60,128	59,231	60,621	62,470	61,304	303,754
Autopsies, n						
Forensic Med. Berlin (B)/Brandenburg (BB)	2685	2428	2486	2499	2505	12,603
Pathology Vivantes (B)	253	236	321	402	386	1598
Total	2938	2664	2807	2901	2891	14,201
Cases of ATAAD, n						
Deutsches Herzzentrum Berlin/Charité Campus Mitte	81	63	85	95	81	405
Forensic Med./pathology Vivantes (B)/Brandenburg (BB)	27	26	34	31	27	145
Total	108	89	119	126	108	550
Incidence ATAAD/100,000 (confidence interval)						
Clinical cases per population	1.4 (1.1–1.7)	1.1 (0.9–1,4)	1.5 (1.2–1.8)	1.6 (1.3–2.0)	1.4 (1.1–1.7)	1.4 (1.3–1.5)
All cases per population	1.8 (1.5–2.2)	1.5 (1.3–1.9)	2.0 (1.7–2.4)	2.1 (1.8–2.6)	1.8 (1.5–2.2)	1.9 (1.7–2.0)
Cases per number of autopsies	919 (632–1340)	976 (667–1426)	1211 (868–1688)	1069 (754–1513)	934 (643–1355)	1021 (869–1200)
Extrapolated cases per population	10.6 (9.8–11.5)	11.1 (10.3–12.0)	14.1 (13.1–15.1)	13.0 (12.1–13.9)	11.0 (10.2–11.9)	11.9 (11.6–12.3)
Calculated autopsy rate (B)/(BB) (%)	4.9	4.5	4.6	4.6	4.7	4.7

Survey of incidence data of ATAAD in Berlin and Brandenburg. Total number of ATAAD cases among all deaths in the population was extrapolated from the incidence of ATAAD among autopsied deaths assuming that the autopsy rate for death by ATAAD is not different from the general autopsy rate. All incidences are presented with 95% confidence intervals.

more likely to lead to forensic autopsy than trauma deaths in older individuals and those in the hospital [23].

On the other hand, clinical autopsies in Brandenburg and smaller private Berlin hospitals were not covered by our data acquisition which means that an unknown number of in-hospital ATAAD cases were not detected. This may, at least partially, equalize the putative bias towards a higher incidence of ATAAD resulting from projecting the rate of ATAAD in the autopsied population towards the total population.

Another putative source of error results from the general problem of low and still declining autopsy numbers in Germany [22]. Thus we had to extrapolate the rate of ATAAD related death in a small autopsied population to the much larger total number of deaths which means that even small deviations in the observed rates produce relatively large differences.

An increase of the current autopsy rate in Germany is undoubtedly warranted, both from a forensic and a pathological point of view and would also have the benefit of allowing more precise epidemiological data.

In summary, ATAAD occurs more frequently than previously known. This has important clinical implications. Of particular relevance in this context is the rapid differential diagnosis of ATAAD and acute coronary syndrome (ACS) or acute myocardial infarction (AMI) in the setting of acute chest pain to allow for appropriate prehospital treatment, i.e. anti-coagulation or no anti-coagulation. In case of suspected ATAAD the patient should be sent to an appropriate institution without delay. In this situation the emergency physician plays a key role that may be decisive for the eventual outcome of these life-threatening events. The gold standard in emergency medical diagnosis includes information on the patient's history, physical examination and ECG interpretation, to gain a rapid overview of the patient's symptoms. On a critical note, "acute chest pain" as the main symptom in the preclinical setting often leads, almost as a "reflex", to pharmacological anti-coagulation. However, the actual number of verified ACS cases is well below the number of preclinical diagnosed patients who receive immediate anti-coagulation. In patients with ATAAD as the cause of chest pain the consequences can be serious for the individual course of the disease in view of iatrogenically suppressed coagulation and simultaneous need for maximally invasive major vascular surgery. We recently reported on the problems of diagnosis of ATAAD in the emergency situation and suggested possible solutions [24]. Against this background, awareness that ATAAD may occur more often than generally assumed may sensitize emergency physicians towards this problem.

Despite currently low autopsy rates, interdisciplinary data analysis combining forensic and pathological autopsy results with in-hospital diagnoses can make a relevant contribution to epidemiological research and generate valid data with implications for changing preclinical and clinical health care strategies. In addition, the data presented here underline the need for larger numbers of forensic and pathological autopsies in Germany.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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2.2 Wundram, M., Falk, V., Eulert-Grehn, J. J., Herbst, H., Thurau, J., Leidel, B. A., Göncz, E., Bauer, W., Habazettl, H. and Kurz, S. D. (2020). Incidence of acute type A aortic dissection in emergency departments. *Scientific Reports,* 10(1), 7434, [online] doi: 10.1038/s41598-020-64299-4.

Die nächste Arbeit untersucht die Häufigkeit von ATAAD im Patientengut der Berliner Notaufnahmen. Der nachfolgende Text entspricht dem Abstrakt der Arbeit „Incidence of acute type A aortic dissection in emergency departments“ (Wundram et al., 2020, S. 1, doi: 10.1038/s41598-020-64299-4).

„Due to the symptoms, patients with acute type A aortic dissection are first seen by the ambulance service and diagnosed at the emergency department. How often an aortic dissection occurs in an emergency department per year has been studied. The incidence in the emergency department may be used as a quality marker of differential diagnostics of acute chest pain. A multi-institutional retrospective study with the municipal Berlin hospital chain Vivantes and its Department of Pathology and the Charité - University Medicine Berlin was performed. From the Berlin Hospital Society, the annual numbers of publicly insured emergency patients were obtained. Between 2006 and 2016, 631 aortic dissections were identified. The total number of patients treated in the emergency departments (n = 12,790,577) was used to calculate the "emergency department incidence." The autopsy data from six clinics allowed an estimate on how many acute type A aortic dissections remained undetected. Across all Berlin hospitals, the emergency department incidence of acute type A aortic dissection was 5.24 cases in 100,000 patients per year. In tertiary referral hospitals and, particularly, in university hospitals the respective incidences were markedly higher (6.7 and 12.4, respectively). Based on the autopsy results, about 50% of the acute type A aortic dissection may remain undetected, which would double the reported incidences. Among different hospital types the emergency department incidences of acute type A aortic dissection vary between 5.93/100,000 and 24.92/100,000".

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Incidence of acute type A aortic dissection in emergency departments

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Due to the symptoms, patients with acute type A aortic dissection are first seen by the ambulance service and diagnosed at the emergency department. How often an aortic dissection occurs in an emergency department per year has been studied. The incidence in the emergency department may be used as a quality marker of differential diagnostics of acute chest pain. A multi-institutional retrospective study with the municipal Berlin hospital chain Vivantes and its Department of Pathology and the Charité - University Medicine Berlin was performed. From the Berlin Hospital Society, the annual numbers of publicly insured emergency patients were obtained. Between 2006 and 2016, 631 aortic dissections were identified. The total number of patients treated in the emergency departments (n = 12,790,577) was used to calculate the "emergency department incidence." The autopsy data from six clinics allowed an estimate on how many acute type A aortic dissections remained undetected. Across all Berlin hospitals, the emergency department incidence of acute type A aortic dissection was 5.24 cases in 100,000 patients per year. In tertiary referral hospitals and, particularly, in university hospitals the respective incidences were markedly higher (6.7 and 12.4, respectively). Based on the autopsy results, about 50% of the acute type A aortic dissection may remain undetected, which would double the reported incidences. Among different hospital types the emergency department incidences of acute type A aortic dissection vary between 5.93/100,000 and 24.92/100,000. Aortic dissection; Incidence; Emergency Department; Epidemiology

Acute type A aortic dissection (ATAAD) is part of the preclinical differential diagnosis of acute chest pain. According to the current literature, the population-based incidence of ATAAD is stated between 2.1 and 16.3 per 100,000 persons[1–12]. It is associated with a high mortality ranging from 26% in surgically treated patients to 58% in medically treated patients[13]. ATAAD is associated with a high risk for post-traumatic stress disorder and has negative effects on the patients' physical and mental health[14]. Aortic dissection usually manifests with sudden thoracic or back pain[13,15]. Increased awareness may further accelerate the diagnostic workup[16]. As the majority of patients with symptoms of an ATAAD are admitted through the emergency department (ED), the emergency staff needs to be aware of the expected incidence of ATAAD. Surgical care of an ATAAD is a time critical event and can only be carried out in specialized clinics[17]. Immediate transportation with a ground-based rescue device to the

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	Berlin	Charité	Vivantes	Other hospitals
Basic data				
Number n (%)	631	171	213	247
male	410 (65.0)	112 (65.5)	142 (66.7)	156 (63.2)
female	221 (35.0)	59 (34.5)	71 (33.3)	91 (36.8)
Age at event, mean±SD in a	61.4 ± 13.8 (23–90)	65 ± 13.9 (23–90)	61 ± 13.4 (28–88)	62 ± 14.1 (23–88)
BMI, mean±SD in kg/m2	27.2 ± 4.9 (16.3–55.56)	26.9 ± 4.6 (18.5–44.2)	26.6 ± 5.6 (17.9–55.6)	26.3 ± 5.6 (16.3–51.9)
Conditions present n (%)				
Arterial hypertension	425 (67.4)	103 (60.2)	153 (71.8)	169 (68.4)
Coronary artery disease	81 (12.8)	18 (10.5)	29 (13.6)	34 (13.8)
Diabetes mellitus type 2	43 (6.8)	9 (5.3)	19 (8.9)	15 (6.1)
Aortic disease (ectasia, aneurysm)	86 (13.6)	20 (11.7)	33 (15.8)	33 (13.4)
Type B dissection	15 (2.4)	6 (3.5)	3 (1.4)	6 (2.4)
Nicotine abuse	190 (30.1)	41 (24)	79 (37.1)	70 (28.3)
Alcohol abuse	32 (5.1)	6 (3.5)	17 (8)	9 (3.6)
Arteriosclerosis	51 (8.1)	13 (7.6)	20 (9.4)	18 (7.3)
Hereditary connective tissue disorder	18 (2.9)	5 (2.9)	7 (3.3)	6 (2.4)
Hypothyreosis	66 (10.5)	18 (10.5)	22 (10.3)	26 (10.5)
Pregnancy	3 (0.5)	2 (2.1)	0 (0)	1 (0.4)
Cocaine abuse	5 (0.8)	2 (2.1)	0 (0)	3 (1.2)

Table 1. Clinical data of all type A aortic dissections treated in Berlin between 2006–2016. The Table shows the Pre-existing medical conditions, average age and gender. The basic data are the mean ± SD with the maximum and the minimum in brackets or absolute numbers with percentages in brackets.

target hospital is the quickest option and is also necessary from a medical law perspective[18,19]. According to the Federal Statistical office, Berlin has 3,613,495 inhabitants and 83 hospitals. The aim of this study was to gather the current knowledge on the incidence of ATAAD among different populations and to determine the true incidence among patients treated in an ED in the region of Berlin.

Results

Emergency department incidence und pathology data. With 12,734,308 ED patients from 2006 to 2016 in Berlin and 631 ATAADs, an ED incidence of 4.96/100,000 was calculated. During the observation period from 2006 to 2016, all these 631 clinical cases of ATAAD were transferred to and treated at the German Heart Center Berlin or the cardiac surgery department of Charité-University Medicine Berlin. Of these, 410 (65%) were men and 221 (35%) were women. The average age was 61.4 ± 13.8 years. The youngest patient was 23 and the oldest patient was 90 years old. The mean body mass index (BMI) was 27.2 ± 4.9 kg/m^2 and ranged from 16.3 to 55.56 kg/m^2. In 425 (67.8%) cases, a pre-existing arterial hypertension was detected. Eighty-one (12.8%) patients had coronary artery disease. In 43 (6.8%) patients, type 2 diabetes mellitus was detected. Pre-existing aortic diseases such as aortic aneurysm or ectasia of the aorta were found in 86 (13.6%) of the patients. Fifteen (2.4%) patients had a Stanford type B dissection in their clinical history. One hundred ninety (30.1%) had a history of nicotine abuse, and 32 (5.1%) patients were alcohol addicted. Arteriosclerosis was found in 51 (8.1%) of the patients. A hereditary connective tissue disorder (Marfan or Ehlers-Danlos) was found in 18 (2.9%) patients. 66 (10.5%) patients were known to have hypothyroidism. There were only three (0.5%) cases of pregnancy and five (0.8%) cases of cocaine abuse.

The Charité and the Vivantes clinics play a major role in the care of critically ill patients. We assigned all patients to the respective clinics in Berlin. We divided them into three groups. The first group includes all Charité patients, the ED group patients from Vivantes clinics formed the second group. The third and last group includes all other EDs in Berlin. Detailed data including the distribution of patient characteristics among different types of hospitals are shown in Table 1. The Charité and the Vivantes clinics provided us with their own ED patient numbers. With our data, it was possible to calculate the exact incidence in the ED for the respective observation periods.

In Table 2 the cases of ATAAD, the population and the incidence are compared for the congruent period from 2010–2016. The first column contains all patients in the Berlin region.

The following columns compare the Charité clinics, the Vivantes clinics and all other hospitals in terms of cases, the emergency department incidence and the extrapolated data.The Charité has 131 ATAAD cases and an ED population of 1,050,994. This results in an incidence of 12.46/100,000. At the Vivantes hospitals, 153 cases of ATAAD were found among 2,112,610 ED patients resulting in an ED incidence of 7.24/100,000. The remaining Berlin hospitals had 5,195,208 ED patients and 154 ATAAD cases. The ED incidence was 2.96/100,000. (Table 2). The information of the pathology department of six Vivantes clinics was used to estimate how many ATAADs

	Berlin	Charité	Vivantes	Other Hospitals
emergency department patients	8,358,812	1,050,994	2,112,610	5,195,208
observation period	2010–2016			
cases of ATAAD	438	131	153	154
extrapolated cases of ATAAD	876	262	306	308
emergency department incidence ATAAD/100,000 (Confidence interval)	5.24 (5.17–5.29)	12.46 (9.2–15.5)	7.24 (6.31–8.21)	2.96 (2.57–3.34)
extrapolated emergency department incidence ATAAD/100,000 (Confidence interval)	10.48 (9.07–11.44)	24.92 (18.05–31.26)	14.48 (12.31–16.01)	5.93 (5.15–6.68)

Table 2. Emergency Department Incidence between 2010 and 2016. The Table 2 shows the population and the cases of ATAAD in the emergency departments of all four groups. The first column contains all patients in the Berlin region. The following columns compare the Charité clinics, the Vivantes clinics and all other hospitals. Incidences were calculated as ATAADs of emergency department cases per 100,000, with the confidence interval in brackets.

Year	Deceased	Pathology Vivantes	Calculated Autopsy Rate	Cases of ATAAD in Autopsy	Extrapolated Cases of ATAAD in all deaths
2010	5288	253	4.78	0	0
2011	5147	236	4.59	2	44
2012	5397	321	5.95	1	17
2013	5717	402	7.03	7	100
2014	5323	386	7.25	2	28
Total	26872	1598	5.95	12	202

Table 3. Pathology Vivantes. The Table 3 presents the cases in the pathology of the Vivantes clinics. The cases of ATAADs in the autopsies were used to extrapolate the cases of ATAAD in all deceased patients in the Vivantes Clinics. Over the five years, 1,598 autopsies were accomplished. Doing this, 12 additional ATAADs could be found. With a calculated autopsy rate of 5.95 and 26,872 deceased patients in total, 202 cases of ATAAD in all deceased could be extrapolated.

went undetected. The ATAAD was not known prior to the autopsy. Compared with the data from the German Heart Institute and the Vivantes clinics, this suggests that only one of every two ATAAD cases was detected. The details are shown in Table 3. Extrapolating this assumption to all hospitals, the incidence of ATAAD in the EDs all over Berlin would increase to 10.48/100,000, to 14.48/100,000 at Vivantes, to 24.92/100,000 at the Charité, and to 5.93/100,000 at all other hospitals in Berlin (Table 2).

Discussion

The literature review has shown that the data on the incidence of ATAAD vary substantially. The study characteristics are summarized in Table 4. It is important to provide an accurate estimation of the incidence and also to consider its development over the years. This may serve as a quality indicator for emergency services, statistical offices, public health offices, legal medicine, and other healthcare providers. The total population of the 14 studies included 1,733,937,352 person years. The indicated incidences of all population-based studies were very heterogeneous and ranged from 2.1 to 16.3/100,000 inhabitants[1–12].

A retrospective study from Rogers *et al.* 2011 roughly estimated an ED incidence for acute aortic dissection in the United States. They assumed 10,000 cases of AAD annually and 100,000,000 ED visits in the same time period. This led to an ED incidence of 10/100,000 patients[20].

Our study confirmed this assumption using exact numbers of ED patients and ATAAD cases.

Another study analyzed the incidence in clinical and forensic autopsies in the regions of Berlin and Brandenburg. The analysis provided 1150.5 cases of ATAAD per 100,000 autopsies[2]. In a retrospective study from Mollo *et al.* in 1983, autopsy reports were analyzed from 1932 to 1981. They could show a relative frequency of 1/168 or an incidence of 595/100,000 autopsies[21]. The incidence rates in the population-based studies were related to AADs without distinction between type A and type B. For this reason, we calculated the incidence for the ATAADs from the given data. A population-based incidence of 2.3/100,000 for all population-based studies was obtained. Due to the high preclinical mortality and missing forensic and clinical autopsy data, the number of unreported cases can safely be assumed to be very high. 26% of the patients who received surgical treatment due to a type A dissection died within the clinic. The mortality of the conservatively treated patients was 58%[13]. The ED incidence in the Berlin area varied over the years, but no sustained increase occurred. Across all 83 hospitals in Berlin, an ED incidence of 4.96/100,000 was calculated for the period from 2006 to 2016. The German Heart Center is responsible for the surgical care of nearly 90% of acute type A aortic dissections in the Berlin region. Looking separately at the largest hospital companies, the incidence at the Vivantes clinics was 7.24/100,000, and at the Charité hospitals it was 12.46/100,000 emergency patients. Hospitals with a higher level of care and a simultaneous “Chest Pain Unit” qualification are increasingly being approached by the ambulance

kind of incidence	Author, Date	Type	Population size × observation years	Time period	Incidence per 100.000
population based	Landenhed *et al.* 2015[5,a]	P	608,240	1923–1950	15
	Sato *et al.* 2005[6,b]	P	1,569,000	1998–1999	4
	Howard et al[7,a].	P	1,020,008	2002–2012	6
	Clouse et al[8,a]	R	1,529,122	1980–1994	3.5
	Olsson *et al.* 2006[4,a]	R	139,200,000	1987–2002	males: 16.3 females: 9.1
	Melvinsdottir *et al.* 2016[9,b]	R	6,381,584	1992–2013	2.53
	Mody et al[10,b].	R	336,781,989	2000–2011	10
	Pacini *et al.* 2013[11,b]	R	36,000,000	2000–2008	4.7
	McClure *et al.* 2018[12,a]	R	167,070,000	2002–2014	4.6
	Yeh *et al.* 2015[3,a]	R	184,383,579	2005–2012	5,6
	Kurz *et al.* 2017[2]	R	29,366,656	2010–2014	11.9
	Reutersberg *et al.* 2019[1,b]	R	729,995,776	2006–2014	2.1
emergency department	Rogers *et al.* 2011[20,c]	R	100,000,000		10
forensic	Kurz *et al.* 2017[2]	R	12,603	2010–2014	1150.5
autopsy	Mollo, Comino, and Passarino 1983[21,c]	R	31,398	1932–1981	595

Table 4. Incidences of ATAAD as Obtained from Literature Search. The Table 4 shows the study characteristics. The Studies are separated by their type of incidence. The second column names the author of the study. The next column includes the study type. The penultimate column presents the population size x observation period. The last column demonstrates the incidence of the acute type A aortic dissection per 100,000. Explanation:study type: P = prospective study, R = retrospective study. [a]Includes thoracic aortic dissections (type A and type B), aneurysm and ruptures. [b]Includes thoracic aortic dissections (type A and type B). [c]Acute Aortic Dissection without separating the different types.

service for the symptom of chest pain. With greater expertise and better occupation in the ED, these institutions generate larger numbers of cases and have a higher incidence of ATAAD in the ED. The study showed higher prevalence with lower incidence of ATAAD in the Vivantes clinics compared to the Charité clinics. This is due to the different number of EDs (Vivantes n = 9, Charité n = 3). The autopsy results and these data led to the conclusion that probably only one in two ATAADs was diagnosed. Following this assumption for the time period from 2010 to 2016, the incidence for all Vivantes clinics increased from 7.24/100,000 to 14.48/100,000. Extrapolating this assumption, the incidence in the Charité increased from 12.46/100,000 to 24.92/100,000. There is only one study that assessed the incidence in EDs in the United States of America. It provides a rough estimateof 10 AAD cases of any type among 100,000 ED patients[20]. We calculated an ED incidence of 5.24 ATAAD/100,000 for Berlin. Under the assumption that only one out of two cases are actually detected, the incidence increases to 10.48/100,000, which is almost identical to the United States of America. This incidence is higher than the average extrapolated population-based incidence in Berlin. In relation to the Berlin population during the study period (37,843,130 person years) and 1262 extrapolated cases of ATAAD, the population-based incidence was 3.3/100,000. The examination of the section material shows a very high number of unreported cases. *In all deceased patients undergoing autopsy, the ATAAD was not known prior to the autopsy. Whether or not ATAAD was causal for death is not known, but, considering the high in-hospital mortality of untreated ATAAD we can assume that it was the cause of death in the majority of cases*[22]. To reduce this number, it would be necessary to take a closer look at the deceased patients of each hospital. A study by Modelmog *et al.* could show that the autopsy findings are not in line with the diagnosis given on the death certificate in 45% of the cases[23]. Burton *et al.* from 2003 pointed out that an autopsy can reveal important and unsuspected diagnoses. The discrepancy between the clinical diagnosis and the findings of the autopsy has decreased over time. But, it remains so high that a continuation of the autopsies is indicated[24].Brinkmann *et al.* provides data on the development of clinicopathologic and forensic autopsy rates between 1994 and 1999. Especially in Berlin, the autopsy rate decreased by 3.9% within 5 years, from 15.3% in 1994 to 11.4% in 1999[25].

The study periods vary between Charité (2010–2016), Vivantes and Berlin (2006–2016). Unfortunately, it was not possible to gather data on the missing years to get equal study periods. The ED population for 2016 was missing and had to be estimated based on the evolution of patient numbers. As a result, the numbers could be under- or overestimated. The autopsy data was provided only from the Vivantes clinics. The overall autopsy rate was 5.95%. This is not enough to provide reliable numbers on undetected cases of ATAAD. Therefore, the extrapolation of these undetected numbers to all Berlin hospitals should be considered with care. For a more detailed assessment, autopsy data from all hospitals in Berlin and the Charité would be necessary. The new data on incidence in EDs should sensitize the hospitals and ambulance services to this acute disease. The goal in preclinical care should be the establishment of a standard operating procedure for the symptom complex of chest pain in which the aortic dissection detection risk score is firmly anchored. There, a special focus should be on patients who are delivered by the ambulance or the rescue service.

Conclusion

Our results underline a higher incidence in the EDs compared with the population-based incidence in the general population of Berlin. The ED incidence in the period from 2010 to 2016 varies between 2.96/100,000 and 12.46/100,000 among different types of hospitals. The population-based incidence for the entire Berlin population from 2010 to 2016 is 3.45/100,000. Specialized clinics show significantly higher case numbers. The ATAAD is a severe disease and it is one of the four differential diagnoses of acute chest pain. Lower than expected incidences may mean that ATAAD remains undetected in a considerable number of patients. The pathology department information showed, that only one in two cases of ATAAD is detected. Under this assumption, the ED incidences and the population-based incidence would be twice as large.

Material and Methods

Study design. The databases PubMed und Google Scholar were used to search for studies on the subject of incidence of aortic dissection. Incidences in the fields of population, ED, pathology autopsies, and forensic medicine were considered. "Acute aortic dissection type A incidence" and "acute aortic dissection at autopsy" were used as search terms. The search on Pubmed and Google Scholar yielded 23,056 studies. The abstracts were screened, and studies were excluded if they dealt with other topics, full-text was not available, or language was different than English or German. Based on these criteria, 23,020 studies were excluded. Twenty-two of the remaining 34 full-text studies fulfilled all criteria for eligibility and met all criteria. The bibliographies of the included studies were explored for further relevant studies. In an additional search, six more relevant studies were identified. Fourteen articles that deal with autopsy-, population-, forensic medicine incidence, and ED incidence of ATAAD are summarized in Table 4, which includes the following information: kind of incidence, author, date, study type, population size and incidence. The study from Kurz *et al.* was considered twice, for a population based incidence and a forensic medicine incidence of ATAAD[2].

Data collection. The only two institutions surgically treating ATAAD in Berlin are the German heart Centre and the Department of Cardiovascular Surgery, Charité- University Medicine Berlin. Thus the number of 631 patients was taken from the archives of these hospitals covering the years 2006 to 2016. To estimate a population of ED patients in Berlin for the years 2006 to 2016, we contacted the two major health care providers, the municipal Berlin hospital chain Vivantes, running nine large hospitals, and the Charité-University Medicine Berlin, with three hospital sites. For Charité-University Medicine hospitals, we received the numbers of ED patients for the years 2010 to 2016 directly from the heads of the respective departments. The Vivantes clinics provided us with the data from 2006 to 2015. The missing data from 2016 had to be calculated based on the annual increase. From the Berlin Hospital Society, we received the annual numbers of publicly insured emergency patients for the years 1998 to 2015. Estimating the rate of privately insured patients at 10%, we added the respective numbers. For the year 2016, no data were available. We therefore extrapolated the number for this year according to the average yearly increment of patient numbers, resulting in a total of 1,268,507 patients in 2016, including private patients.

Ethics approval and consent to participate. The study was approved by the Ethics Committee of Charité-Universitätsmedizin Berlin (Ethics Subcommittee 2 of Campus Virchow-Klinikum, registration number: EA2/126/14) and complies with the Declaration of Helsinki. An informed consent by the patient to participate in the study was not necessary on the part of the ethics committee.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

M.W., H.H., S.D.K. were responsible for the study concept and design. M.W., V.F., H.H., J.T., B.L., E.G., W.B., S.D.K. performed the acquisition of the data. M.W., H.H., S.D.K. analyzed and interpreted the data. M.W., H.H., S.D.K. wrote the manuscript.M.W., V.F., J.J.E.G., H.H., J.T., B.L., E.G., W.B. H.H., S.D.K. performed a critical revision of the manuscript for important intellectual content. The statistical expertise, and acquisition of funding was performed by M.W., H.H. and S.D.K. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Um ein besseres Verständnis für den zeitlichen Ablauf in der Versorgung von ATAAD Patienten zu bekommen, wurden in der nachfolgenden Arbeit die Symptome und deren Einfluss auf die Versorgung genauer untersucht. Der nachfolgende Text entspricht dem Abstrakt der Arbeit „Acute Type A Aortic Dissection: Aortic Dissection Detection Risk Score in emergency care – surgical delay because of initial misdiagnosis" (Zaschke et al., 2020, S. 40, doi: 10.1177/2048872620914931).

„***Background:*** *Acute type A aortic dissection requires immediate surgical treatment, but the correct diagnosis is often delayed. This study aimed to analyse how initial misdiagnosis affected the time intervals before surgical treatment, symptoms associated with correct or incorrect initial diagnosis and the potential of the Aortic Dissection Detection Risk Score to improve the sensitivity of initial diagnosis.*

Methods: *We conducted a retrospective analysis of 350 patients with acute type A aortic dissection. Patients were divided into two groups: initial misdiagnosis (group 0) and correct initial diagnosis of acute type A aortic dissection (group 1). Symptoms were analysed as predictors for the correct or incorrect initial diagnosis by multivariate analysis. Based on these findings, the Aortic Dissection Detection Risk Score was calculated retrospectively; a result ⩾2 was defined as a positive score.*

Results: *The early suspicion of aortic dissection significantly shortened the median time from pain to surgical correction from 8.6 h in patients with an initial misdiagnosis to 5.5 h in patients with the correct initial diagnosis (p<0.001). Of all acute type A aortic dissection patients, 49% had a positive Aortic Dissection Detection Risk Score. Of all initial misdiagnosed patients, 41% had a positive score (⩾2). The presence of lumbar pain (p<0.001), any paresis (p=0.037) and sweating (p=0.042) was more likely to lead to the correct initial diagnosis.*

Conclusion: *An early consideration of acute aortic dissection may reduce the delay of surgical care. The suggested Aortic Dissection Detection Risk Score may be a useful tool to improve the preclinical assessment".*

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Acute type A aortic dissection: Aortic Dissection Detection Risk Score in emergency care – surgical delay because of initial misdiagnosis

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Abstract

Background: Acute type A aortic dissection requires immediate surgical treatment, but the correct diagnosis is often delayed. This study aimed to analyse how initial misdiagnosis affected the time intervals before surgical treatment, symptoms associated with correct or incorrect initial diagnosis and the potential of the Aortic Dissection Detection Risk Score to improve the sensitivity of initial diagnosis.

Methods: We conducted a retrospective analysis of 350 patients with acute type A aortic dissection. Patients were divided into two groups: initial misdiagnosis (group 0) and correct initial diagnosis of acute type A aortic dissection (group 1). Symptoms were analysed as predictors for the correct or incorrect initial diagnosis by multivariate analysis. Based on these findings, the Aortic Dissection Detection Risk Score was calculated retrospectively; a result $\geqslant 2$ was defined as a positive score.

Results: The early suspicion of aortic dissection significantly shortened the median time from pain to surgical correction from 8.6 h in patients with an initial misdiagnosis to 5.5 h in patients with the correct initial diagnosis ($p<0.001$). Of all acute type A aortic dissection patients, 49% had a positive Aortic Dissection Detection Risk Score. Of all initial misdiagnosed patients, 41% had a positive score ($\geqslant 2$). The presence of lumbar pain ($p<0.001$), any paresis ($p=0.037$) and sweating ($p=0.042$) was more likely to lead to the correct initial diagnosis.

Conclusion: An early consideration of acute aortic dissection may reduce the delay of surgical care. The suggested Aortic Dissection Detection Risk Score may be a useful tool to improve the preclinical assessment.

Keywords

Aortic dissection, misdiagnosis, time intervals, Aortic Dissection Detection Risk Score

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Introduction

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular emergency with an incidence of about 2.9–11.9 cases/100,000 individuals/year.[1–3] Because of the high mortality rate of 1–2% per hour after symptom onset, immediate surgical treatment is necessary.[2,4–7] Acute aortic dissections are part of the acute aortic syndrome (AAS) and were first described over 200 years ago.[8] Typical of ATAAD is an abrupt onset of a tearing or ripping pain in the chest or back.[6,7,9] In general, the clinical presentation is diverse, often unspecific and can mimic other more common conditions such as acute coronary syndrome (ACS), which is the most common misdiagnosis in patients with ATAAD.[10–12]

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Because of the symptomatic overlap and the higher incidence of ACS (100–200 times more common), the correct diagnosis is often delayed.[9,13,14] In 2010 the American Heart Association (AHA) guidelines for the diagnosis and management of patients with thoracic aortic disease listed 12 high-risk markers to identify patients with acute aortic dissection.[15] These risk factors are stratified into three categories, resulting in the easily manageable Acute Aortic Dissection Detection Risk Score (ADDRS). The score is intended to support the early diagnosis of AAS in preclinical settings as well as in emergency rooms.

In our retrospective study we analysed the rate of correct or incorrect initial diagnosis of ATAAD and its impact on the delay until surgery. In addition, we analysed which clinical symptoms were associated with a correct or incorrect initial diagnosis of ATAAD and how a consistent application of the ADDRS could have affected the rate of correct diagnosis and subsequent patient care.

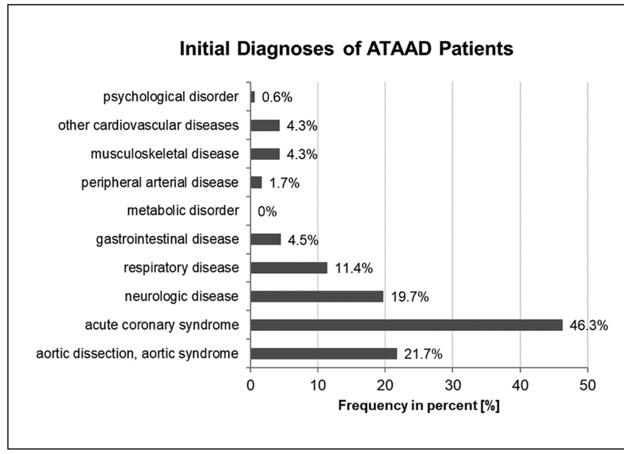

Figure 1. Distribution of documented first diagnoses of 350 acute type A aortic dissection (ATAAD) patients. More than one diagnosis was noted in 64 cases.

Methods

Within the study period between January 2012–December 2016, 415 patients with non-iatrogenic type A aortic dissection according to the Stanford classification were transferred to our institution for surgical treatment. Twenty-one patients were excluded for a period of more than 14 days between the onset of symptom and diagnosis. Forty-four patients were excluded from the analyses because the initial diagnosis was not documented in the patient file or there was a lack of data needed for the calculation of the ADDRS, resulting in 350 patients with non-iatrogenic ATAAD that were finally included in the analysis. The German Heart Center Berlin is specialised in the treatment of cardiovascular diseases, including the surgery of ATAAD. All patients were primarily admitted to another regional hospital before transfer to this institution.

Data were collected from electronic and analogue patient files. The emergency protocols and medical reports from the referring regional hospitals were also analysed. The relevant time intervals were defined as: pain onset and admission to the primary hospital, pain onset and diagnosis, admission to the primary hospital and diagnosis, diagnosis and surgery, and the overall time interval between pain onset and the start of surgery (pain-cut-time (PCT)). In addition, we analysed demographics and risk factors. Symptoms, as documented by the primary medical contact, were recorded: pain, dyspnoea, sweating, paresis of any kind, cyanosis, convulsion, nausea, reduced consciousness, dizziness, aphasia, ataxia and vision disorders. The pain was described by localization and quality. Angina pectoris like pain was defined as a retrosternal pressure or tightness.

Patients were divided into two groups according to the appropriateness of the initial diagnosis (group 0 (n=274) initial misdiagnosis, group 1 (n=76) aortic dissection as sole or differential diagnosis included in initial workup). The initial diagnosis is defined as the diagnosis of the first physician with patient contact (on-site emergency physician or physician in the emergency room). Initial diagnosis refers to the presumed diagnosis of the emergency physician before the extended imaging or invasive diagnostic process. In addition to the correct initial diagnosis (aortic dissection or AAS) the other documented initial diagnoses were assigned to 10 categories, as listed in Figure 1.

The groups were compared concerning the time intervals until surgery (e.g. time from pain onset to diagnosis). Furthermore, we analysed which symptoms were associated with the correct or wrong initial diagnosis.

The ADDRS was retrospectively evaluated taking into account the risk markers of the three categories (predisposing conditions, pain features and physical findings) as described in the AHA guidelines of 2010.[15] For each category, one point can be awarded if at least one risk marker of the category applies. A result of ADDRS=0 means a low risk and ADDRS=1 an intermediate risk for an acute aortic dissection. Patients with an ADDRS$\geqslant$2 have a high risk of an acute aortic event. Patients were divided in ADDRS negative (ADDRS$\leqslant$1) and ADDRS positive (ADDRS$\geqslant$2) groups.

All statistical analyses were carried out using SigmaStat (included in SigmaPlot, Version 13.0, Systat Software GmbH) and SPSS Statistics (Version 24, IBM). Values of p less than 0.05 ($p<0.05$) were considered statistically significant.

Continuous variables are presented as means and standard deviation or median and first and third quartile, as appropriate. To compare the time intervals between the two groups we used the Mann-Whitney U test. Categorical variables were compared by chi-square tests. In order to identify symptoms which are independently associated with the correct initial diagnoses we used univariable and multivariable

Table 1. Patients' characteristics.

Variables	Overall n=350[a]	Group 0 n=274[a]	Group 1 n=76[a]	p Value
Demographics				
Age, mean±SD	63.2 ± 13.2	62.7 ± 13.4	65.1± 12.4	0.162
Gender (male), *n* (%)	222 (63.4)	175 (63.9)	47 (61.8)	0.746
Patient history, *n* (%)				
Hypertension	250 (72.7)	197 (73.2)	53 (70.7)	0.659
Coronary heart disease	43 (12.5)	35 (13.0)	8 (10.7)	0.594
Diabetes mellitus	28 (8.1)	24 (8.9)	4 (5.3)	0.322
Hypothyreosis	46 (13.3)	37 (13.7)	9 (12.0)	0.709
Aortic disease	39 (11.3)	26 (9.6)	13 (17.3)	0.062
Positive family history	10 (2.9)	8 (3.0)	2 (2.7)	0.877
Previous type B dissection	7 (2.0)	5 (1.9)	2 (2.7)	0.646
Marfan syndrome	3 (0.9)	3 (1.1)	1 (1.3)	0.357
Drug abuse				
Nicotine	102 (30.3)	86 (32.7)	16 (21.6)	0.067
Alcohol	15 (4.4)	12 (4.6)	2 (3.9)	0.835
30-Day mortality, *n* (%)	59 (16.9)	49 (17.9)	10 (13.2)	0.337

SD: standard deviation.
Patients' characteristics are listed for the whole cohort (overall) and for patients with an initial misdiagnosis (group 0) and an initial correct diagnosis (group 1) of aortic dissection. Thirty-day mortality is defined as the period after surgery.
[a]Denominators reflect only the number of patients from whom information was available.

logistic regression. Only the variables with $p<0.1$ in the univariable analyses were included in the multivariable analyses. The initial multivariable logistic model was optimised according to the Akaike information criterion by stepwise elimination of covariables with least association with outcome. The study was approved by the local ethics committee of the Charité University Medicine Berlin (EA2/126/14) and performed in accordance with the Declaration of Helsinki. Informed consent of the individual patients was not required for this retrospective analysis.

Results

A total of 350 patients were included in the statistical analyses. Patient characteristics are presented in Table 1.

Initial diagnosis

Correct initial diagnosis of aortic dissection was noted for 76 of 350 patients (group 1, 21.7%), while initial misdiagnosis occurred for 274 patients (group 0, 78.3%). The most frequently documented initial diagnosis was ACS (46.3%; n=162). The second most frequent initial misdiagnoses were neurological diseases (19.7%, n=69), followed by respiratory diseases (11.4%, n=40). Figure 1 shows the frequencies of documented initial diagnoses.

Symptoms

Table 2 outlines the symptoms and pain localizations associated with the initial diagnosis. In univariable logistic regression, angina pectoris like pain ($p<0.001$) was associated with initial misdiagnosis. Conversely, the symptoms sweating (p=0.043), paresis of any kind (p=0.003), pain between the scapulae (p=0.034), along the thoracic spine (p=0.029), and in the lumbar region ($p<0.001$) were positively associated with the correct initial diagnosis of aortic dissection.

In multivariable logistic regression (Table 3), lumbar pain ($p<0.001$), paresis of any kind (p=0.037) and sweating (p=0.042) were independently associated with the correct initial diagnosis and angina pectoris ($p<0.001$) was an independent predictor for initial misdiagnosis. Pain between the scapulae was associated with a trend towards the correct initial diagnosis (p=0.072).

Time intervals after pain onset

Group 0 (initial misdiagnosis) and group 1 (correct initial diagnosis) were compared regarding the time intervals following the onset of pain until surgery. All intervals except the time between pain onset and admission to the primary hospital (p=0.282) were significantly lower in group 1 (Figure 2). The median time interval from pain onset to diagnosis was 4.0 h in group 0 (Q1–Q3 2.4–10.4 h) and 2.1 h in group 1 (Q1–Q3 1.5–3.2 h; $p<0.001$) and the median time interval from admission to the primary hospital to diagnosis was 2.0 h in group 0 (Q1–Q3 0.8–5.1 h) and 0.6 h in group 1 (Q1–Q3 0.3–1.4 h; $p<0.001$). Furthermore, the median time interval from diagnosis to cut (surgery) was noted as 4.1 h in group 0 (Q1–Q3 3.2–5.0 h) and 3.4 h in group 1 (Q1–Q3 2.6–3.9 h; $p<0.001$). Finally, the

Table 2. Symptoms.

Variables	Overall n=350[a]	Group 0 n=274[a]	Group 1 n=76[a]	p Value
Pain localization, *n* (%)				
Thorax/chest	240 (68.8)	189 (69.2)	51 (67.1)	0.724
Angina pectoris	123 (35.5)	110 (40.4)	13 (17.6)	<0.001
Head	30 (8.6)	22 (8.1)	8 (10.5)	0.497
Mandibula	39 (11.2)	32 (11.8)	7 (9.2)	0.533
Neck	59 (17.0)	47 (17.3)	12 (15.8)	0.760
Thoracic spine	66 (19.0)	45 (16.5)	21 (27.6)	0.029
Lumbar spine	33 (9.4)	16 (5.9)	17 (22.4)	<0.001
Between scapulae	40 (11.5)	26 (9.6)	14 (18.4)	0.032
Abdomen	62 (17.9)	44 (16.2)	18 (23.7)	0.134
Left arm	22 (6.3)	19 (7.0)	3 (3.9)	0.336
Other limb	31 (8.9)	22 (8.1)	9 (11.8)	0.310
Other symptoms, *n* (%)				
Reduced consciousness	77 (22.1)	62 (22.6)	15 (19.7)	0.580
Dyspnoea	88 (25.2)	73 (26.7)	15 (19.7)	0.214
Nausea	75 (21.5)	58 (21.2)	17 (22.4)	0.833
Sweating	88 (25.2)	62 (22.7)	26 (34.2)	0.041
Cyanosis	8 (2.3)	4 (1.5)	4 (5.3)	0.050
Convulsions	9 (2.6)	8 (2.9)	1 (1.3)	0.432
Dizziness	60 (17.1)	48 (17.6)	12 (15.8)	0.714
Aphasia	13 (3.7)	10 (3.6)	3 (3.9)	0.903
Ataxia	2 (0.6)	2 (0.7)	0 (0)	0.455
Vision disorder	25 (7.1)	21 (7.7)	4 (5.3)	0.472
Any paresis	103 (29.4)	70 (25.5)	33 (43.4)	0.002

Symptoms are listed for the whole cohort (overall) and for patients with initial misdiagnosis (group 0) and initial correct diagnosis (group 1) of aortic dissection.
[a]Denominators reflect only the number of patients from whom information was available.

Table 3. Multivariable logistic regression.

Variables	Odds ratio	95% CI	p Value
Pain, lumbar region	4.38	1.94 - 9.90	<0.001
Angina pectoris	0.31	0.16 - 0.61	<0.001
Sweating	1.86	1.02 - 3.37	0.042
Any paresis	1.85	1.04 - 3.31	0.037
Pain, scapulae	2.03	0.94 - 4.39	0.072

CI: confidence interval.
Results of the multivariable logistic regression model on the association of symptoms or pain localization with correct initial diagnosis are listed. While angina pectoris like pain is associated with a higher rate of initial misdiagnosis, sweating and pain in the lumbar region independently favour correct initial diagnosis.

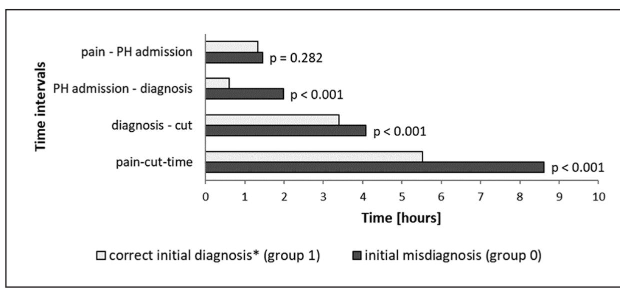

Figure 2. Distribution of the different time intervals (in median). Denominators reflect only the number of patients from whom information was available. PH: primary hospital. *Aortic dissection at least as differential diagnosis.

median PCT (time interval from pain onset to surgery) was 8.6 h in group 0 (Q1–Q3 6.3–16.4 h) and only 5.5 h in group 1 (Q1–Q3 4.5–7.9 h; $p<0.001$).

ADDRS

The retrospective analysis of the ADDRS revealed that 178 patients initially had a negative (ADDRS⩽1) and 172 a positive score (ADDRS⩾2) (51% vs 49%). As is obvious from data in Table 4, the rate of correct initial diagnoses increased with increasing ADDRS, from 5.1% in patients with an ADDRS=0 to 56.2% in patients with a score=3. However, among the 172 patients with a positive ADDRS of ⩾2, 113 patients (65.7%) still received an incorrect initial diagnosis.

Discussion

In this retrospective study including patients with ATAAD, we were able to show that initial misdiagnosis is a common problem that significantly prolongs the time to necessary surgical correction. The symptoms lumbar pain, sweating

Table 4. Relationship of Aortic Dissection Detection Risk Score (ADDRS) and initial diagnosis.

ADDRS	ADDRS-result	Initial misdiagnosis *n*=274	Correct initial diagnosis *n*=76	Total	Total
Negative	0	37 (94.9%)	2 (5.1%)	39	178
	1	124 (89.2%)	15 (10.8%)	139	
Positive	2	106 (67.9%)	50 (32.1%)	156	172
	3	7 (43.8%)	9 (56.2%)	16	

Distribution of the ADDRS results with respect to the correct or incorrect initial diagnosis. The black frame represents the patients who have the potential to receive a correct initial diagnosis using the ADDRS.

and paresis were associated with a correct suspected diagnosis. On the other hand, angina pectoris like pain was associated with more frequent initial misdiagnosis. This is also reflected by the fact that ACS was the most common initial diagnosis in patients with ATAAD (46% of all cases).

Retrospectively, 41% of all patients with an initial misdiagnosis presented with a positive ADDRS result (ADDRS⩾2). Thus, a large number of patients may profit from a consistent application of the ADDRS during the first physician contact.

Symptoms

Previous studies reported chest pain as a potential predictor for misdiagnosis.[16,17] These results are confirmed by our data where angina pectoris like pain was associated with initial misdiagnosis. Angina pectoris is the main symptom of ACS and due to the higher incidence compared to acute aortic dissection, a significant association of angina pectoris with the initial misdiagnosis is easy to understand, but at the same time it is a major problem. In addition, back pain has been reported to lead to a significantly faster correct diagnosis.[10] This observation matches well with our result that lumbar pain is positively associated with correct initial diagnosis of ATAAD. In addition we were able to show, that any paresis also induced emergency physicians to consider an aortic dissection.

Initial diagnosis

The wide variety of symptoms, which are associated with acute aortic dissection, make it difficult to establish the correct diagnosis. In previous studies, the rates of initial misdiagnosis ranged from 16–39%.[11,17–19] In this study, initial misdiagnosis occurred more frequently in 78.3%. This obvious difference may be explained by the fact that we considered the first suspected diagnosis made by the first physician contact (including emergency physicians outside of the hospital). In contrast, most other studies used the diagnosis made at the emergency department as the 'first diagnosis', which was mostly reached after completion of the whole diagnostic workup. The most common misdiagnosis in this study was the acute coronary syndrome with 46.3%. This result is in agreement with that of Hirata et al. where 41.7% of the 127 ATAAD patients initially received this diagnosis. Also, neurological and respiratory emergencies (16% and 14%) were similarly reported as differential diagnoses.[19]

ADDRS

To facilitate the identification of an acute aortic dissection, the ADDRS was introduced in 2011.[20] In our study, a positive ADDRS (ADDRS⩾2) was retrospectively found in 49.2% of all cases. Another 40% of all ATAAD patients had an intermediate risk of aortic dissection (ADDRS=1). An ADDRS result with zero points was found in about 11%. These results are comparable to those of Rogers et al., Nazerian et al. and Gorla et al., in which the frequency for ADDRS=0 ranged between 1.2–8.9%, for ADDRS=1 between 35.3–58.4% and for ADDRS>1 between 32.6–63.5%.[20–23] Thus, we can confirm the statement of Nazerian et al. that an ADDRS=0 does not exclude an acute aortic dissection with certainty.[21] But consequently, an early application of the ADDRS could increase the rate of correct initial diagnosis from 22–49%, which could significantly shorten the time interval until the necessary surgery for numerous aortic dissection patients.

We also analysed the ADDRS result in relation to the initial diagnoses. Of 274 patients with initial misdiagnosis, approximately 41% had a positive ADDRS (ADDRS⩾2) and thus a high risk of acute aortic dissection. In these patients, had the score been used, aortic dissection could have been considered as a differential diagnosis already before reaching the emergency room or before onset of the extensive diagnostic procedure. This could have potentially paved the way for a faster diagnostic workup and hence shortened the PCT in some of these patients. If the ADDRS had been applied early, initial misdiagnosis due to ADDRS⩾1 could have been avoided in two out of three cases (65.7%). In this context, it must also be mentioned that this would produce many patients as false positives and expose them to radiological overtesting.[24] One reason for this is the low specificity, especially for a score of ADDRS⩾1, which ranges between 26.4–64.6%.[21–23] Furthermore, a low positive predictive value for an ADDRS

Table 5. Time intervals in comparison to other studies.

	Pain – PH admission hours	PH admission – diagnosis hours	Diagnosis – cut hours
Our study	1.5 vs 1.3	2.0 vs 0.6	4.1 vs 3.4
Rapezzi et al.	1.3	1.95	-
Hirata et al.	-	1.5	-
Harris et al.	-	4.3	4.3

PH: primary hospital.
Time intervals from our study are given for group 0 versus group 1.

⩾1, as in Nazerian et al. of only 39%, leads to a significant expansion of the diagnostic workup in many emergency room patients with suspected aortic dissection. On the one hand, this means that 61% of the patients with a positive score (ADDRS⩾2) have no AAS, but are still exposed to potential complications from further workups like computed tomography (CT) angiography, such as radiation or contrast-induced anaphylaxis or nephropathy.[23] On the other hand, for a small number of patients with AAS, this could mean an early and correct diagnosis, which could potentially save lives. This illustrates the dilemma between misdiagnosis of ATAAD patients and overtesting of non-AAS patients.

Gorla et al. and Nazerian et al. attempted to improve the accuracy of ADDRS through a combination with biomarkers (D-dimers), especially in patients with ADDRS=0. The combination of an ADDRS=0 with a negative test for D-dimers could be considered to standardise the diagnostic exclusion of ATAAD, so a CT angiography would not be necessary.[22,23] This requires a systematic application of the ADDRS. As already shown above, our data suggest that a routine implementation of the score in the daily clinical practice may still need to be improved.

Based on our findings we believe that the ADDRS may be helpful in the preclinical setting to assess the risk of an acute aortic dissection and to document it as a potential diagnosis before reaching the emergency department. Once ATAAD is on the list of differential diagnoses, it may trigger a faster and more directed workup in the emergency room. A combination with other easily available diagnostic procedures (such as transthoracic echocardiography (TTE) and the determination of D-dimers) in addition to the ADDRS could be used here to avoid unnecessary CT angiographies. Zhan et al. analysed a positive diagnostic rate of aortic dissection of 97.9% with TTE.[25] That means that TTE could be a fast and widely available alternative to CT angiography in the case of a positive ADDRS, provided that physicians with sufficient experience in TTE are available. A detailed history in terms of the pain (onset, duration, severity, radiation and quality) and its documentation are very important and reduce the risk of misdiagnosis.[26] This history is included in the ADDRS and should be supplemented by a brief physical examination including bilateral blood pressure measurement and a check for femoral pulse difference, which can easily be accomplished in the preclinical setting.

Time intervals

We found no previous studies analysing the different time intervals after onset of pain until surgery in relation to the initial diagnosis of patients with ATAAD but there are a number of articles describing these time intervals in general (Table 5).[10,19,27] Rapezzi et al. found similar time intervals from pain to admission to a primary hospital and from admission to diagnosis. But, Rapezzi et al. included all patients with aortic dissection – the rate of ATAAD was only 27%.[27] Additionally Hirata et al. report a similar median time interval from admission to diagnosis.[19] Harris et al. established, in their study of 751 patients, a time interval from admission to the emergency department to diagnosis of 4.3 h and a time interval from diagnosis to surgery of 4.3 h. They also described a reduction of the time interval from diagnosis to surgery when the patient had typical symptoms (such as chest, back or leg pain).[10] The initial mention of aortic dissection as a differential diagnosis not only leads to significantly shorter times until the final diagnosis of ATAAD, but also to a significantly shorter time interval between diagnosis and surgery. Obviously, the expectation of an aortic dissection triggers a more directed workup by initiating faster patient transfer and appropriate imaging. A rapid patient transfer to a hospital for surgery is also important, but is often delayed and requires good organization.[28]

Limitations

Our study shares all the common limitations of a retrospective analysis, including missing data. The rationale of the first physician contact that led to the initial clinical assessment, and subsequently to the correct or incorrect diagnosis is usually not documented. Our study population was first treated in primary hospitals with different diagnostic workup algorithms and possibilities and then transferred to our institution with a confirmed diagnosis. The assessment and treatment in these hospitals differed, which may have influenced the relevant time intervals. Patients who died before arriving at our institution were not registered in the study.

Conclusion

Approximately 41% of all ATAAD patients with an initial misdiagnosis had a positive ADDRS (ADDRS$\geqslant$2) and thus a high risk of aortic dissection. These patients would have had a higher likelihood of getting the correct diagnosis by consistently applying the ADDRS in the preclinical setting. For this reason, our data suggests that the routine use of the ADDRS should be encouraged. However, a prospective study would be necessary to confirm that this would shorten the time until surgery. Our analysis showed a significant delay of surgical care in cases of initial misdiagnosis. With a mortality of 1–2% per hour in the first 24–48 h after the onset of pain,[2,4] the early consideration of aortic dissection as a differential diagnosis may improve outcomes. The first physician contact thus plays a key role in drawing attention to the possibility of an acute aortic dissection even before reaching the emergency department. Here, the ADDRS could be a supportive tool.

With a short, focused history on pain specifics and pre-existing conditions of the patient's aorta or heart or their family members, as well as a brief clinical examination including measuring of bilateral blood pressure and checking neurological status, the ADDRS is an easy manageable tool to estimate the risk of an acute aortic dissection.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Die nachfolgende Arbeit untersucht die Lebensqualität nach einer ATAAD. Der nachfolgende Text entspricht dem Abstrakt der Arbeit „Health-related quality of life of patients after surgery for acute Type A aortic dissection" (Adam et al., 2018, S. 48, doi: 10.1093/icvts/ivy036).

*„**OBJECTIVES:** Acute Type A aortic dissection (ATAAD) and the ensuing surgical therapy may be experienced as a traumatic event by patients. This study aimed at analyzing the prevalence of post-traumatic stress disorder (PTSD) and the physical and mental well-being of survivors of surgically treated ATAAD.*

***METHODS:** A total of 393 survivors were contacted and asked to fill in various health questionnaires.*

***RESULTS:** Two hundred and ten (53%) patients returned the questionnaires. The mean follow-up was 51 ± 27.8 months. The results showed that 67.6% had high blood pressure, 12.9% had pre-existing diseases of the aorta and 31.5% or 27% of these groups were at risk for PTSD according to the health questionnaires. Duration of intensive care unit or hospital stay had no effect on the risk for PTSD. According to the questionnaire, Short Form 12, physical and mental well-being was significantly reduced in the patients compared to a large German norm sample, even after adjustment for differences in age between the 2 cohorts. Physical activity prior to the event was associated with im- proved physical and mental well-being but did not reduce the risk for PTSD.*

***CONCLUSIONS:** Emergency surgery for ATAAD is associated with high risk for PTSD, which seems to negatively affect physical and mental well-being. More efforts should be directed at prevention and early diagnosis and therapy of PTSD. This study has evaluated 8-year trends in the presentation, diagnosis and outcomes such as physical and mental measures and prevalence rates of PTSD in patients who have undergone an emergency operation for ATAAD".*

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Health-related quality of life of patients after surgery for acute Type A aortic dissection

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Abstract

OBJECTIVES: Acute Type A aortic dissection (ATAAD) and the ensuing surgical therapy may be experienced as a traumatic event by patients. This study aimed at analysing the prevalence of post-traumatic stress disorder (PTSD) and the physical and mental well-being of survivors of surgically treated ATAAD.

METHODS: A total of 393 survivors were contacted and asked to fill in various health questionnaires.

RESULTS: Two hundred and ten (53%) patients returned the questionnaires. The mean follow-up was 51 ± 27.8 months. The results showed that 67.6% had high blood pressure, 12.9% had pre-existing diseases of the aorta and 31.5% or 27% of these groups were at risk for PTSD according to the health questionnaires. Duration of intensive care unit or hospital stay had no effect on the risk for PTSD. According to the questionnaire, Short Form 12, physical and mental well-being was significantly reduced in the patients compared to a large German norm sample, even after adjustment for differences in age between the 2 cohorts. Physical activity prior to the event was associated with improved physical and mental well-being but did not reduce the risk for PTSD.

CONCLUSIONS: Emergency surgery for ATAAD is associated with high risk for PTSD, which seems to negatively affect physical and mental well-being. More efforts should be directed at prevention and early diagnosis and therapy of PTSD. This study has evaluated 8-year trends in the presentation, diagnosis and outcomes such as physical and mental measures and prevalence rates of PTSD in patients who have undergone an emergency operation for ATAAD.

Keywords: Acute Type A aortic dissection • Post-traumatic stress disorder • Quality of life

INTRODUCTION

Without surgical intervention, acute Type A aortic dissection (ATAAD) is in most cases a fatal condition that is characterized by splitting of the ascending aorta wall layers [1] and may cause typical symptoms such as excruciating pain radiating into the jaw and back, atypical angina pectoris symptoms or neurological deficits such as syncope, hemiparesis/hemiplegia or paraparesis/paraplegia [2]. ATAAD is not rare, and the incidence has been recently estimated at 11.9/100 000 per year. ATAAD should therefore be considered in prehospital differential diagnosis of patients with acute chest pain [3, 4]. Usually the final diagnosis is based on imaging techniques such as transoesophageal or transthoracic echocardiography or computed tomography [5].

For patients with serious health conditions such as ATAAD, the subsequent diagnostic and therapeutic procedures and the stay in the intensive care unit (ICU) are often associated with fear and can trigger a post-traumatic stress disorder (PTSD) [6]. PTSD is common due to the strong stressors to which the patients are exposed in the ICU. PTSD displays specific symptoms such as repeatedly experienced flashbacks, depression and anxiety disorders that, by definition, will persist for at least 1 month [7]. PTSD is recognized as a serious psychiatric disorder in our society and as a discrete condition [8]. The prevalence of PTSD can vary according to the different illnesses, e.g. up to 15% after myocardial infarction [9] and has been found to amount to 5–63% [6] after a stay in the ICU. In general, PTSD is diagnosed more frequently in the case of female and younger patients [10, 11].

Although numerous studies on PTSD are available, there are no long-term studies on the relationship between surgically treated ATAAD and PTSD. The aim of this study, therefore, was to determine how the condition of ATAAD, the major emergency surgery and the subsequent ICU stay were experienced by the patients and affected their later life.

PATIENTS AND METHODS

The study was approved by the local ethics committee. Written informed consent of patients was obtained. In addition to the available clinical patient data from the inpatient stay, the findings from 4 questionnaires to be filled out by the patients were evaluated.

Patient selection

During the study period between 2006 and 2013, a total of 665 patients underwent treatment for ATAAD at the German Heart Centre Berlin. During this period, patients were operated on mainly in deep hypothermia (84%). For cerebral protection, retrograde (75%) or, occasionally, antegrade (6%) perfusion was applied. Aortic valve reconstruction was performed in 40.5% of patients, aortic valve replacement with bioprosthesis in 5.7% and with mechanical prosthesis in 24%. At least this latter cohort would require postoperative anticoagulation. New neurological complications were coma in 2.9%, cerebral or spinal ischaemia in 18.4% and peripheral ischaemic neuropathy in 8% of patients. A total of 272 patients died postoperatively before follow-up (FU); 393 survivors of surgery for ATAAD could be located, were contacted in a letter and, in case of lacking response, by telephone and were asked to complete a battery of questionnaires that included a clinical questionnaire, the Short Form 12 Health Survey (SF-12), the Post-traumatic Diagnostic Scale (PDS), the Post-traumatic Stress Scale 14 (PTSS-14) and the health questionnaire 'Questionnaire on the person'. Two hundred and ten patients returned the questionnaires (overall response rate of 53%) but not all of them completed all of the 4 questionnaires.

Questionnaires

Sociodemographic questionnaire. Demographic variables included age, gender, years of education, employment and marital status. The employment status was divided into paid work and no paid work (retired or unemployed). Marital status was categorized as single, married, divorced or widowed.

There are several psychometric tests to diagnose PTSD.

Short Form-12 Health Survey. Health-related quality of life was assessed by the SF-12, a standardized questionnaire with established psychometric validity. Health domains such as physical functioning, role limitations due to physical health, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional health or mental health (psychological distress and psychological well-being) were measured by the SF-12 [12]. The 2 main scales, the Mental Component Summary (MCS) and the Physical Component Summary (PCS) are generated from the SF-12 and analysed as continuous variables [13]. The SF-12 data were compared with data from a normative German population ($n = 6676$) used for the validation of the SF-12 in Germany [14].

Post-traumatic Diagnostic Scale. Edna Foa, in 1995, developed and validated the PDS, a self-reported questionnaire consisting of 49 items. To date, it is regarded as the gold standard for PTSD diagnosis [15]. The PDS may be scored by hand or by a computer program and has a sensitivity of 0.89 [16].

Patients were asked to provide information on their traumatic experiences and about the symptoms of PTSD such as nightmares, memories of their experiences and social activity. The PDS is also used to determine the level of severity of PTSD. This is based on the total point value from the third part, which can lie between 0 and 51: 0–10 points is classified as mild, 11–20 points as moderate, 21–35 points as moderate to severe and >35 points as a severe form of PTSD [17, 18].

Post-traumatic Stress Scale 14. PTSS-14 is a short test to diagnose PTSD and is based on international diagnosis criteria (Diagnostic and Statistical Manual of Mental Disorders - IV-textrevision). Suspected PTSD is diagnosed at a total number of 40 or more points [19], and preventive contact with a doctor or psychologist should then be recommended. The test is divided into 2 parts. Part 1 consists of 4 questions and concerns the memory of the illness itself and the hospital stay. Part 2 consists of 14 questions that relate to the present state of health and ask about typical reactions that can arise after stress and were not apparent previously [15].

Statistical analyses

Descriptive statistics were produced based on demographic and psychometric data (PTSS-14, PDS and SF-12). For group comparisons such as PTSD-positive versus PTSD-negative patients, patients with versus without sports or patients versus norm sample, the χ^2 test or the Student's *t*-test was used as appropriate. Comparisons of MCS and PCS between patients and the norm sample according to age groups were performed by 2-way analysis of variance. All statistical analyses were performed with IBM SPSS Statistics (SPSS, Inc., Chicago, IL, USA) for Windows.

RESULTS

In total, 393 questionnaires were sent to patients affected by ATAAD. Two hundred and ten of these patients agreed to take part in the study and returned the questionnaires; 188 (90%) of the 210 patients completed the SF-12, 206 (98.1%) patients the PTSS-14 and 159 (75.7%) the PDS in full. The mean FU was 51 ± 27.8 (range 36–120) months after surgery. The mean operative time was 410 ± 172 min, mean stay on the ICU was 4.7 ± 8 days, mean operative temperature was 17 ± 7.3 °C and mean time on cardiopulmonary bypass was 225 ± 80 min. Rethoracotomy was performed in 9 (1.3%) cases.

Demographics and clinical characteristics

Of the 210 participants, 132 (62.9%) were men and 78 (37.1%) were women. The average age at the time of surgery was 59.1 ± 12.3 years. The youngest patient was operated on at 27 years and the oldest at 90 years. One hundred and forty-two (67.6%) of the patients had high blood pressure and 4 (1.9%) patients had Marfan syndrome. One patient was pregnant. The total risk profile for the entire patient cohort is listed in Table 1. Further statistics show that 98.1% were Caucasian, 65.7% were married, 68.6% lived with their family or partner, 42.4% had successfully graduated from secondary school or had higher education, 51% were retired at the time of the study and 15.7% were

Table 1: Pre-existing conditions of ATAAD patients

Categories	ATAAD patients
Number of patients (2006–2013)	210
Average age (years)	59.1 ± 12.3
Male gender	132 (63)
BMI (kg/m^2)	26.9 ± 4.5
Hypertension	142 (67.6)
Diabetes mellitus	6 (2.9)
Hypothyroidism	22 (10.5)
Positive family history of aortic dissection	11 (5.2)
Marfan syndrome	4 (1.9)
Diseases of the aorta in patient history	27 (12.9)
Coronary heart disease	23 (11)
Arteriosclerosis	10 (4.8)
Nicotine	61 (29)
Alcohol	13 (6.2)
Cocaine	0
Pregnancy	1 (0.5)
Replacement of parts of the aorta in patient history	4 (2)
Aortic valve replacement	4 (1.9)
Mitral valve replacement	3 (1.4)
Coronary angiography	11 (5.2)
Coronary bypass	2 (1)
Neurological deficits (preoperatively)	72 (41.4)

Pre-existing medical conditions, average age and gender as derived from the patient files are listed. Data are presented as either mean ± SD or *n* (%) in brackets.

ATAAD: Acute Type A aortic dissection; BMI: body mass index; SD: standard deviation.

Table 2: Questionnaire on the person: sociodemographic data

Questions	*n* (%)
Ethnic group: White	206 (98.1)
Living with partner/family	144 (68.6)
Education	
Secondary school	89 (42.4)
College	63 (30)
Current professional status	
Retired	107 (51)
Unemployed	10 (4.8)
Employed	46 (21.9)
Incapacitated	39 (18.5)
Currently able to walk	189 (90)
Dependent on the help of others	33 (15.7)
Sport before ATAAD operation	81 (38.6)

Demographic variables included years of education, employment, marital status and some current health situations.

ATAAD: Acute Type A aortic dissection.

dependent on the help of others for physical care, dressing or eating (Table 2).

Short Form-12 Health Survey

In total, 188 patients completed the self-report questionnaire SF-12 in full. The results are compared to those of the German norm sample (normal population) from 1998 ($n = 6676$) [14]. The evaluation shows an average PCS of 48.2 ± 8.8 for the subjects in the norm sample vs 37.2 ± 10.9 for the ATAAD patients ($P < 0.001$). The average MCS of the norm sample was 51.4 ± 8.6 compared to 48.9 ± 11.6 for the ATAAD patients ($P < 0.001$; Table 3). These differences were similar for men and women.

Table 3: Comparison of the PCS and MCS scales of the German norm sample versus those of ATAAD patients

Population	*n*	AM ± SD	*P*-value
PCS			
Norm sample	6676	48.2 ± 8.8	<0.001
ATAAD patients	188	37.2 ± 10.9	
Norm sample (male)	3269	49.1 ± 8.2	<0.001
ATAAD patients (male)	121	37.5 ± 11.5	
Norm sample (female)	3407	47.3 ± 9.2	<0.001
ATAAD patients (female)	67	36.5 ± 10	
MCS			
Norm sample	6676	51.4 ± 8.6	<0.001
ATAAD	188	48.9 ± 11.6	
Norm sample (male)	3269	52.5 ± 7.8	<0.001
ATAAD patients (male)	121	50 ± 11.1	
Norm sample (female)	3407	50.3 ± 9.1	0.002
ATAAD patients (female)	67	46.9 ± 12.2	

PCS and MCS from ATAAD patients are compared with those of the German norm sample by gender from 1998 [14]. Data are numbers of patients (*n*), AM ± SD and *P*-value. Comparisons by age groups are presented in Figs 1 and 2.

AM: arithmetic mean; ATAAD: Acute Type A aortic dissection; MCS: Mental Component Summary; PCS: physical component summary; SD: standard deviation.

Comparison of the age groups

Because patients were considerably older than the subjects of the norm sample, PCS and MCS were additionally analysed according to the age groups from 21–30 years up to >70 years. The age group of 41–50 years is equally represented in ATAAD patients and the standard sample. In younger age groups, ATAAD patients are under-represented, with only 1 patient <30 years of age, while patients are over-represented in older age groups.

In the norm sample, the MCS remains largely unchanged up to 60 years, with a slight increase beyond this age (Fig. 1). In 31–40-year-old ATAAD patients, the MCS is similar to that of the norm sample, but it is considerably lower in 41–50-year-old patients and then roughly follows the development in the norm sample, yet on this lower level.

The PCS continuously decreased with increasing age in both the standard sample and ATAAD patients (Fig. 2). However, patients present with consistently lower values across all age groups ($P = 0.005$ to $P < 0.001$). The relative difference between the standard sample and the ATAAD patients is more pronounced for the PCS than for the MCS.

Post-traumatic Stress Scale 14 and Post-traumatic Diagnostic Scale

In total, 206 (98.1%) patients completed the questionnaire PTSS-14 in full, and 159 (75.7%) patients completed the questionnaire PDS in full. Sixty-five (31.5%) patients achieved a score total of 40

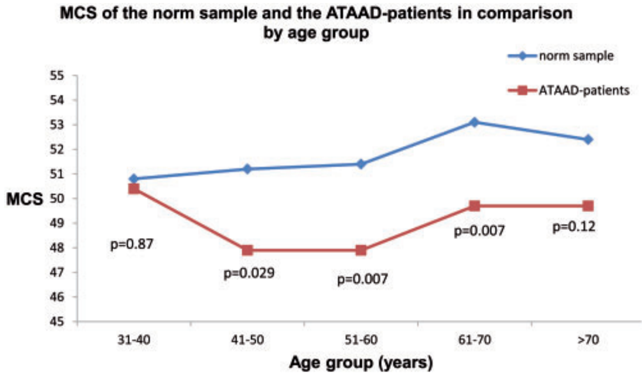

Figure 1: MCS from ATAAD patients between 2006 and 2013 is compared with that of the German norm sample by their age group from year 1998 [14]. Data are MCS value, age (years) and *P*-value. In 31–40-year-old ATAAD patients, the MCS is similar to that of the norm sample; it is considerably lower in 41–50-year-old patients and then roughly follows the development in the norm sample, yet on this lower level. ATAAD: Acute Type A aortic dissection; MCS: Mental Component Summary.

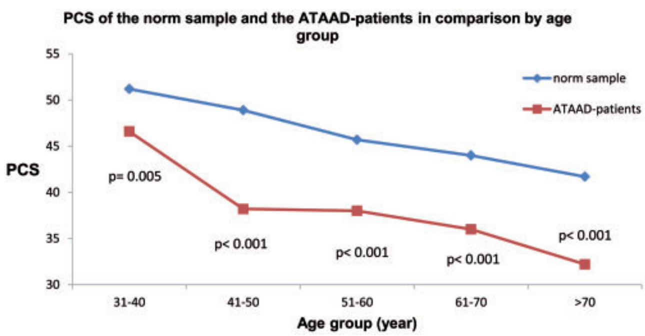

Figure 2: PCS from ATAAD patients between 2006 and 2013 is compared with that of the German norm sample by their age group from year 1998 [14]. Data are PCS value, age group (years) and the *P*-value. A decrease of the PCS value in the ATAAD group and the German norm sample with increasing age is demonstrated. ATAAD: Acute Type A aortic dissection; PCS: Physical Component Summary.

or higher in the PTSS-14, indicating the possibility of PTSD and 43 (27%) patients were at risk of PTSD according to PDS criteria (Table 4).

In Table 4, sociodemographic data and PTSD symptoms such as nightmares, depression, sleep problems and memories of the illness itself are listed for both questionnaires.

There is a trend towards more women ($P = 0.42$ by PTSS-14), for younger ($P = 0.1$ by PTSS-14), unemployed ($P = 0.35$ by PTSS-14) and disabled patients being affected by PTSD. The differences were not statistically significant, except in patients with reduced mobility ($P = 0.002$ by PTSS-14). Patients with positive PTSS-14 or PDS results presented with significantly lower PCS and MCS as obtained from the SF-12 self-report questionnaires ($P < 0.001$ by PTSS-14 and PDS).

It is evident from Table 4 that roughly half of the patients at risk for PTSD had violent fear and panic and approximately a third experienced severe pains when they remember the illness itself and the hospital stay. Sexual activity is reduced significantly in patients positive for PTSD results ($P = 0.004$).

Physical activity and quality of life

Eighty-one (39%) patients participated in sport before their ATAAD operation. The parameters are listed in Table 5. They tended to be 1 year younger, presented with a significantly higher PCS ($P = 0.02$) and MCS ($P = 0.015$) and were less frequently incapacitated ($P = 0.03$) compared to the 'without sport' group. Nightmares and depression occurred at a similar rate, but sleep problems were less common in the group with preoperative sports ($P = 0.04$).

Relationship between length of intensive care unit stay and post-traumatic stress disorder

One objective of this study was to determine whether there is a connection between the length of stay in the ICU and the PTSD risk. This was analysed using both the PTSS-14 and PDS questionnaires.

Patients at risk for PTSD according to the PTSS-14 (positive 87 h, negative 127 h; $P = 0.68$) or PDS (positive 92 h, negative 95 h; $P = 0.5$) did not present with longer ICU stay.

In order to account for a possible influence of the duration of FU on our results, we also divided patients into 2 groups according to the FU time. Among the patients operated between 2006 and 2009 ($n = 85$), 29.4% were positive for PTSS-14 and 21% for PDS. Similarly among patients operated between 2010 and 2013 ($n = 125$), 32% were positive for PTSS-14 and 20% were positive for PDS. Contrary to our expectations, this study did not show a decrease in the likelihood of PTSD with time.

DISCUSSION

Previous publications had a small number of patients in comparison with this study [20, 21].

The PCS and MCS of our patients were compared with various other diseases examined in the 1998 'Health Survey' in Germany [14]. ATAAD (48.9) patients have a lower MCS than patients with other diseases (asthma 50.3, diabetes mellitus 50.2, cancer 49.3 and stroke 50.1). Patients with depression (42.9) and eating disorder (43.8) showed the lowest MCS.

The physical situation indicates a different outcome. The highest PCS came from the eating disorder patients (46.8). Patients with ATAAD present a PCS of 37.1. Compared to patients with other diseases such as asthma (46.1), diabetes mellitus (41.3) and cancer (44.2), ATAAD patients were mentally fitter but in a poorer physical condition.

The most recent study found that 32% of post-dissection patients experienced depression [21]. In contrast, 25.8% of ATAAD patients self-reported depression due to their ATAAD and 24.8% of ATAAD patients indicate that ATAAD has negatively affected their sexual activity; according to Chaddha *et al.* [21], it was 33%.

In a previous study, durations of ward and ICU stays were suggested to influence the later quality of life of the patients after surgery [22]. This was not confirmed here. The results differ only slightly, and the deviations are not significant, so that a connection between the parameters could not be reliably established.

Patients without sports activities before the event were more often incapacitated, had more sleep problems and lower MCS and PCS scores. Although the incidence of PTSD was not different, one may conclude that the general quality of life after the operation is positively influenced by regular physical activity.

Limitations

The following limitations exist regarding this study. Two different questionnaires were used for PTSD diagnosis. PDS contains more

Table 4: Results of the PTSS-14 and the PDS according to patient conditions

Parameters	PTSS-14 positive	PTSS-14 negative	*P*-value	PDS positive	PDS negative	*P*-value
n (%)	65 (31.5)	141 (68.4)		43 (27)	116 (72.9)	
Male	37 (57)	94 (67)	0.42	26 (60)	76 (66)	0.34
Female	28 (43)	47 (33)		17 (40)	40 (34)	
Average age (years)	56.9 ± 12.2	59.7 ± 12	0.10	55.3 ± 10.9	57.8 ± 12.6	0.25
BMI (kg/m^2)	26.6	27	0.51	27.3	26.9	0.30
PCS	31.7 ± 7.9	39.9 ± 11.2	<0.001	31.3 ± 9.7	39.1 ± 10.9	<0.001
MCS	37.9 ± 9.3	54.3 ± 8.4	<0.001	39.9 ± 10.4	51.6 ± 10.4	<0.001
Living with partner/family	42 (64.6)	99 (70.2)	0.52	27 (62.8)	82 (70.7)	0.45
Retired	26 (40)	78 (55.3)	0.06	16 (37.2)	55 (47.4)	0.33
Unemployed	5 (7.7)	5 (3.5)	0.35	4 (19)	5 (4.3)	0.41
Incapacitated	23 (35.3)	16 (11.3)	0.001	14 (32.6)	18 (15.5)	0.03
Currently able to walk	52 (80)	134 (95)	0.002	34 (79.1)	110 (94.8)	0.007
Dependent on outside help	12 (18.5)	19 (13.5)	0.47	9 (20.9)	16 (13.8)	0.39
Participated in sport before their ATAAD operation	21 (32.3)	59 (41.5)	0.25	15 (34.9)	48 (41.4)	0.57
Reduced sexual activity	31 (58)	21 (21)	0.004	29 (70)	22 (21)	<0.001
In memory (disease event or hospitalization)						
Nightmares	44 (67.7)	48 (34)	<0.001	28 (65.1)	40 (34.5)	0.001
Violent fear and panic	50 (76.9)	36 (25.5)	<0.001	29 (67.4)	37 (31.9)	<0.001
Severe pain	30 (46.2)	43 (30.5)	0.004	22 (51.2)	41 (35.3)	0.10
Dyspnoea	36 (55.4)	35 (24.8)	<0.001	29 (67.4)	31 (26.7)	<0.001
Neurological deficits (preoperatively)	25 (38.5)	47 (33.3)	0.57	17 (39.5)	34 (29.3)	0.30
Currently I suffer						
Sleep problems (very often to always)	17 (27)	11 (7.9)	<0.001	10 (24.4)	12 (10.6)	0.07
Nightmares (very often to always)	6 (9.2)	1 (0.7)	0.006	5 (11.9)	1 (0.9)	0.007
Depression (very often to always)	16 (24.6)	0	<0.001	12 (29.2)	3 (2.6)	<0.001

Sociodemographic data, health activity and PTSD symptoms, such as nightmares, pain, dyspnoea and depression from patients who completed PTSS-14 and PDS. Most of these symptoms were included in the questionnaires for diagnosis of PTSD and are listed here to identify the items contributing most to the diagnosis. The parameters are presented as *n* (%). The average age, the PCS and MCS values are presented as mean ± SD and *P*-value.

ATAAD: Acute Type A aortic dissection; BMI: body mass index; MCS: Mental Component Summary; PCS: Physical Component Summary; PDS: Post-traumatic Diagnostic Scale; PTSD: post-traumatic stress disorder; PTSS-14: Post-traumatic Stress Scale 14; SD: standard deviation.

Table 5: Preoperative sport versus without sport

Parameters	Sport	Without sport	*P*-value
n (%)	81 (39)	125 (61)	
Male	53 (41)	76 (59)	0.60
Female	28 (36)	49 (64)	
Average age (years)	58.2 ± 13	59.4 ± 11.7	0.56
BMI (kg/m^2)	26.4 ± 4.4	27.1 ± 4.7	0.38
PTSD according to PDS	15 (18.5)	27 (21.6)	0.72
PTSD according to PTSS-14	21 (26)	43 (34.4)	0.26
PCS	39.6 ± 12.2	35.6 ± 9.6	0.02
MCS	51.3 ± 11	47.1 ± 11.5	0.015
Incapacitated	9 (11.1)	30 (24)	0.03
Currently able to walk	74 (91.4)	112 (89.6)	0.86
Dependent on outside help	11 (13.6)	20 (16)	0.78
Patients experiencing currently			
Sleep problems (very often to always)	5 (6.2)	21 (16.8)	0.04
Nightmares (very often to always)	1 (1.2)	5 (4)	0.47
Depression (very often to always)	5 (6.2)	10 (8)	0.83

General data and PTSD symptoms from ATAAD patients compared according to their sports activity before surgery. Data are either mean ± SD or numbers of patients with percentages in brackets.

ATAAD: Acute Type A aortic dissection; BMI: body mass index; MCS: mental component summary; PCS: physical component summary; PDS: Post-traumatic Diagnostic Scale; PTSD: post-traumatic stress disorder; PTSS-14: Post-traumatic Stress Scale 14; SD: standard deviation.

questions, is divided up repeatedly and is more difficult to complete than PTSS-14 (14 items), though the result is more specific and exact. Not all patients completed the questionnaire in full (PTSS-14 98.1% and PDS 75.7%). Therefore, we could not determine quality of life for all patients. Also, questionnaires filled in by patients have diagnostic limitations: questions may be understood differently by different individuals and not all aspects of quality of life are covered. Qualitative interviews might provide better insights, but such an approach on a large number of patients would be beyond the scope of this study. Some patients were not aware of how dangerous ATAAD is; as such, the surgery was not considered a traumatic experience. Because the findings were based on a retrospective analysis and not on preoperative data, quality of life of the patients before the operation could not be judged. ATAAD affects older patients in majority (on average 59 years old). In the evaluated cohort of patients, there was only 1 patient in the age group 21–30 years, meaning that any reasonable comparison with the norm sample was not feasible in this age group. In 31.5% of the ATAAD patients, there is a suspicion of PTSD according to PTSS-14 and in 27% according to PDS. The most frequently used questionnaire, PDS, is more specific than the questionnaire PTSS-14 for the diagnosis of PTSD. The agreement between the 2 questionnaires is 77%.

The distinction between the positive and negative responses of PTSS-14 is 1.2–2.8. The items contributing to the differentiation of >2.3 points, such as depression, frequent mood swings, painful memories of the time in hospital, poor future prospects, contribute most to the discrimination against the PTSD. On the contrary, some items with a differentiation of <1.5 points contribute the least. These include feelings of dullness, irritability, guilt feelings, avoidance of places and memories of the time in hospital.

CONCLUSION

In conclusion, our study supports the hypothesis that ATAAD occurs in the elderly and influences the later outcome of patients both physically and mentally. There is no significant relationship between ICU stay and PTSD. Finally, PTSD is often diagnosed too late or is not recognized.

Future perspective

Three approaches were established to prevent the development of PTSD in the patients in future:

1. As almost half of the PTSD-positive patients complained of nightmares, dyspnoea and severe fear and pain when remembering the illness itself and the hospital stay, sufficient analgesics and anxiolytics should be prescribed for patients as well as operative care as rapidly as possible, also in the case of older patients.
2. Even with a high level of operative care, the postoperative quality of life of patients is not sufficiently known, despite annual check-ups. At the German Heart Center Berlin, all ATAAD patients should fill out the PTSS-14 questionnaires during the inpatient stay and again during the check-ups, so that the long-term quality of life can be assessed and, especially in the case of younger patients, psychological support can be provided in the ward and the development of PTSD prevented [20].
3. This study demonstrates that patients engaged in sports before their ATAAD operation have a higher quality of life and experience less PTSD. Thus, patients who want to improve their cardiovascular health should be generally encouraged to practice physical activity [21].

Conflict of interest: none declared.

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In der nachfolgenden Arbeit wird der Einfluss der linksventrikulären Herzfunktion auf das Outcome bei Patienten mit einer ATAAD untersucht. Der nachfolgende Text entspricht dem Abstrakt der Arbeit „Left Ventricular Systolic Dysfunction in Patients With Type-A Aortic Dissection Is Associated With 30-Day Mortality" (Thurau et al., 2019a, S. 51, doi:10.1053/j.jvca.2018.07.046).

„***Objective:*** *The aim of this study was to analyze preoperative and postoperative echocardiographic parameters in patients with type-A acute aortic dissection (ATAAD) and to analyze whether impaired preoperative left ventricular function was associated with short- and long-term survival. To enable multivariable analysis, established risk factors of ATAAD were analyzed as well.* ***Design:*** *Retrospective single-center study.* ***Setting:*** *The German Heart Center Berlin.*

Participants: *The retrospective data of 512 patients with ATAAD who were treated between 2006 and 2014 were analyzed.*

Interventions: *None.*

Measurements and Main Results: *Preoperative versus postoperative left ventricular ejection fraction (LVEF), right ventricular ejection fraction, left ventricular end-diastolic diameter, and right ventricular end-diastolic diameter were not significantly different, and the mean values were within the reference ranges. Because of the surgical intervention, incidences and severities of aortic regurgitation and pericardial effusion decreased. In multivariable logistic analysis, the authors identified age (odds ratio [OR] 1.04, $p < 0.001$), preoperative LVEF < 35% (OR 2.20, $p = 0.003$), any ischemia (Penn non-Aa) (OR 2.15, $p < 0.001$), and longer cardiopulmonary bypass time (OR 1.04, $p < 0.001$) as independent predictors of 30-day mortality. Cardiopulmonary resuscitation, tamponade, or shock, and pre-existing cardiac disease, were not predictors of death.* ***Conclusion:*** *After surgery, aortic insufficiency and pericardial effusion decreased, whereas cardiac functional parameters did not change. Severe LV dysfunction was identified as a new independent predictor of 30-day mortality".*

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Original Article

Left Ventricular Systolic Dysfunction in Patients With Type-A Aortic Dissection Is Associated With 30-Day Mortality

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Objective: The aim of this study was to analyze preoperative and postoperative echocardiographic parameters in patients with type-A acute aortic dissection (ATAAD) and to analyze whether impaired preoperative left ventricular function was associated with short- and long-term survival. To enable multivariable analysis, established risk factors of ATAAD were analyzed as well.
Design: Retrospective single-center study.
Setting: The German Heart Center Berlin.
Participants: The retrospective data of 512 patients with ATAAD who were treated between 2006 and 2014 were analyzed.
Interventions: None.
Measurements and Main Results: Preoperative versus postoperative left ventricular ejection fraction (LVEF), right ventricular ejection fraction, left ventricular end-diastolic diameter, and right ventricular end-diastolic diameter were not significantly different, and the mean values were within the reference ranges. Because of the surgical intervention, incidences and severities of aortic regurgitation and pericardial effusion decreased. In multivariable logistic analysis, the authors identified age (odds ratio [OR] 1.04, $p < 0.001$), preoperative LVEF ≤35% (OR 2.20, $p = 0.003$), any ischemia (Penn non-Aa) (OR 2.15, $p < 0.001$), and longer cardiopulmonary bypass time (OR 1.04, $p < 0.001$) as independent predictors of 30-day mortality. Cardiopulmonary resuscitation, tamponade, or shock, and pre-existing cardiac disease, were not predictors of death.
Conclusion: After surgery, aortic insufficiency and pericardial effusion decreased, whereas cardiac functional parameters did not change. Severe LV dysfunction was identified as a new independent predictor of 30-day mortality.

Key Words: type-A aortic dissection; predictors of perioperative mortality; echocardiography; left ventricular dysfunction; left ventricular ejection fraction

TYPE-A acute aortic dissection (ATAAD) is a frightening and severe disease. In the authors' region of the German Federal States of Berlin and Brandenburg, the population-based incidence recently has been estimated at 11.9/100,000 per year,[1] and the mortality per hour is said to be 1% to 2% after the onset of symptoms.[2] Therefore, fast diagnosis and surgical therapy of ATAAD are required to improve outcomes.[3] Even after successful surgery, mortality is about 18%.[4] Numerous studies have attempted to identify risk factors for short-term postoperative mortality, such as age,

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cardiopulmonary resuscitation, renal dysfunction, migrating chest pain, or pulse deficit.[5-12] In addition, the Penn classification has been established to enable stratification of patients by operative mortality risk: Penn Aa (no ischemia), Penn Ab (localized ischemia), Penn Ac (generalized ischemia), and Penn Ab+c (combined ischemia).[13]

Although computed tomography is the gold standard for diagnosis of ATAAD, many articles attribute a diagnostic role to transthoracic echocardiography or transesophageal echocardiography.[14-16] Particularly in cases of immobile or highly unstable patients, echocardiography becomes indispensable.

Although some of these articles report the left ventricular ejection fraction (LVEF),[14] precise and comprehensive data on cardiac function in patients with ATAAD are lacking. Thus, it is also unclear whether cardiac function parameters may affect postoperative mortality. Specifically, the authors hypothesized that impaired preoperative left ventricular function determined as LVEF <50% would be associated with increased 30-day mortality. In addition, the authors also differentiated between moderately (LVEF 36% to 49%) and severely (LVEF ≤35%) impaired LV function.

Therefore, the aim of this study was to determine comprehensive cardiac function parameters of a large number of ATAAD patients by retrospective analyses of echocardiography reports and to assess whether these were associated with 30-day mortality or long-term survival. To enable multivariable analyses, patient characteristics, symptoms (ischemia, tamponade, shock), and data concerning the surgical treatment (cardiopulmonary bypass [CPB] time, surgical procedures) were retrieved from the hospital database.

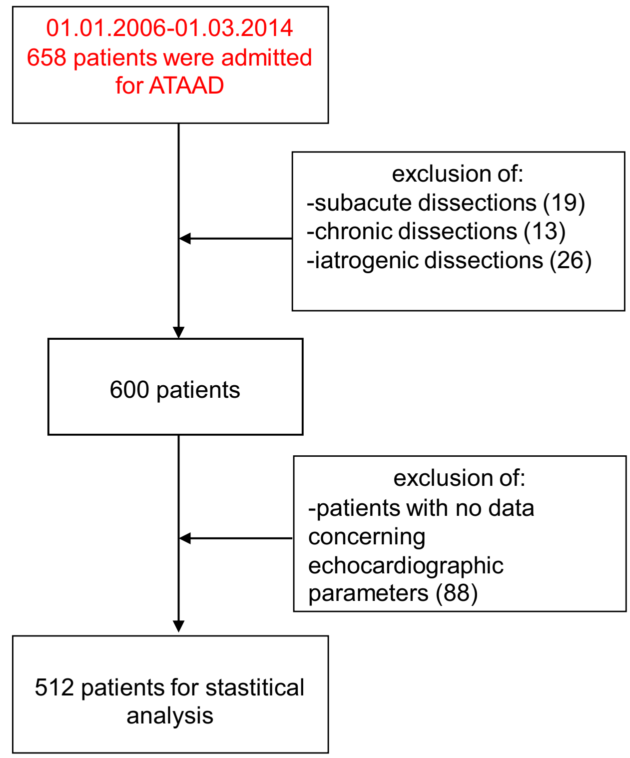

Figure 1. Patient flow and recruitment.

Materials and Methods

The authors retrospectively examined echocardiography reports (mostly transthoracic echocardiography) of 512 consecutive patients with ATAAD treated at the German Heart Center Berlin between January 2006 and 2014. In 2006, systematic documentation of patients with ATAAD was initiated at the authors' institution. Therefore, the authors included patients from this date on.

The patient flow and recruitment in this study, including all reasons and numbers of the excluded patients, is illustrated in Fig. 1. Intraoperative transesophageal echocardiograph was used mostly for additional up-to-date information of surgeons and for monitoring. Ventricular dimensions were not documented systematically. Therefore, the authors used preoperative and scheduled postoperative echocardiography data. The study was approved by the local ethics committee; informed consent was waived for this retrospective analysis. The parameters examined were left and right ventricular end-diastolic diameters (LVEDD and RVEDD, respectively), LVEF and right ventricular ejection fraction (RVEF), the diameters of the aortic annulus and of the ascending aorta, aortic and mitral valve regurgitation, and pericardial effusion. Missing data of the ascending aortic diameter were completed by manual measurements from stored echocardiographic loops using the EchoPAC program. Preoperative and postoperative data were compared. The first in-hospital postoperative echocardiography report, which was in most cases from the first and none later than the third postoperative day, was used for this comparison.

Baseline characteristics of the patients were collected from the electronic patient files: age; sex; body weight and height; date of birth; pre-existing diseases such as hypertension, hypothyreosis, diabetes, arteriosclerosis, coronary heart disease, family history of aortic disease, previous type-B aortic dissection, or Marfan syndrome; smoking status; and abuse of alcohol or cocaine. In addition, the patient's symptoms of shock, tamponade, coma, and cardiopulmonary resuscitation were collected. Renal, myocardial, intestinal, cerebral, spinal, and extremity ischemia were documented in the authors' database. When at least 1 of these organs was affected by ischemia, this was defined as "any ischemia" according to the Penn classification. Data concerning pulse state, neurological state, and the surgical procedures also were retrieved from the electronic patient files.

Deep hypothermic circulatory arrest with antegrade cerebral perfusion was applied in 86.6% of patients. Surgical procedures were dependent upon the extent of the dissection. In the case of involvement of the sinus of Valsalva, an aortic root replacement with conduit (including valve) or David procedure (preservation of aortic valve) was performed. As stated in Table 4, where surgical procedures are listed, aortic valve reconstruction was performed in 44% of the authors' patient cohort.

According to the up-to-date literature, the following parameters were included in the multivariable logistic regression model: age, any ischemia (= Penn non-Aa),[13] cardiogenic shock or tamponade, pre-existing aortic disease, pre-existing cardiac disease, cardiopulmonary resuscitation, CPB time, LVEF ≤35%, and partial arch repair.

Date of death was identified using the data from the residents' registration offices of the federal states Berlin and Brandenburg. The primary outcome parameter was 30-day mortality, but long-term survival additionally was examined.

All statistical analyses were carried out using SigmaStat (Systat Software GmbH, Erkrath, Germany). Statistical significance was assumed at $p < 0.05$. Preoperative versus postoperative values were compared by the Wilcoxon rank sum test or chi-square test. In case of multiple comparisons, p values were adjusted according to Bonferroni-Holm. Intergroup comparisons were done by Kruskal-Wallis test followed by Dunn's post hoc all pairwise comparisons. Stepwise backward multivariable logistic regression was used to identify independent predictors of 30-day mortality. Only variables presenting with $p < 0.1$ in univariable analyses were included in the initial multivariable model. Kaplan-Meier curves were used to illustrate effects of LVEF on long-term survival.

Results

Patient Population

Five hundred twelve patients who were treated operatively at the German Heart Center Berlin between 2006 and 2014 were analyzed statistically. Sixty-seven percent were male. The mean age was 60.8 years, ranging from 23 to 90 years. Mean body weight was 83.6 kg, ranging from 44 to 180 kg, and the mean height was 175 cm with a spread from 138 to 213 cm; 74.0% of the patients had hypertension, 12.3% coronary heart disease, and 32.1% a history of smoking. The complete list of patient characteristics is presented in Table 1.

Because patient recruitment covered a period of 9 years, the authors analyzed outcome and incidence of LV dysfunction according to the time periods 2006 to 2010 and 2010 to 2014. The authors detected no major differences. In the earlier group, 30-day mortality was 20%, and moderate and severe LV dysfunction were present in 15% and 5% of patients, respectively. In the later cohort, the respective numbers are 23%, 14%, and 5%.

Cardiac Function

Mean preoperative LVEF was 56.5 ± 10.3%; however, in 149 patients (29.1%) LVEF was below the lower normal limit of 52% for females or 54% for males.[17,18] Mean preoperative RVEF was 57.0 ± 8.4% and below the lower limit of 38% (19) in 12 patients (2.3%). Mean LVEDD was 47.8 ± 7.5 mm and above the normal limit of 58 mm for males or 52 mm for females[17,18] in 56 (11.3%) cases. Mean RVEDD was 28.3 ± 3.9 mm and above the normal limit of 42 mm[19] in 0 (0%) cases. All these values remained essentially unchanged after surgery (LVEF: 55 ± 11.6%, RVEF: 54.6 ± 10.2%, LVEDD: 46.5 ± 7.4 mm, RVEDD: 29 ± 3.8 mm). Preoperative aortic or mitral insufficiency (grade I-IV) was noted in, respectively, 81.5% and 33.5% of patients. The incidence of aortic insufficiency (AI) was reduced to 29.1% (26.5% AI grade I, 2.1% AI II, and 0.5% AI III) after surgery.

Preoperative pericardial effusions were present in 52.7% of patients and this rate was reduced to 32.1% after surgery. The mean preoperative ascending aortic diameter, available for 401 patients, was 46.3 ± 11.6 mm; the mean aortic annulus diameter, available for 358 patients, 26.3 ± 5.5 mm. Three hundred seventy-two (92.8%) patients had a higher ascending aortic diameter than the normal limit of 34 mm for males and

Table 1
Baseline Characteristics

	Overall	LVEF ≤35	LVEF 36-49	LVEF ≥50	p
Age (y)	60.8 ± 13.4	61.6 ± 12.9	65 ± 13.9	60.3 ± 13.3	0.054
Male	343 (67)	14 (56)	31 (64.6)	298 (67.9)	0.438
Height (cm)	175 ± 9.7	171.7 ± 7.6	174.4 ± 11.8	174.8 ± 9.6	0.226
Body weight (kg)	83.6 ± 18.7	84.1 ± 18.3	85.4 ± 21.5	83.3 ± 18.4	0.788
BMI (kg/cm^2)	27.3 ± 5.0	28.3 ± 4.5	28.0 ± 6.6	27.1 ± 4.8	0.290
Diseases					
Hypertension	374 (74.0)	21 (84)	34 (73.9)	319 (73.5)	0.507
CAD	62 (12.3)	5 (20)	9 (19.1)	48 (11.1)	0.132
Diabetes	35 (6.9)	3 (12)	3 (6.5)	29 (6.7)	0.592
Aortic disease	81 (16)	5 (20)	6 (13)	70 (16.1)	0.741
Family history positive for aortic diseases	17 (3.4)	1 (4)	2 (4.3)	14 (3.2)	0.908
Type B aortic dissection	17 (3.4)	1 (4)	0 (0)	16 (3.7)	0.413
Smoking history	162 (32.1)	11 (44)	8 (17.4)	143 (33)	0.042
Arteriosclerosis	48 (9.5)	4 (16)	6 (13)	38 (8.8)	0.336
Marfan syndrome	14 (2.8)	1 (4)	3 (6.5)	10 (2.3)	0.236
Hypothyreosis	48 (9.5)	3 (12)	2 (4.3)	43 (9.9)	0.431
Drug abuse					
Alcohol	34 (6.7)	2 (8)	5 (10.9)	27 (6.2)	0.473

NOTE. Patient characteristics at admission to the authors' institution are listed as means ± standard deviation or numbers with percentages in brackets. Percentages refer to the actual number of patients with information on the respective parameter.
Abbreviations: BMI, body mass index; CAD, coronary artery disease.

Table 2
Preoperative Heart Function in Patients With ATAAD

	Overall	LVEF ≤35	LVEF 36-49	LVEF ≥50	p
LVEF (%)	56.5 ± 10.3	27.2 ± 8.8	41.7 ± 2.4	59.8 ± 5.9	n.a.
RVEF (%)	57.0 ± 8.4	45.4 ± 13.5*	50.2 ± 11.1*	58.3 ± 6.8	<0.001
LVEDD (mm)	47.8 ± 7.5	52.4 ± 7.9*	48.4 ± 8.5	47.5 ± 7.3	0.011
RVEDD (mm)	28.3 ± 3.8	28.4 ± 5.0	28.3 ± 3.9	28.2 ± 3.7	0.943
Aortic regurgitationGrade 0, n (%)	91 (18.5)	6 (26.1)	8 (16.7)	76 (18.1)	0.145
Grade I, n (%)	145 (29.5)	5 (21.7)	10 (20.8)	130 (31.0)	
Grade II, n (%)	156 (31.8)	6 (26.1)	17 (35.4)	133 (31.7)	
Grade III, n (%)	96 (19.6)	5 (21.7)	13 (27.1)	78 (18.6)	
Grade IV, n (%)	3 (0.6)	1 (4.3)	0 (0)	2 (0.5)	
Mitral regurgitation Grade 0, n (%)	307 (66.5)	12 (54.5)	26 (55.3)	269 (68.4)	0.317
Grade I, n (%)	140 (30.3)	8 (36.4)	20 (42.6)	112 (28.5)	
Grade II, n (%)	14 (3.0)	2 (9.1)	1 (2.1)	11 (2.8)	
Grade III, n (%)	1 (0.2)	0 (0)	0 (0)	1 (0.3)	
Pericardial effusion, n (%)	268 (52.7)	10 (40)	31 (66)	226 (51.8)	0.120

NOTE. Echocardiographic (mostly transthoracic echocardiography) findings at admission to the authors' institution are listed as means ± standard deviation or numbers with percentages in brackets. Percentages refer to the actual number of patients with information on the respective parameter.
Abbreviations: LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RVEDD, right ventricular end-diastolic diameter; RVEF, right ventricular ejection fraction.

31 mm for females.[17,18] Aortic annulus diameter was above the limit of 29 mm for males and 25 mm for females[17,18] in 87 (24.3%) patients. Table 2 shows the preoperative echocardiographic parameters in detail.

Furthermore, patients were divided into 3 groups according to preoperative LVEF: severe LV dysfunction with LVEF ≤35% (n = 25), moderate LV dysfunction with LVEF 36%-49% (n = 48), and normal LV function with LVEF ≥50% (n = 439). The authors compared these groups according to the 30-day mortality (Table 3). Both severe LV dysfunction and moderate dysfunction were associated with significantly increased 30-day mortality (52% and 33%, respectively, *v* 18.7%; Table 3). In contrast, mortality was similar between both groups with severe or moderate LV dysfunction.

Eleven of 25 patients with severe LV dysfunction with LVEF ≤35% presented with myocardial ischemia (44%) versus 56 out of 468 patients with only moderate or no LV dysfunction (12%, $p < 0.001$).

Symptoms and Surgical Procedures

Patient symptoms like cardiogenic shock, tamponade, ischemia, and cardiopulmonary resuscitation and the performed surgical procedures are listed in Table 4.

Table 3
Preoperative LVEF and 30-Day Mortality

Preoperative LVEF (%)	Patients (n)	30-Day Mortality, n (%)
≤35	25	13 (52)*
36%-49%	48	16 (33)*
≥50	439	82 (18.7)

NOTE. Overall p from chi-square test: <0.001.
Abbreviations: LVEF, left ventricular ejection fraction.
* Adjusted $p < 0.05$ in single group comparisons versus ≥50%.

Table 4
Symptoms and Surgical Procedures

Preoperative symptoms and surgical procedures, n (%)	
Cardiogenic shock	68 (13.8)
Tamponade	74 (15.0)
Coma	15 (3.0)
Acute kidney injury	30 (6)
Myocardial ischemia	67 (13.6)
Limb ischemia	115 (23.4)
Intestinal ischemia	39 (8)
Cerebral ischemia	58 (11.8)
Spinal ischemia	11 (2.2)
Any ischemia (Penn non-Aa)	225 (45.6)
Cardiopulmonary resuscitation	7 (1.4)
CPB time, mean ± SD	253.0 ± 88.7
Surgical procedures, n (%)	
Partial arch repair	103 (20.9)
Aortic valve reconstruction	217 (44)
Arch replacement + frozen elephant trunk	15 (3.0)
Arch reconstruction	58 (11.8)
Aortic root reconstruction	300 (60.9)
Supracoronary conduit	369 (74.8)
Aortic valve replacement + supracoronary conduit	20 (4.1)
Bypass (CABG)	47 (9.5)
Moderate hypothermia	33 (6.7)
Deep hypothermia	427 (86.6)

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; SD, standard deviation.

Furthermore, the authors analyzed the associations between LVEF and cardiopulmonary resuscitation, LVEF and cardiogenic shock, and LVEF and coronary artery bypass graft. Sixteen percent of the patients with severe LV dysfunction (≤ 35%), none of the patients with moderate LV dysfunction, and 0.7% of the patients with a LVEF >50% had cardiopulmonary resuscitation ($p < 0.001$). Forty-eight percent of the patients with severe LV dysfunction had a cardiogenic shock versus 22.9% and 10.7% for the patients with, respectively,

Table 5
Independent Predictors of 30-Day Mortality

Variables	Odds Ratio	95% CI	p
Age (y)	1.04	1.03-1.05	<0.001
Preoperative LVEF ≤ 35%	2.20	1.31-3.72	0.003
Any ischemia (Penn non-Aa)	2.15	1.62-2.87	<0.001
Longer CPB times (10 min)	1.04	1.03-1.06	<0.001

NOTE. Multiple logistic regression analysis was used to identify independent predictors of 30-day mortality.
Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction.

moderate or no LV dysfunction ($p < 0.001$). Coronary artery bypass graft was noted in 28%, 10.4%, and 8.3% of the patients with, respectively, severe, moderate, and normal LV dysfunction ($p < 0.005$).

Predictors of 30-Day Mortality

One hundred eleven of the 512 patients (21.7%) died within 30 days after surgery.

In multivariable analysis, the authors identified age (OR 1.04, $p < 0.001$), preoperative LVEF ≤35% (OR 2.2, $p = 0.003$), ischemia (Penn non-Aa) (OR 2.15, $p < 0.001$), and longer CPB times (OR 1.04, $p < 0.001$) as independent predictors of 30-day mortality (Table 5). LV and RV diameters were not associated with mortality.

Long-Term Survival

Kaplan-Meier curves for patients (Fig. 2) with preoperative LVEF ≥50% versus 36% to 49% and ≤35% confirm that 30-day survival was reduced similarly in both groups with impaired LV systolic function. This difference was preserved until 5 years after surgery ($p = 0.001$). Between 1 and 4 months after surgery, there was a trend toward higher mortality in patients with severe versus moderate LV dysfunction, which was, however, not significant.

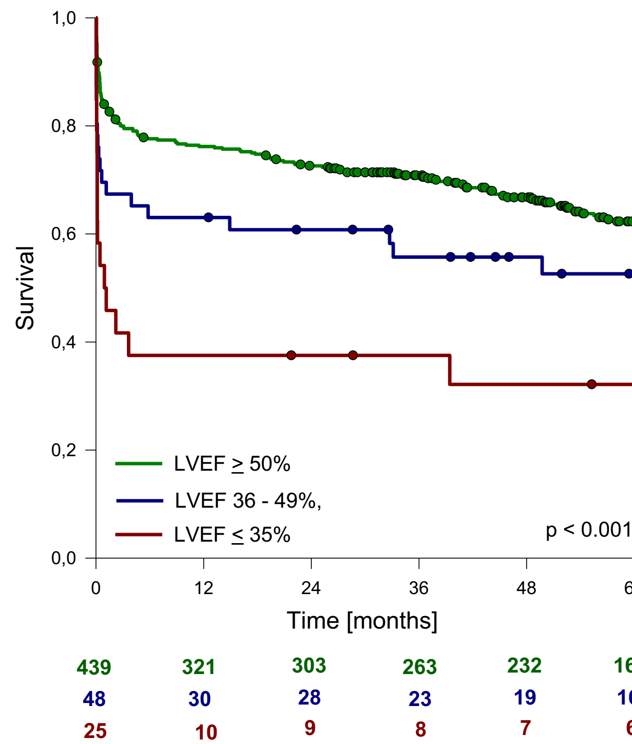

Figure 2. Kaplan-Meier survival curves show survival of patients with preoperative LVEF ≥50% (*green line*) compared to those with LVEF 36% to 49% (*blue line*) and LVEF ≤35%. Censored patients are indicated by *dots*. The numbers of patients at risk are indicated in the respective colors beneath the x-axis in 12-month intervals. The difference in survival between groups occurred mostly during the early postoperative period; later on, the survival curves run roughly in parallel. Adjusted p is < 0.05 for both groups with reduced LVEF versus LVEF ≥50%.

Discussion

This study investigated independent predictors of 30-day mortality (21.7%) in a large cohort of patients with ATAAD. As a main result, the parameters age ($p < 0.001$), LVEF ≤35% ($p = 0.003$), any ischemia (Penn non-Aa) ($p < 0.001$), and longer CPB times ($p < 0.001$) were found to be associated independently with 30-day mortality.

The 30-day mortality of 21.7% in the cohort is within the range of reports from previously studied large patient cohorts of 16.9% to 32.5%,[8,9,12] suggesting that the results also may be representative for other cardiac surgery centers. Also, the high prevalence of the most common risk factor for aortic dissection, i.e. arterial hypertension, in the patient cohort of 74.0%, is similar to that found in large registry databases.[7]

Previous analyses on predictors of 30-day mortality concentrated on the following parameters: cardiopulmonary resuscitation, malperfused organ systems, migrating chest pain, pulse deficit, hypotension, or neurological deficits. In addition, age and renal dysfunction were associated with survival.[8,11] According to the mentioned parameters, the authors included in the multivariable logistic regression model the following variables: age ($p < 0.001$), any ischemia (Penn non-Aa) ($p < 0.001$), cardiogenic shock or tamponade, pre-existing aortic disease, pre-existing cardiac disease, cardiopulmonary resuscitation, CPB time ($p < 0.001$), partial arch as surgical procedure, and LVEF ≤35% ($p = 0.003$). The International Registry of Aortic Dissection was used for several studies examining predictors of death: Rampoldi et al. and Tsai et al. identified the variables age, history of aortic valve replacement, hypotension, shock or tamponade, migrating chest pain, and any pulse deficit as predictors of in-hospital postoperative mortality.[6,7] International Registry of Aortic Dissection data also were used to create scores for risk stratification of AADA patients.[6,9] Leontyev et al. also created a score, named the Leipzig-Halifax scorecard, using multiple logistic regression on data from a dual-center study.[10] In this scorecard the following variables, which were predictors of the 30-day mortality, were included: age, critical preoperative state, ischemia syndrome, and coronary artery disease. In this study, the authors could confirm the parameters age

($p < 0.001$) and ischemia ($p < 0.001$) as predictors of the 30-day mortality, but did not find a significantly worse outcome for patients having coronary artery disease. Another study created a classification of ischemia presentation in ATAAD called Penn classification: Penn Aa (no ischemia), Penn Ab (localized ischemia), Penn Ac (generalized ischemia), and Penn Abc (combined ischemia).[13] The authors included the ischemia data in the study as non-Aa (any ischemia) and could find a significantly worse outcome in patients with any ischemia ($p < 0.001$).

Conzelmann et al. used registry data from 2,137 patients and identified age, coma, cardiopulmonary resuscitation, ischemic organ systems, and longer operating times as independent predictors of 30-day mortality.[8] The authors also investigated the variables age ($p < 0.001$), ischemia ($p < 0.001$), and longer operating times (longer CPB times) ($p < 0.001$) in the analysis and could confirm the results from Conzelmann et al. In contrast to this study, the authors did not find an association between cardiopulmonary resuscitation or coma and mortality.

Kaplan-Meier curves show that impaired LV function also is associated with long-term survival. The difference occurred clearly in the early postoperative period and curves run roughly in parallel thereafter. Therefore, the authors limited the multivariable analysis to 30-day postoperative mortality and found that only severe but not moderate LV dysfunction was associated independently with short time survival. An effect of LV dysfunction with LVEF <50% on in-hospital mortality already has been claimed by Chiappini et al. by univariable analysis of 487 patients (OR 1.97, $p = 0.014$).[12] This is confirmed by the authors' own data, where even moderate LV dysfunction is associated with 30-day mortality, however only in the univariable analysis as evident from the Kaplan-Meier analysis. The novel result from the authors' study is that after adjusting for patient characteristics, symptoms, and surgical procedures by multivariable analysis, only severe LV dysfunction remained an independent predictor of 30-day mortality.

Although the mean preoperative cardiac function values LVEF, RVEF, LVEDD, and RVEDD were well within the reference ranges, a substantial number of patients presented with pathological values; however, only reduced LVEF proved to be an independent predictor of 30-day mortality. The observation that these values remained essentially unchanged after surgery for AADA suggests that they represent conditions that are independent of the acute event. In contrast, the rate of patients with AI decreased from 81.5% preoperatively to 29.1% postoperatively, with most of the remaining cases being grade 1, which may explain why this parameter was not associated with 30-day mortality. This marked decrease of AI may be attributed to surgical reconstruction or implantation of an aortic valve prosthesis during surgery for ATAAD. Pericardial effusion also decreased after surgery from 52.7% to 32.1%; however, persisting effusion was not associated with 30-day mortality.

This study shares the common limitations of all retrospective studies, mainly that only variables can be included that are available from the hospital records. Furthermore, the echocardiographic analysis was done by different physicians, leading to a possible variation in the technique of measurement. In addition, including only patients from a single center might lead to a patient selection bias, and the results need to be validated in an independent patient cohort.

Conclusion

The present study identified severely impaired preoperative LVEF as a strong independent predictor of 30-day mortality after surgery for ATAAD. Although the number of patients who thus are affected is rather small (5% in this cohort), the risk of death is more than doubled in these patients. If this finding was confirmed in further studies, the authors suggest including preoperative LVEF in future risk stratification algorithms.

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Letters to the Editor

Poor Prognosis of Left Ventricular Systolic Dysfunction in Patients With Type-A Aortic Dissection

To the Editor:

I read with great interest the article by Thurau et al. in the *Journal of Cardiothoracic and Vascular Anesthesia*.[1] In this study, the authors analyzed factors of affecting 30-day mortality in 512 patients with type-A aortic dissection with special reference to impaired preoperative left ventricular function. In multivariable logistic analysis, adjusted odds ratio (95% confidence intervals) of age, preoperative left ventricular ejection fraction ≤35%, any ischemia (Penn non-Aa), and longer cardiopulmonary bypass time for 30-day mortality were 1.04 (1.03-1.05), 2.20 (1.31-3.72), 2.15 (1.62-2.87), and 1.04 (1.03-1.06), respectively. I have 2 concerns about the study.

First, the authors also presented a long-term mortality risk in patients with poor left ventricular systolic dysfunction. They conducted a 5-year follow-up, and I wonder if there are specific risk factors for long-term mortality. Chen et al. reported that there was a U-shaped relationship between admission serum potassium levels and both in-hospital death and long-term mortality.[2] Namely, adjusted hazard ratios of potassium levels under 3.5 and ≥4.5mmol/L for in-hospital and long-term mortality significantly increased. In addition, surgical intervention was a strong protective factor for both in-hospital and long-term mortality. There is a need of speculating the mechanism of these parameters for affecting mortality.

Second, the authors recognized no significant change of left or right ventricular ejection fraction and left or right ventricular end-diastolic diameter before and after surgical intervention. Does this mean that risk factor on survival had already been determined by these cardiac dysfunctions? Are there any strategies to improve these functional parameters by surgical intervention or medication?

Further comprehensive studies are needed to verify the net effect of left ventricular systolic dysfunction on prognosis in patients with type-A aortic dissection, by considering serum potassium levels and kidney function.[2]

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Conflict of interest

The author declares no conflict of interest.

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Response: The Effects of Cardiac Dysfunction on Survival After Surgery for Type A Aortic Dissection

To the Editor:

With great interest we read the comments of Kawada[1] regarding our recent study on the detrimental effects of cardiac dysfunction on survival after surgery for type A aortic dissection.[2] He raises 2 important issues. Firstly, he draws our attention toward the negative effects of out-of-the-normal-range serum potassium concentrations on in-hospital and long-term survival,[3] which we had not addressed in our analysis. We assume that in Chen's institution, as well as in ours, out-of-range potassium levels are normalized during patient treatment. That raises the question of whether the observed increase in mortality is due to the detrimental effects of too-high or too-low potassium levels or rather to the underlying conditions that induced the out-of-range levels. Low potassium is often due to treatment with diuretics, and the major indications would be chronic kidney disease, hypertension, or chronic cardiac failure. High potassium levels may result from renal failure or from treatment with potassium-sparing

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diuretics (for indications, see above). In the multivariate analysis, Chen et al. adjusted for estimated glomerular filtration rate, that is, kidney disease, but not for the other conditions, which had not been significantly related to mortality in univariate analyses.[3] Although hypertension was not related to mortality in our analysis, left ventricular dysfunction had a strong effect on mortality.[2] In conclusion, the data published by Chen et al. and the data available from our study do not sufficiently explain the mechanisms by which out-of-range potassium levels would affect mortality.[2,3] We are aware of the protective effect of surgery on survival. Therefore, all patients included in our study underwent surgery.[2]

It is correct that cardiac dysfunction was already present at patient admission and did not change after surgery.[2] Since aortic regurgitation and pericardial effusion were surgically treated, we assumed that cardiac dysfunction was a chronic condition of these patients that persisted after surgery and cannot be surgically treated. Nevertheless, increased awareness of the high risk of these patients, especially during the first few postoperative months, should induce intensified surveillance. In addition, optimization of medical therapy according to current guidelines for treatment of cardiac failure might help to increase survival.

Conflict of Interest

There are no conflicts of interest.

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2.6 Otten, A., Kurz, S. D., Anwar, S., Potapov, E., Krall, C., O'Brien, B., Habazettl, H., Krabatsch, T. and Kukucka, M. (2018). Prognostic value of 3-dimensional echocardiographical heart volume assessment in patients scheduled for left ventricular assist device implantation. *European Journal of Cardio-Thoracic Surgery*, 54(1), 169-175, [online] doi:10.1093/ejcts/ezy002

Um die Rolle der Rechtsherzfunktion nach der Implantation eines linksventrikulären Unterstützungssystems besser verstehen zu können, wurde in der nachfolgenden Arbeit mittels dreidimensionalen Ultraschall der Einfluss des Herzvolumens genauer untersucht. Der nachfolgende Text entspricht dem Abstrakt der Arbeit „Prognostic value of 3-dimensional echocardiographical heart volume assessment in patients scheduled for left ventricular assist device implantation“(Otten et al., 2018, S.169, doi: 10.1093/ejcts/ezy002).

*„**OBJECTIVES:** Left ventricular assist device (LVAD) support is an increasingly important and successful therapeutic option for patients with end-stage heart failure. As chronic heart failure progresses, the left and right ventricles adapt by enlarging its volume and patients present for LVAD implantation with varying degrees of dilatation. By quantitatively assessing right ventricular (RV) and left ventricular (LV) volumes using 3D transoesophageal echocardiography and correlating the findings with clinical outcomes, we aim to investigate the prognostic value of LV and RV volumes for early survival after LVAD implantation.*

***METHODS:** This is a single-centre, non-randomized diagnostic cohort study using prospectively collected clinical and 3D echocardiographic data from 65 patients scheduled for LVAD implantation, using centrifugal pumps for long-term support (HeartWare and HeartMate 3). The primary end-point for this study is 60-day mortality, with longer term survival as a secondary end-point.*

***RESULTS:** We divided our cohort group into survivors and non-survivors at 60 days [49 patients (75%) and 16 patients (25%), respectively]. Right to left end-diastolic ratio assessed by 2D echocardiography was significantly higher in the 60-day non-survivors group (0.70 ± 0.09 vs 0.62 ± 0.11; P = 0.01). Indexed end-diastolic volume parameters (LV, RV and overall heart) showed significant differences among the groups and were higher in the 60-day survivors group (LV volume 154 ± 51 ml/m² vs 110 ± 40 ml/m², P = 0.004; RV volume 96 ± 27 ml/m² vs 80 ± 23 ml/m², P = 0.05; heart 250 ± 64 ml/m² vs 190 ± 57 ml/m², P= 0.003). To investigate haemodynamic and echocardiographic parameters, the right to left end-diastolic ratio and indexed RV end-diastolic*

volume were associated with 60-day mortality in the logistic regression analysis. The Kaplan-Meier survival curves for patients with indexed RV end-diastolic volume >82 ml/m^2 vs indexed RV end-diastolic volume <_82 ml/m^2 showed better 1-year survival (P = 0.005) for the group with more RV dilatation.

CONCLUSIONS: *Patients with moderately increased end-diastolic RV volume index carry a higher postoperative risk, while severe RV dilatation seems to be protective. In future, postoperative management of patients with moderately dilated RVs should be focused on adjusting individually appropriate LVAD flows and providing frequent follow-up".*

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Prognostic value of 3-dimensional echocardiographical heart volume assessment in patients scheduled for left ventricular assist device implantation

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Abstract

OBJECTIVES: Left ventricular assist device (LVAD) support is an increasingly important and successful therapeutic option for patients with end-stage heart failure. As chronic heart failure progresses, the left and right ventricles adapt by enlarging its volume and patients present for LVAD implantation with varying degrees of dilatation. By quantitatively assessing right ventricular (RV) and left ventricular (LV) volumes using 3D transoesophageal echocardiography and correlating the findings with clinical outcomes, we aim to investigate the prognostic value of LV and RV volumes for early survival after LVAD implantation.

METHODS: This is a single-centre, non-randomized diagnostic cohort study using prospectively collected clinical and 3D echocardiographic data from 65 patients scheduled for LVAD implantation, using centrifugal pumps for long-term support (HeartWare and HeartMate 3). The primary end-point for this study is 60-day mortality, with longer term survival as a secondary end-point.

RESULTS: We divided our cohort group into survivors and non-survivors at 60 days [49 patients (75%) and 16 patients (25%), respectively]. Right to left end-diastolic ratio assessed by 2D echocardiography was significantly higher in the 60-day non-survivors group (0.70 ± 0.09 vs 0.62 ± 0.11; $P = 0.01$). Indexed end-diastolic volume parameters (LV, RV and overall heart) showed significant differences among the groups and were higher in the 60-day survivors group (LV volume 154 ± 51 ml/m^2 vs 110 ± 40 ml/m^2, $P = 0.004$; RV volume 96 ± 27 ml/m^2 vs 80 ± 23 ml/m^2, $P = 0.05$; heart 250 ± 64 ml/m^2 vs 190 ± 57 ml/m^2, $P = 0.003$). To investigate haemodynamic and echocardiographic parameters, the right to left end-diastolic ratio and indexed RV end-diastolic volume were associated with 60-day mortality in the logistic regression analysis. The Kaplan–Meier survival curves for patients with indexed RV end-diastolic volume >82 ml/m^2 vs indexed RV end-diastolic volume ≤82 ml/m^2 showed better 1-year survival ($P = 0.005$) for the group with more RV dilatation.

CONCLUSIONS: Patients with moderately increased end-diastolic RV volume index carry a higher postoperative risk, while severe RV dilatation seems to be protective. In future, postoperative management of patients with moderately dilated RVs should be focussed on adjusting individually appropriate LVAD flows and providing frequent follow-up.

Keywords: End-stage heart failure • Left ventricular assist device • 3D echocardiography • Right ventricular volume • Survival

INTRODUCTION

Long-term mechanical circulatory support, most commonly left ventricular assist device (LVAD) implantation, has rapidly matured to provide the best alternative to heart transplantation and is a viable therapeutic option with an acceptable evidence base supporting its indication (Class IIa) [1] for patients with refractory heart failure (HF). Patients classified as the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) [2] Stage D continue to develop severe HF symptoms, despite guideline-directed medical therapy. Further clinical stratification of this patient subgroup to 7 clinical profiles was developed by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [3] working group.

As chronic HF progresses, systolic and diastolic function deteriorates, and the left and right ventricles adapt by enlarging and

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increasing intraventricular volumes. This ventricular remodelling is initially beneficial for stroke volume (SV), but in the later stages of disease, detrimental effects prevail. There is evidence that progressive chamber enlargement is associated with poor prognosis [4]. Conversely, reverse remodelling achieved by optimal medical therapy improves outcomes, and such a reversal is considered to be the primary treatment goal [4]. Variability in disease progression, therapy and patient factors results in appreciable differences in the degree of right ventricular (RV) and left ventricular (LV) dilatation in patients scheduled for elective LVAD implantation.

The early survival after LVAD implantation is still critical and depends on patient selection, timing of the implantation and postoperative management. Among a plethora of factors, acute exacerbation and severity of HF and early right ventricular dysfunction or failure (RVF) are recognized as indicators for increased risk of early death after implantation. RVF occurs in 10–40% of patients who have undergone LVAD implantations [5–8].

Recently, the quality of myocardial imaging techniques has improved considerably, and magnetic resonance imaging has become the gold standard in quantification of RV and LV volumes. Furthermore, 3D echocardiography allows direct quantification of chamber volumes without assumptions on ventricular geometry, yet with less technical effort compared with magnetic resonance imaging. Previous studies have shown that quantitative measurements obtained with 3D echocardiographic data are well validated against magnetic resonance imaging-based data [9–11]. Thus, immediate quantitative measurements of ventricular volume and function are readily available from preprocedural 3D imaging using transoesophageal echocardiography for patients undergoing LVAD implantation.

However, the putative effect of the degree of preoperative RV or LV remodelling or dilatation on survival after LVAD implantation has not been systematically assessed until now.

The aim of our study was to assess preprocedural LV and RV volumes, as a product of remodelling and its therapeutic reversal, in patients scheduled for LVAD implantation and to investigate whether there was any prognostic value of these 3D echocardiographic parameters for early postoperative survival.

PATIENTS AND METHODS

Patients

This is a single-centre, case–control study using prospectively collected clinical and echocardiographic data from 65 patients scheduled for LVAD implantation at the German Heart Centre Berlin between May 2015 and March 2016. The study was approved by the institutional review board, and all patients gave informed consent.

Clinical data

The database was searched for preoperative descriptive parameters (age, gender and body mass index), parameters specific for end-organ dysfunction (creatinine, bilirubin and pro-b-type natriuretic peptide) and for postimplantation haemodynamic data within the first 48 postoperative hours (central venous pressure, cardiac output, inotropic support and mixed venous saturation).

Procedure

Sixty-five patients with Stage D HF were listed for LVAD implantation. The same heart team performed the procedure and perioperative care according to the institutional standard operating procedures. Particular attention was paid to early recognition and therapy of RVF. Patients who were at increased risk for the development of RVF, as identified by the preprocedural echocardiographic right to left end-diastolic ventricular size ratio [5], were primarily treated with inhaled nitric oxide. Our institutional criteria for post-procedural diagnosis of RVF, previously published in the iNOT study [12], were as follows: cardiac output <2.0 l/min/m^2, mixed venous saturation <55%, mean arterial pressure <50 mmHg, high pharmacological RV support and echocardiographically determined RV dilatation with simultaneously collapsed left atrium and left ventricle. If a patient met one or more of these criteria, the intraoperative decision was made for temporary RVAD implantation after weaning from cardiopulmonary bypass.

Echocardiography

According to the updated recommendation by the American Society of Echocardiography and the European Association of Cardiovascular Imaging for chamber quantification [13], standard transoesophageal views for assessment of right and left ventricles are acquired and digitally stored using Vivid E9 (GE) and Epiq 7 (Philips) Ultrasound machines. Preprocedural echocardiography was performed about 45 min after the induction of anaesthesia in steady state prior to the onset of surgery. The 3D workflow starts with an optimized 2D 4-chamber view with the left ventricle aligning in the middle of the sector and is followed by full 3D imaging. Appropriate depth and lateral and elevational widths are adjusted to render the complete left ventricle visible. To achieve the necessary frame rate of more than 30 frames per second, multibeat acquisition of 4–6 beats is used. To avoid stitching artefacts, ventilation was paused after preoxygenation with 100% oxygen. The apnoeic pause is limited to <60 s. Similarly, the 3D workflow for the right ventricle starts with a 4-chamber view and turning of the probe to the right to optimize the 2D image of the right ventricle (Fig. 1A). After commencing 3D acquisition, full volume and pulmonary valve visibility are checked and multibeat acquisition is performed as described earlier.

Analysis of the preprocedural transoesophageal echocardiography data was performed by an experienced echocardiographer who was blinded to the outcome parameters. For comprehensive LV and RV volumetric quantitative evaluation (Fig. 1B), standard TOMTEC tools were used (TOMTEC Imaging Systems, Unterschleissheim, Germany). This software is based on surface quantification of chamber volumes in each frame of the stored data, and measurement is independent of geometric assumptions for ventricular geometry. Linear dimensions, areas, volumes and functional parameters for the left and right ventricles were evaluated.

Clinical outcome

The major focus of this study is early postoperative outcome with the primary end-point of 60-day mortality and a secondary end-point of long-term survival.

Statistical analysis

Patients were stratified according to 60-day mortality and divided into 60-day survivors and 60-day non-survivors. The Mann–

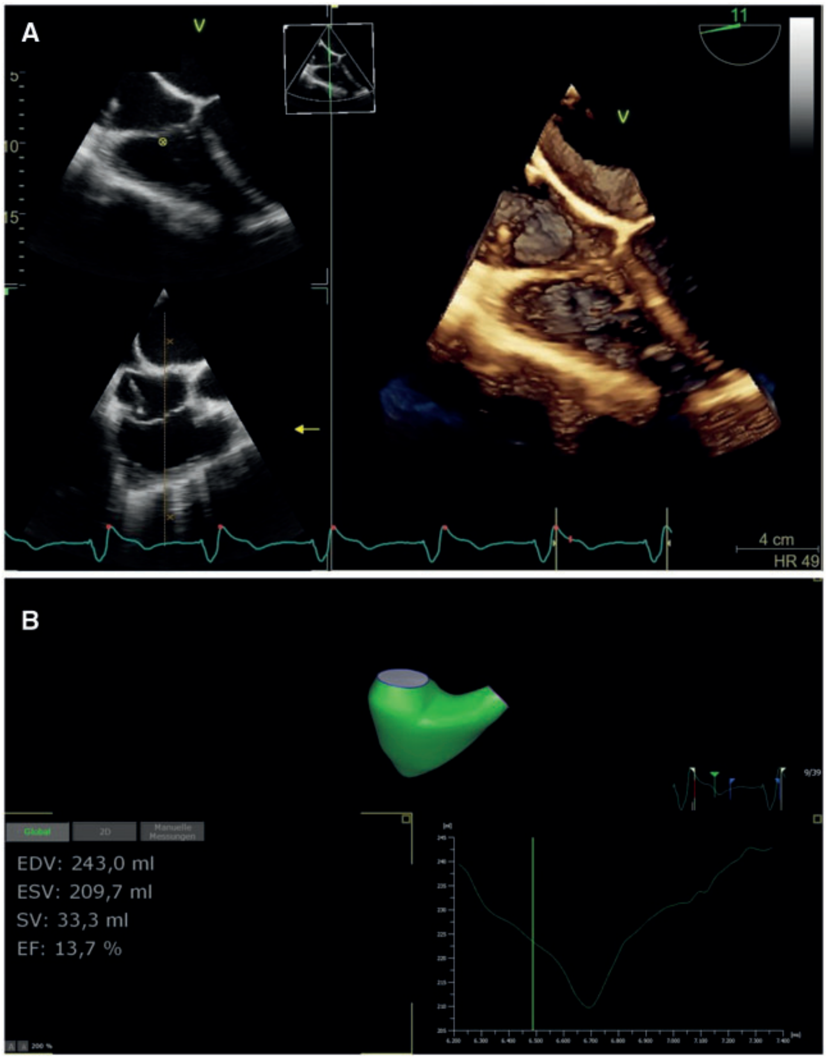

Figure 1: (**A**) 2D preparation (left) for 3D multibeat full-volume image (right). (**B**) Surface quantification of right ventricle using TOMTEC software. EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; SV: stroke volume.

Whitney *U*-test and the Fisher's exact test were used to compare the patient groups. Optimal cut-offs for putative prognostic parameters of 60-day mortality were determined by receiver operating characteristics curves and Youden's J-statistic. Independent predictors of 60-day mortality were identified by multivariable logistic regression analysis. Predictors of long-term survival were identified by the multivariable Cox regression proportional hazards model. In both cases, variables presenting with $P < 0.1$ in univariable analyses were included in the initial multivariable models, which were then optimized according to the Akaike information criterion by backwards stepwise elimination of variables. Biventricular chamber end-diastolic volume index was removed from the models because of co-linearity with indexed LV end-diastolic volume (LVEDVi). The Kaplan–Meier survival curves are presented to illustrate the difference in mortality between patients with severely versus moderately dilated RVs.

RESULTS

A total of 65 patients scheduled for LVAD implantation met the inclusion criteria. Four primary pathologies caused end-stage HF in this patient cohort: 39 patients had dilated cardiomyopathy (CMP), 24 patients had an ischaemic CMP, 1 patient was diagnosed with hypertrophic obstructive CMP and 1 patient developed CMP after therapy for oncological disease. All patients were implanted with the latest generation of centrifugal LVAD continuous-flow technology. In 46 patients, HeartWare HVAD (HeartWare, Framingham, MA, USA) devices were used, and 19 patients received a HeartMate 3 (St. Jude Medical, St Paul, MN, USA). Sixty-three implantations were performed conventionally using a cardiopulmonary bypass, whereas in the remaining 2 patients, a novel minimal invasive technique using a bilateral approach without cardiopulmonary bypass was applied [14]. Additional elective surgical procedures were necessary in 22 patients: persistent foramen ovale/atrial septal defect closure (10 patients), tricuspid valve repair (5 patients), aortic valve replacement (3 patients), LV thrombectomy (4 patients) and left atrial appendage occlusion (1 patient).

Sixteen patients died within 60 days after implantation. Thus, we divided our cohort group into 60-day survivors (49 patients, 75%) and 60-day non-survivors (16 patients, 25%). Post-procedural RVF occurred in 18 patients [survivors 12 (24.5%), non-survivors 6 (37.5%); $P = 0.191$]. Temporary right ventricular assist device (RVAD;

CentriMag, Levitronix LLC, Waltham, MA, USA) implantation was performed in 10 patients [survivors 5 (10%), non-survivors 5 (31%)]. Five RVADs were implanted on the day of surgery, 3 on the following day and 2 on Day 4. The only major difference in preoperative data was noted for LVEF, which was significantly lower in patients requiring RVAD (10.4 ± 1.3 vs 15.1 ± 0.3, $P = 0.03$). In 3 of the 5 survivors, RVAD was explanted after 14, 20 and 23 days, respectively, and these patients are still alive. Two patients were converted to RVAD HeartWare after 29 und 75 days: 1 patient died 376 days later, and the other is still alive. The 5 non-survivors died on RVAD after 2, 3, 5, 15, and 19 days, respectively. In the group diagnosed with dilated CMP, 6 (15%) patients died, and among those with ischaemic cardiomyopathy, mortality was 42% (10 patients). Causes of death were multiorgan failure (9 patients), RVF (6 patients) and generalized cerebral oedema (1 patient).

Table 1 summarizes the clinical and demographic characteristics of both groups. The only significant difference between the groups was higher average age of 60-day non-survivors (62 ± 12 vs 55 ± 12, $P = 0.02$). There were no significant differences in gender distribution, body mass index, INTERMACS profiles (ranging from 2 to 4) and the indicators for end-organ dysfunction.

Table 2 describes the postoperative course. The following parameters were used to reflect the postoperative haemodynamic status in the first 48 h after LVAD implantation: minimal mean arterial pressure, minimal cardiac index, lowest mixed venous saturation, maximal central venous pressure and maximal inotropic support [15]. Patients in the 60-day non-survivors group required significantly higher maximal inotropic support (68 ± 51 vs 36 ± 20; $P = 0.02$).

Table 3 shows quantitative parameters from preprocedurally acquired echocardiographic recordings. There was no difference in linear dimensions of RV, but LV end-diastolic diameter was lower in the non-survivors group (6.72 ± 0.83 vs 7.69 ± 1.25; $P = 0.007$) and the right to left end-diastolic ratio (R/L ratio) was significantly higher in the 60-day non-survivors group (0.70 ± 0.09 vs 0.62 ± 0.11; $P = 0.01$). There were no significant differences in functional parameters acquired in 2D (tricuspid annulus plane systolic excursion and fractional area change) and by 3D echocardiography (SV index, LV global longitudinal strain and RV free wall longitudinal strain).

However, LV, RV and overall heart end-diastolic volumes were found to be significantly different between the 2 groups. Values for chamber volumes are given as body surface-adjusted indices and are higher in the 60-day survivors group (LV volume 154 ± 51 ml/m^2 vs 110 ± 40 ml/m^2, $P = 0.004$; RV volume 96 ± 27 ml/m^2 vs 80 ± 23 ml/m^2, $P = 0.05$; heart 250 ± 64 ml/m^2 vs 190 ± 57 ml/m^2, $P = 0.003$). Supplementary Material, Fig. S1 shows

Table 1: Patient characteristics

	60-day survivors	60-day non-survivors	*P*-value
Number of patients	49 (75)	16 (25)	
Male gender	40 (82)	14 (88)	0.74
Age (years)	55 ± 12	62 ± 12	0.02
BMI (kg/m^2)	26 ± 6	27 ± 6	0.39
DCMP	33 (67)	6 (37.5)	0.035
ICMP	14 (29)	10 (62.5)	
INTERMACS 2	22 (45)	11 (69)	0.24
INTERMACS 3	19 (39)	4 (25)	
INTERMACS 4	8 (16)	1 (6)	
Creatinine (mg/dl)	1.5 ± 0.7	2.0 ± 1.3	0.41
Bilirubin (mg/dl)	1.7 ± 1.4	2.5 ± 2.3	0.28
GOT (U/l)	127 ± 270	950 ± 2998	0.10
GGT (U/l)	169 ± 126	153 ± 140	0.49
Lactate (mg/dl)	11.4 ± 10.7	15.7 ± 27.4	0.63
Pro-BNP (pg/ml)	8586 ± 8246	16146 ± 16686	0.15

Data are presented as means ± SD or as *n* (%).

BMI: body mass index; DCMP: dilated cardiomyopathy; GGT: gamma-glutamyl transpeptidase; GOT: glutamate oxalate transaminase; ICMP: ischaemic cardiomyopathy; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; pro-BNP: pro-b-type natriuretic peptide; SD: standard deviation.

Table 2: Postoperative course

	60-day survivors	60-day non-survivors	*P*-value
Minimal MAP 48 h (mmHg)	61 ± 5	58 ± 6	0.11
Minimal CI 48 h (l/m^2)	4.3 ± 1.0	3.6 ± 1.2	0.07
Maximal CVP 48 h (mmHg)	15.9 ± 4.0	18.3 ± 5.5	0.07
cvSO$_2$ 48h Min (%)	65 ± 10	71 ± 7	0.04
Maximal inotropic score 48 h	36 ± 20	68 ± 51	0.02
Secondary RVAD	5 (10)	5 (31)	0.10

Data are presented as means ± SD or as *n* (%).

CI: cardiac index; CVP: central venous pressure; cvSO$_2$: central venous oxygen saturation; MAP: mean arterial pressure; RVAD: right ventricular assist device; SD: standard deviation.

Table 3: Echocardiographic parameters

	60-day survivors	60-day non-survivors	*P*-value
RVEDD (cm)	4.71 ± 0.79	4.68 ± 0.80	0.71
LVEDD (cm)	7.69 ± 1.25	6.72 ± 0.83	0.007
R/L ratio	0.62 ± 0.11	0.70 ± 0.09	0.01
FAC (%)	17.4 ± 8.8	20.0 ± 7.5	0.31
TAPSE (mm)	13.6 ± 5.5	12.6 ± 4.5	0.59
LVEDVi (ml/m^2)	154 ± 51	110 ± 40	0.004
LVESVi (ml/m^2)	134 ± 48	92 ± 36	0.003
LVSVi [ml/m^2]	19.8 ± 7.9	18.4 ± 9.6	0.43
LVEF (%)	13.7 ± 5.3	16.9 ± 6.8	0.11
LV GLS (%)	-3.9 ± 2.0	-4.7 ± 3.4	0.16
RVEDVi (ml/m^2)	96 ± 27	80 ± 23	0.05
RVESVi (ml/m^2)	75 ± 23	61 ± 21	0.06
RVSVi (ml/m^2)	21.2 ± 9.2	19.1 ± 6.7	0.45
RVEF (%)	22.4 ± 8.3	24.7 ± 9.8	0.47
RV GLS (%)	-9.6 ± 4.0	-10.5 ± 5.3	0.75
Heart EDVi (ml/m^2)	250 ± 64	190 ± 57	0.003
R/L EDV ratio	0.67 ± 0.23	0.76 ± 0.23	0.16

Data are presented as means ± SD.

EDV: end-diatolic volume; FAC: fractional area change; GLS: global longitudinal strain; EDVi: indexed sum of RV and LV end-diastolic volumes; LV: left ventricular; LVEF: LV ejection fraction; LVSVi: indexed LV stroke volume; LVEDD: LV end-diastolic diameter; LVEDVi: indexed LV end-diastolic volume; LVESVi: indexed LV end-systolic volume; R/L ratio: ratio of RVEDD over LVEDD; R/L EDV ratio: ratio of RV and LV end-diastolic volumes; RV: right ventricular; RVEDD: RV end-diastolic diameter; RVEF: RV ejection fraction; RVESVi: indexed RV end-systolic volume; RVSVi: indexed RV stroke volume; SD: standard deviation; TAPSE: tricuspid annulus plane systolic excursion.

concordance between linear dimension (RV end-diastolic diameter) and volume of RV (RV end-diastolic volume).

The inflection points for maximal differentiation of echocardiographic parameters for risk identification of 60-day mortality are listed in Table 4. All were determined by construction of receiver operating characteristics curves and selected at the maximum sum of sensitivity and specificity. Results of univariable prescreening for ratios (linear and volume values) and end-diastolic values for RV, LV and heart volumes show a potential to predict 60-day mortality.

The Kaplan–Meier survival curves (Fig. 2) for patients with indexed right ventricular end-diastolic volume (RVEDVi) >82 ml/m^2 vs RVEDVi ≤82 ml/m^2 show better 1-year survival ($P = 0.005$), with a pronounced difference occurring within the first 60 days after LVAD implantation.

Table 4: 60-Day mortality according to selected echocardiographic parameters cut-offs

Cut-off	<Cut-off	≥Cut-off	*P*-value
R/L ratio: 0.67	5 of 41 (12)	11 of 24 (46)	0.006
R/L EDV: 0.80	7 of 43 (16)	8 of 17 (47)	0.021
LVEDVi: 144 ml/m^2	13 of 32 (41)	2 of 28 (7)	0.003
RVEDVi: 82 ml/m^2	10 of 24 (42)	6 of 42 (14)	0.018
Heart EDVi: 256 ml/m^2	14 of 38 (37)	1 of 22 (5)	0.005

Data are presented as numbers with percentages in brackets.
EDVi: indexed sum of RV and LV end-diastolic volumes; LVEDVi: indexed LV end-diastolic volume; R/L EDV: RV to LV end-diastolic volume ratio; R/L ratio: RV to LV end-diastolic diameter ratio; RVEDVi: indexed RV end-diastolic volume.

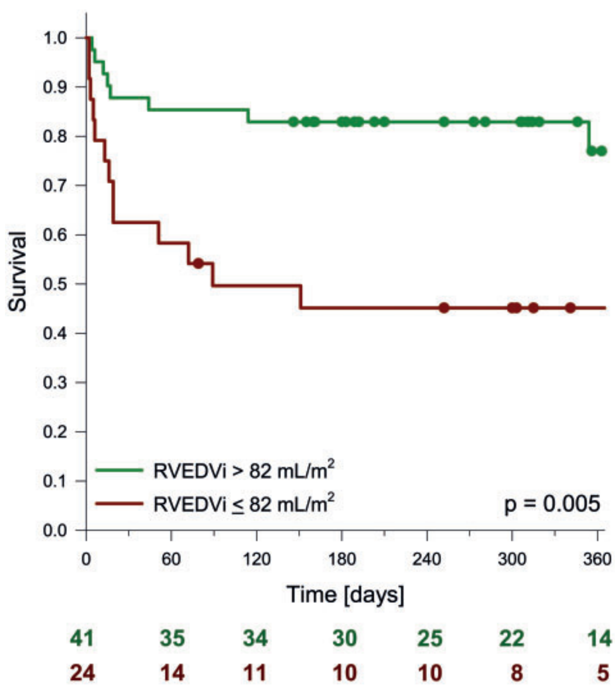

Figure 2: The Kaplan–Meier survival curve over 360 days for patients with pre-procedural moderate (red) and severe right ventricular dilatation (green). RVEDVi: indexed right ventricular end-diastolic volume.

The variables initially included in the logistic regression analysis for 60-day mortality were age, ischaemic versus dilatative CMP, R/L ratio >0.67, R/L end-diastolic volume >0.80, RVEDVi ≤82 ml/m^2, LVEDVi ≤144 ml/m^2 and creatinine concentration. Only R/L ratio and RVEDVi ≤82 ml/m^2 were independently associated with 60-day mortality (Table 5). The variables initially included in the Cox proportional hazards model for long-term survival were age, ischaemic versus dilatative CMP, R/L ratio >0.67, R/L end-diastolic volume >0.80, RVEDVi ≤82 ml/m^2, LVEDVi ≤144 ml/m^2 and creatinine and bilirubin concentrations. In addition to R/L ratio and RVEDVi, age was associated with long-term survival (Table 6).

DISCUSSION

The first major finding of our study in patients scheduled for LVAD implantation is that the right ventricle in all patients was severely dilated (92 ± 27 ml/m^2) compared with normal values (61 ± 13 ml/m^2) [13] and RV ejection fraction was severely reduced at 23 ± 9%.

The second important, and somewhat surprising, finding is that more severe RV (indexed end-diastolic volume >82 ml/m^2) dilatation was seemingly advantageous for early outcome following LVAD implantation.

Ventricular remodelling, measured as chamber enlargement, is a primary adaptive process in chronic global or regional myocardial impairment. Although this compensatory mechanism is beneficial in HF patients to maintain SV, the long-term effect is disadvantageous [16]. Interventions limiting ventricular dilatation (remodelling) and neurohumoral activation are associated with improved survival [17]. Patients in Stage D, such as in our study, present with substantial LV and RV dilatation as a common final

Table 5: Results of the multivariable logistic regression model for 60-day mortality

	OR	95% CI	*P*-value
R/L ratio >0.67	11.07	1.86–66.03	0.008
RVEDVi ≤82 ml/m^2	7.69	1.29–45.67	0.025
LVEDVi ≤144 ml/m^2	3.08	0.52–18.21	0.215

CI: confidence interval; OR: odds ratio; R/L ratio: RV to LV end-diastolic diameter ratio; RVEDVi: indexed RV end-diastolic volume; LVEDVi: indexed LV end-diastolic volume.

Table 6: Results of the multivariable Cox regression proportional hazards model for long-term survival

	HR	95% CI	*P*-value
Age (years)	1.07	1.00–1.13	0.039
R/L ratio >0.67	3.60	1.42–9.09	0.007
RVEDVi ≤82 ml/m^2	4.42	1.68–11.70	0.003

CI: confidence interval; HR: hazard ratio; R/L ratio: RV to LV end-diastolic diameter ratio; RVEDVi: indexed RV end-diastolic volume.

pathway for different pathologies, different therapies and variability in disease progression.

In the setting of LVAD implantation, the main therapeutic aim is to increase cardiac output, determined by LVAD flow, to normal values. This haemodynamic change leads to a major increase of venous return to the right ventricle. This immediate increase in RV preload may exceed the mechanically unsupported ability of the right ventricle to increase its SV accordingly, resulting in RV failure after LVAD implantation. We expected that right ventricles with less remodelling (i.e. less dilatation) would be able to better deal with this increase of venous return. Unfortunately, our data showed an unexpected protective effect of more advanced RV dilatation. We can only speculate as to why seemingly more severely dilated right ventricles with greater RVEDVi confer a benefit on short-term survival. In addition to increasing RV preload, LVAD implantation also induces a marked decrease of RV afterload due to the resolved LV congestion [18]. It seems possible that right ventricles with greater dilation profit more from the decreased afterload, while the relative increase in preload is smaller due to the greater baseline volume prior to LVAD implantation.

Thus, more severely remodelled/dilated RVs might be able to better deal with the increase of venous return due to LVAD implantation.

Kiernan *et al*. [19] used 3D echocardiography in 26 patients for assessment of RV volumes and suggested RVEDVi >62 ml/m^2 as a predictor of RVF after LVAD implantation, which seems to contradict our findings. However, that study essentially compared patients with normal RV size to patients with moderately increased RV, while in our cohort patients with severely dilated RV were compared to patients with moderately increased RV volumes.

The 60-day mortality of 25% is higher than that reported in the INTERMACS registry. This may be explained by the low preprocedural INTERMACS profiles of our patient cohort, with 51% of patients presenting with profile 2 and 35% with profile 3. Nearly all deaths (15, 94%) were due to RVF or multiorgan failure. Despite the use of standard operating procedures for early management of RVF, early mortality also depends on the timing of surgery, the clinical preoperative patient status and general postoperative management.

In our previous study, we presented R/L ratio as a valuable predictor of RVF after LVAD implantation [5]. Our results were later confirmed by Vivo *et al*. [20] with nearly the same cut-off value for R/L ratio (0.75 vs 0.72). In this study, R/L ratio is also predictive for 60-day mortality.

Limitations

Our study shares all the typical limitations of retrospective analyses, which include severe weaknesses of a *post hoc* design and analysis, the inability to harvest data on all important variables/risk factors and to standardize the indication for the primary intervention [21]. Yet the variables that were included in our final multivariate models have been shown to have an impact on 60-day survival.

We analysed a mixed patient population including both ischaemic and dilated aetiology of CMP. Because ischaemic CMP was associated with higher mortality while dilated CMP may result in greater RV or LV volumes, this could severely bias our results towards greater mortality among patients with only moderately dilated right or left ventricle. Therefore, we analysed ventricular dimensions according to the aetiology of CMP and did not detect any difference: RVEDVi (92.6 ± 28.3 vs 91.5 ± 26.7 ml/m^2); LVEDVi (143 ml/m^2 in both groups) and LV end-diastolic diameter (7.5 vs 7.4 cm in patients with dilated versus ischaemic CMP). Nevertheless, we included the aetiology of CMP in the initial multivariable models; however, it was not confirmed as an independent predictor of mortality.

Another limitation is the relatively small number of patients. However, patients were treated by the same heart team within a relatively short observation time for this type of therapy and all received technically similar centrifugal LVAD devices from only 2 manufacturers, which may be expected to result in a rather homogeneous patient cohort. Nevertheless, at best, these data can be used to inform a prospective controlled trial to confirm the relevance of cardiac chamber volume parameters for risk stratification of patients undergoing LVAD implantation and to develop effective therapeutic strategies accordingly.

CONCLUSION

3D echocardiography is established as a valuable tool for volume measurements, independent of assumptions on chamber geometry and readily available in preprocedural examinations prior to LVAD implantation. Moderately increased RVEDVi identified patients with higher early and late postoperative risks, while severe RV dilatation seemed to be protective. In future, postoperative management of patients with moderately dilated RV should be focussed on adjusting individually appropriate LVAD flow and providing frequent follow-ups.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: none declared.

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3 Diskussion

Die ATAAD ist ein vielschichtiges Krankheitsbild und die Weichenstellung für die komplexe Versorgung erfolgt schon weit vor dem operativen Eingriff. Eine genaue Analyse der einzelnen präklinischen Versorgungsabschnitte und eine exakte Betrachtung der epidemiologischen Daten sind die Voraussetzungen für ein besseres Verständnis der Erkrankung und um daraus eine strukturierte, optimierte Versorgung für betroffene Patienten zu entwickeln. Ein weiterer bedeutender Faktor ist die genaue Kenntnis der Region und des Einzugsgebietes. Die durchgeführten wissenschaftlichen Arbeiten haben sich weitestgehend an der Region Berlin-Brandenburg orientiert, da das Deutsche Herzzentrum Berlin die einzige herzchirurgische Klinik für dieses Gebiet ist. Die Region Berlin-Brandenburg hat ungefähr sechs Millionen Einwohner (Statistisches Bundesamt, 2014). Dadurch eignet sie sich insbesondere für Kohortenstudien und Interventionsstudien im Bereich der herzchirurgischen präklinischen Versorgung. Die wissenschaftliche Herangehensweise beginnt mit der Feststellung der Inzidenz der Erkrankung in der genannten Region. Die Inzidenz ist für die Versorgungsforschung zur akuten Aortendissektion von essenzieller Bedeutung. Auf Basis der Zahlen zur Inzidenz ist es beispielweise möglich, die tatsächlich klinisch diagnostizierten Fälle mit den zu erwartenden Fällen abzugleichen. Diese zu erwartenden Fallzahlberechnungen, z. B. für eine bestimmte Region, lassen sich als unabhängiger Qualitätsindikator in der präklinischen Diagnostik von akuten Aortendissektionen nutzen.

Die erste vorgestellte Arbeit hat die tatsächliche Inzidenz der ATAAD in einer bevölkerungsbasierten Studie untersucht. Die wahre Inzidenz der akuten Typ-A-Aortendissektion ist aufgrund der Pathophysiologie der Erkrankung im deutschen System zur statistischen Erfassung von Krankheiten und Sterbefällen aktuell nicht möglich. In Europa und Deutschland wird die statistische Inzidenz auf ca. 2–16 Fälle pro 100 000 Einwohner und Jahr geschätzt (Mészáros et al., 2000; Olsson et al., 2006; Howard et al., 2013; Pacini et al., 2013; Statistisches Bundesamt, 2014). Durch die Auswertung der Obduktionsberichte aller gerichtsmedizinischen Institute und eines großen pathologischen Instituts in der Region konnten erstmalig auch alle präklinischen Fälle identifiziert werden. Basierend auf diesen Ergebnissen wurde die regionale Inzidenz der ATAAD in Höhe von 11,9 Fällen pro 100 000 Einwohner berechnet (Kurz et al., 2017). Dies ist für alle weiteren Arbeiten auf diesem Gebiet die erste wichtige Grundlage. Anhand der Berechnungen ergibt sich für die Region Berlin-Brandenburg eine erwartete Zahl von etwa 720 Fällen pro Jahr. Die Obduktion von ungeklärten Todesfällen und die Auswertung von klinischen Obduktionen ist ein wichtiger

Qualitätsprozess bei der statistischen Erhebung von Erkrankungshäufigkeiten im Bereich der Herz-Kreislauf-Medizin (Brinkmann, Du Chesne and Vennemann, 2002; Statistisches Bundesamt, 2014; Kurz et al., 2021).

Aufgrund der akuten Symptomatik haben Patienten mit einer ATAAD in der Regel den ersten Kontakt mit dem Rettungsdienst. Die weitere Behandlung und Diagnostik erfolgt in der Notaufnahme des ersten angefahrenen Krankenhauses (Primärkrankenhaus). Ziel der zweiten vorgestellten Arbeit war es zu untersuchen, wie häufig das Ereignis einer ATAAD in einer Notaufnahme pro Jahr auftritt. Hierzu wurden die Daten von insgesamt 12 790 577 Patienten über einen Zeitraum von 13 Jahren (2006 bis 2016) ausgewertet. In allen Berliner Krankenhäusern lag die berechnete Inzidenz der ATAAD in der Notaufnahme bei 5,24 Fällen pro 100 000 Notfallpatienten pro Jahr. An den Berliner Universitätskliniken waren die Inzidenzen deutlich höher. Hier lagen sie bei 6,7 bzw. 12,4 Fällen pro 100 000 Notfallpatienten (Wundram et al., 2020). Brustschmerz ist ein dringliches Symptom in einer Notaufnahme, das für das Team häufig eine schwierige diagnostische Aufgabe darstellt. Möckel et al. konnten 2013 in einer Untersuchung von 34 333 Patienten einer zentralen Notaufnahme in Berlin zeigen, dass 11,5 % der Patienten das Symptom Brustschmerz aufwiesen (Möckel et al., 2013; Bruno et al., 2015; Möckel and Störk, 2017). Auch hier kann sich die prognostizierte Gesamtzahl der jährlich zu erwartenden Patienten in einer Notaufnahme mit der richtigen Diagnose einer ATAAD als möglicher Qualitätsindikator für die Differenzialdiagnostik des akuten Brustschmerzes eignen (Wundram et al., 2020).

Bei der ATAAD ist das klinische Bild des Patienten häufig nicht eindeutig. Die Diagnose ist oft schwierig und führt immer wieder zu einer Verzögerung der operativen Versorgung (Butler et al., 1991; Harris et al., 2011; Froehlich et al., 2018). Eine der Hauptursachen für eine verzögerte Diagnostik ist das Auftreten von unterschiedlichen initialen klinischen Symptomen (Harris et al., 2011; Froehlich et al., 2018; Zaschke et al., 2020). In der dritten vorgestellten Arbeit von Zaschke et al. wurden die initiale Symptomatik und der diagnostische Verlauf genauer untersucht. Ergänzend wurde analysiert, welche Symptome im Zusammenhang mit einer korrekten oder falschen Erstdiagnose assoziiert waren. Außerdem wurde das Potenzial des Aortic Dissection Detection Risk Score (ADDRS) bei der Verbesserung der Sensitivität der Erstdiagnose erforscht (Zaschke et al., 2020). Die korrekte Erstdiagnose einer ATAAD wurde bei 76 von 350 untersuchten Patienten (Gruppe 1, 21,7 %) festgestellt, während anfängliche Fehldiagnosen bei 274 Patienten (Gruppe 0, 78,3 %) auffielen. Die häufigste dokumentierte Erstdiagnose war das akute

Koronarsyndrom (ACS) mit 162 Fällen (46,3 %). Die zweithäufigste initiale Fehldiagnose stellten bei 69 Patienten neurologische Erkrankungen (19,7 %) dar, gefolgt von akuten Atemwegserkrankungen bei 40 Patienten (11,4 %) (Zaschke et al., 2020). Zusammenfassend wurde somit festgestellt, dass die Rate der initialen Fehldiagnosen bei 78,3 % liegt. Die häufigste Fehldiagnose ist mit 49,4 % das akute Koronarsyndrom (Zaschke et al., 2020).

Bei den Versorgungszeiten nach dem akuten Schmerzereignis konnten weitere aufschlussreiche Beobachtungen gemacht werden. Die Gruppe 0 (initiale Fehldiagnose) und die Gruppe 1 (korrekte initiale Diagnose) wurden bezüglich der Zeitintervalle in der Versorgung genauer miteinander verglichen. Alle Zeitintervalle, außer die Zeit zwischen Schmerzbeginn und Aufnahme im Primärkrankenhaus (p = 0,282), waren in Gruppe 1 signifikant kürzer. In der Gesamtübersicht der Versorgungszeit eignet sich am besten das Zeitintervall der medianen ‚Pain-Cut-Time' (PCT, Zeitintervall vom Beginn der Schmerzen bis zur Operation) mit 8,6 Stunden in Gruppe 0 (Q1 – Q3: 6,3–16,4 h) und 5,5 Stunden in Gruppe 1 (Q1 – Q3: 4,5–7,9 h; p < 0,001) zum besseren Verständnis der verzögerten Versorgungsproblematik (Zaschke et al., 2020).

Die ebenfalls durchgeführte retrospektive Auswertung des ADDRS ergab, dass 178 Patienten zunächst einen negativen ADDRS < 1 hatten und 172 Patienten einen positiven Score > 2 (51 % vs. 49 %). Die Rate von korrekten Erstdiagnosen stieg mit zunehmendem ADDRS von 5,1 % bei Patienten mit einem ADDRS = 0 auf bis zu 56,2 % bei Patienten mit einem ADDRS Score von drei Punkten. Unter den 172 Patienten mit einem positivem ADDRS Score > 2 erhielten 113 Patienten (65,7 %) immer noch eine falsche initiale Verdachtsdiagnose (Zaschke et al., 2020). Durch die hohen Patientenzahlen, die starke Arbeitsbelastung und die teilweise geringe Erfahrung der jüngeren Kolleginnen und Kollegen kommt es bei akuten Aortendissektionen bis zur definitiven Diagnostik häufig zu erheblichen Behandlungsverzögerungen von teilweise mehr als acht Stunden (Butler et al., 1991; Rapezzi et al., 2008; Harris et al., 2011). In einer Auswertung von ATAAD Daten aus dem IRAD wurden sogar Behandlungsverzögerungen zwischen Menschen mit unterschiedlicher Hautfarbe festgestellt (Rapezzi et al., 2008).

Um die klinische Versorgung bei einer ATAAD besser zu verstehen, teilt man diese idealerweise in fünf Versorgungsabschnitte ein (vgl. Abb. 4, eigene Abbildung). Im ersten Versorgungsabschnitt stehen Patienten mit einem arteriellen Hypertonus und ihre hausärztliche Versorgung im Fokus. Da es sich beim Großteil der betroffenen Patienten um Hypertoniker handelt, besteht die Möglichkeit, durch Sensibilisierungsmaßnahmen – z. B. in der Hausarztpraxis – die Patienten rund um das Thema ‚plötzlicher Brustschmerz' besser aufzuklären. Hier sind beispielsweise regelmäßige Veranstaltungen und Flyer zum Themenkomplex Hypertonie ein wesentlicher Baustein. Im Rahmen der zunehmenden Digitalisierung im Gesundheitswesen rücken auch Werkzeuge wie die digitale Patientenakte und Gesundheitsanwendungen auf dem Smartphone immer mehr in den Fokus. Der Patient verwaltet seine Patientendaten selbst, Anwendungen werden zunehmend durch künstliche Intelligenz unterstützt. Dadurch wird der Patient auch frühzeitig in differenzialdiagnostische Überlegungen eingebunden, da der Patient Hinweise auf eventuell bestehende Vorerkrankungen und Risikofaktoren besser kommunizieren kann. Frühzeitige differenzialdiagnostische Hinweise an beispielweise das Personal vom Rettungsdienst oder in den Notaufnahmen sind für den zeitlichen Ablauf bei einer akuten Aortendissektion entscheidend und können die Zeit zwischen dem Ereignis und der definitiven chirurgischen Versorgung verkürzen (Zaschke et al., 2020). Die Verbesserung des ersten Versorgungsabschnittes ist Aufgabe der hausärztlichen Versorgung, der Rettungsstellen und des Rettungsdienstes.

Der zweite Versorgungsabschnitt ist durch die rasche und zügige Verlegung des Notfallpatienten gekennzeichnet. Hier lassen sich in der Regel keine weiteren Zeitgewinne generieren. Die nächstgelegene Rettungsstelle mit der Möglichkeit zu einer EKG-getriggerten CT-Angio-Untersuchung gehört fraglos zu den zentralen Faktoren bei der Transportentscheidung. In Berlin wurde am Virchow-Klinikum der Charité eine Schwerpunktaufnahme für Fälle mit Verdacht auf ein akutes Aortensyndrom geschaffen. Hegt der Rettungsdienst oder der Notarzt den Verdacht auf ein akutes Aortensyndrom, so kann er mit Voranmeldung die Notaufnahme direkt anfahren.

Damit stehen im dritten Versorgungsabschnitt die betroffene Person und ihre Anamnese im Fokus. Eine genaue Schmerzanamnese und die Erfassung der begleitenden klinischen Symptome sind für die weiteren diagnostischen Schritte entscheidend. Ein erstes validiertes Tool ist hierfür der ADDRS der American Heart Association (AHA) aus dem Jahre 2011 (Rogers et al., 2011). Dieser Score ergibt sich aus der Beantwortung dreier einfacher Fragenblöcke rund um die Anamnese zur Aorta. Die drei Fragenblöcke beinhalten Fragen zur Aortenanamnese (Voroperationen, familiäre Aortenerkrankungen u. a.), zur Schmerzanamnese (plötzlicher Vernichtungsschmerz mit wanderndem Charakter u. a.) und zum klinischen Untersuchungsbefund des Patienten (neurologische Ausfälle, Zeichen von Malperfusionsstörungen u. a). Der ADDRS erzeugt jedoch auch eine hohe Rate an falsch positiven Patienten. Dies führt zu mehr Fällen in der CT-Diagnostik und damit zu einem sogenannten ‚Overtesting'. Um diesen Score weiterzuentwickeln, wurde er in den vergangenen Jahren im Rahmen zahlreicher Arbeiten um wesentliche Punkte ergänzt. Dazu zählen die Labordiagnostik (D-Dimere, Troponin), Röntgenuntersuchungen des Brustkorbes und das Point-of-Care-Ultraschallverfahren. Eine weitere sehr aktuelle Arbeit zum besseren Verständnis des diagnostischen Ablaufs wurde 2021 im „Journal of the American Society of Cardiology“ publiziert. Hier werden in einer sehr guten grafischen Übersicht der organisatorische Prozess und die Einbindung weiterer diagnostischer Verfahren bis zur Diagnosestellung einer ATAAD gezeigt (Vilacosta et al., 2021). Im Hinblick auf die praktischen Fertigkeiten wird auch hier auf die konsequente Anwendung von Point-of-Care-Diagnostik, z. B. in Form von fokussierter transthorakaler Sonographie (FOKUS), deutlich hingewiesen. Es geht bei der Anwendung von Sonographieverfahren in der Notaufnahme nicht um einen ausführlichen Sonographiebefund, sondern – speziell bei akutem Thoraxschmerz – um die Darstellung von neu aufgetretenen, potenziell lebensbedrohlichen Veränderungen im Bereich des Herzens, wie z. B. einen neu aufgetretenen Perikarderguss oder ein neu aufgetretenes Aortenklappenvitium. Dies dient als Hinweis, welchem weiteren diagnostischen Verfahren der Patient als nächstes zugeführt werden sollte. Die Anwendung von fokussierter Ultraschalldiagnostik sollte mittlerweile zum Standardverfahren im Rahmen der diagnostischen Abläufe von plötzlich aufgetretenen, akuten Brust- und Rückenschmerzen gehören.

Der vierte Versorgungsabschnitt beschreibt die Sekundärverlegung des Patienten in eine herzchirurgische Klinik. Hier gilt die Einhaltung der gesetzlichen Hilfsfrist von 15 Minuten bei der Disposition eines geeigneten Rettungsmittels zur Verlegung (Kurz et al., 2020). Ein Notfallpatient ist so lange Notfallpatient, bis er eine geeignete Klinik erreicht hat, um dort einer definitiven Versorgung zugeführt zu werden. Bei Patienten mit einer akuten Aortendissektion ist die Zeit der entscheidende Faktor für das Überleben. Es spielt keine Rolle, ob der Patient boden- oder luftgebunden verlegt wird. Jedoch ergeben luftgebundene Transporte erst ab einer Distanz zur Zielklinik von mehr als 75–90 Kilometer einen zeitlichen Gewinn und sie machen im Vergleich zum bodengebundenen Transport keinen Unterschied in der Letalität (Matschilles et al., 2018). Es ist zur Verlegung des Patienten überdies nicht notwendig, diesen aufwendig zu verkabeln. Ein oder zwei periphere Zugänge sind ausreichend. Der Blutdruck des Patienten sollte nicht mehr als 120 mmHg betragen und eine großzügige Schmerzbekämpfung mittels Opioidanalgetika (z. B. Morphin) sollte erfolgen. Falls für die Verlegung des Patienten kein Notarzt zur Verfügung steht, sollte der Transport mit dem nächstverfügbaren RTW durchgeführt werden (Kurz et al., 2020).

Der fünfte Abschnitt nach Ankunft in der Zielklinik kennzeichnet sich durch einen raschen Transport des Patienten in den Operationsraum. Durch die Organisation über des Aortentelefons des Deutschen Herzzentrums Berlin (DHZB) sind alle wesentlichen Bilddaten und die Vorgeschichte des Patienten bereits übermittelt worden. Somit kann die Operation im Vorfeld organisiert und geplant werden. Die OP-Teams bestehen in der Regel aus bis zu 16 Personen. Damit sie jederzeit einsatzbereit sein können, ist ein hoher technischer und organisatorischer Aufwand erforderlich.

Die akute Typ-A-Aortendissektion und der darauffolgende herzchirurgische Eingriff können von Patienten als traumatisches Ereignis erlebt werden. In der vierten vorgestellten Arbeit wurde das Ziel verfolgt, die Prävalenz der posttraumatischen Belastungsstörung (PTSD) und das körperliche und geistige Wohlbefinden von Patienten nach einer ATAAD zu analysieren. Insgesamt wurden 393 Überlebende kontaktiert und gebeten, verschiedene Fragebögen auszufüllen (Adam et al., 2018). Dabei handelte es sich um einen Fragebogen zur Abfrage soziodemografischer Daten, einen Gesundheitsfragebogen in Kurzform (SF-12) zur Erhebung der gesundheitsbezogenen Lebensqualität, einen Fragebogen zur Erfassung von posttraumatischen Belastungsstörungen (Post-traumatic Diagnostic Scale, PDS) und einen letzten Fragebogen zur Erfassung von posttraumatischem Stress (Post-traumatic Stress Scale 14). Von den kontaktierten Patienten schickten 210 Personen (53 %) die Fragebögen ausgefüllt zurück. Die mittlere Nachbeobachtungszeit betrug 51,0 ± 27,8 Monate. Die Dauer des Aufenthaltes auf der Intensivstation oder des Gesamtaufenthalts im Krankenhaus hatte keinen Einfluss auf das Risiko einer PTSD (Adam et al., 2018). Insgesamt ist eine ATAAD jedoch mit einem hohen Risiko für PTSD verbunden. Darüber hinaus scheint sich die Erkrankung ebenfalls langfristig auf die körperliche und geistige Verfassung der Patienten auszuwirken. Es sind jedoch weitere Untersuchungen im Hinblick auf die Prävention, Früherkennung und die Therapie von PTSD bei Patienten mit einer ATAAD notwendig, um dies abschließend beurteilen zu können. Jede herzchirurgische Klinik, die eine größere Anzahl von Patienten mit einer ATAAD pro Jahr versorgt, sollte eine spezielle Sprechstunde für diese Patientengruppe anbieten. Auch eine psychosoziale Betreuung sollte als fester Bestandteil der Versorgung implementiert werden.

In der fünften vorgestellten Arbeit wurden präoperative und postoperative echokardiographische Parameter bei Patienten mit einer ATAAD untersucht (Thurau et al., 2019a). Auch postoperative kardiale Einschränkungen haben gravierende Folgen für die Lebensqualität der betroffenen

Patienten. Es wurde untersucht, ob eine Beeinträchtigung der präoperativen linksventrikulären Funktion mit einem kurz- und langfristigen Überleben assoziiert war. Um eine multivariable Analyse zu ermöglichen, wurden etablierte Risikofaktoren der ATAAD analysiert. Hierzu wurden retrospektiv die Daten von 512 Patienten mit ATAAD aus den Jahren 2006 bis 2014 ausgewertet. In der multivariablen logistischen Analyse zeigte sich, dass Alter (Odds Ratio [OR] 1,04, p < 0,001), eine präoperative LVEF von ≤ 35 % (OR 2,20, p = 0,003), jede Ischämie (Penn class non-Aa) (OR 2,15, p < 0,001) und eine längere kardiopulmonale Bypasszeit (OR 1,04, p < 0,001) als unabhängige Risikofaktoren für die 30-Tage-Sterblichkeit zu werten sind. Damit konnte erstmalig herausgearbeitet werden, dass eine eingeschränkte linksventrikuläre Pumpfunktion einen zusätzlichen unabhängigen Risikofaktor für die 30-Tage-Sterblichkeit bei einer ATAAD darstellt (Thurau et al., 2019a).

Wie in der vorgenannten Arbeit beschrieben, ist die linksventrikuläre Herzfunktion ein ernst zu nehmender Indikator der 30-Tage-Sterblichkeit bei einer akuten TYP-A-Dissektion. In der an sechster Stelle vorgestellten Arbeit wurden am Beispiel eines linksventrikulären Unterstützungsgeräts (LVAD) die Auswirkungen der Rechtsherzfunktion genauer untersucht (Otten et al., 2018). Ein LVAD-System ist eine zunehmend bedeutsame und erfolgreiche Therapieoption für Patienten mit terminaler Herzinsuffizienz. Wenn die chronische Herzinsuffizienz fortschreitet, passen sich der linke und der rechte Ventrikel an, indem sie ihr Volumen vergrößern, und die Patienten stellen sich mit unterschiedlichen Dilatationsgraden für die LVAD-Implantation vor. Durch die quantitative Bestimmung des rechtsventrikulären (RV) und linksventrikulären (LV) Volumens mittels transösophagealer 3-D-Echokardiographie und der Korrelation der Befunde mit den klinischen Ergebnissen wurden die LV- und RV-Volumina für das Überleben nach LVAD-Implantation als prognostische Marker identifiziert. In dieser Untersuchung wurden die Fälle von insgesamt 65 Patienten ausgewertet. Das Design war eine monozentrische, nicht randomisierte diagnostische Kohortenstudie mit prospektiv gesammelten klinischen und 3-D-echokardiographischen Daten von Personen, bei denen eine LVAD-Implantation geplant war und Zentrifugalpumpen zur Langzeitunterstützung (HeartWare^{TM} und HeartMate 3^{TM}) eingesetzt wurden. Als primärer Endpunkt dieser Studie wurde die 60-Tage-Sterblichkeit definiert. Das langfristige Überleben wurde als zweiter Endpunkt festgelegt. Die Kohortengruppe wurde nach sechzig Tagen unterteilt in Überlebende (49 Patienten, 75 %) und Nichtüberlebende (16 Patienten, 25 %). Das rechts-links-enddiastolische Verhältnis war in der 60-Tage-nicht-überlebenden-Gruppe signifikant höher (0,70 ± 0,09 vs. 0,62 ± 0,11; P = 0,01). Die indexierten enddiastolischen

Volumenparameter (LV, RV und Gesamtherz) zeigten signifikante Unterschiede zwischen den Gruppen und waren in der 60-Tage-überlebenden-Gruppe höher (LV-Volumen 154 ± 51 ml/m^2 vs. 110 ± 40 ml/m^2; P = 0,004. RV-Volumen 96 ± 27 ml/m^2 vs. 80 ± 23 ml/m^2; P = 0,05. Herz 250 ± 64 ml/m^2 vs. 190 ± 57 ml/m^2; P = 0,003) (Otten et al., 2018).

Zusammenfassend wurde somit festgestellt, dass Patienten mit einem mäßig erhöhten enddiastolischen RV-Volumenindex ein höheres postoperatives Sterblichkeitsrisiko haben. Eine schwere RV-Dilatation scheint sich hingegen protektiv auszuwirken. Diese Studie zeigt, dass auch die Rechtsherzfunktion ein zusätzlich weiterer wertvoller Ansatz im präklinischen Assessment von ATAAD sein kann, um das perioperative Risiko besser einschätzen zu können.

Es gibt zahlreiche Faktoren, die die Versorgung von Patienten mit einer ATAAD beeinflussen. Als sogenannte kritische Faktoren konnten in aktuellen Publikationen die Anzahl der durchgeführten Aorteneingriffe pro Jahr, die Erfahrung des operierenden Chirurgen, die regionale Versorgungsstruktur, Kenntnisse über die Häufigkeit der Erkrankung, Patientencharakteristika und der präoperative Status als unmittelbare Variablen, die das Outcome beeinflussen, identifiziert werden (Reutersberg et al., 2019; O'Hara et al., 2020; Benedetto et al., 2021). Es ist dringend erforderlich, einen weltweiten Versorgungs- und Entscheidungsstandard für die ATAAD festzulegen. Public-Health-Ansätze (Versorgungsforschung) sind dringend notwendig, um auch die präklinische Sterblichkeit, die aktuell bei fast 50 % liegt, deutlich zu senken (Hirst, Johns and Kime, 1958; Moon, 2009; Lauterbach et al., 2001). Bei einer Inzidenz von 11,9 Fällen pro 100 000 Einwohner ist derzeit in Deutschland (83,2 Millionen Einwohner, Statistisches Bundesamt, 2021; Stand 30.09.2021) mit ca. 9900 Patienten und in Europa (447,7 Millionen Einwohner, Statistisches Bundesamt, 2021; Stand 2021) mit ca. 53 276 Patienten pro Jahr zu rechnen. Mehr als die Hälfte der Patienten versterben (50 %), bevor Sie ein spezialisiertes Zentrum erreichen (Mahase, 2020). Die Steigerung der Awareness beispielsweise in den Notaufnahmen und eine Änderung des Manchester-Triage-Systems (MTS) sind dringend zu adressierende Ansätze in der Versorgung. Das MTS enthält in der aktuellen Fassung bei Brustschmerz keinen Hinweis auf die Differenzialdiagnose eines akuten Aortensyndroms. Obwohl mittlerweile erwiesen ist, dass bei Patienten, die mit Brustschmerz in die Notaufnahme eingeliefert werden, dieser in nur 20 % der Fälle auf ein akutes Koronarsyndrom zurückzuführen ist, müssen auch andere Differenzialdiagnosen dringend besser adressiert werden. Bei 78,8 % der Patienten mit einem ATAAD wird initial nicht die richtige Diagnose gestellt und 46,3 % der ATAAD-Patienten werden initial als akutes Koronarsyndrom behandelt (Zaschke et al., 2020). Sie erhalten aufgrund der Verdachtsdiagnose eines akuten Koronarsyndroms Antikoagulantien im Verlauf ihrer Behandlung. Dies hat für Patienten mit einer ATAAD fatale Folgen. Es kommt zu Blutungskomplikationen und einer erhöhten Sterblichkeit (Davis et al., 2005; Lentini and Perrotta, 2011; Zschaler et al., 2018a; Xue et al., 2019). Die unterschiedlichen nationalen Versorgungsstrukturen bei der Behandlung einer ATAAD erfordern dringend eine Risikostratifizierung der einzelnen Versorgungsschritte und einen weltweit gültigen standardisierten mehrsprachigen Leitfaden.

4 Zusammenfassung

Die akute Aortendissektion Typ A (ATAAD) gehört in der heutigen Notfallmedizin zu den komplexesten und anspruchsvollsten Krankheitsbildern und ist mit einer hohen interdisziplinären Anforderung an alle beteiligten Berufsgruppen verbunden. Bessere Kenntnis über die pro Jahr zu erwartenden Fälle in einer medizinisch versorgten Region und die Analyse der einzelnen präklinischen Versorgungsabschnitte, sowie Kenntnisse der Epidemiologie sind elementare Grundlagen, um Versorgungsabläufe Durch die interdisziplinäre und häufig auch überregionale Zusammenarbeit entstehen unterschiedlichste Herausforderungen. Um diesen gesamten interdisziplinären und überregionalen Prozess besser koordinieren zu können, hat sich das Aortentelefon als Hotline in der Region Berlin-Brandenburg bewährt. Ferner konnte gezeigt werden, dass Obduktionen weiterhin einen bedeutsamen qualitativen Anteil am epidemiologischen Verständnis von Erkrankungen darstellen. Epidemiologische Daten eignen sich somit bei einer ATAAD sehr gut als Qualitätsindikator für die zu erwartende Fallzahl einer herzchirurgisch versorgten Region. Notaufnahmen oder Rettungsstellen sind wichtige Weichensteller für die weitere Diagnostik und Behandlung von Patienten mit einer ATAAD. Epidemiologische Fallzahlen eignen sich bei einer ATAAD demnach auch, um beispielweise die zu erwartenden Gesamtzahl der Patienten in einer Notaufnahme besser zu überwachen. Zusätzliche Maßnahmen wie beispielweise Schulungen zur Steigerung der Awareness für das Krankheitsbild der ATAAD lassen sich somit auch gezielter einsetzen.

Die zunehmende Digitalisierung, elektronische Patientenakten, Gesundheitsanwendungen auf Smartphones und anderen Endgeräten werden in Zukunft eine immer größere Rolle in der Patientenversorgung spielen und die frühzeitige Diagnostik der Erkrankung einer ATAAD weiter verbessern. Jedoch sind dringend weltweite Standards für die gesamte Versorgungsstrecke von Patienten mit einer ATAAD erforderlich. Es ist die Aufgabe der großen Fachgesellschaften und der nationalen Gesundheitssysteme, hierfür die notwendige Aufmerksamkeit zu generieren. Bei der transnationalen Forschung und der Umsetzung von Forschungsergebnissen in die Gesundheitsversorgung von ATAAD besteht dringender Handlungsbedarf.

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7 Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
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- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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