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Influence of Meteorological Conditions on the Incidence of Spontaneous Acute Aortic Dissection

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LIST OF ABBREVIATIONS

-	℃	Degree Celsius
-	A	Type A dissection
-	A+B	Type A and type B dissections
-	AWST	Automatic weather station
-	B	Type B dissection
-	CABG	Coronary artery bypass grafting
-	CRP	C-reactive protein
-	CT	Computed tomography
-	DD	Code for wind direction
-	ECG	Electrocardiogram
-	FF	Code for wind speed
-	Fig.	Figure
-	hPa	Hectopascal
-	ICD	International classification of diseases
-	IRAD	International Registy of Aortic Dissections
-	IVUS	Intravascular ultrasound
-	LDH	Lactate dehydrogenase
-	m/s	Meters per second
-	mm	Millimeter
-	MMP	Matrix metalloproteinase
-	N	Number
-	p	p-value
-	Std.	Standard
-	WBC	White blood cells
-	WEWA	Manned weather station

ZUSAMMENFASSUNG

EINLEITUNG

Die chronobiologische Periodizität kardiovaskulärer Erkrankungen sowie der Einfluss, den meteorologische Bedingungen auf deren Inzidenz nehmen, sind insbesondere für die häufigeren Krankheitsbilder bereits nachgewiesen.

Für akute Aortendissektionen wurden ebenfalls jahreszeitliche Schwankungen beschrieben, die weitgehend denen der übrigen kardiovaskulären Erkrankungen entsprechen. Ein Einfluss meteorologischer Faktoren – insbesondere von Temperatur und Luftdruck - auf die Inzidenz akuter Aortendissektionen konnte ebenfalls mehrfach demonstriert werden, doch wurden unterschiedliche Methoden angewandt und unterschiedliche und teils widersprüchliche Ergebnisse publiziert, sodass insgesamt ein inhomogenes Bild resultiert.

Deshalb wurden retrospektiv die während des 6-jährigen Zeitraums zwischen dem 01.07.2004 und dem 31.06.2010 am Universitätsklinikum Tübingen behandelten Fälle spontaner akuter Aortendissektionen im Hinblick auf eine Korrelation mit den an den Tagen ihres Auftretens sowie definierten Zeiträumen zuvor herrschenden Witterungsbedingungen analysiert. Da bekannt ist, dass sich der Mensch an die herrschenden klimatischen Verhältnisse anpasst und davon ausgegangen werden kann, dass rapide Veränderungen meteorologischer Bedingungen am ehesten zu markanten Reaktionen führen, wurde zudem untersucht, ob den Aortendissektionen akute Veränderungen der Witterungsbedingungen vorangegangen und ob die Zeitintervalle vor dem Auftreten der Dissektionen durch eine größere Variabilität der meteorologischen Messwerte gekennzeichnet waren, als die entsprechenden Vergleichsintervalle. Darüber hinaus wurde überprüft, ob die verschiedenen Typen von Aortendissektionen in unterschiedlichem Ausmaß von den herrschenden meteorologischen Bedingungen beeinflusst werden.

Bei den untersuchten Parametern handelt es sich primär um Temperatur und Luftdruck. Weitere Einflussfaktoren wie die relative Luftfeuchtigkeit, die Niederschlags- sowie die Windverhältnisse wurden als sekundäre Parameter berücksichtigt, da davon ausgegangen wird, dass sie weniger als eigenständige Risikofaktoren für das Auftreten akuter Aortendissektionen in Frage kommen, sondern eher zum Kältestress, einem der zentralen Mechanismen, über den meteorologische Bedingungen Einfluss auf das Auftreten akuter Aortendissektionen nehmen, beitragen.

In der Literatur finden sich verschiedene Theorien dazu, wie die Inzidenz akuter kardiovaskulärer Ereignisse durch meteorologische Faktoren beeinflusst werden kann, wobei der Schwerpunkt auch hier größtenteils auf Temperatur und Luftdruck liegt:

- Temperaturbedingte Veränderungen der sympathovagalen Regulation der kardiovaskulären Funktion im Sinne einer Sympathikusaktivierung und Katecholaminausschüttung als Folge von Kältestress sind schon seit längerer Zeit gut erforscht. Auch spontane akute Aortendissektionen könnten bei Vorliegen einer prädisponierten Aortenwand durch die aus der Sympathikusaktivierung und Katecholaminausschüttung resultierenden Steigerungen des systemischen Blutdrucks begünstigt werden.

- Temperaturbedingte Veränderungen der hämorheologischen Eigenschaften sind ebenfalls umfangreich vorbeschrieben. Bei niedrigen Temperaturen werden Steigerungen der Fibrinogen- und Serumlipidspiegel, der Erythrozytenzahl sowie der Thrombozytenaggregabilität und der Aktivität verschiedener Gerinnungsfaktoren verzeichnet, woraus eine Hyperkoagulabilität und erhöhte Blutviskosität resultieren, die das Auftreten kardiovaskulärer Ereignisse begünstigen. Im Kontext akuter Aortendissektionen könnte eine erhöhte Blutviskosität über eine Steigerung der auf die Aortenwand einwirkenden Scherkräfte begünstigend wirken.

- Luftdruckbedingte Blutdruckschwankungen wurden mehrfach postuliert und könnten ebenfalls als Auslöser spontaner akuter Aortendissektionen in

Frage kommen, konnten im Gegensatz zu temperaturbedingten Blutdruckschwankungen jedoch nicht eindeutig nachgewiesen werden.

- Luftdruckbedingte Steigerungen transmuraler Druckgradienten sollen aus einer Verringerung des extravasalen Drucks bzw. des Gewebedrucks resultieren, die mit dem Absinken des Luftdrucks einhergeht, wobei ein höherer Druckgradient einer höheren Belastung der Aortenwand entsprechen und folglich deren Dissektion bei Vorliegen prädisponierender Faktoren begünstigen soll.

- Veränderungen des proteolytischen Gleichgewichts innerhalb der Aortenwand könnten ebenfalls durch Veränderungen der herrschenden Druckbelastungen ausgelöst werden. In diesem Zusammenhang werden insbesondere die Metalloproteinasen und deren Inhibitoren beschrieben, deren Gleichgewicht sich infolge geänderter Druckverhältnisse innerhalb der Aortenwand soweit verschieben könnte, dass der Abbau von Matrixkomponenten in einem solchen Ausmaß zunimmt, dass prädisponierte Abschnitte der Aortenwand dissezieren können.

DATEN

An patientenbezogenen Daten wurden das Geschlecht, das Alter zum Zeitpunkt der Dissektion, prädisponierende Faktoren, relevante Begleiterkrankungen sowie vorangegangene herzchirurgische Eingriffe oder Operationen im Bereich der Aorta dokumentiert.

An dissektionsbezogenen Daten wurden der Dissektionstyp (nach Stanford-Klassifikation) sowie das Datum, die Zeit und der Ort des ersten Auftretens von Symptomen wie auch jegliche weiteren relevanten Informationen zu den Umständen des Auftretens der Aortendissektion erfasst.

Die meteorologischen Daten wurden vom Deutschen Wetterdienst des Bundesministeriums für Verkehr, Bau und Stadtentwicklung bezogen. Verwendet wurden die Daten von neun meteorologischen Stationen, die das

Studiengebiet adäquat abdecken und jeweils komplette Datensätze mit allen benötigten Daten liefern. Diese umfassten in Stundenintervallen registrierte Werte für:

- Lufttemperatur in 0,1℃
- Luftdruck auf Stationshöhe in 0,1 hPa
- Luftfeuchtigkeit in %
- Stundenhöhe des Niederschlags in 0,1 mm
- 10-Minuten-Mittel der Windgeschwindigkeit in 0,1 m/s
- Windrichtung in 36-teiliger Windrose

STATISTISCHE AUSWERTUNG

Aus den Werten der einzelnen Stationen wurden für das gesamte Studiengebiet und die verschiedenen untersuchten Intervalle für die primären Parameter (Temperatur und Luftdruck) Minimum-, Maximum- und Mittelwerte und für die sekundären Parameter (Luftfeuchtigkeit, Niederschlags- und Windverhältnisse) Mittelwerte errechnet.

Die statistische Auswertung erfolgte unter Anwendung nichtparametrischer Methoden (Wilcoxon-Test).

ERGEBNISSE

Studienpopulation

Die Studienpopulation umfasste nach Ausschluss von 5 Patienten, für die das Datum der Aortendissektion nicht eindeutig festgestellt werden konnte, 156 Patienten (108 männlich, 48 weiblich, 122 Typ A-Dissektionen, 34 Typ B-Dissektionen). Das mittlere Alter der Patienten bei Auftreten der Aortendissektion betrug 61,48 ± 12,32 Jahre. Bei Frauen traten akute Aortendissektionen in höherem Alter als bei Männern auf. Patienten mit akuter Typ B-Dissektion waren im Mittel älter als Patienten mit akuter Typ A-

Dissektion. Eine arterielle Hypertonie war bei 66,7% der Patienten dokumentiert, vorbestehende Aortenaneurysmen bei 19,9% und ein Marfan-Syndrom bei 2,6%. 5,8% der Patienten waren an Herz und/oder Aorta voroperiert.

Auftretenshäufigkeit und Variabilität im Jahresverlauf

Für die gesamte Studienpopulation sowie die Patienten mit Typ A-Dissektion konnte die höchste Inzidenz an Aortendissektionen im März und die niedrigste im August verzeichnet werden. Typ B-Dissektionen traten am häufigsten im April und gleichermaßen selten im Januar, Juli und Oktober auf.

Eine jahreszeitliche Häufung aller akuten Aortendissektionen sowie der Typ A-Dissektionen war im Winter zu verzeichnen, während die Inzidenz im Sommer am niedrigsten war. Akute Typ B-Dissektionen zeigten die höchste Inzidenz im Frühling und waren über die übrigen Jahreszeiten hinweg etwa gleichmäßig verteilt.

Temperatur

Die Mittel-, Mindest- und Höchstwerte für das gesamte Studiengebiet zeigten für die gesamte Studienpopulation sowie für die Untergruppe der Typ A-Dissektionen insofern einen vergleichbaren Trend, als die Temperaturen an Tagen, an denen Aortendissektionen auftraten, sowie während der vorangegangenen Intervalle jeweils niedriger als während der Vergleichszeiträume an und vor Tagen ohne Auftreten von Aortendissektionen waren. Diese Ergebnisse waren großteils statistisch signifikant. Für die Untergruppe der Typ B-Dissektionen zeigten sich ebenfalls durchgehend niedrigere Mittel- und Mindestwerte, während die Temperaturhöchstwerte während einiger der untersuchten Intervalle vor Typ B-Dissektionen höher als während der Vergleichszeiträume waren. Allerdings erreichten die Ergebnisse für die Untergruppe der Typ B-Dissektionen keine statistische Signifikanz.

Die gebietsweite maximale Temperaturdifferenz als Maß für die Temperaturschwankungsbreite war an Tagen, an denen Dissektionen auftraten, sowie während der vorangegangenen Intervalle für die gesamte Studienpopulation sowie für die Untergruppe der Typ A-Dissektionen unerwarteterweise großteils niedriger als während der Vergleichszeiträume. Für die Untergruppe der Typ B-Dissektionen hingegen zeigte sich großteils eine höhere Temperaturschwankungsbreite während der den Dissektionen zugeordneten Zeiträume im Vergleich zu den Vergleichszeiträumen, wobei die Ergebnisse für die B-Dissektionen wiederum keine statistische Signifikanz erreichten, während jene für die gesamte Studienpopulation und die Typ A-Dissektionen teilweise statistisch signifikant waren.

Ein relevantes Absinken der lokalen mittleren Temperaturen während der den Dissektionen vorangegangenen Tage konnte nicht nachgewiesen werden.

Luftdruck

Die Mittel-, Minimum- und Maximumdruckwerte für das gesamte Studiengebiet zeigten für die gesamte Studienpopulation sowie die Untergruppen der Typ A- sowie der Typ B-Dissektionen weitgehend einheitliche Ergebnisse. Die Druckwerte waren an Tagen, an denen Aortendissektionen auftraten, sowie während der vorangegangenen Intervalle jeweils niedriger, als während der Vergleichszeiträume.

Die gebietsweite Schwankungsbreite der Luftdruckwerte war an Tagen, an denen Dissektionen auftraten, sowie während der vorangegangenen Intervalle für die gesamte Studienpopulation sowie für die Untergruppe der Typ A-Dissektionen erwartungsgemäß höher, als in den Vergleichszeiträumen. Für die Untergruppe der Typ B-Dissektionen hingegen zeigte sich ein gegenläufiges Ergebnis mit einer geringeren Schwankungsbreite während der den Dissektionen zugeordneten Zeiträume gegenüber den Vergleichszeiträumen.

Die Analyse der Luftdruckentwicklung während der den Aortendissektionen vorangegangenen Zeiträume ergab keine signifikanten Ergebnisse.

Luftfeuchtigkeit

Die relative Luftfeuchtigkeit war während der den Aortendissektionen zugeordneten Intervalle großteils höher, als während der Vergleichszeiträume. Ein abweichendes Ergebnis ergab sich mit geringeren Luftfeuchtigkeitswerten während der den Dissektionen zugeordneten Intervalle für die Untergruppe der Typ B-Dissektionen.

Niederschlag

Bezüglich der Niederschlagsmengen konnten weder statistisch signifikante Ergebnisse erzielt, noch ein eindeutiger Trend identifiziert werden. Dies gilt sowohl für die gesamte Studienpopulation, als auch für die Untergruppen der Typ A- und Typ B-Dissektionen.

Windgeschwindigkeit

Die Windgeschwindigkeit war während der den Aortendissektionen zugeordneten Intervalle höher, als während der Vergleichsintervalle. Vergleichbare Ergebnisse konnten auch für die Untergruppen der Typ A- und Typ B-Dissektionen festgestellt werden. Während die Ergebnisse für die gesamte Studienpopulation sowie die Typ A-Dissektionen teilweise statistisch signifikant waren, erreichten die Ergebnisse für die Typ B-Dissektionen erneut keine statistische Signifikanz.

Windrichtung

Ein Zusammenhang zwischen dem Auftreten von Aortendissektionen und der Windrichtung konnte nicht nachgewiesen werden.

DISKUSSION UND SCHLUSSFOLGERUNGEN

Eine Variabilität der Auftretenshäufigkeit von Aortendissektionen im Jahresverlauf konnte nachgewiesen werden. Insbesondere konnte eine

Häufung der Aortendissektionen während der kalten Jahreszeit demonstriert werden, was die Ergebnisse bestätigt, die auch von anderen Autoren für die Auftretenshäufigkeit von Aortendissektionen berichtet wurden.

Darüber hinaus stimmen diese Ergebnisse mit der jahreszeitlichen Varianz überein, die für verschiedene andere akute kardiovaskuläre Ereignisse nachgewiesen wurde. Auch die negative Korrelation, die die meisten Autoren zwischen akuten kardiovaskulären Ereignissen einschließlich Aortendissektionen und den herrschenden Temperatur- und Luftdruckwerten feststellen konnten, ließ sich anhand unserer Daten nachvollziehen.

Nicht bestätigen hingegen ließ sich die Hypothese einer Korrelation zwischen dem Auftreten akuter Aortendissektionen und vorangegangenen markanten Temperatur- oder Luftdruckabfällen. Allerdings konnte nachgewiesen werden, dass die maximale Luftdruckdifferenz als Ausdruck der maximalen Amplitude der Luftdruckschwankungen während der den Dissektionen zugeordneten Zeitintervalle größer war, als während der Vergleichszeiträume, was darauf schließen lässt, dass markante Luftdruckschwankungen tatsächlich Einfluss auf das Auftreten akuter Aortendissektionen nehmen könnten.

Aufgrund der Studienlage ist einerseits davon auszugehen, dass meteorologische Einflüsse sich auf das Auftreten von akuten Pathologien der Aorta einschließlich Aortendissektionen auswirken, und andererseits sind moderne diagnostische Verfahren auf breiter Basis verfügbar, um spezifisch gefährdete Patienten zu identifizieren. Deshalb wäre es denkbar, das Wissen über das erhöhte Risiko prädisponierter Patienten, in der kalten Jahreszeit eine Aortendissektion zu erleiden, auch in Therapieentscheidungen wie z.B. die zeitliche Planung elektiver aortenchirurgischer oder interventioneller Eingriffe einfließen zu lassen, Patienten durch entsprechende Dosisanpassung ihrer antihypertensiven und insbesondere ß-blockierenden Medikation gegen akute, aus einer Sympathikusaktivierung durch Kältestress resultierende Blutdruckanstiege abzuschirmen und Empfehlungen zur Vermeidung akuter Temperatur- oder Luftdruckänderungen auszusprechen.

1 INTRODUCTION

1.1 MOTIVATION AND OBJECTIVES

Chronobiological periodicity as well as the influence of meteorological conditions on the frequency of occurrence of cardiovascular disease have both been subject to and proven by extensive scientific investigation. Variations in the incidence of acute aortic syndrome have similarly received a fair amount of scientific attention and been demonstrated in large study populations.

The influence of meteorological conditions on the occurrence of acute aortic syndrome, in contrast, has so far been studied by few groups of investigators only, who additionally applied different methods and focused on different acute aortic pathologies as well as different meteorological parameters, on the whole rendering an inhomogeneous picture and reporting partly conflicting results.

The present study is therefore dedicated to examining the influence of meteorological conditions on the occurrence of acute aortic dissection in order to contribute to providing a more complete account of the biometeorological aspects of acute aortic disease.

1.2 GENERAL CONSIDERATIONS AND HYPOTHESES TO BE TESTED

When evaluating the influence of meteorological conditions on the incidence of acute aortic dissection, it is essential to keep in mind that aortic dissection is a multifactorial process that usually occurs in predisposed individuals, has already been demonstrated to be subject to chronobiological rhythmicity and can be triggered by a variety of different stimuli.

Meteorological conditions therefore represent only one factor influencing the frequency of occurrence of acute aortic dissection. In practice, they most certainly interact with a multitude of other factors. Their contribution may range from rendering the aortic walls of predisposed individuals more prone to injury during certain periods than during others to actually triggering dissection themselves by negatively influencing the forces acting on the aortic wall.

Against this background, the present study was undertaken to test the hypothesis that there exists a negative correlation between temperature and atmospheric pressure, the two meteorological parameters generally considered to exert an influence on the frequency of occurrence of acute aortic pathologies, on the one hand, and the incidence of acute aortic dissection, on the other. Further meteorological conditions such as relative air humidity, precipitation and wind were taken into account as secondary parameters contributing to cold stress rather than as relevant factors influencing the frequency of occurrence of acute aortic dissection by themselves.

Statistical evaluation was designed in such a way as to include meteorological conditions prevailing not only at the date of dissection, but also during a number of defined periods preceding the date of onset of symptoms.

This also enabled testing of a second hypothesis according to which acute aortic dissections tend to be preceded by changes in meteorological conditions, the rationale underlying this second hypothesis being that prolonged exposure of humans to particular meteorological factors is known to induce adaptive processes, while changes tend to provoke more striking responses.

Further investigating the relevance of changes in meteorological conditions, a third hypothesis assuming that the periods preceding acute aortic dissections are characterized by greater fluctuations in temperature and atmospheric pressure than periods not preceding acute aortic dissections was formulated. This hypothesis was tested by comparing the maximum amplitudes of the temperature and atmospheric pressure differences during the defined periods preceding acute aortic dissections and the maximum amplitudes during the reference periods not preceding aortic dissections.

Finally, it may be assumed that different types of acute aortic dissections are characterized by different degrees of susceptibility to meteorological factors.

Therefore, the study population was divided into subgroups according to the Stanford type of dissection, and each of the hypotheses was tested not only for the entire study population, but also for the two subgroups comprising patients with Stanford type A and type B dissections, respectively.

When interpreting the results of the present study, it is essential to keep in mind that different individuals may respond differently to meteorological influences and that the intensity of response to environmental conditions is known to be altered by parameters such as gender and patient age as well as by presence or absence of certain predisposing or risk factors, medication, level of physical activity, etc.

1.3 DESIGN

The present study is designed as a single–center retrospective investigation of all cases of spontaneous acute aortic dissection that presented at our hospital in the 6–year period from 01 July 2004 to 30 June 2010.

The study area is the area served by our hospital during this period with respect to acute aortic pathologies and defined by the geographical locations of the meteorological stations assigned to each of the cases as shown below.

1.4 COMPLIANCE WITH APPLICABLE STATUTORY AND ETHICAL REQUIREMENTS

Medical data used for the purpose of the present study were obtained strictly adhering to the principle of patient anonymity and observing our ethical obligation to maintain confidentiality as far as medical information relating to our patients is concerned. Compliance with the applicable data protection regulations was ensured. Case-related information was retrieved from our hospital’s electronic database without contacting patients or disclosing patient identity at any stage of the investigation.

2 AORTIC DISSECTION

2.1 HISTORY

Aortic dissection is a disastrous cardiovascular event that only came to be properly understood and distinguished from aortic aneurysm in the 18th and 19th centuries. [1] In literature, there seems to be a certain amount of disagreement as to who was the first to report a case of aortic dissection. The earliest description is frequently attributed to Sennertus (1650) [2], while Jean–Pierre Maunoir (1802) [3] is usually credited with having coined the term “dissection”. [4]

Some of the earliest accounts of the presenting symptoms and further fate of patients presenting with acute aortic dissection, as well as of the pathology of their aortic walls found at autopsy, impressively reflect the defining characteristics of the condition as they are still valid today. One of the most famous cases ever is that of the English King George II, who succumbed to acute aortic dissection in 1760 and was autopsied by his physician, Frank Nicholls, who rendered a detailed account of the late king’s condition in 1761, describing the essential morphologic characteristics of classic aortic dissection with pericardial tamponade:

> *“…the pericardium was found distended with a quantity of coagulated blood, nearly a pint …; the whole heart was very soon necessarily so compressed as to prevent any blood contained in the veins from being forced into the auricles; therefore, the ventricles were found absolutely void of blood…; and in the trunk of the aorta we found a transverse fissure on its inner side, about an inch and a half long, through which some blood had recently passed under its external coat and formed an elevated ecchymosis.”* [5]

Published in the same year, Giovanni Battista Morgagni’s masterpiece *“De sedibus, et causis morborum”* contains further early accounts of aortic dissection, one of them featuring *“a man who had been too much given to the exercise of tennis and the abuse of wine”* and *“in consequence of both these irregularities”* died of a dissected aneurysm. [6]

More than 3 centuries post mortem, this particular patient continues to be remembered as an early example illustrating the fatal course aortic aneurysms and dissections used to take before surgical treatment became an option. At the *Bologna Ospedale degli Incurabili* to which he was admitted in or about the year 1704, he was ordered *“to keep himself still, and to think seriously and piously of his departure from this mortal life”* which was known to *be “very near at hand, and inevitable”.* This turned out to be correct, and at dissection Morgagni found

> *“a large aneurysm, into which the anterior part of the curvature of the aorta itself being expanded, had partly consumed the upper part of the sternum, the extremities of the clavicles which lie upon it, and the neighbouring ribs … And where the bones had been consumed or affected with the caries, there not the least traces of the coats of the arteries remained: to which, in other places, a thick substance every where adhered internally, resembling a dry and lurid kind of flesh, distinguished with some whitish points; and this substance you might easily divide into many membranes, as it were, one lying upon another … [7]*

In 1826, the French physician René Théophile Hyacinthe Laënnec published a report entitled *“Anévrysme disséquant de l’aorte, chez un sujet attaqué d’hypertrophie simple du ventricule droit”* in his *“Traité de l’auscultation mediate”* on the case of a woman who suffered aortic dissection and was admitted to hospital in 1817.

Describing a combination of transient gastric symptoms accompanied by persisting neurologic pathology in the absence of chest, back or abdominal pain, this early account impressively reflects the characteristic and often misleading variety of presenting symptoms. In his autopsy report, Laënnec described a classic aortic dissection with an intimal tear and an intimal flap resulting in a double barrel aorta:

> *"La crosse de l'aorte, dilatée de manière a pouvoir contenir une pomme de moyen volume, était incrustée de quelques plaques osseuses. L'aorte descendante, à environ deux pouces de son origine, présentait intérieurement une fente transversale, occupant les deux tiers de son contour cylindrique, et intéressant seulement ses membranes interne et fibrineuse. Les bords de cette division étaient amincis, inégaux et comme déchires par endroits … au premier coup d'œil on aurait pu croire que la cavité de l'aorte était divisée par une cloison médiane. "* [8]

Thomas Bevill Peacock furnished another remarkably complete description of the condition in the 1840s [1], while Swaine and Latham became famous for the first ante-mortem diagnosis of aortic dissection, reporting the case of a 51 year old man previously known to have mitral and aortic valve regurgitation, who in 1855

> *"…. was … seized with a sudden violent pain "as though", to use his own words, "my chest was torn open from side to side by some outward force". It was instantly followed by a second "agonizing" pain, which seemed to dart from mid–sternum down the left of the spinal column … The next … occurrence was loss of power in the left inferior extremity, and very soon after in the right also. Carried into his house, for a brief interval he became bereft of consciousness; but not until after a repetition of the lacerating pain, referred, this time, not to the anterior, but to the posterior part of the thorax, from scapula to scapula.* [9]

Swaine correctly diagnosed a dissecting aneurysm. The patient, in whom a mass *"the size of a goose's egg"* had became palpable over the aortic bifurcation, died three months later after a period of initial improvement. [1]

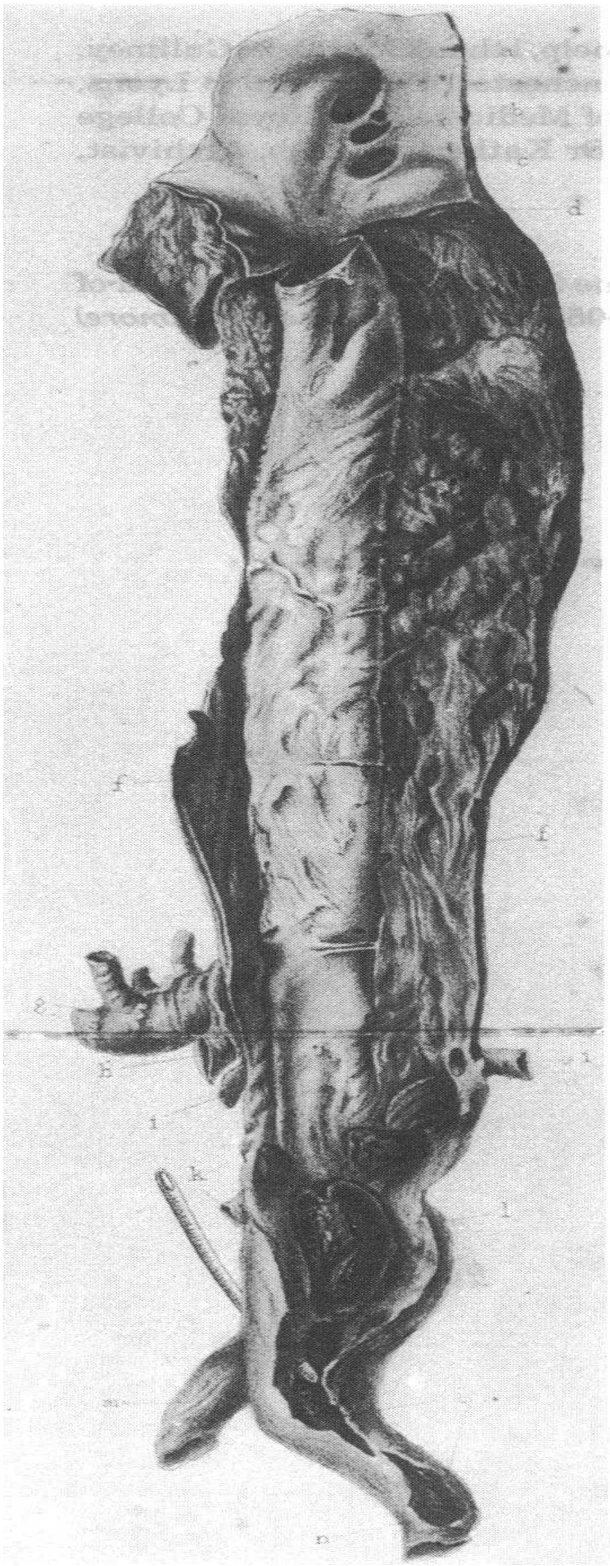

Fig 1. Dissecting aneurysm of the aorta laid open (Swaine's case, 1856), reproduced from Doyle L. Three important early case reports on dissecting aneurysm of the aorta: one each from Dublin, Paris and York. J R Soc Med 1992; 85:169-172

Overall, however, aortic dissection remained a mostly post-mortem diagnosis for quite some time thereafter. Treatment in those few cases where aortic dissection was suspected or diagnosed ante-mortem remained an extremely frustrating task for physicians, because an efficient surgical method of repair was not available and therapy in those patients in whom dissection did not take a rapidly lethal course was symptomatic only. Survival depended on whether the destructive process within the aortic wall progressed or came to a halt and on the extent to which branch vessels were occluded and malperfusion of organs or limbs present.

The earliest surgical treatment of acute aortic dissection is usually attributed to Gurin, who performed the first aortic fenestration procedure by creating a re–entrant window to decompress the true aortic lumen in order to restore iliac perfusion in a patient in 1935. [10] Similar interventions as well as a number of attempts to repair intimal as well as adventitial tears in the aortic wall were performed and published in the following years, but the outcomes reported were poor. A new milestone was not reached until 1955, when DeBakey, Cooley and Creech reported a series of patients in whom they had succeeded in closing the medial split and restoring aortic continuity. [11] [12]

On the whole, surgical options remained limited until modern technologies and, in particular, cardiopulmonary bypass were introduced, marking the beginning of the modern era of cardiac and aortic surgery. The most noteworthy names associated with the development of surgical management of aortic dissection are those of Stanley Crawford (1922–1992), Denton Cooley (b. 1920), and, especially, Michael DeBakey (1908—2008), who introduced innovative surgical procedures and defined diagnostic and therapeutic principles from the 1950's onwards. DeBakey acquired additional fame for suffering aortic dissection at the age of 97 and undergoing some of the very procedures he had devised many years before.

Since the early days of aortic surgery, modern materials and technologies have facilitated surgical procedures and offered new and increasingly interdisciplinary approaches including endovascular and hybrid procedures, thus considerably expanding the spectrum of methods available to address aortic pathology. On the whole, aortic dissection, together with its causes and risk factors, has come to be better understood but nevertheless continues to be feared as a devastating cardiovascular event frequently leaving the patient in a life–threatening condition while presenting physicians with considerable challenges.

2.2 DEFINITION AND CLASSIFICATION OF AORTIC DISSECTION

Aortic dissection results either from rupture of the intimal layer of the aortic wall with blood subsequently entering a false lumen forming between the layers of the aortic wall and separated from the true lumen by an intimal flap, or, less frequently, from a penetrating atherosclerotic ulcer or an intramural hemorrhage or hematoma. In each case, the force of the blood flow acting on the layers of the aortic wall will force these further apart, allowing the dissection to propagate in an antegrade or retrograde fashion. In case of communicating dissections, blood may flow from the true into the false lumen and vice versa through tears in the intimal flap, while non–communicating dissections are characterized by the absence of such tears. [13] [14] [15] Partial or complete thrombus formation may occur in lumens without blood flow and has recently been proposed as an essential prognostic factor. [16] [17] Rupture through the adventitia, finally, will cause severe hemorrhage frequently resulting in death from pericardial tamponade or hypovolemic shock unless immediate surgical relief is provided.

Aortic dissection may be spontaneous, traumatic or iatrogenic. Traumatic dissection results from direct or indirect trauma to the aorta, while iatrogenic dissection is most frequently caused by injuries inflicted in the course of cardiac surgery or catheter–based interventions but may also occur, for example, as a consequence of cardiopulmonary resuscitation. Classification is usually based on anatomical location and time from onset. Acute aortic dissection is defined as an event of aortic dissection diagnosed within 14 days from the onset of symptoms, whereas after a period of more than 14 days from onset, aortic dissection is referred to as chronic. [13] [14] The term “subacute” may be used to refer to aortic dissections more than two weeks but less than two months old. [4]

For classification of aortic dissections based on the respective parts of the aorta affected, several systems have been proposed of which the two outlined below are most commonly used.

According to the Stanford classification, type A dissections involve the ascending aorta, while type B dissections affect only the descending aorta distal to the origin of the left subclavian artery. [18] DeBakey et al. differentiated between type I dissections involving both the ascending and the descending aorta, type II dissections affecting only the ascending aorta, and type III dissections limited to the descending aorta. [19] [20] Subsequent authors subdivided DeBakey’s type III into types IIIa and IIIb depending on involvement of the thoracic or abdominal sections of the descending aorta, respectively. [21]

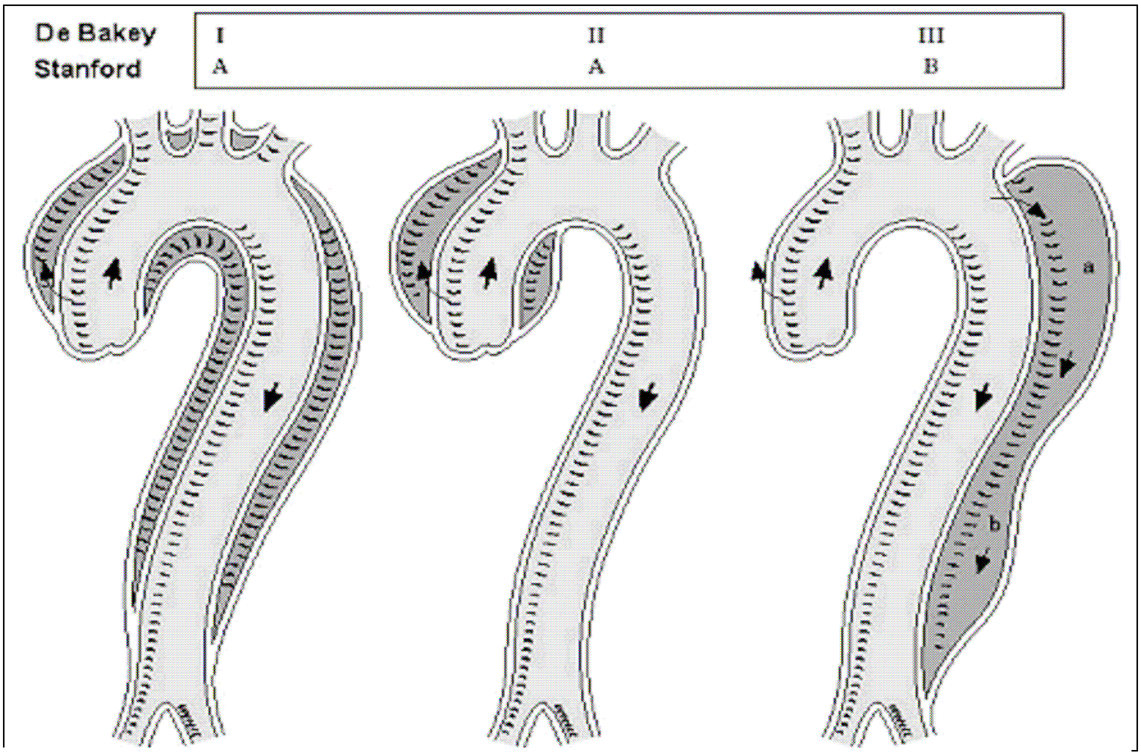

Fig. 2. DeBakey / Stanford classes, including subdivision of DeBakey III / Stanford B into thoracic and abdominal types (a and b). Reproduced from Erbel et al. Diagnosis and management of aortic dissection. Recommendations of the Task Force on Aortic Dissection. European Society of Cardiology. Eur Heart J 2001;22,1642-1681

More recently, a new classification was proposed by the European Society of Cardiology in its Task Force Report based on the assumption that intramural hemorrhage, intramural hematoma and penetrating aortic ulcers represent early stages or subtypes of aortic dissection.

Class 1 of this new classification represents classic aortic dissection with an intimal flap between the true and the false lumen and may be subdivided, depending on presence or absence of tears in the intimal flap, into communicating and non-communicating dissections. Medial disruption secondary to intramural hemorrhage or formation of an intramural hematoma is defined as class 2, and discrete/subtle dissection without hematoma showing an eccentric bulge at the tear site as class 3. Plaque ruptures leading to aortic ulceration and penetrating aortic atherosclerotic ulcers with surrounding hematoma are combined into class 4, and iatrogenic and traumatic dissections, finally, into class 5. [22]

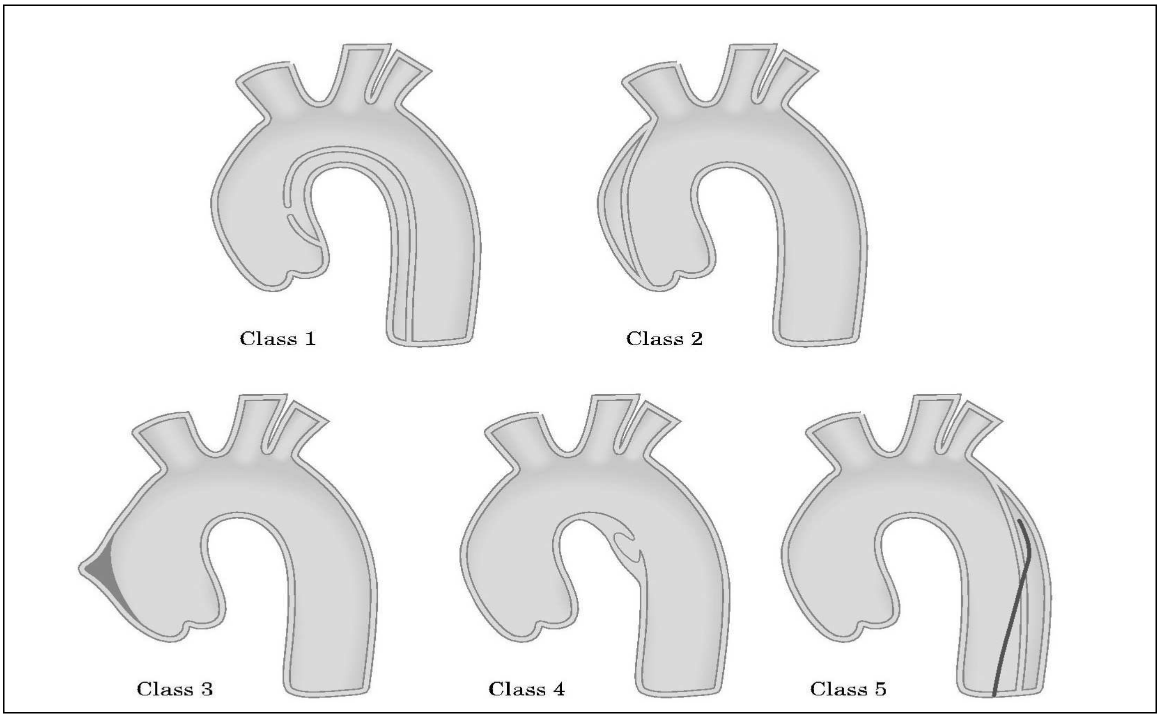

Fig. 3. Differentiation of classes 1-5 of aortic dissection. Reproduced from Svensson LG, Labib SB, Eisenhauer AC, Butterly JR. Intimal Tear Without Hematoma: An Important Variant of Aortic Dissection That Can Elude Current Imaging Techniques. Circulation 1999;99:1331-1336

The different subtypes or stages of aortic dissection may progress into classic aortic dissection and lead to contained or, in the worst case, frank aortic rupture. On the other hand, regression as well as healing may also be observed. [13]

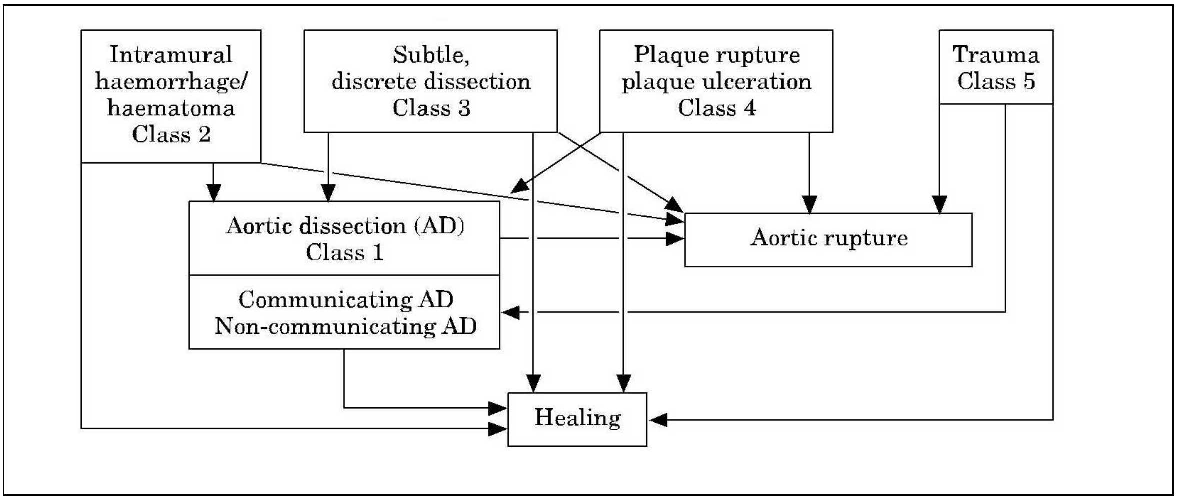

Fig. 4. Progression or regression of aortic dissection classes. Reproduced from Erbel et al. Diagnosis and management of aortic dissection. Recommendations of the Task Force on Aortic Dissection. European Society of Cardiology. Eur Heart J 2001;22,1642-1681

Acute aortic syndrome, finally, is a term that may be used to designate the entire spectrum of acute aortic pathologies including not only the various types of dissection but also other acute processes such as aneurysmal leak or rupture or traumatic injury to the aorta as may result from rapid deceleration or direct trauma. [23]

2.3 DEMOGRAPHIC ASPECTS, INCIDENCE AND FREQUENCY OF MISDIAGNOSIS OF ACUTE AORTIC DISSECTION

The incidence figures reported for aortic dissection vary greatly. The estimated incidence is usually reported to range from 5 to 30 cases per million people per year. Incidence in the USA alone is estimated to amount to at least 7000 cases per year. In large series of autopsies, the prevalence of aortic dissection ranged from 0.2 to 0.8%, lower figures being reported only rarely. Different authors additionally found men to be affected more frequently than women and indicated ratios between 2:1 and 5:1. [4] [14] [15] [24] [25] [26] [27]

Excluding aortic dissection in pregnant women, syndromic patients or individuals with heritable aortic conditions, patients presenting with spontaneous acute aortic dissection are typically hypertensive males in their sixth or seventh decades of life and usually present after acute onset of pain. Those diagnosed with Stanford type B dissection tend to be older than those affected by Stanford type A dissection, and affected females tend to be older than affected males. The mean age reported by Hagan et al. in 2000 for the 464 subjects included in the International Registry of Aortic Dissection, for example, was 63.1 ± 14.0 years. Patients diagnosed with type A dissection were reported to be younger (61.2 ± 14.1 years) than patients presenting with type B dissection (66.3 ± 13.2 years). [15] Auer et al., in a review of the incidence, natural history and impact of surgery of aortic dissection, found age peaks for type A and type B dissections at 50 to 55 years and 60 to 70 years, respectively. [26] In general, type A dissection was found to be more common than type B dissection, and spontaneous dissection more frequent than iatrogenic or traumatic dissections. The shares of acute and chronic aortic dissections in overall incidence figures are reported to be approximately two thirds and one third, respectively. [13] [14] [15][27] [28] [29] [30]

Increasing incidence figures for acute aortic pathology including aortic dissections were published over the past few decades. [25] [30] These increases may be accounted for, in addition to aging populations and increasing cardiovascular morbidity, by a combination of a higher index of suspicion, continuous further development and improvement of diagnostic tools, as well as development and increasingly stringent application of diagnostic algorithms reducing the number of cases going undiagnosed.

When reporting on the incidence of acute aortic dissections, it is additionally important to keep in mind that figures based on hospital admissions most certainly underestimate actual prevalence, as a considerable number of patients succumbing to acute aortic dissection die before admission to hospital or before diagnosis. The share of out–of-hospital deaths secondary to acute aortic dissection is estimated to amount to approximately one fifth of cases. Olsson et al., in a series covering the period from 1987 to 2002 and comprising 14,229 subjects diagnosed with thoracic aortic dissection or aneurysm, for example, reported a share of 22% of patients not reaching the hospital alive. [25] Mészáros et al. found, in a population-based longitudinal study covering a period of 27 years and a study population of 106,500 individuals, that a share of 21% of those diagnosed with aortic dissection died out of hospital. [28]

Another fairly high share of aortic dissections is reported to be misdiagnosed as myocardial infarctions, sudden cardiac deaths and the like in the absence of a post mortem examination. In a series comprising 236 cases from 1980 to 1990, Spittell et al., for example, found that a correct ante-mortem diagnosis was made in less than half of the cases. [24] More recently, lower but still significant figures were published for the share of aortic dissections initially misdiagnosed. Hansen et al. found, in a series of 66 patients in Toronto, that 39% of aortic dissections were misdiagnosed, the most frequent misdiagnosis being acute coronary syndrome. [31] These findings are confirmed by an investigation by Asouhidou et al. in Greece, who reported a share of 31% of acute aortic dissections being misdiagnosed as either myocardial or cerebral infarctions [32]. Similar results were published by Patel et al., according to whom dissection may be overlooked in up to 39% of cases [33], and by English et al. who, publishing a case report, reviewed literature and came to the conclusion that aortic dissection is a post–mortem diagnosis in at least one third of cases. [34] A similar share of one third of aortic dissections never being diagnosed was also published by Roberts et al. based on an analysis of 40 necropsy patients. [35]

2.4 PREDISPOSING FACTORS AND TRIGGERS OF SPONTANEOUS AORTIC DISSECTION

Male sex, pregnancy and old age have been identified as general risk factors of aortic dissection. The two conditions seen in the majority of patients presenting with spontaneous aortic dissection are arterial hypertension and atherosclerosis though there seems to be a certain amount of disagreement as to whether atherosclerosis itself does in fact represent an independent risk factor.

Arterial hypertension, reported to be present in up to more than 85% of patients presenting with aortic dissection, increases wall stress and weakens the aortic wall. In the long run, this can cause aneurysm formation and render the vessel wall prone to dissection while at the same time, together with hyperlipidemia, obesity, smoking and diabetes, which are usually also listed as risk factors for aortic dissection, contributing to the development of atherosclerosis. [13] [14] [15] [28]

Spontaneous aortic dissection is frequently seen to be triggered by acute surges in systemic blood pressure. This explains why it may be associated with intense physical exertion or profound emotional stress [36] [37], consumption of drugs such as cocaine or amphetamine [38] [39] [40] [41], discontinuation of antihypertensive medication or withdrawal of beta blocking agents [42], or various other stimuli, including chronobiological and meteorological factors, capable of increasing release of or enhancing response to endogenous catecholamines.

Dissection tends to occur in locally weakened sections of the aortic wall such as may result from presence of an aortic aneurysm or occurrence of a traumatic event including previous surgical or interventional procedures such as, in particular, aortic valve replacement, aortic cannulation or cross–clamping, application of an intraaortic balloon pump, coronary catheterization, or percutaneous valvuloplasty or valve implantation. Increased vulnerability may furthermore be associated with malformations such as a bicuspid aortic valve, anuloaortic ectasia, aortic coarctation or arch hypoplasia.

Additionally, the layers of the aortic wall may be rendered vulnerable by degenerative, infectious, inflammatory, immunological or toxic processes such as cystic medial necrosis, bacterial or fungal aortitis, luetic aortitis, Takayasu's aortoarteritis, giant cell arteritis, aortitis associated with rheumatoid disease, Ormond's or Behcet's disease or inflammatory abdominal aortic aneurysms. Chromosomal aberrations such as Noonan syndrome or Turner syndrome as well as heritable connective tissue disorders such as Marfan or Ehler–Danlos syndrome and familial forms of thoracic aortic aneurysms, aortic dissections, anuloaortic ectasia or bicuspid aortic valves also put patients at an increased risk of suffering acute aortic pathology including, in particular, aortic dissection. [13] [14] [15] [27] [26] [43] [44] [45] [46]

2.5 SYMPTOMS OF ACUTE AORTIC DISSECTION

Victims of acute aortic dissection who are still conscious and in an adequate state of mind upon admission to hospital frequently describe an event of acute and excruciating pain, often felt to be ripping, tearing or sharp, marking the onset of dissection. Anterior chest pain is usually reported by patients with type A dissection, while type B dissection tends to be characterized by interscapular, back or abdominal pain, and neck or jaw pain represent possible manifestations of aortic arch dissection. Additionally, pain is often described to be migratory, the location of most intense pain shifting as the dissection propagates along the aorta. Syncope is another frequent symptom and may result from severe pain, cardiac tamponade, dysrhythmia, hypovolemia, acute cardiac failure, obstruction of cerebral vessels, or activation of aortic baroreceptors.

Pain as the leading symptom may, however, be absent altogether or may be accompanied and/or followed by a wide variety of further symptoms. This is because dissections of the ascending aorta may include damage at the level of the aortic valve or the coronary arteries, while dissections of the aortic arch may affect the epiaortic vessels. Dissections of the descending aorta, finally, may propagate into or obliterate visceral, renal or spinal arteries and/or extend into the aortic bifurcation or beyond. In each case, additional damage, symptoms and complications attributable to involvement of different regions and organ systems may be encountered. Patients with spontaneous acute aortic dissection may therefore present with signs and symptoms of shock, pericardial effusion, hemopericardium or pericardial tamponade, cardiac low output or congestive heart failure secondary to acute aortic valve incompetence, myocardial ischemia/infarction, stroke-like symptoms, altered mental status, coma, spinal ischemia, acute renal failure, visceral ischemia, limb ischemia, as well as a myriad of other manifestations.

2.6 DIAGNOSIS OF ACUTE AORTIC DISSECTION

2.6.1 Physical examination

Reflecting the wide range of different manifestations of aortic dissection, physical examination may yield a multitude of different findings. An aortic regurgitant murmur or wide pulse pressure may be suggestive of aortic valve incompetence, while a pulse deficit or paradoxical pulse as well as muffled heart sounds or jugular venous distension may be indicative of increasing pericardial effusion or impending pericardial tamponade. Low blood pressure, tachycardia and reduced alertness may announce developing shock or, once again, pericardial tamponade. Acute congestive heart failure will manifest itself in the form of dyspnea and wheezing due to pulmonary edema, elevated jugular venous pressure, and other symptoms of congestion. Cerebrovascular malperfusion may produce any of the multitudes of signs of cerebral ischemia, while spinal ischemia may cause acute and severe back pain, flaccid limb weakness, paralysis, sensory loss and the like. Ischemia of the limbs will produce the findings usually associated with obliteration of peripheral arteries including coldness, paleness, numbness, pain and absence of peripheral pulses, while persistent abdominal pain and increasing lactate levels are indicative of visceral ischemia. Fever is not a common finding but can occur due to the release of pyrogenic substances from the aortic wall. [13] As the symptoms of acute aortic dissection may mimic a multitude of different conditions and physical findings may be suggestive of a variety of other diseases or may be absent altogether, further diagnostic tools need to be employed.

2.6.2 Further diagnostic methods

Chest radiography may show mediastinal widening, abnormalities of the aortic contour, a tracheal shift or distortion of the left main bronchus, displacement of intimal calcifications into the aortic lumen, or pleural effusions, while unspecific abnormalities or signs of myocardial infarction resulting from occlusion of coronary arteries in the course of dissection may be present in the 12–lead electrocardiogram. However, authors investigating larger series of patients reported absence of pathological chest radiography and/or ECG findings in a considerable share of cases. [13] [14] [15] [47] [48] [49] Contrast enhanced CT and (transesophageal) echocardiography represent further commonly used diagnostic tools, while aortography and magnetic resonance imaging are less frequently applied [50] [51]. Intravascular ultrasound (IVUS) is a catheter–based method that may be used to visualize the aortic wall from within [52], and coronary arteriography may be performed to assess coronary ostial involvement and to determine whether or not significant coronary disease requiring concomitant CABG to prevent poor outcome is present.

Laboratory testing is of minor importance as results are usually unspecific. However, an elevated WBC count or elevated CRP, LDH or bilirubin levels may be interpreted as indicative of the presence of a large wound surface or hematoma [14], while elevated concentrations of smooth muscle myosin heavy chain [53] [54], serum soluble elastin fragments [55], creatine kinase BB isozyme [56] and plasma fibrin D–dimer [57] [58] have been suggested as more specific indicators of aortic dissection.

2.7 MANAGEMENT OF ACUTE AORTIC DISSECTION

2.7.1 Management of acute Stanford type A dissection

Patients presenting with acute Stanford type A dissection are mostly considered to require emergent surgical repair. The balance between surgical risk and the hazard of aortic rupture and the disastrous consequences resulting therefrom usually speaks in favor of surgery. In a small minority of cases, however, surgery is not performed due to advanced age, excessive frailty or a forbiddingly high level of comorbidity resulting in unacceptable surgical risk, patient refusal or death before surgery. In some cases, surgery must be delayed, for example, when there is concern that administration of heparin for cardiopulmonary bypass will result in serious cerebral or other bleeding complications.

Recently, some of the novel approaches offered by the endovascular techniques originally devised to address pathologies of the descending aorta have also been evaluated as treatment options for the ascending aorta and the aortic arch including acute type A dissection. Moreover, medical therapy is coming to be discussed as an alternative to immediate surgical or interventional therapy in hemodynamically stable, asymptomatic patients with acute type A dissection. The existence of chronic type A dissections, after all, demonstrates that acute type A dissection may be survived and take a benign course in patients who do not succumb to dissection during the acute period. Consequently, it may be assumed that certain patients might, in fact, not need to be exposed to the inherent risks of emergent therapy, the notion of avoiding the adverse effects of cardiopulmonary bypass and the bleeding complications frequently associated with emergent aortic procedures being additionally intriguing. [59] [60] [61] [62]

The majority of patients presenting with acute type A dissection, however, still undergo emergent surgery. The aim of surgical therapy primarily consists in preventing the fatal consequences of aortic rupture, i.e. hypovolemic shock or pericardial tamponade, or of cardiac low output secondary to severe aortic regurgitation or myocardial infarction in the case of involvement of coronary arteries.

Surgical therapy in principle consists of removing the section of the aortic wall containing the primary intimal tear(s). This is usually achieved by replacing the ascending aorta using either a tubular aortic prosthesis with or without concomitant aortic valve repair or a composite graft with a mechanical or biological aortic valve prosthesis attached to it so as to restore aortic valve competence and redirect the blood flow into the true lumen. Depending on the extent of the damage and the intraoperative findings, the surgical procedure may additionally include implantation of coronary arteries into the graft, CABG, arch repair, partial or total arch replacement, interventions at the level of the epiaortic vessels including debranching, as well as a variety of other adjunct procedures recently also including endovascular techniques. [13] [14] [23] [26] [33] [63] [64] [65]

Routinely performed during cardioplegic cardiac arrest on cardiopulmonary bypass, surgical treatment of acute type A dissection may additionally involve different levels of hypothermia, different cannulation methods, different methods of selective cerebral perfusion or even total circulatory arrest.

In summary, there exists a considerable variety of surgical procedures that may be applied. These are supplemented by increasingly refined and well-tested endovascular methods so that the treatment of acute Stanford type A dissection is therefore turning into an interdisciplinary rather than a purely surgical task. There is a variety of surgical, hybrid and endovascular approaches to choose from that can be individualized on a patient-to-patient basis. They may be applied to address any portion of the aorta as well as its branch vessels and can implemented in the form of one-stage or multiple-stage procedures as deemed to be most favorable under the circumstances given in each individual case.

2.7.2 Management of acute Stanford type B dissection

In contrast to Stanford type A dissection, where the necessity of emergent surgical treatment (with or without concomitant or subsequent endovascular intervention) has largely been undisputed until recently and timely surgical therapy has generally been shown to improve outcome, acute Stanford type B dissections frequently do not require surgical or interventional treatment. Instead, a medical approach is recommended where the condition of the patient is sufficiently stable, as type B dissections are known to frequently take a favorable natural course by developing into chronic forms.

There is wide consensus that open surgical therapy, known to be associated with considerable morbidity and mortality rates, is only indicated to prevent life–threatening complications or where other treatment options are not feasible or have failed. According to a set of criteria stipulated by the Task Force on Aortic Dissection of the European Society of Cardiology in 2001, surgery in patients with acute type B dissections is only required in the case of aortic rupture or impending aortic rupture, persistent, intractable pain or a rapidly expanding aortic diameter. Dissection in a previously aneurysmatic aorta and impairment of the blood flow to an organ or limb were listed as further possible surgical emergencies. [13]

Confirmed by a vast majority of authors at the time of their publication [14] [23] [26] [66], these criteria have undergone a process of re-evaluation in order to accommodate for endovascular repair techniques. These were first described by Parodi et al. [67] and Volodos et al. [68] two decades ago and have meanwhile evolved into viable and routinely applied options supplementing medical treatment and open surgical therapy of Stanford type B dissections. Encouraging results with lower mortality and complication rates for endovascular repair than for open surgery published by growing numbers of authors have led to a major paradigm shift as far as the treatment algorithms for Stanford type B dissections are concerned. A significant body of evidence currently speaks in favor of endovascular repair as a therapy offering safety as well as efficacy for patients with type B dissections amenable to endovascular techniques. [69] [70] [71] [72]

2.8 MORTALITY

Acute aortic dissection is still associated with high overall as well as in–hospital mortality rates. This applies, in particular, to acute type A dissection, which according to a common rule of thumb carries a mortality of 1-2 % per hour unless emergent surgical treatment is provided. This is more or less confirmed by a number of reviews where highest in–hospital mortality rates amounting to nearly 60% are reported for patients with type A dissection not receiving surgery. In–hospital mortality rates of patients with type A dissection undergoing surgical treatment are lower but vary greatly depending on the location and extent of dissection and involvement of branch vessels as well as the patient's pre–operative condition, age and level of co–morbidity. The lowest in–hospital mortality rates are usually reported for patients with type B dissection receiving medical treatment, while in–hospital mortality of patients undergoing surgical therapy of type B dissection is reported to be considerably higher, in particular in patients with renal or visceral ischemia or peripheral vascular ischemic complications. [13] [14] [15] [23] [26]

The investigators of the International Registry of Aortic Dissections reported an overall in–hospital mortality of 25.1% for patients undergoing surgery for type A dissections, listing a history of previous aortic valve replacement, migratory chest pain, hypotension (as a sign of shock), preoperative tamponade and limb ischemia as independent predictors of operative mortality. The overall in–hospital mortality indicated by the IRAD for patients requiring surgery for type B dissections authors is 29.3%. Surgical mortality in this patient group was found to be associated with preoperative coma or altered consciousness, partial thrombosis of the false lumen, evidence of periaortic hematoma, an excessive diameter of the descending aorta, right ventricular dysfunction at surgery, and shortness of the interval between the onset of symptoms and surgery. Age >70 years and preoperative shock/hypotension were listed as independent predictors of surgical mortality. [66] [73]

3 CHRONOBIOLOGY AND BIOMETEOROLOGY

3.1 DEFINITIONS

3.1.1 Chronobiology

Chronobiology is defined as the science of investigating and objectively quantifying phenomena and mechanisms of the biological time structure including the rhythmic manifestations of life. [74] Medical chronobiology, as a subspecialty, correspondingly focuses on understanding how biological rhythms influence the occurrence and severity of manifestation of disease, how rhythmicity or periodicity of medical phenomena can be integrated into predictive models, or how adjustment to natural rhythms can contribute to prevention or enhance therapy. On the whole, the evolvement of terms such as “chronopathology”, “chronotherapy”, “chronodiagnostics”, “chronopharmaceutics”, “chronoepidemiology”, “chronorisk”, and many more illustrates a high degree of awareness of the fact that there is a time–related dimension to many aspects of modern medicine and that a transition has occurred from a static to a more dynamic concept of health, disease and treatment. [75]

3.1.2 Biometeorology

Biometeorology represents an interdisciplinary science investigating the interactions between atmospheric processes and living organisms. The most important question that biometeorology answers is how weather and climate impact living creatures. Biometeorology is, in other words, concerned with describing and understanding the effect of weather and climate on living organisms and their activities and condition. [76]

Medical biometeorology can therefore be applied to investigate phenomena such as fluctuations in the frequency of occurrence or severity of disease that are not or insufficiently explained by other factors such as biorhythmicity and for which variations in meteorological conditions are suspected to be responsible or, at least, co–responsible.

3.2 HISTORY

Chronobiology and biometeorology are fields of investigation that have evolved, though not formally designated as such, since ancient times and refer not only to human beings, but to all manifestations of life.

Recorded recognition of biological rhythms in plants and animals, for example, dates back to at least 5000 B.C. Rhythmic variations in the frequency of occurrence of certain conditions, diseases and death were observed at various times throughout history, and early medicine in different parts of the world explicitly encompassed the notion of temporal patterns of health and disease. [77] [78]

The recognition that environmental factors in the form of the weather influence health and disease goes back to the very beginnings of mankind. The conceptions of the nature of these influences varied greatly over the centuries, ranging from the superstitious beliefs and weather gods of early civilizations to the rational explanations modern science is able to furnish.

An essential role in the development of biometeorology and chronobiology is attributed to the Greek philosophers. Eager to disclose the secrets of nature and life, they investigated the relationship between health and disease, on the on hand, and the natural environment, on the other.

They came to the conclusion that the human body is not an entity in itself but that its functioning is inseparable from the natural environment. Therefore, they not only postulated that the environment must be considered in all matters of health and disease but also were the first to systematically describe the way the atmosphere and its changes affect the functioning of the human body. [79]

The probably most famous early commitment to the influence of environmental and meteorological conditions on human health was laid down by the Greek physician Hippocrates (circa 460-375 BC) who has come to be thought of as the very Father of Medicine.

In his famous treatise “On Airs, Waters, and Places”, he wrote:

> *Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces for they are not all alike, but differ much from themselves in regard to their changes. Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality* … *And in particular, as the season and the year advances, he can tell what epidemic diseases will attack the city, either in summer or in winter, and what each individual will be in danger of experiencing from the change … And if it shall be thought that these things belong rather to meteorology, it will be admitted, on second thoughts, that astronomy contributes not a little, but a very great deal, indeed, to medicine.* [80]

In his humoral theory, Hippocrates similarly observed what may be understood as a correlation between the onset and course of illnesses, on the one hand, and the seasons of the year and the prevailing meteorological conditions, on the other, linking four humors (blood, yellow bile, black bile and phlegm) with the four seasons and four pairs of qualities (warm and moist, warm and dry, cold and dry, cold and moist). His theories lived on and were subsequently adopted and refined by influential scholars in many countries so that the Hippocratic ideas influenced the practice of medicine over a considerable period of time.

Later, resistance to traditional philosophy and science began to grow, and by the end of the sixteenth century, the connection between meteorology and medicine was nearly forgotten. Progress in medicine and the natural sciences occurred at an ever faster pace over the next two centuries, and with increasing knowledge available, scholars once again became interested in the relationship between environmental conditions and disease. In 1777, the Dutch Academy of Science offered a prize for the best essay on the subject of the possible influence of the weather on the occurrence of diseases and stimulated interest in the subject, as did the Royal Academy in England and the Societas Meteorologica Palatina in Germany. [79]

Additionally, scholars also began to look for scientific explanations for the chronobiological phenomena that had been observed and described for centuries, and Jean–Jacque d'Ortous de Mairan's discovery that the movement of plant leaves follows a circadian rhythm in 1729 finally marked the advent of modern chronobiology. [81] Nearly 100 years later, the doctoral thesis of the French pharmacist Julien Joseph Virey, published in 1814 under the title "*Ephémérides de la vie humaine, ou recherches sur la révolution journalière, et la périodicité de ses phénomènes dans la santé et les maladies"*, became another milestone in the development of chronobiology. Dedicated to biological rhythms, Virey's thesis demonstrated that human mortality exhibits rhythmicity and earned Virey the title of the father of modern chronobiology. [82] [83]

Alexander von Humboldt (1769-1859) recognized that "*climate comprises all atmospheric changes which clearly excite our organs*" and set another milestone with his study "*Kosmos"*, as did Hoffmann (1746), Finke (1795) and Schnurren (1813) by implementing the first statistical studies on the relation of diseases to particular climates. Hufeland (1782-1836), Carus (1789-1869), Schönlein (1793-1864), Wunderlich (1815-1878), Ackermann (1810-1873) and Von Pettenkofer (1818-1901) further contributed to the development of biometeorology by publishing works on the relationship between weather and morbidity and the influence of weather and climate on the organism. [79]

The formal establishment of biometeorology as a scientific discipline dates back to the early 1950s, when groups of scientists in America and Europe became interested in combining biology and meteorology, which resulted in the establishment of the International Society of Biometeorology. [84]

Since these early beginnings, a vast body of literature has been published on chronobiology and biometeorology. Both have established themselves as highly complex and rapidly developing scientific disciplines in their own right representing, as a consequence of the multitude of different manifestations of life characterized by chronobiological rhythmicity or subject to meteorological influence, interdisciplinary fields of investigation that also and importantly interact with medicine.

Chronobiological investigations were thus conducted with respect to many of the most frequent pathological conditions and have shown periodicities with peak rates at different times of the day or of the year for many diseases.

Biometeorological investigations, on the other hand, were designed to shed light on possible connections between various illnesses and weather conditions such as temperature, atmospheric pressure, air humidity, or variations thereof, and succeeded in establishing, beyond a doubt, clear and statistically significant correlations between meteorological influences and various pathologies.

3.3 CHRONOBIOLOGICAL AND BIOMETEOROLOGICAL ASPECTS OF CARDIOVASCULAR DISEASE

Today, a large body of evidence substantiates that cardiovascular events do not occur randomly but are subject to chronobiological periodicity, and that a time-related dimension must also be taken into account as far as risk, prevention and therapy of cardiovascular disease are concerned. [85] [86] [87] [88] [89] [90] [91]

There has, for example, been extensive research into the chronobiological aspects of transient myocardial ischemia [92] [93], myocardial infarction [94] [95] [96] [97], sudden cardiac death [98] [99] [100] [101] [102], pulmonary thromboembolism [103] [104] [105] [106], cerebral hemorrhage and infarction [107] [108] [109], various arrhythmias and heart blocks [110] [111] [112] and even a number of acute cardiovascular conditions of more recent interest such as tako–tsubo cardiomyopathy [113] [114]. Overall, it has been shown that acute cardiovascular events follow a circadian pattern characterized by a marked morning peak and a circannual pattern essentially showing a winter peak and a summer trough. Only few authors reported results differing from these common findings or were unable to establish statistically significant circadian, weekly, monthly or circannual periodicity at all in their respective study populations.

In addition to chronobiological rhythmicity, an impact of meteorological conditions on cardiovascular disease has been demonstrated beyond a doubt, a considerable body of literature clearly demonstrating correlations between weather conditions and the occurrence of, for example, acute episodes of ischemic heart disease, myocardial infarction, cerebral infarction and thromboembolic events. [115] [116] [117] [118] [119] [120] [121] [122]

3.4 CHRONOBIOLOGICAL AND METEOROLOGICAL ASPECTS OF ACUTE AORTIC PATHOLOGIES

Acute aortic syndrome, representing one of the less frequent acute cardiovascular events, has received a fair amount of attention with respect to its chronobiological aspects. Most authors suggest a circadian pattern resembling that of the other cardiovascular diseases with a peak in the morning and, according to some, an additional peak in the evening. [123] [124] [125] [126] [127] [128] [129]

As far as circannual variation in the occurrence of acute pathologies of both the ascending and the descending aorta is concerned, a number of studies have yielded a certain variety of findings, with peaks most frequently being reported to occur during the winter season. However, some authors also suggested peaks during other seasons or identified different peaks for different types of acute aortic pathologies or for conditions affecting different sections of the aorta or reported absence of statistically significant peaks altogether. [130] [131] [132] [133] [134] [135] [136]

Fewer projects were dedicated to investigating the influence of meteorological conditions on acute aortic pathologies. Nevertheless, a number of investigators studied possible correlations between meteorological conditions and the onset of acute aortic conditions, mostly focusing on temperature and atmospheric pressure. The results they report show a marked degree of variation, overall suggesting that the incidence of acute aortic pathologies does indeed correlate with changes in meteorological conditions while only a minority of authors were not able to establish such associations. [137] [138] [139] [140] [141] [142] [143]

3.5 PATHOMECHANISMS SUGGESTED TO EXPLAIN THE INFLUENCE OF METEOROLOGICAL CONDITIONS ON CARDIOVASCULAR DISEASE

Once a correlation between meteorological conditions and the frequency of occurrence of cardiovascular pathologies had been established, investigators began to explore how changes in meteorological conditions could possibly trigger cardiovascular events. Although the influence of meteorological conditions on cardiovascular events has not yet been fully elucidated, important advances have been made in that a number of pathomechanisms were suggested which may also be useful in explaining the impact of meteorological influences on the frequency of occurrence of acute aortic dissection.

3.5.1 Temperature–related variation of the sympathovagal balance of cardiovascular regulation

Today, there is a substantial body of literature describing a shift of the sympathovagal balance towards sympathetic activity in the morning as well as during the cold season. In the morning, it is attributed, in addition to endogenous biorhythmicity, to the effects of awakening, assuming the upright position and starting daily activities. In the cold season, it is mainly understood as a consequence of exposure to cold stress. [144] [145] [146] [147] [148] [149]

Activation of the sympathetic nervous system and the consecutive surge in endogenous catecholamine levels are known to cause an increase in heart rate, vascular tone and blood pressure, thus increasing cardiac work, oxygen consumption and myocardial stress and, on the whole, the likelihood of occurrence of acute cardiovascular events.

In the context of acute aortic dissection, this particular pathomechanism is relevant in that surges in blood pressure increase both the shear forces and the expansive forces acting on the aortic wall. In combination, these forces may render vulnerable sections of the aortic wall prone to injury.

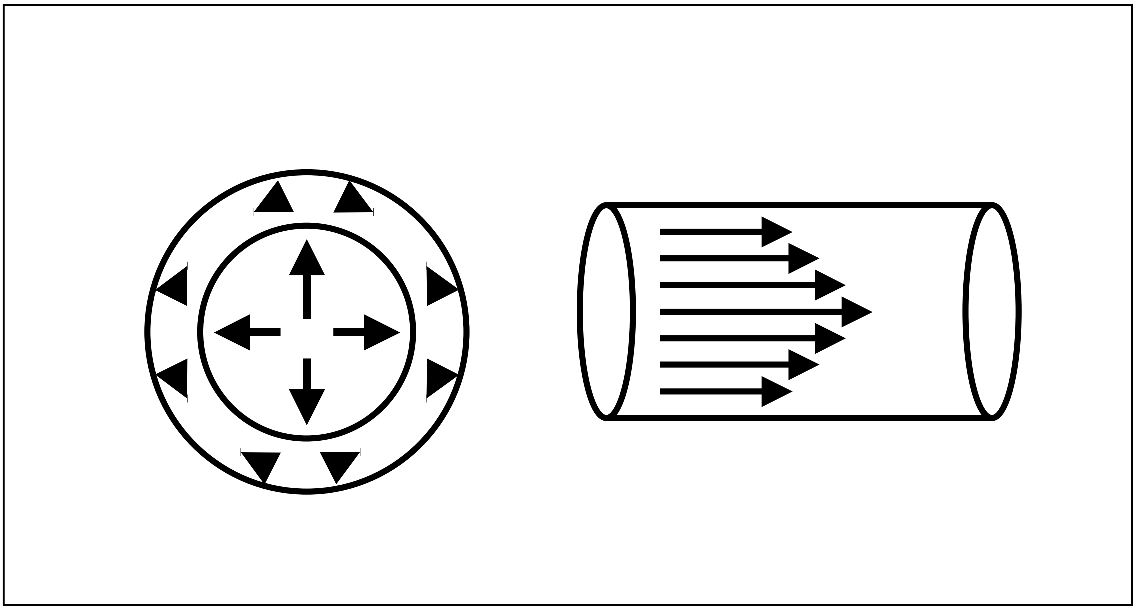

Fig. 5. Expansive forces and shear forces acting on the aortic wall

Interestingly, aging has been shown to modify the adverse cardiovascular responses to cold stress. The effect of cooling was found to be more pronounced in older than in younger adults, the augmented systolic blood pressure elevations in older subjects being explained by greater stiffness of their central arteries. [150]

Several authors additionally postulated that arterial stiffness increases not only with age, but also during cold stress and that the cold–induced surge in blood pressure is therefore greater in central than in peripheral arteries. [151] This means that cold–induced surges in systolic blood pressure in the aorta may be higher than one might expect on the basis of peripheral blood pressure measurements. Consequently, the stress on the aortic wall that is caused by surges in blood pressure occurring in response to cold stress and the risk of injury resulting from temperature changes may very well be underestimated.

Several groups of investigators furthermore demonstrated occurrence of adaptive processes, which may explain why increases in systolic blood pressure in response to lower temperatures were found to be less pronounced in colder than in warmer countries. It also explains why studies conducted in areas with higher long-term mean temperatures more frequently report detrimental effects of temperature drops than similar projects implemented in colder regions. [120] [152] [153] [154]

3.5.2 Temperature–related variation of hemorheologic properties

Temperature–related variations in hemorheologic properties are also well–recognized and largely undisputed. Increases in coagulability and blood viscosity caused by hemoconcentration and elevated fibrinogen and serum lipid levels, erythrocyte count, platelet aggregability and coagulation factor activity have all been reported to occur as a consequence of exposure to low temperatures and to contribute to a higher incidence of cardiovascular events during the cold season. [155] [156] [157] [158] [159] [160] [161]

In connection with acute aortic dissection, the increase in viscosity, with hypercoagulability contributing to it, is of interest in that higher viscosity augments the shear stress acting on vessel walls. Shear stress, in contrast to the expansive force exerted by blood pressure, represents the tangential force of the flowing blood that acts on the innermost layer of the arterial wall and may therefore be associated with lacerations resulting in dissection. [162] [163] [164]

3.5.3 Atmospheric pressure-related variation of blood pressure

In contrast to the effect of temperature on blood pressure, which has been extensively studied and conclusively proven, there is still a considerable degree of uncertainty as to whether or not atmospheric pressure is capable of exerting a relevant influence on blood pressure independently of concomitant temperature changes.

Jehn et al. studied the effect of atmospheric pressure on blood pressure and observed increasing atmospheric pressure to be associated with a slight decrease in 24h and daytime blood pressure variability as well as a slight increase in nighttime blood pressure variability. However, they were not able to report statistically significant results, which they partly attributed to the fact that there was little variability in their barometric pressure data so that a significant correlation was difficult to establish. [165]

Similarly, Weinbacher et al., reporting a negative association between atmospheric pressure and blood pressure in non–responders to antihypertensive treatment, were only able to report a weak correlation, their study being limited by a small sample size. [166]

Okumiya et al. studied a larger population of 406 subjects and reported that 42.1% of the subjects investigated showed a significant correlation between atmospheric pressure and systemic blood pressure. However, the correlation was positive in approximately half of the subjects found to respond to atmospheric pressure, and negative in the remaining half. [167]

Therefore, the question whether or not and how exactly blood pressure is influenced by changes in atmospheric pressure must be considered to remain an issue for future research.

3.5.4 Atmospheric pressure–related variation of transmural pressure gradients

The transmural stress a blood vessel is exposed to depends on the pressure gradient across the vessel wall, which results from the difference between intraluminal pressure (blood pressure) and extravascular pressure.

As the extravascular pressure varies with atmospheric pressure, it has been hypothesized that not only an increase in blood pressure, but also a drop in atmospheric pressure resulting in lower extravascular pressure may increase the transmural pressure gradient and, consequently, the transmural stress acting on the vessel wall, thus rendering vulnerable vessel walls prone to injury. [138]

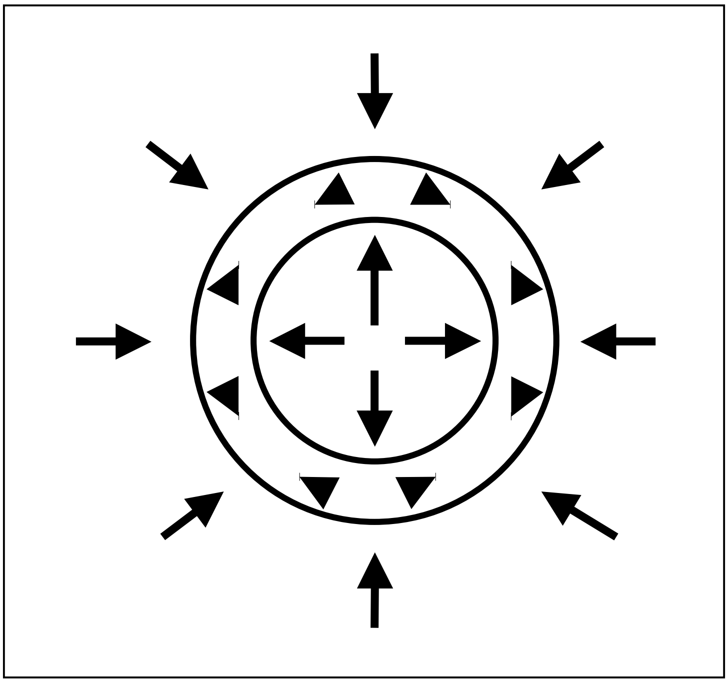

Fig.6. Blood pressure and extravascular pressure resulting in the net expansive force acting on the aortic wall

3.5.5 Atmospheric pressure-related variation of arterial blood gas concentrations

Several groups of investigators recently pointed out, in a number of studies evaluating the role of atmospheric pressure-related changes with regard to the incidence of acute aortic pathologies and quoting a study by Burnett et al. [168], that arterial blood gas concentrations currently represent the only physiological parameter conclusively proven to be positively associated with atmospheric pressure. However, they were not able to furnish an explanation as to how reduced arterial oxygen tension resulting from drops in atmospheric pressure may contribute to increasing the incidence of acute aortic pathologies. [138] [139] [141]

3.5.6 Modification of the proteolytic balance within the arterial wall induced by changes in meteorological conditions

A group of authors, investigating aortic aneurysms and pointing out that aneurysmal rupture in their study group was preceded by atmospheric pressure changes within the 24-hour period preceding the acute event, recently hypothesized that altered pressure patterns acting on the aortic wall as a consequence of drops in atmospheric pressure may activate lytic factors. They pointed out that a number of previous studies demonstrated that changes in atmospheric pressure and/or mechanical stress may indeed modify the release of certain substances from or the expression of certain genes within vascular wall cells, thus exerting an adverse effect on the proteolytic balance within the aortic wall. [138]

In this context, a special role is usually attributed to the matrix metalloproteinases (MMP), a group of proteolytic enzymes associated with degradation of the extracellular matrix known to play a significant role in the development of aortic aneurysms as well as a variety of other pathological processes.

This may also be relevant with a view to aortic dissection, as elevated levels of MMP activity have been shown to be present in tissue samples of acutely dissected aortic wall. The secretion and/or activity of the MMPs and their inhibitors have moreover been demonstrated to be modified by a variety of different factors including mechanical stretch and shear stress, and have additionally been found capable of changing acutely in response to stress factors. [169] [170] [171] [172]

Therefore, it may be worth while to examine whether or not changes in meteorological conditions are capable of changing pressure patterns within the aortic wall to such a degree that the balance between the MMPs and their inhibitors is shifted until degradation of extracellular matrix components occurs and the strength of previously weakened sections of the aortic wall decreases beyond a critical threshold.

Similarly, the effect of meteorological changes on other factors involved in maintaining the proteolytic balance within and the integrity of the aortic wall is still largely unknown and may warrant further investigation.

4 METHODS

Accessing the electronic database of our hospital, all patients presenting with aortic dissections in the 6-year period from 01 July 2004 to 30 June 2010 were identified on the basis of the respective ICD codes:

- I71.00 Dissection of aorta, unspecified site, without mention of rupture
- I71.01 Dissection of aorta, thoracic, without mention of rupture
- I71.02 Dissection of aorta, abdominal, without mention of rupture
- I71.03 Dissection of aorta, thoracoabdominal, without mention of rupture
- I71.04 Dissection of aorta, unspecified site, ruptured
- I71.05 Dissection of aorta, thoracic, ruptured
- I71.06 Dissection of aorta, abdominal, ruptured
- I71.07 Dissection of aorta, thoracoabdominal, ruptured

All cases containing any of the ICD codes above were reviewed. Cases were only included if a confirmed diagnosis of acute aortic type A or type B dissection was present, i.e. if acute aortic dissection had been established beyond a doubt either surgically, or on the basis of diagnostic imaging (usually contrast-enhanced CT), or by means of a post-mortem examination.

Diagnostic measures performed at external hospitals prior to referral to our clinic were accepted as equal where documentation of findings was considered to be sufficiently detailed and reliable and/or where imaging studies had been made available.

Chronic, iatrogenic and traumatic dissections as well as a number of cases found to be miscoded were excluded. For the remaining cases, patient-related, dissection-related and meteorological data were obtained as described below.

4.1 PATIENT-RELATED DATA

For each patient, the following data were retrieved, complying with the applicable data protection regulations and strictly observing our ethical obligation to maintain confidentiality and patient anonymity:

- gender
- age at onset of dissection
- predisposing factors
- relevant concomitant disease
- history of previous cardiac or aortic surgery

4.2 DISSECTION-RELATED DATA

For each incidence of dissection, the following information was retrieved:

- type of dissection
- date of onset of symptoms, if available
- time of onset of symptoms, if available
- place of onset of symptoms, i.e. the patient's place of residence or any other place of onset specified in the patient records
- any relevant further information such as circumstances of or activity at the time of onset of symptoms

4.2.1 Type of dissection

The type of dissection was determined on the basis of diagnostic imaging, intraoperative findings and/or post mortem examination applying the Stanford method of classification.

4.2.2 Date of onset

Defined as the date when acute symptoms occurred for the first time as reported by the patient, the patient's relatives, witnesses to the incident or the referring physician, the date of onset was indicated in the medical records in the majority of the cases. A number of cases where the date of onset was not explicitly stated or not sufficiently clear because patients, relatives, witnesses or referring physicians were not able or failed to indicate the date of onset, for example because dissection was painless, were excluded.

4.2.3 Time of onset

Information as to the time of onset of symptoms was indicated in a fairly large share of the cases reviewed. However, a precise hour of the day was stated in a minority of cases only, while the remaining medical records contained accounts too vague to be used for statistical evaluation purposes.

4.2.4 Place of onset

Assuming that people's daily activities usually occur within a radius from their homes sufficiently limited to be covered by the nearest meteorological station, each patient's place of residence was, in the absence of information to the contrary, defined as the geographic reference point on the basis of which each case was assigned to the nearest meteorological station so as to define the study area and to determine area-wide values.

In those cases where patients suffered dissection at a relevant distance from their respective places of residence, the place of onset was recorded as indicated by the patient, the patient's relatives, witnesses to the acute onset of dissection or the referring physician and used for reference purposes.

4.3 METEOROLOGICAL DATA

Meteorological information was obtained from the German Meteorological Service (Deutscher Wetterdienst), which is the official meteorological institution operated by the German Federal Ministry of Transport, Building and Urban Affairs and provides meteorological data for scientific as well as commercial applications from an extensive network of meteorological stations.

The network of the German Meteorological Service comprises different types of meteorological installations ranging from weather stations manned 24 hours a day and providing full data records including information on the type and amount of precipitation, the speed and direction of wind, atmospheric pressure as well as maximum, minimum and mean daily temperature values, to unmanned recording facilities providing only some of the parameters needed for the purposes of the present study.

The geographic reference points defined as indicated above are covered by the nine meteorological stations indicated below, which each supply a full set of meteorological data:

- Station 10727 Karlsruhe (until 2008)
- Station 10731 Rheinstetten (from 2008 onward)
- Station 10736 Muehlacker
- Station 10738 Stuttgart-Echterdingen
- Station 10742 Oehringen
- Station 10815 Freudenstadt
- Station 10818 Klippeneck
- Station 10838 Ulm
- Station 10929 Konstanz

A number of further meteorological facilities suggested by the German Meteorological Service for our project as they are also located within the study area had to be excluded because their data records do not contain full information. Their data records lacked, in particular, atmospheric pressure readings, which are, however, essential for the purpose of the present study, because atmospheric pressure is specifically investigated as one of the two primary meteorological parameters assumed to exert an influence on the occurrence of acute aortic dissection.

For each patient, the meteorological station located nearest to the respective geographic reference point was determined and assigned to the case. A rough calculation of the mean distances between the geographic reference points and the respective meteorological stations assigned to them performed for orientation purposes showed that the mean distance between each geographic reference point and the respective meteorological station assigned to it is 25±10 km. Therefore, it can be assumed that meteorological conditions within the study area are adequately reflected.

Cases were assigned to the meteorological stations as shown below:

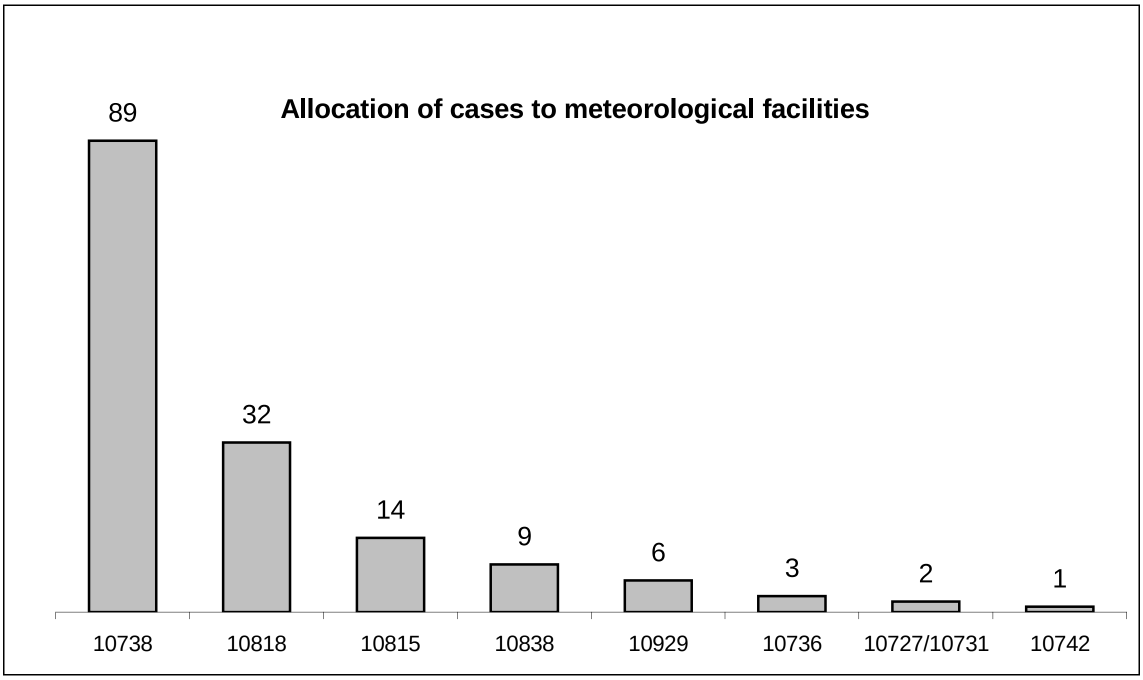

Fig. 7. Allocation of cases to meteorological stations

As shown in Fig. 8 below, the University Hospital of Tuebingen is located fairly in the center of the study area roughly delineated by drawing connecting lines between eight of the meteorological stations. The remaining station not included in the contour, Stuttgart–Echterdingen (10738), is located in an eccentric position within the study area, the latter representing the region served by our department with respect to severe aortic pathologies.

The meteorological station of Stuttgart–Echterdingen (10738) additionally plays a special role in that more than half of all cases of acute aortic dissection (57%) that occurred during the study period were allocated to it. This is because this particular station serves Stuttgart and its surroundings, which together represent the most densely populated zone of the study area from which the largest share of patients with acute aortic dissections are referred to our hospital. The meteorological station of Karlsruhe (10727) was put out of operation and replaced by a facility located at Rheinstetten nearby (10731) in 2008.

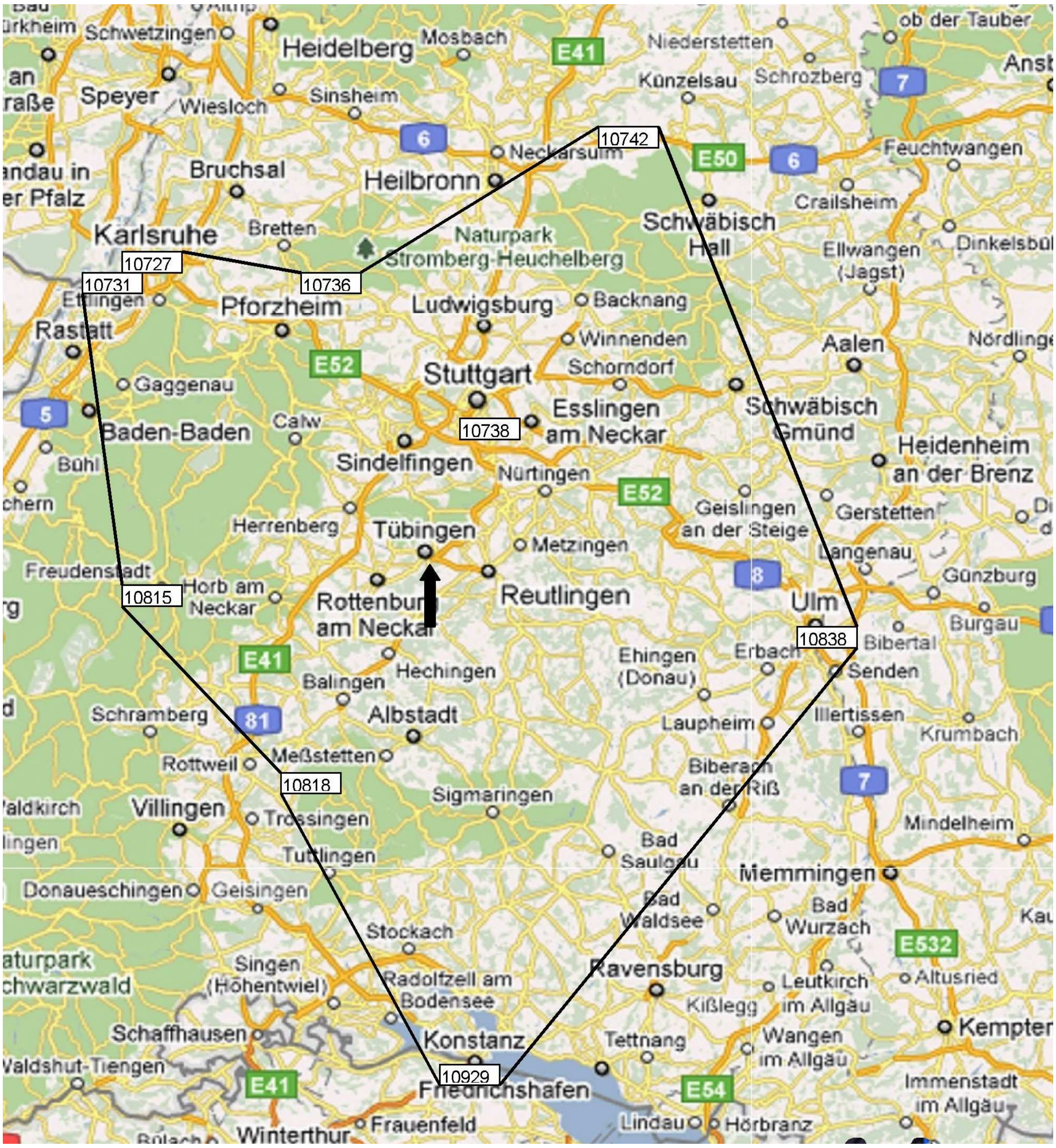

Fig. 8. Enlarged view (underlying map adaped from Google Maps 2010) of the area covered by the present study roughly outlined by connecting the meteorological stations assigned to and located at a maximum distance of 55 km and a mean distance of 25 ± 10 km from the places of onset of acute aortic dissections

Meteorological station	N of dissections	N of type A dissections	N of type B dissections	N of dissections in male patients	N of dissections in female patients
Karlsruhe	1	1	0	0	1
Rheinstetten	1	0	1	1	0
Muehlacker	3	2	1	3	0
Stuttgart-Echterdingen	89	68	21	57	32
Oehringen	1	1	0	0	1
Freudenstadt	14	14	0	10	4
Klippeneck	32	26	6	26	6
Ulm	9	6	3	7	2
Konstanz	6	4	2	4	2
Total	**156**	**122**	**34**	**108**	**48**

Table1. Study population 01 Jul 2004 through 30 Jun 2010: distribution by meteorological station, type of dissection and gender

Station	Name	Coordinates	Height above sea level
10727	Karlsruhe (WEWA)	49:02 N 08:22 O	112m
10731	Rheinstetten	48:58 N 08:20 O	116m
10736	Muehlacker (AWST)	48:58 N 08:52 O	244m
10738	Stuttgart– Echterdingen	48:41 N 09:14 O	371m
10742	Oehringen (WEWA)	49:12 N 09:31 O	276m
10815	Freudenstadt(WEWA)	48:27 N 08:25 O	797m
10818	Klippeneck (AWST)	48:06 N 08:45 O	973m
10838	Ulm (AWST)	48:23 N 09:57 O	567m
10929	Konstanz (WEWA)	47:41 N 09:11 O	443m

Table 2. Geographic coordinates of the meteorological stations

4.3.1 Meteorological parameters provided by the meteorological stations

The meteorological data from the nine meteorological stations indicated above were singled out from a very extensive body of data provided by the German Meteorological Service for the study area for the entire six-year period covered by the present study.

Each of the nine meteorological stations provided the following meteorological parameters in the form of hourly readings from 00:00 to 23:00 hours each day:

- air temperature in 0.1°C
- atmospheric pressure at the designated station elevation in 0.1 hPa
- relative air humidity in %
- hourly precipitation in 0.1 mm
- speed of wind (FF) as ten minute mean in 0.1 m/s
- direction of wind (DD) in tens of degrees

4.3.2 Meteorological parameters used for statistical evaluation

For the purpose of investigating differences in meteorological conditions between days with and without occurrence of acute aortic dissection, the temperature and atmospheric pressure readings provided by the meteorological stations on an hourly basis were used to determine mean, maximum and minimum meteorological values for each 24-hour interval during the study period.

For relative air humidity as well as direction and speed of wind, only daily mean values and for precipitation only daily total values were calculated from the hourly readings, as these factors are considered to be secondary and to contribute to cold stress rather than exerting a significant influence on the occurrence of acute aortic pathologies on their own. Therefore, analysis of relative air humidity, wind and precipitation was limited to checking for significant trends that might merit closer analysis of either of them as an independent factor triggering acute aortic pathologies.

4.3.2.1 Temperature

- Minimum temperature recorded at each meteorological station during each 24-hour period
- Maximum temperature recorded at each meteorological station during each 24-hour period
- Mean temperature at each meteorological station during each 24-hour period

4.3.2.2 Atmospheric pressure at the designated station elevation

- Minimum atmospheric pressure recorded at each meteorological station during each 24-hour period
- Maximum atmospheric pressure recorded at each meteorological station during each 24-hour period
- Mean atmospheric pressure at each meteorological station during each 24-hour period

4.3.2.3 Relative air humidity

- Mean relative air humidity at each meteorological station during each 24-hour period

4.3.2.4 Precipitation

- Total precipitation at each meteorological station during each 24-hour period

4.3.2.5 Wind speed

- Mean wind speed at each meteorological station during each 24-hour period

4.3.2.6 Wind direction

- Mean direction of wind at each meteorological station during each 24-hour period

5 STATISTICAL EVALUATION

5.1 GENERAL

Statistical evaluation was performed using the SPSS 17.0 Statistical Package. Consulting regarding the most appropriate methods of statistical testing to be applied was provided by the Department of Medical Biometry of the University of Tuebingen.

The dissections included in the present study occurred on a total of 153 days within the study period, including three days on which two patients with acute aortic dissection each were admitted. To be able to account separately for each dissection occurring on these days, it was decided to duplicate each of the three days concerned, which was deemed to be of neglectable effect and therefore admissible in view of the large total number of days evaluated. Consequently, the total day count reported is 2194 instead of 2191 for the total period of six years.

Non-parametric testing methods were applied as the data collected do not fit a normal distribution.

Allocation of cases to the meteorological stations is shown in Table 3 below. Mean values were not weighted to reflect the uneven distribution of cases, as patients must be assumed to have moved within the study area during the various periods preceding the onset of acute aortic dissection so that application of unweighted area-wide mean values appeared more appropriate.

10742	10727/10731	10736	10929	10838	10815	10818	10738
0.06%	0.13%	1.9%	3.8%	5.8%	9.0%	20.5%	57.1%

Table 3. Allocation of cases to meteorological stations

Median values are indicated to provide an impression of the actual magnitude and practical relevance of the differences in meteorological conditions prevailing on and preceding days with vs. days without occurrence of acute aortic dissection.

5.2 APPLICATION OF AREA-WIDE VALUES

Temperature, atmospheric pressure, relative air humidity, precipitation as well as wind speed and direction were evaluated using area-wide meteorological values covering the entire study area. For this purpose, area-wide minimum and maximum as well as mean temperature and atmospheric pressure values were determined for each of the periods evaluated from the 24-hour values calculated from the readings provided by each of the nine meteorological stations. For relative air humidity, wind speed and wind direction, area-wide mean values were determined from the local 24-hour mean values. Area-wide mean precipitation values were calculated from the local 24-hour precipitation totals derived from the hourly readings provided by the nine meteorological stations.

5.3 COMPARISON BETWEEN METEOROLOGICAL CONDITIONS PREVAILING ON AND PRECEDING DAYS WITH VS. DAYS WITHOUT OCCURRENCE OF ACUTE AORTIC DISSECTION

The Wilcoxon test was applied to compare temperature, atmospheric pressure, relative air humidity, precipitation as well as wind direction and speed prevailing on days on which acute aortic dissection occurred, as well as on days 1, 2 and 3 and during the weeks and months preceding them, on the one hand, and the corresponding parameters on and preceding days without acute aortic dissection, on the other.

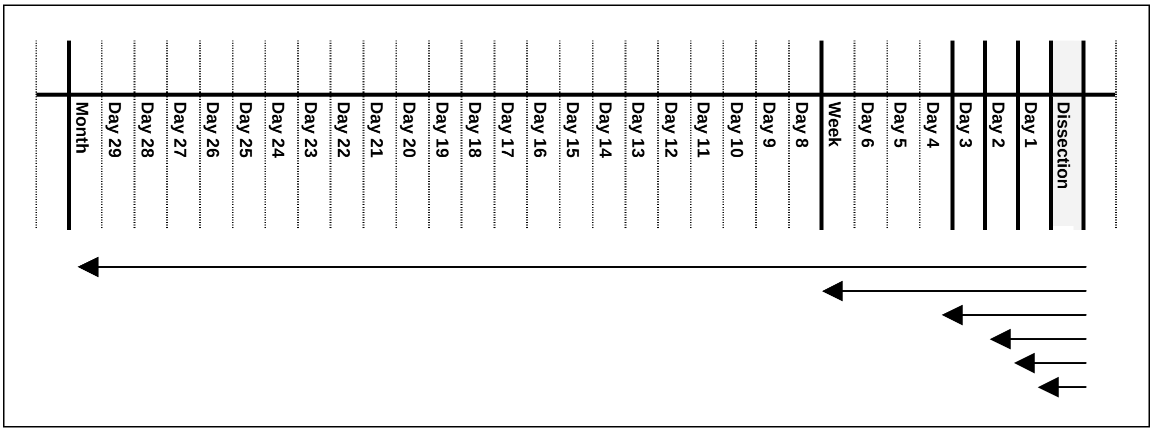

Fig. 9. Time intervals defined for statistical evaluation purposes: day of dissection and days 1, 2, 3, week and month preceding dissection

5.4 EVALUATION OF FLUCTUATIONS IN METEOROLOGICAL CONDITIONS DURING PERIODS PRECEDING ACUTE AORTIC DISSECTION

5.4.1 Comparison between maximum temperature and atmospheric pressure amplitudes on and preceding days with vs. days without acute aortic dissection

Assuming that acute aortic dissection may tend to be triggered by short-term changes in meteorological conditions and that fluctuations in meteorological conditions may be at least as relevant as absolute levels, the maximum amplitudes of temperature and atmospheric pressure, i.e. the two primary parameters evaluated, were calculated for each day of the study period as well as for days 1, 2, 3 and the week and month preceding each day by subtracting the minimum from the maximum values previously determined for the respective periods. The maximum amplitudes on and preceding days with vs. days without dissection were subsequently compared applying the Wilcoxon test.

5.4.2 Analysis of local temperature and atmospheric pressure development during the 4-day interval preceding and including the date of dissection

Additionally, local mean daily temperature and atmospheric pressure values on days on which acute aortic dissection occurred as well as on days 1, 2 and 3 preceding dissection were compared so as to determine whether or not a trend towards increases or drops in temperature or atmospheric pressure during the days preceding the onset of dissection can be discerned.

6 RESULTS

6.1 DESCRIPTION OF THE STUDY POPULATION

6.1.1 Number of dissections and distribution by gender and type

In the 6–year period between 01 July 2004 and 30 June 2010, a total of 161 patients (thereof 110 (68.3%) male and 51 (31.7%) female) were admitted to our hospital with acute spontaneous aortic dissection.

Acute aortic dissections 01 Jul 2004 through 30 Jun 2010 Distribution by gender			
Gender	**Frequency**	**Percent**	**Cumulative percent**
Female	51	31.7	31.7
Male	110	68.3	100.0
Total	161	100.0	100.0

Table 4. Acute aortic dissections 01 Jul 2004 through 30 Jun 2010: distribution by gender

126 (78.3 percent) patients were diagnosed with type A dissection, while dissections in the remaining 35 patients (21.7%) were classified as type B, type A being defined, according to the Stanford classification, as any dissection involving the ascending aorta while type B was defined as any dissection involving only the descending aorta distal to the left subclavian artery.

Acute aortic dissections 01 Jul 2004 through 30 Jun 2010 Distribution by Stanford type			
Type	**Frequency**	**Percent**	**Cumulative percent**
Type A	126	78.3	78.3
Type B	35	21.7	100.0
Total	161	100.0	100.0

Table 5. Acute aortic dissections 01 Jul 2004 through 30 Jun 2010: distribution by Stanford type

Acute type A dissections occurred in 87 (69.05%) male and 39 female (30.95%), acute type B dissections in 23 male (65.7%) and 12 female (34.3%) patients.

Acute aortic dissections 01 Jul 2004 through 30 Jun 2010 Distribution by Stanford type and gender			
	Gender		
Type	Female	Male	Total
Type A	39	87	126
Type B	12	23	35
Total	51	110	161

Table 6. Acute aortic dissections 01 Jul 2004 through 30 Jun 2010: distribution by Stanford type and gender

The ratio of acute type A to acute type B dissections was 3.6 : 1. Male to female ratios determined were 2.2 : 1 for acute aortic dissections irrespective of Stanford type, 2.2 : 1 for acute type A dissections and 1.9 : 1 for acute type B dissections.

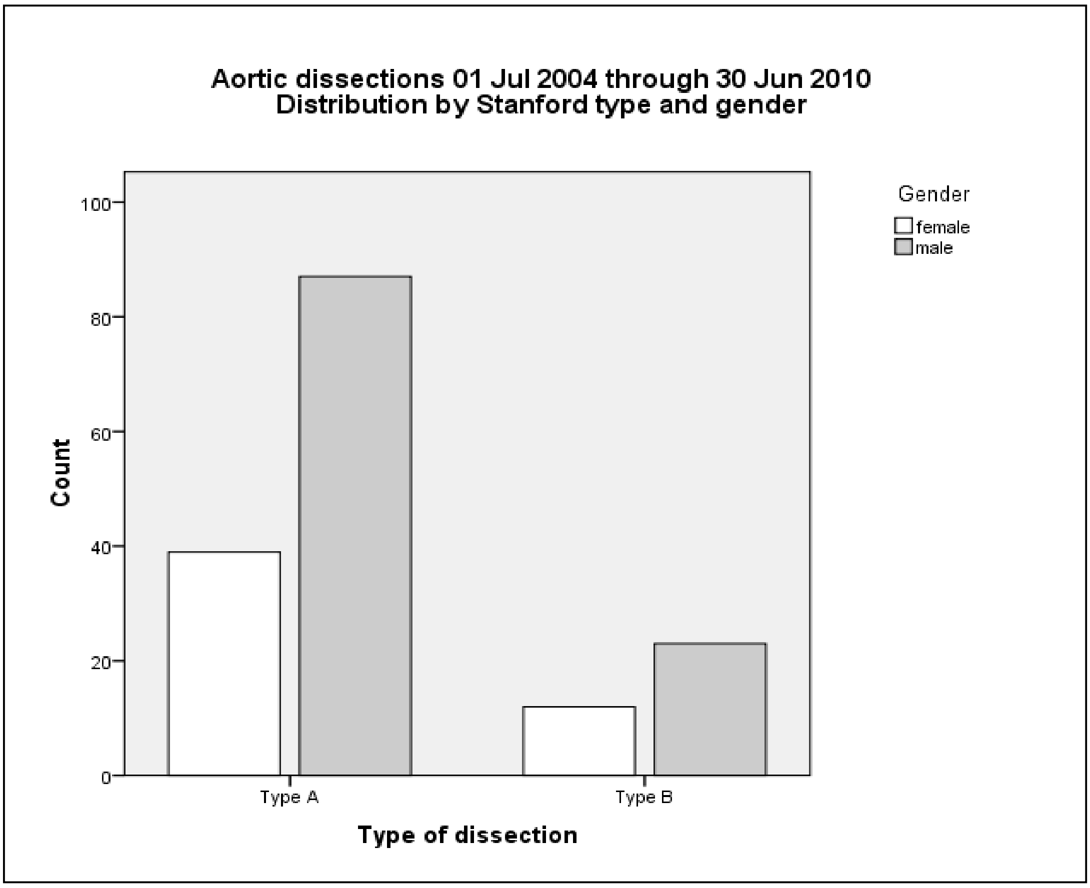

Fig. 10. Acute aortic dissections 01 Jul 2004 through 30 Jun 2010: 126 acute Stanford type A dissections, thereof 87 in male and 39 in female patients; 35 acute Stanford type B dissections, thereof 23 in male and 12 in female patients

After exclusion of 5 patients (3.1%) for whom the date of onset of symptoms could not be determined with a sufficient degree of certainty, the study population comprised 156 patients (108 male (69.2%) and 48 female (30.8%)).

Study population 01 Jul 2004 through 30 Jun 2010 Distribution by gender			
Gender	**Frequency**	**Percent**	**Cumulative percent**
Female	48	30.8	30.8
Male	108	69.2	100.0
Total	156	100.0	100.0

Table 7. Study population 01 Jul 2004 through 30 Jun 2010, distribution by gender

The shares of acute type A and type B dissections were 122 (78.2%) and 34 (21.8%), respectively.

Study population 01 Jul 2004 through 30 Jun 2010 Distribution by Stanford type			
Type	**Frequency**	**Percent**	**Cumulative percent**
Type A	122	78.2	78.2
Type B	34	21.8	100.0
Total	156	100.0	100.0

Table 8. Study population 01 Jul 2004 through 30 Jun 2010: distribution by Stanford type

Acute type A dissections occurred in 86 (70.5%) male and 36 female (29.5%), acute type B dissections in 22 male (64.7%) and 12 female (35.3%) patients.

Study population 01 Jul 2004 through 30 Jun 2010 Distribution by Stanford type and gender			
Type	**Gender**		
	Female	**Male**	**Total**
Type A	36	86	122
Type B	12	22	34
Total	48	108	156

Table 9. Study population 01 Jul 2004 through 30 Jun 2010: distribution by Stanford type and gender

The ratio of acute type A to acute type B dissections was 3.6 : 1. Male to female ratios determined were 2.3 : 1 for acute aortic dissections irrespective of Stanford type, 2.4 : 1 for acute type A dissections and 1.8 : 1 for acute type B dissections.

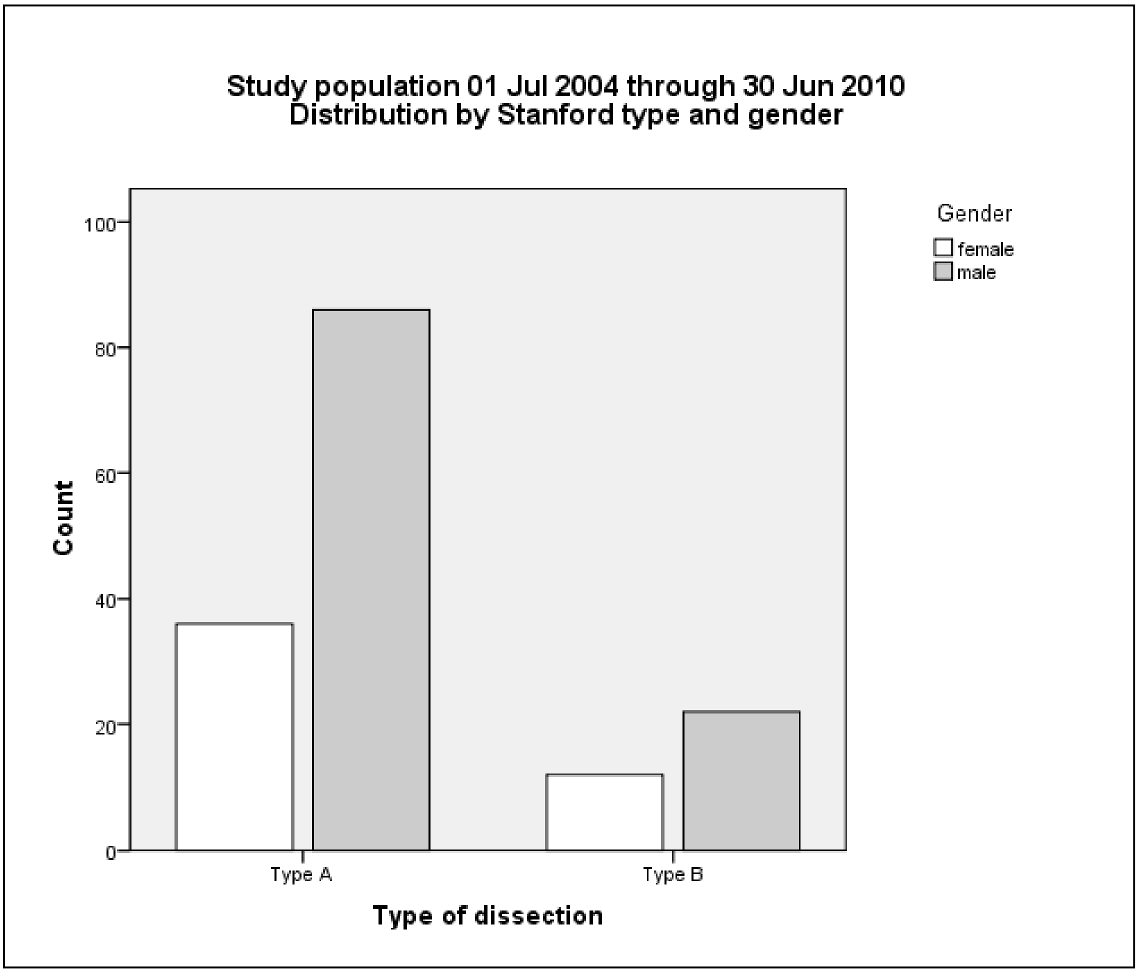

Fig. 11. Study population 01 Jul 2004 through 30 Jun 2010: 122 acute Stanford type A dissections, thereof 86 in male and 36 in female patients; 34 acute Stanford type B dissections, thereof 22 in male and 12 in female patients

6.1.2 Age structure of the study population

The age values indicated represent patient age at the date of onset of symptoms. Age distributions were analyzed by gender as well as by type of dissection, indicating age values as mean ± standard deviation and including the range covered by of each of the age groups.

On the whole, women presenting with acute aortic dissection tended to be older than men, and patients with acute type B dissection older than patients with acute type A dissection.

Study population 01 Jul 2004 through 30 Jun 2010 Patient age at date of onset						
		N	**Minimum**	**Maximum**	**Mean**	**Std. deviation**
Total acute aortic dissections		**156**	**23.82**	**87.16**	**61.48**	**12.32**
	Male	108	34.42	86.86	60.49	11.58
	Female	48	23.82	87.16	63.69	13.73
	Type A	122	23.82	86.86	60.62	12.10
	Type B	34	36.91	87.16	64.57	12.83
Acute type A dissections		**122**	**23.82**	**86.86**	**60.62**	**12.10**
	Male	86	34.42	86.86	60.20	11.48
	Female	36	23.82	85.41	61.62	13.56
Acute type B dissections		**34**	**36.91**	**87.16**	**64.57**	**12.83**
	Male	22	36.91	82.50	61.65	12.13
	Female	12	44.84	87.16	69.93	12.81

Table 10. Study population 01 Jul 2004 through 30 Jun 2010: mean, minimum and maximum ages at date of onset, by type of dissection and gender

Mean age at the date of onset of symptoms was 61.48 ± 12.32 years (range 23.82 – 87.16) for the entire study population irrespective of gender and type of dissection.

Male patients presented at a mean age of 60.49 ± 11.58 years (range 34.42 – 86.86), while female patients were admitted for acute aortic dissection irrespective of Stanford type at a mean age of 63.72 ± 13.73 (range 23.82 – 87.16).

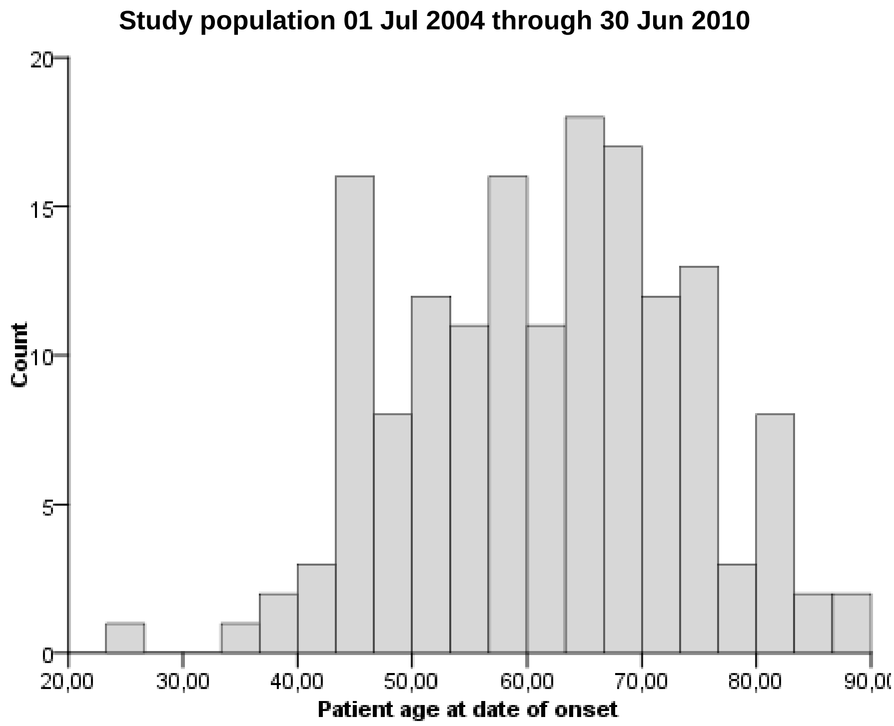

Fig. 12. Study population 01 Jul 2004 through 30 Jun 2010: patient age at date of dissection

The mean age determined for patients presenting with acute type A dissection was 60.62 ± 12.10 (range 23.82 – 86.86).

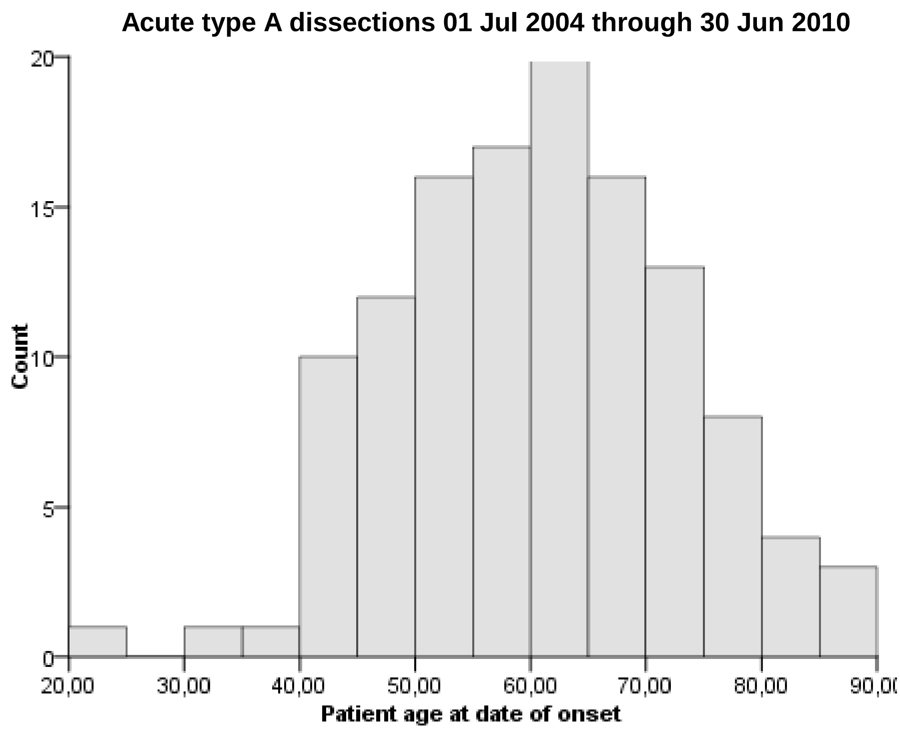

Fig. 13. Acute type A dissections 01 Jul 2004 through 30 Jun 2010: patient age at date of dissection

Men with acute type A dissection presented at a mean age of 60.20 ± 11.48 (range 24.42 – 86.86), while women admitted for acute type A dissection were aged 61.64 ± 13.56 (range 23.82 – 85.41).

Patients diagnosed with acute type B dissection were aged 64.57 ± 12.82 (range 36.91 – 87.16), the mean age determined for male patients being 61.65 ± 12.13 (range 36.91 – 82.50) while women were 69.93 ± 12.83 (range 44.84 – 87.16) years old.

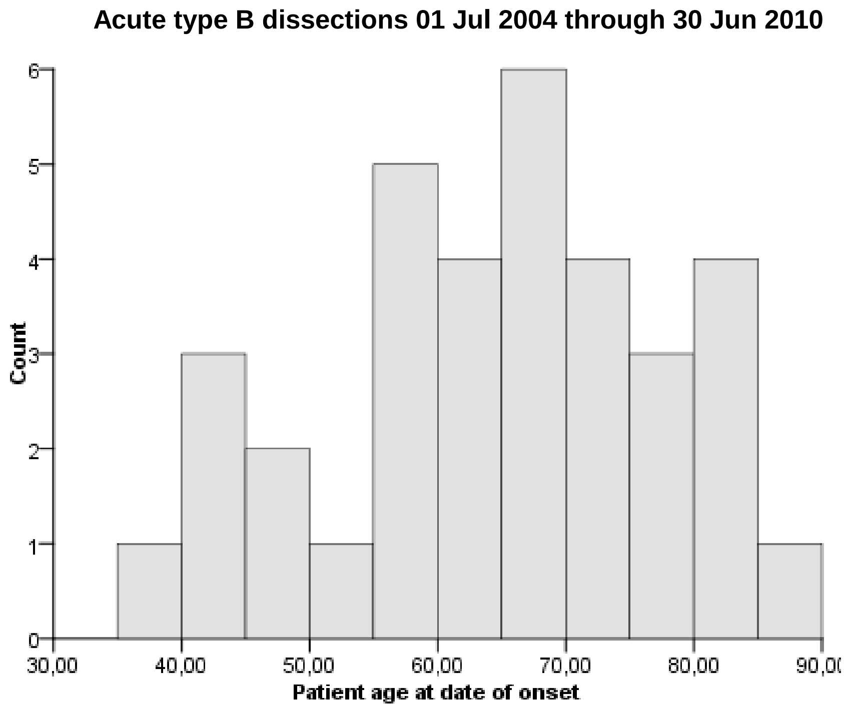

Fig. 14. Acute type B dissections 01 Jul 2004 through 30 Jun 2010: patient age at date of dissection

6.1.3 Cardiovascular risk profile, predisposing factors and relevant comorbidities

The majority of patients were either admitted directly to our hospital on an emergency basis or referred as emergencies from peripheral hospitals. Evaluation of the medical documentation available showed that the admitting or referring physicians frequently indicated presence or absence of arterial hypertension and other generally known predisposing factors of aortic dissection such as preexisting aortic aneurysms, connective tissue diseases, other inherited or congenital conditions or a history of cardiac or aortic surgery but more often than not failed to provide complete and accurate information on the patients' full cardiovascular risk profile, other medical history and medication. Scanning of patient records for presence of atherosclerosis, diabetes, smoking or medication such as antihypertensive or beta-blocking substances therefore yielded information too incomplete and imprecise to be used for statistical evaluation. Fairly complete information was obtained, however, on a number of specific risk factors of aortic dissection.

A history of arterial hypertension was indicated in 104 patients (66.7%). An aortic aneurysm (including aneurysms in syndromic individuals and patients with a history of previous cardiac or aortic surgery) was present in 31 cases (19.9%), and confirmed or strongly suspected Marfan syndrome in 4 cases (2.6%). Additionally, the study population comprised one patient (0.6%) suffering from systemic lupus who had been on steroid treatment for many years, one case of Turner syndrome (0.6%) and one patient (0.6%) with a congenital aortic anomaly (right aortic arch and right–sided descending aorta, with dissected Kommerell diverticle).

Study population 01 Jul 2004 through 30 Jun 2010 Predisposing factors and concomitant diseases		
	Frequency	**Percent**
Arterial hypertension	104	66.7
Preexisting aneurysm	31	19.9
Previous surgery	9	5.8
Marfan	4	2.6
Systemic lupus + steroid treatment	1	0.6
Turner syndrome	1	0.6
Congenital aortic anomaly	1	0.6

Table 11. Study population 01 Jul 2004 through 30 Jun 2010: predisposing factors and relevant comorbidities

Cases where acute aortic dissection occurred in sufficiently close temporal association with cardiac or aortic surgery to be considered as iatrogenic in nature were excluded, which left 9 patients (5.8%) with previous cardiac or aortic surgery. Four patients had a history of previous aortic valve replacement four, five, nine and 15 years prior to the dissection, respectively (in one case performed eight months after surgical treatment of an aortic isthmus stenosis). Two patients presented after replacement of the ascending aorta, in one case with a tubular graft four months before the dissection, and in the second case with a composite graft five years before being readmitted. Two patients diagnosed with mega aorta syndrome had previously undergone replacement of the ascending aorta and proximal arch six years and thoracoabdominal aortic replacement 10 years before the dissection, respectively. One further patient presented after previous arch repair and replacement of the descending aorta seven years before the dissection.

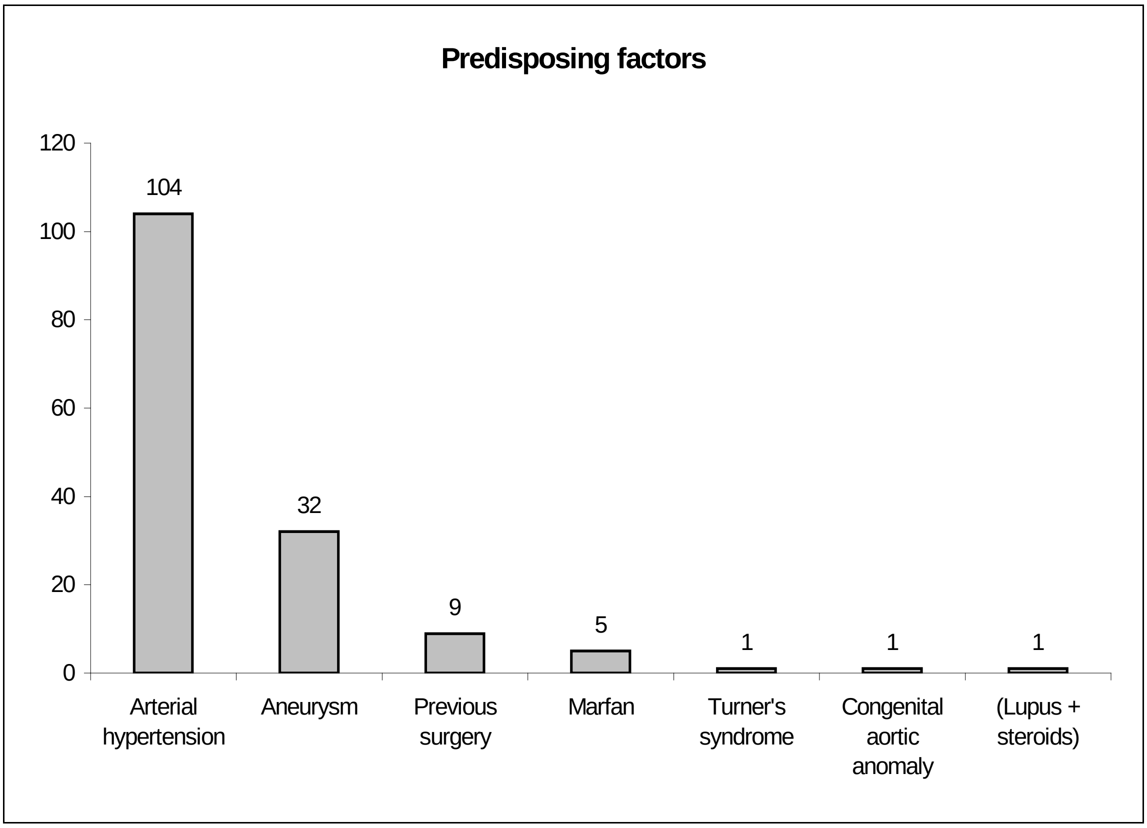

Fig.15. Study population 01 Jul 2004 through 30 Jun 2010: distribution of risk factors and relevant comorbidities

On the whole, the risk factors most frequently associated with acute aortic dissection, i.e. arterial hypertension, pre–existing aortic aneurysms, previous aortic or cardiac surgery and connective tissue diseases prevailed. Some other factors frequently quoted in literature as predisposing to or triggering acute aortic dissection were not encountered at all throughout the entire six–year period. There was, for example, not a single case of aortic dissection during pregnancy, associated with drug consumption or involving profound emotional stress or excessive physical exertion though a considerable share of cases were reported to have occurred during moderate physical activity.

6.2 FREQUENCY AND CIRCANNUAL VARIATION OF OCCURRENCE

Allocation of the cases to the twelve calendar months yielded the percentages indicated below, showing peak incidence of acute aortic dissection irrespective of the Stanford type in the month of March (19 cases, 12.2%) while incidence was lowest in August (8 cases, 5.1%). In other words, peak monthly incidence of acute aortic dissection irrespective of Stanford type was 2.4 times as high as the lowest monthly incidence rate.

Study population 01 Jul 2004 through 30 Jun 2010 Distribution of acute aortic dissections by month			
Month	**Frequency**	**Percent**	**Cumulative percent**
January	10	6.4	6.4
February	16	10.3	16.7
March	19	12.2	28.8
April	17	10.9	39.7
May	10	6.4	46.2
June	9	5.8	51.9
July	13	8.3	60.3
August	8	5.1	65.4
September	16	10.3	75.6
October	14	9.0	84.6
November	9	5.8	90.4
December	15	9.6	100.0
Total	156	100.0	100.0

Table 12. Study population 01 Jul 2004 through 30 Jun 2010: distribution of acute aortic dissections by month

Separate allocation of acute type A and B dissections to the months of the year showed a similar trend for acute type A dissections as for acute aortic dissections irrespective of Stanford type, with a different distribution pattern for acute type B dissections. This may be explained by the fact that acute type A dissections (N = 122) account for more than three quarters (78.2%) of all dissections (N = 156) included in the present study.

Acute type A dissections showed peak incidence in March (16 cases, 13.1%) and lowest incidence in August (4 cases, 3.3%), while acute type B dissections occurred with highest frequency in April (8 cases, 23.5%) and with equally low frequency (1 case, 2.9%) in the months of January, July and October. The monthly peak incidence reported for acute type A dissections (13.1%) is 4 times as high as the lowest monthly incidence rate and lower than the peak incidence rate reported for acute type B dissections (23.5%), the latter being 8 times as high as the lowest monthly incidence rate for type B dissections.

Study population 01 Jul 2004 through 30 Jun 2010 Distribution of acute type A and B dissections by month			
	Type of dissection		
Month	**Type A**	**Type B**	**Total**
January	9	1	10
February	13	3	16
March	16	3	19
April	9	8	17
May	7	3	10
June	6	3	9
July	12	1	13
August	4	4	8
September	13	3	16
October	13	1	14
November	7	2	9
December	13	2	15
Total	122	34	156

Table 13. Study population 01 Jul 2004 through 30 Jun 2010: distribution of acute type A and B dissections by month

A comparison between the monthly distribution curves for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections is shown in Fig. 16 below. The curves illustrate the similarity between the distribution patterns identified for acute aortic dissections irrespective of Stanford type and acute type A dissections, both showing peak incidence in March and lowest incidence in August.

The curve representing occurrence of acute type B dissections impressively deviates from the distribution patterns for acute aortic dissections irrespective of Stanford type and acute type A dissections with a peak in April and a secondary peak in August coinciding with the period of lowest incidence demonstrated for total and type A dissections.

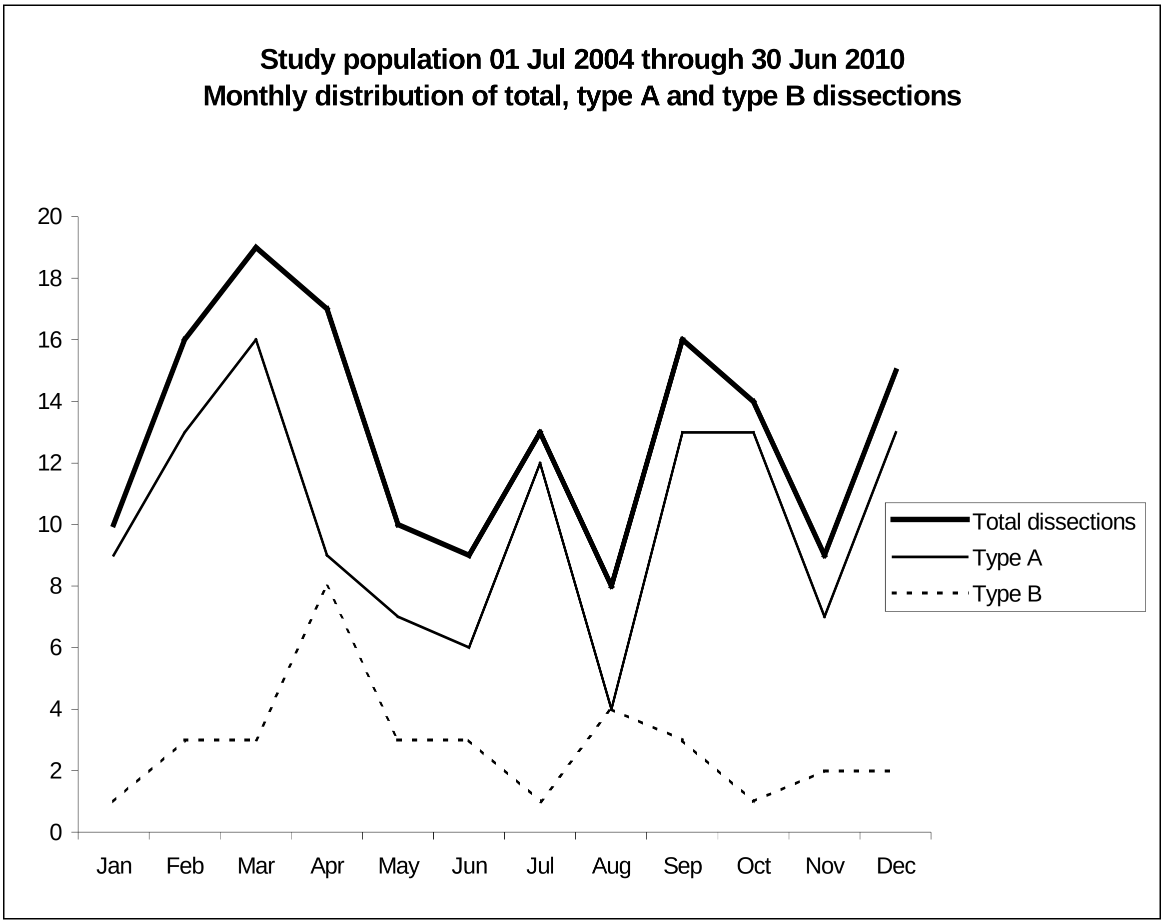

Fig. 16. Study population 01 Jul 2004 through 30 Jun 2010: monthly distribution of acute aortic dissections, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Additionally, the dates of onset were allocated to the 4 calendar seasons, the seasons for this purpose being defined as

- Winter, from December 21st through March 20th
- Spring from March 21st through June 20th
- Summer from June 21st through September 20th
- Autumn from September 21st through December 20th.

As expected and described for cardiovascular events in general, aortic dissections irrespective of Stanford type showed a peak in winter with 46 cases, (29.5%) and a trough in summer with 34 cases (21.8%) while the frequency of occurrence was fairly equal in spring (23.7%) and autumn (25.0%).

The highest seasonal incidence rate (46 cases of acute aortic dissections in winter) was 1.4 times as high as the lowest (24 cases of acute aortic dissection in summer).

Study population 01 Jul 2004 through 30 Jun 2010 Seasonal distribution of acute aortic dissection			
Season	**Frequency**	**Percent**	**Cumulative percent**
Winter	46	29.5	29.5
Spring	37	23.7	53.2
Summer	34	21.8	75.0
Autumn	39	25.0	100.0
Total	156	100.0	100.00

Table 14. Study population 01 Jul 2004 through 30 Jun 2010: seasonal distribution of acute aortic dissection

Allocation of acute type A and B dissections to the four seasons, like allocation to the twelve months of the year, showed a similar trend for acute type A dissections as for acute aortic dissections irrespective of Stanford type, once again with a different distribution pattern identified for type B dissections.

Study population 01 Jul 2004 through 30 Jun 2010 Seasonal distribution of acute aortic dissection			
Season	Type of dissection		Total
	Type A	Type B	
Winter	38	8	46
Spring	24	13	37
Summer	27	7	34
Autumn	33	6	39
Total	122	34	156

Table 15. Study population 01 Jul 2004 through 30 Jun 2010: seasonal distribution of acute type A and acute type B dissections

Acute type A dissections showed a peak in winter (38 cases, 31.2%) with a trough in spring (24 cases, 19.7%), the highest seasonal incidence rate being 1.6 times as high as the lowest. Acute type B dissections showed a peak of 13 cases (38.2%) in spring and a fairly even distribution over the remaining parts of the year with 8 cases (23.5%) in winter, 7 cases (20.6%) in summer and 6 cases (17.6) in autumn. The peak seasonal incidence of acute type B dissection was 2.2 as high as the lowest seasonal incidence rate. Reflecting the findings described above for monthly incidence rates, the peak identified for acute type B dissections (38.2%) was higher than the peak determined for acute type A dissections (31.2%).

A comparison between the seasonal distribution curves for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections is shown in Fig. 17 below.

The curves once again show similar distribution patterns for acute aortic dissections irrespective of Stanford type and acute type A dissections, both showing peak incidence in winter and a trough during the warmer seasons, while the curve representing occurrence of acute type B dissections shows a deviating distribution pattern with a delayed peak in spring.

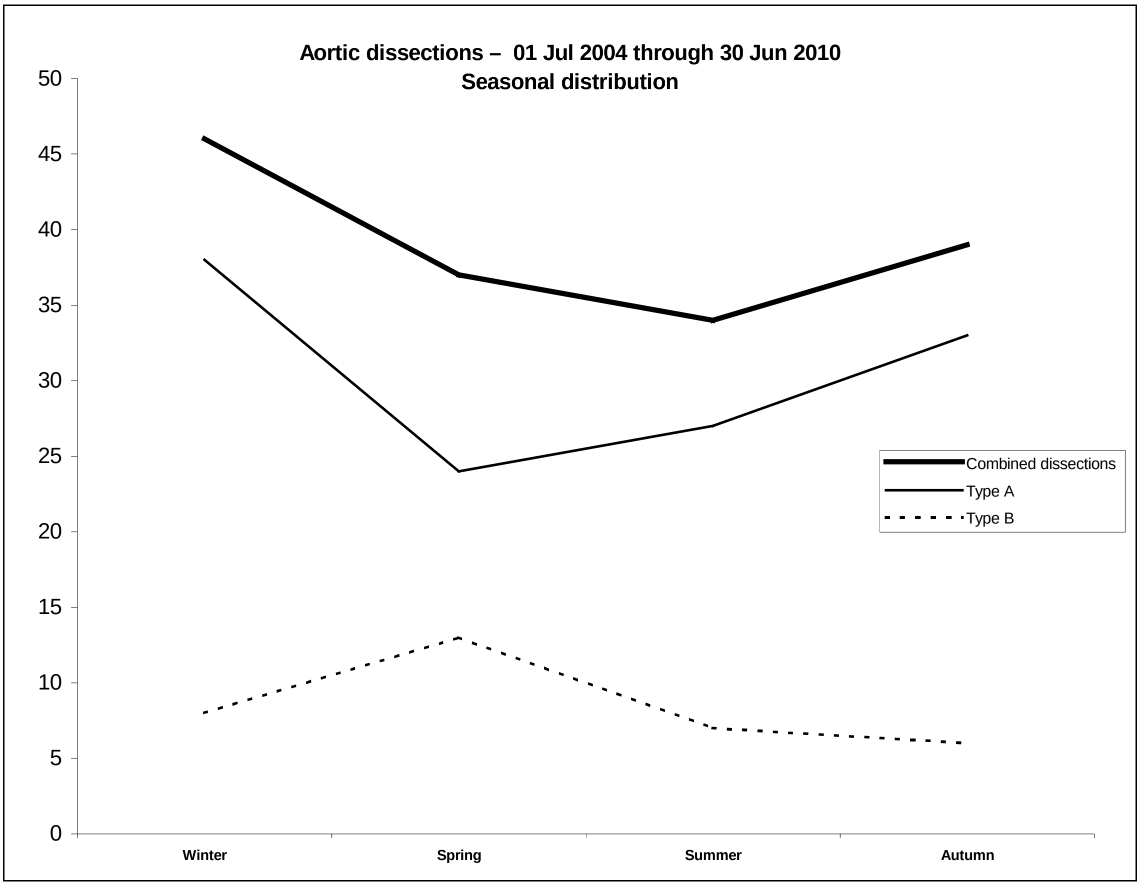

Fig. 17. Study population 01 Jul 2004 through 30 Jun 2010: seasonal distribution of acute aortic dissections, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.3 LOCAL CLIMATE AND METEOROLOGICAL CHARACTERISTICS OF THE STUDY AREA

Our hospital is located in Tuebingen, in the state of Baden–Wuerttemberg in the south–western part of Germany. Like the rest of Germany, Baden-Wuerttemberg is characterized by a warm, temperate, fully humid mid-latitude climate mostly classified as Cfb according to the Koeppen-Geiger Climate Classification System as shown in Fig. 18:

- C = warm, temperate
- f = fully humid
- b = warm summer [173]

Mostly westerly winds steer humid air masses inward from the Atlantic Ocean throughout the year. An oceanic influence, decreasing from the northwest to the southeast, is responsible for fairly mild winters and moderately hot summers. Considerable local differences, however, are caused by the characteristic topography of our region. [174] [175]

To ensure that these local differences are adequately reflected, meteorological information was not obtained from one central meteorological institution only, but was initially requested from 27 meteorological stations. Of these, however, only nine facilities were found to provide a full set of meteorological data including temperature, atmospheric pressure, air humidity, precipitation as well as wind speed and wind direction readings.

Therefore, and because the mean distance between these nine meteorological stations and the geographic reference points determined on the basis of the information contained in the medical records reviewed was found to be roughly 25±10 km, it was decided to exclude the stations not providing full data records, assuming that the nine stations selected cover the study area in such a way that local differences are reflected with an adequate degree of accuracy.

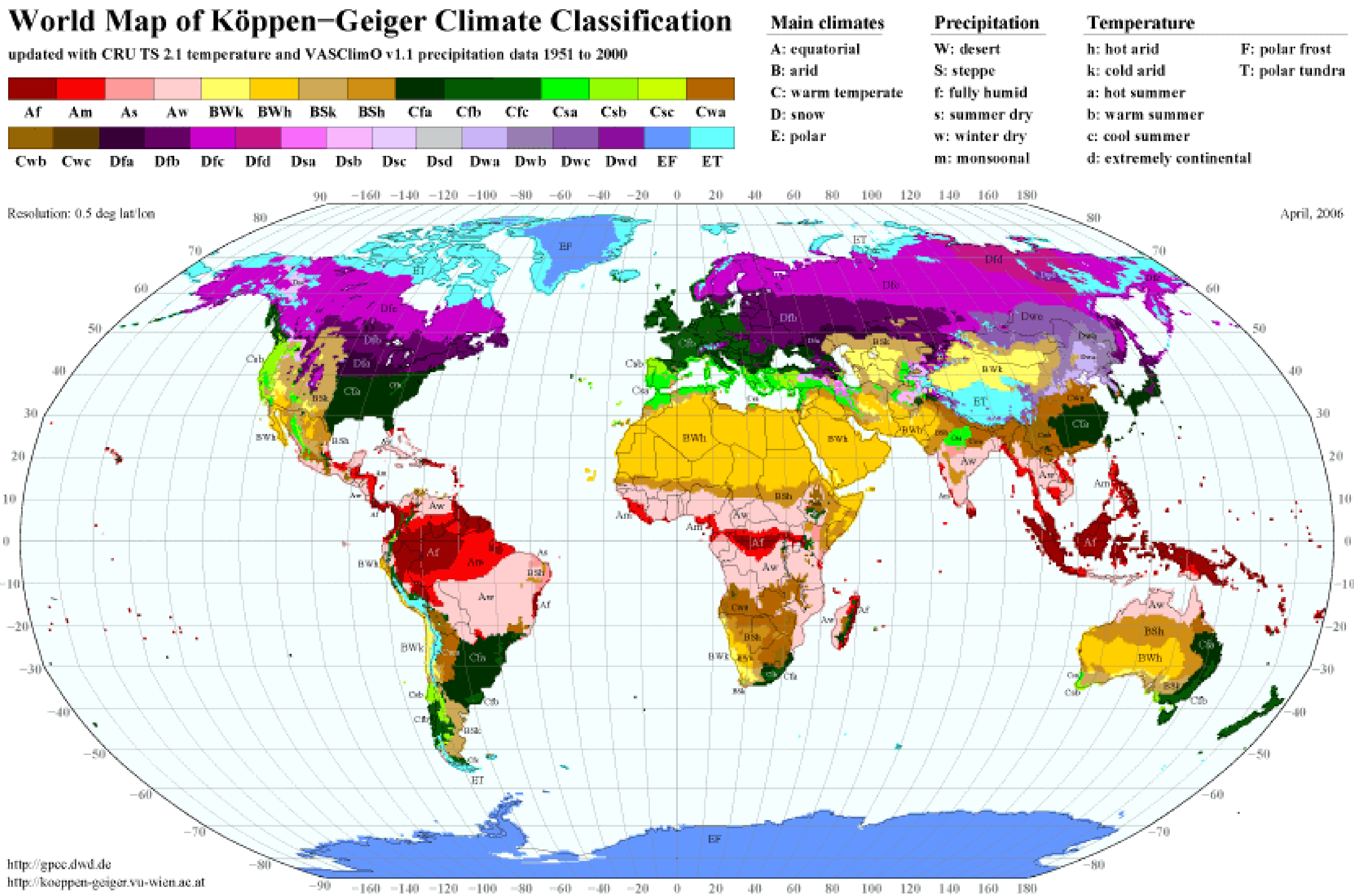

Fig. 18. Koeppen–Geiger Climate Classification System. Reproduced from Kottek M, Grieser J, Beck C, Rudolf B, Rubel F. World Map of Koeppen-Geiger Climate Classification updated. Meteorol Z 2006;15:259– 263

6.4 TEMPERATURE

The following area-wide parameters were determined on the basis of the local 24-hour values calculated from the readings obtained from the nine meteorological stations:

- minimum temperature on each day of the study period
- maximum temperature on each day of the study period
- mean temperature on each day of the study period
- temperature amplitude on each day of the study period

- minimum temperature on day 1 preceding each day
- maximum temperature on day 1 preceding each day
- mean temperature on day 1 preceding each day
- temperature amplitude on day 1 preceding each day

- minimum temperature on day 2 preceding each day
- maximum temperature on day 2 preceding each day
- mean temperature on day 2 preceding each day
- temperature amplitude on day 2 preceding each day

- minimum temperature on day 3 preceding each day
- maximum temperature on day 3 preceding each day
- mean temperature on day 3 preceding each day
- temperature amplitude on day 3 preceding each day

- minimum temperature during the week preceding each day
- maximum temperature during the week preceding each day
- mean temperature during the week preceding each day
- temperature amplitude during the week preceding each day

- minimum temperature during the month preceding each day
- maximum temperature during the month preceding each day
- mean temperature during the month preceding each day
- temperature amplitude during the month preceding each day

6.4.1 Comparison between temperature prevailing on and preceding days with vs. days without occurrence of acute aortic dissection

6.4.1.1 Association between temperature and acute aortic dissection irrespective of Stanford type

Application of the Wilcoxon test showed that area-wide mean temperatures were significantly lower on days when patients presented with acute aortic dissection than on days when no cases of acute aortic dissection occurred (p=0.21). Similarly, area-wide mean temperature values were lower on days 1, 2 and 3 as well as during the weeks and months preceding days with vs. days without occurrence of acute aortic dissection. The p-values returned by the Wilcoxon test were 0.018, 0.036, 0.041 and 0.024 for days 1, 2, 3 and the 7-day interval, respectively, while the difference for the 30-day interval was not statistically significant with a p-value of 0.086 (Tables 16, 17).

Area-wide minimum and maximum temperatures were also lower on and preceding days with vs. days without acute aortic dissection. The results for minimum temperatures reached statistical significance only for days with vs. days without acute aortic dissection and days 1 preceding them. The p-values returned for minimum temperatures on days with vs. days without acute aortic dissection and days 1, 2 and 3 and the weeks and months preceding them were 0.008, 0.039, 0.072, 0.056, 0.066 and 0.202, respectively (Tables 18, 19). The differences between the maximum temperatures on and preceding days with vs. days without acute aortic dissection were more relevant in that statistical significance was reached by the results for all intervals other than the 30-day period (p=0.041, 0.016, 0.021, 0.013, 0.027, 0.090) (Tables 20, 21).

6.4.1.2 Association between temperature and acute type A dissection

As could be expected, acute type A dissections, accounting for more than two thirds of all dissections included in the present study, showed a pattern closely resembling that described above for acute aortic dissections irrespective of Stanford type. Area-wide mean temperature values were lower on and preceding days with vs. days without acute type A dissection, with p-values of 0.014, 0.019, 0.054, 0.046, 0.019 and 0.057 being returned by the Wilcoxon test for days with vs. days without acute type A dissection and days 1, 2, 3 and the weeks and months preceding them, respectively (Tables 16, 17).

Area-wide minimum and maximum temperatures also reflect this trend towards lower temperatures on and preceding days with vs. days without occurrence of type A dissection. Confirming the results obtained for acute aortic dissections irrespective of Stanford type, maximum as well as minimum temperatures were lower on days with as well as during the intervals preceding occurrence of acute type A dissection. However, not all differences were statistically significant, the results for type A dissections resembling the results for acute aortic dissections irrespective of Stanford type in that results for maximum temperatures reached statistical significance more consistently than results obtained for minimum temperatures. The p-values returned by the Wilcoxon test for minimum temperatures on days with vs. days without acute type A dissection and days 1, 2 and 3 and the weeks and months them were 0.014, 0.072, 0.116, 0.066, 0.044 and 0.181 respectively (Tables 18, 19). The corresponding p-values for maximum temperatures were 0.019, 0.010, 0.027, 0.015, 0.012 and 0.053 (Tables 20, 21).

6.4.1.3 Association between temperature and acute type B dissection

Area-wide mean temperature values on days with acute type B dissection as well as on days 1, 2 and 3 and during the weeks and months preceding them were also lower than the corresponding values on and preceding days without occurrence of acute type B dissection. However, in contrast to the results indicated above for acute aortic dissections irrespective of Stanford type and acute type A dissections, the difference was not statistically significant for any of the intervals evaluated (Tables 16, 17). No statistically significant results were returned by the Wilcoxon test for differences in area-wide minimum and maximum temperatures either, minimum temperatures (Tables 18, 19) being lower and maximum temperatures (Tables 20, 21) mostly lower on and preceding days with acute type B dissection.

	A+B	N	Mean Rank	Sum of Ranks	A	N	Mean Rank	Sum of Ranks	B	N	Mean Rank	Sum of Ranks
Mean temperature on each day with vs. without dissection	No	2038	1106.10	2254241.50	No	2072	1105.53	2290664.00	No	2160	1097.91	2371492.50
	Yes	156	985.09	153673.50	Yes	122	961.07	117251.00	Yes	34	1071.25	36422.50
	Total	2194			Total	2194			Total	2194		
Mean temperature on day 1 preceding each day	No	2038	1106.32	2254683.00	No	2072	1105.21	2290000.00	No	2160	1098.43	2372598.00
	Yes	156	982.26	153232.00	Yes	122	966.52	117915.00	Yes	34	1038.74	35317.00
	Total	2194			Total	2194			Total	2194		
Mean temperature on day 2 preceding each day	No	2038	1105.36	2252723.50	No	2072	1103.83	2287131.00	No	2160	1098.85	2373507.50
	Yes	156	994.82	155191.50	Yes	122	990.03	120784.00	Yes	34	1011.99	34407.50
	Total	2194			Total	2194			Total	2194		
Mean temperature on day 3 preceding each day	No	2038	1105.14	2252284.00	No	2072	1104.05	2287584.50	No	2160	1098.43	2372614.50
	Yes	156	997.63	155631.00	Yes	122	986.32	120330.50	Yes	34	1038.25	35300.50
	Total	2194			Total	2194			Total	2194		
Mean temperature during week preceding each day	No	2038	1105.94	2253896.00	No	2072	1105.21	2289995.00	No	2160	1098.06	2371816.00
	Yes	156	987.30	154019.00	Yes	122	966.56	117920.00	Yes	34	1061.74	36099.00
	Total	2194			Total	2194			Total	2194		
Mean temperature during month preceding each day	No	2038	1103.93	2249817.00	No	2072	1103.74	2286941.00	No	2160	1097.59	2370791.00
	Yes	156	1013.45	158098.00	Yes	122	991.59	120974.00	Yes	34	1091.88	37124.00
	Total	2194			Total	2194			Total	2194		

Table 16. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean temperature values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Mean temperature on each day with vs. without dissection	Mean temperature on day 1 preceding each day	Mean temperature on day 2 preceding each day	Mean temperature on day 3 preceding each day	Mean temperature during week preceding each day	Mean temperature during month preceding each day
Mann-Whitney U	141427.500	140986.000	142945.500	143385.000	141773.000	145852.000
Wilcoxon W	153673.500	153232.000	155191.500	155631.000	154019.000	158098.000
Z	-2.300	-2.357	-2.101	-2.043	-2.254	-1.719
Asymp. Sig. (2-tailed)	.021	.018	.036	.041	.024	.086

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	109748.000	110412.000	113281.000	112827.500	110417.000	113471.000
Wilcoxon W	117251.000	117915.000	120784.000	120330.500	117920.000	120974.000
Z	-2.448	-2.350	-1.928	-1.995	-2.349	-1.900
Asymp. Sig. (2-tailed)	.014	.019	.054	.046	.019	.057

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	35827.500	34722.000	33812.500	34705.500	35504.000	36529.000
Wilcoxon W	36422.500	35317.000	34407.500	35300.500	36099.000	37124.000
Z	-.244	-.545	-.793	-.550	-.332	-.052
Asymp. Sig. (2-tailed)	.808	.586	.428	.583	.740	.958

Table 17. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean temperature values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissection irrespective of Stanford type, acute type A and acute type B dissections

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Minimum temperature on each day with vs. without dissection	No	2038	1107.44	2256955.50	No	2072	1105.58	2290771.00	No	2160	1099.12	2374099.50
	Yes	156	967.69	150959.50	Yes	122	960.20	117144.00	Yes	34	994.57	33815.50
	Total	2194			Total	2194			Total	2194		
Minimum temperature on day 1 preceding each day	No	2038	1105.22	2252440.50	No	2072	1103.41	2286275.00	No	2160	1099.11	2374080.50
	Yes	156	996.63	155474.50	Yes	122	997.05	121640.00	Yes	34	995.13	33834.50
	Total	2194			Total	2194			Total	2194		
Minimum temperature on day 2 preceding each day	No	2038	1104.23	2250422.00	No	2072	1102.66	2284714.00	No	2160	1098.90	2373623.00
	Yes	156	1009.57	157493.00	Yes	122	1009.84	123201.00	Yes	34	1008.59	34292.00
	Total	2194			Total	2194			Total	2194		
Minimum temperature on day 3 preceding each day	No	2038	1104.66	2251299.00	No	2072	1103.53	2286508.50	No	2160	1098.47	2372705.50
	Yes	156	1003.95	156616.00	Yes	122	995.14	121406.50	Yes	34	1035.57	35209.50
	Total	2194			Total	2194			Total	2194		
Minimum temperature during week preceding each day	No	2038	1104.39	2250738.50	No	2072	1104.11	2287708.50	No	2160	1097.66	2370945.00
	Yes	156	1007.54	157176.50	Yes	122	985.30	120206.50	Yes	34	1087.35	36970.00
	Total	2194			Total	2194			Total	2194		
Minimum temperature during month preceding each day	No	2038	1102.28	2246442.50	No	2072	1101.88	2283105.50	No	2160	1097.80	2371252.00
	Yes	156	1035.08	161472.50	Yes	122	1023.03	124809.50	Yes	34	1078.32	36663.00
	Total	2194			Total	2194			Total	2194		

Table 18. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide minimum temperature values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Minimum temperature on each day with vs. without dissection	Minimum temperature on day 1 preceding each day	Minimum temperature on day 2 preceding each day	Minimum temperature on day 3 preceding each day	Minimum temperature during week preceding each day	Minimum temperature during month preceding each day
Mann-Whitney U	138713,500	143228,500	145247,000	144370,000	144930,500	149226,500
Wilcoxon W	150959,500	155474,500	157493,000	156616,000	157176,500	161472,500
Z	-2,656	-2,063	-1,799	-1,914	-1,840	-1,277
Asymp. Sig. (2-tailed)	.008	.039	.072	.056	.066	.202

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	109641.000	114137.000	115698.000	113903.500	112703.500	117306.500
Wilcoxon W	117144.000	121640.000	123201.000	121406.500	120206.500	124809.500
Z	-2.463	-1.802	-1.573	-1.837	-2.013	-1.336
Asymp. Sig. (2-tailed)	.014	.072	.116	.066	.044	.181

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	33220.500	33239.500	33697.000	34614.500	36375.000	36068.000
Wilcoxon W	33815.500	33834.500	34292.000	35209.500	36970.000	36663.000
Z	-.955	-.950	-.825	-.574	-.094	-.178
Asymp. Sig. (2-tailed)	.340	.342	.409	.566	.925	.859

Table 19. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide minimum temperature values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissection irrespective of Stanford type, acute type A and acute type B dissections

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Maximum temperature on each day with vs. without dissection	No	2038	1105.16	2252306.50	No	2072	1105.18	2289923.50	No	2160	1097.36	2370298.00
	Yes	156	997.49	155608.50	Yes	122	967.14	117991.50	Yes	34	1106.38	37617.00
	Total	2194			Total	2194			Total	2194		
Maximum temperature on day 1 preceding each day	No	2038	1106.49	2255030.00	No	2072	1105.95	2291537.00	No	2160	1097.87	2371408.00
	Yes	156	980.03	152885.00	Yes	122	953.92	116378.00	Yes	34	1073.74	36507.00
	Total	2194			Total	2194			Total	2194		
Maximum temperature on day 2 preceding each day	No	2038	1106.10	2254240.50	No	2072	1104.78	2289101.00	No	2160	1098.64	2373054.50
	Yes	156	985.09	153674.50	Yes	122	973.89	118814.00	Yes	34	1025.31	34860.50
	Total	2194			Total	2194			Total	2194		
Maximum temperature on day 3 preceding each day	No	2038	1106.83	2255727.50	No	2072	1105.48	2290564.50	No	2160	1098.65	2373078.00
	Yes	156	975.56	152187.50	Yes	122	961.89	117350.50	Yes	34	1024.62	34837.00
	Total	2194			Total	2194			Total	2194		
Maximum temperature during week preceding each day	No	2038	1105.75	2253519.50	No	2072	1105.74	2291090.00	No	2160	1097.38	2370344.50
	Yes	156	989.71	154395.50	Yes	122	957.58	116825.00	Yes	34	1105.01	37570.50
	Total	2194			Total	2194			Total	2194		
Maximum temperature during month preceding each day	No	2038	1103.85	2249638.00	No	2072	1103.85	2287181.50	No	2160	1097.39	2370371.50
	Yes	156	1014.60	158277.00	Yes	122	989.62	120733.50	Yes	34	1104.22	37543.50
	Total	2194			Total	2194			Total	2194		

Table 20. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide maximum temperature values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Maximum temperature on each day with vs. without dissection	Maximum temperature on day 1 preceding each day	Maximum temperature on day 2 preceding each day	Maximum temperature on day 3 preceding each day	Maximum temperature during week preceding each day	Maximum temperature during month preceding each day
Mann-Whitney U	143362.500	140639.000	141428.500	139941.500	142149.500	146031.000
Wilcoxon W	155608.500	152885.000	153674.500	152187.500	154395.500	158277.000
Z	-2.046	-2.403	-2.299	-2.494	-2.205	-1.696
Asymp. Sig. (2-tailed)	.041	.016	.021	.013	.027	.090

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	110488.500	108875.000	111311.000	109847.500	109322.000	113230.500
Wilcoxon W	117991.500	116378.000	118814.000	117350.500	116825.000	120733.500
Z	-2.339	-2.576	-2.218	-2.433	-2.510	-1.936
Asymp. Sig. (2-tailed)	.019	.010	.027	.015	.012	.053

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	36418.000	35912.000	34265.500	34242.000	36464.500	36491.500
Wilcoxon W	2370298.000	36507.000	34860.500	34837.000	2370344.500	2370371.500
Z	-.082	-.220	-.670	-.676	-.070	-.062
Asymp. Sig. (2-tailed)	.934	.826	.503	.499	.944	.950

Table 21. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide maximum temperature values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.4.2 Fluctuations in temperature during periods preceding acute aortic dissection

6.4.2.1 Maximum temperature amplitudes on and preceding days with vs. days without acute aortic dissection

While it was hypothesized that days with and preceding occurrence of acute aortic dissection may be characterized by more significant fluctuations in temperature than days without and not preceding acute aortic dissection, evaluation of the amplitudes between area-wide minimum and maximum temperatures on and preceding days with vs. days without acute aortic dissection did not confirm that assumption. Instead, temperature amplitudes turned out to be higher on days with vs. days without acute aortic dissection irrespective of Stanford type but lower on days preceding acute type A dissection. Lower temperature amplitudes were also demonstrated for all periods preceding both acute aortic dissections irrespective of Stanford type and acute type A dissections. p-values of 0.799, 0.081, 0.082, 0.013, 0.081 and 0.245 were returned by the Wilcoxon test for acute aortic dissections irrespective of Stanford type, while the p-values obtained for acute type A dissections were 0.518, 0.010, 0.033, 0.006, 0.020 and 0.085 (Tables 23, 24).

For acute type B dissections, differences on and preceding days with dissections were shown to be higher during all periods other than day 3 preceding days with vs. days without dissection. However, the results for acute type B dissections did not reach statistical significance (Tables 23, 24).

6.4.2.2 Local temperature development during the 4-day interval preceding and including the date of dissection

To test whether or not the onset of acute aortic dissection tends to be preceded by drops in temperature, the development of local mean temperature values on the days preceding dissection was analyzed and, for total dissections irrespective of Stanford type as well as for acute type A dissections, in fact showed local mean temperatures continuously decreasing during the 3 days preceding the onset of dissection with the lowest mean temperature prevailing on the day of onset (Table 22).

Similar to the other analyses of temperature performed so far, the results obtained for type B dissections once again differed from those for acute aortic dissections irrespective of Stanford type and acute type A dissections. Acute type B dissections, in fact, showed a practically opposite pattern with temperatures increasing rather than decreasing during the period leading up to the onset of dissection, highest mean temperature being recorded on the day of onset (Table 22).

In this respect, attention must be called to the fact that temperature values are indicated in 0.1℃ and that day-to-day differences as well as the temperature variation throughout the entire 4-day period are extremely low and probably of no practical relevance.

	Type A+B	Minimum	Maximum	Mean	Std. Deviation
Local mean temperature on day of onset	156	-102.25	223.42	75.03	80.92
Local mean temperature on day 1 preceding onset	156	-127.96	223.71	75.39	79.12
Local mean temperature on day 2 preceding onset	156	-92.63	228.92	78.33	79.42
Local mean temperature on day 3 preceding onset	156	-95.00	238.46	78.37	79.23
	Type A				
Local mean temperature on day of onset	122	-102.25	223.42	70.60	84.54
Local mean temperature on day 1 preceding onset	122	-127.96	223.71	72.39	83.47
Local mean temperature on day 2 preceding onset	122	-55.54	238.46	76.26	82.00
Local mean temperature on day 3 preceding onset	122	-92.63	228.92	76.93	82.70
	Type B				
Local mean temperature on day 2 preceding onset	34	-92.13	177.42	83.34	67.20
Local mean temperature on day 3 preceding onset	34	-95.00	178.33	85.94	68.98
Local mean temperature on day 1 preceding onset	34	-59.21	169.13	86.16	60.90
Local mean temperature on day of onset	34	-44.75	195.83	90.95	64.94

Table 22. Study area 01 Jul 2004 through 30 Jun 2010: Mean local temperature development preceding onset of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections. Days ranked by temperature from lowest to highest, temperature indicated in 0.1℃.

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Mean temperature amplitude on each day with vs. without dissection	No	2038	1096.55	2234765.00	No	2072	1099.62	2278420.00	No	2160	1094.56	2364260.00
	Yes	156	1109.94	173150.00	Yes	122	1061.43	129495.00	Yes	34	1283.97	43655.00
	Total	2194			Total	2194			Total	2194		
Mean temperature amplitude on day 1 preceding each day	No	2038	1104.03	2250004.50	No	2072	1105.97	2291563.00	No	2160	1095.54	2366356.50
	Yes	156	1012.25	157910.50	Yes	122	953.70	116352.00	Yes	34	1222.31	41558.50
	Total	2194			Total	2194			Total	2194		
Mean temperature amplitude on day 2 preceding each day	No	2038	1104.00	2249957.00	No	2072	1104.49	2288501.00	No	2160	1096.93	2369371.00
	Yes	156	1012.55	157958.00	Yes	122	978.80	119414.00	Yes	34	1133.65	38544.00
	Total	2194			Total	2194			Total	2194		
Mean temperature amplitude on day 3 preceding each day	No	2038	1106.85	2255751.50	No	2072	1106.48	2292624.50	No	2160	1097.70	2371042.00
	Yes	156	975.41	152163.50	Yes	122	945.00	115290.50	Yes	34	1084.50	36873.00
	Total	2194			Total	2194			Total	2194		
Mean temperature amplitude during week preceding each day	No	2038	1104.03	2250007.50	No	2072	1105.13	2289839.00	No	2160	1096.33	2368083.50
	Yes	156	1012.23	157907.50	Yes	122	967.84	118076.00	Yes	34	1171.51	39831.50
	Total	2194			Total	2194			Total	2194		
Mean temperature amplitude during month preceding each day	No	2038	1101.76	2245396.00	No	2072	1103.15	2285727.00	No	2160	1096.10	2367584.00
	Yes	156	1041.79	162519.00	Yes	122	1001.54	122188.00	Yes	34	1186.21	40331.00
	Total	2194			Total	2194			Total	2194		

Table 23. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean temperature amplitudes on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissection irrespective of Stanford type, acute type A and acute type B dissections

Test statistics: Grouping variable: Occurrence of dissection

	Mean temperature amplitude on each day with vs. without dissection	Mean temperature amplitude on day 1 preceding each day	Mean temperature amplitude on day 2 preceding each day	Mean temperature amplitude on day 3 preceding each day	Mean temperature amplitude during week preceding each day	Mean temperature amplitude during month preceding each day
Mann-Whitney U	157024.000	145664.500	145712.000	139917.500	145661.500	150273.000
Wilcoxon W	2234765.000	157910.500	157958.000	152163.500	157907.500	162519.000
Z	-.254	-1.744	-1.738	-2.498	-1.744	-1.140
Asymp. Sig. (2-tailed)	.799	.081	.082	.013	.081	.254

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	121992.000	108849.000	111911.000	107787.500	110573.000	114685.000
Wilcoxon W	129495.000	116352.000	119414.000	115290.500	118076.000	122188.000
Z	-.647	-2.580	-2.130	-2.736	-2.326	-1.722
Asymp. Sig. (2-tailed)	.518	.010	.033	.006	.020	.085

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	30380.000	32476.500	35491.000	36278.000	34203.500	33704.000
Wilcoxon W	2364260.000	2366356.500	2369371.000	36873.000	2368083.500	2367584.000
Z	-1.730	-1.158	-.335	-.121	-.687	-.823
Asymp. Sig. (2-tailed)	.084	.247	.737	.904	.492	.411

Table 24. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean temperature amplitudes on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.4.3 Summary of findings

The findings regarding temperatures prevailing on and preceding days with vs. days without occurrence of acute aortic dissection are summarized in Tables 25 and 26 below for dissections irrespective of Stanford type, type A and type B dissections, respectively. The medians of the area-wide mean temperature values are shown in Table 27 to provide an impression of the actual magnitude of the temperature differences observed.

Comparison between area-wide temperature values yielded consistent and mostly statistically significant results for acute dissections irrespective of Stanford type as well as for acute type A dissections in that area-wide mean as well as area-wide maximum and minimum values were all found to be lower on and preceding days with occurrence of dissection than on and preceding days on which no dissection occurred. Results obtained for type B dissections equally showed lower area-wide mean and lower area-wide minimum temperature values, while maximum temperatures were found to be higher during three of the six intervals investigated. However, the results obtained for type B dissections did not reach statistical significance(Table 25).

Area-wide temperature amplitudes were mostly lower on and preceding days with occurrence of acute aortic dissection irrespective of type and acute type A dissection, a higher temperature amplitude being reported only for days with vs. days without acute aortic dissection irrespective of type. Temperature amplitudes on days with acute type B dissection as well as on days 1 and during the weeks and months preceding them were higher than during the corresponding periods pertaining to days without type B dissection. Lower amplitudes were reported for day 3 and the week preceding days with vs. days without type B dissection. The results for type B dissections were once again not statistically relevant (Table 26).

Relevant drops in local mean temperature in the course of the days preceding the onset of dissection were not demonstrated (Table 22).

	Day with vs. day without dissection			Day 1 preceding each day			Day 2 preceding each day			Day 3 preceding each day			Week preceding each day			Month preceding each day		
	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B
Area-wide mean temperature	↓	↓	(↓)	↓	↓	(↓)	↓	(↓)	(↓)	↓	↓	(↓)	↓	↓	(↓)	(↓)	(↓)	(↓)
Area-wide minimum temperature	↓	↓	(↓)	↓	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	↓	(↓)	(↓)	(↓)	(↓)
Area-wide maximum temperature	↓	↓	(↑)	↓	↓	(↓)	↓	↓	(↓)	↓	↓	(↓)	↓	↓	(↑)	(↓)	(↓)	(↑)

Table 25. Study area 01 Jul 2004 through 30 Jun 2010: Summary of results for temperatures prevailing on and preceding days with vs. days without acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

	Day with vs. day without dissection			Day 1 preceding each day			Day 2 preceding each day			Day 3 preceding each day			Week preceding each day			Month preceding each day		
	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B
Area-wide temperature amplitude	(↑)	(↓)	(↑)	(↓)	↓	(↑)	(↓)	↓	(↑)	↓	↓	(↓)	(↓)	↓	(↑)	(↓)	(↓)	(↑)

Table 26. Study area 01 Jul 2004 through 30 Jun 2010: Summary of results for area–wide temperature amplitudes on and preceding days with vs. days without acute aortic dissections, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Tables 25, 26. Summary of results:

↑ = higher, statistically significant
↓ = lower, statistically significant
(↑) = higher, not statistically significant
(↓) = lower, not statistically significant

☐ = result confirming hypothesis
■ (grey) = result deviating from hypothesis

	A+B	N	Median	A	N	Median	B	N	Median
Median of area–wide mean temperature on each day with vs. without dissection	No	2038	98.25	No	2072	98.25	No	2160	97.77
	Yes	156	83.38	Yes	122	76.10	Yes	34	93.13
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean temperature on day 1 preceding each day	No	2038	98.56	No	2072	98.28	No	2160	97.79
	Yes	156	78.64	Yes	122	72.20	Yes	34	93.57
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean temperature on day 2 preceding each day	No	2038	98.70	No	2072	98.41	No	2160	98.07
	Yes	156	80.23	Yes	122	79.05	Yes	34	100.52
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean temperature on day 3 preceding each day	No	2038	98.20	No	2072	98.18	No	2160	97.79
	Yes	156	86.12	Yes	122	79.28	Yes	34	85.28
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean temperature during week preceding each day	No	2038	97.88	No	2072	97.93	No	2160	97.16
	Yes	156	80.24	Yes	122	72.03	Yes	34	91.13
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean temperature during month preceding each day	No	2038	100.76	No	2072	100.64	No	2160	99.51
	Yes	156	86.73	Yes	122	81.40	Yes	34	104.66
	Total	2194		Total	2194		Total	2194	

Table 27. Study area 01 Jul 2004 through 30 Jun 2010: Medians of area–wide mean temperatures on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.5 ATMOSPHERIC PRESSURE

The following area-wide parameters were determined on the basis of the local 24-hour values calculated from the readings obtained from the nine meteorological stations:

- minimum atmospheric pressure on each day of the study period
- maximum atmospheric pressure on each day of the study period
- mean atmospheric pressure on each day of the study period
- atmospheric pressure amplitude on each day of the study period

- minimum atmospheric pressure on day 1 preceding each day
- maximum atmospheric pressure on day 1 preceding each day
- mean atmospheric pressure on day 1 preceding each day
- atmospheric pressure amplitude on day 1 preceding each day

- minimum atmospheric pressure on day 2 preceding each day
- maximum atmospheric pressure on day 2 preceding each day
- mean atmospheric pressure on day 2 preceding each day
- atmospheric pressure amplitude on day 2 preceding each day

- minimum atmospheric pressure on day 3 preceding each day
- maximum atmospheric pressure on day 3 preceding each day
- mean atmospheric pressure on day 3 preceding each day
- atmospheric pressure amplitude on day 3 preceding each day

- minimum atmospheric pressure during the week preceding each day
- maximum atmospheric pressure during the week preceding each day
- mean atmospheric pressure during the week preceding each day
- atmospheric pressure amplitude during the week preceding each day

- minimum atmospheric pressure during the month preceding each day
- maximum atmospheric pressure during the month preceding each day
- mean atmospheric pressure during the month preceding each day
- atmospheric pressure amplitude during the month preceding each day

6.5.1 Comparison between atmospheric pressure prevailing on and preceding days with vs. days without occurrence of acute aortic dissection

6.5.1.1 Association between atmospheric pressure and acute aortic dissection irrespective of Stanford type

Area-wide mean atmospheric pressure values were lower on and preceding days when acute aortic dissection irrespective of Stanford type occurred than on days when acute aortic dissection did not occur. Statistical significance, however, was only reached by the result for the 30-day interval (p=0.035) (Tables 29, 30).

Area-wide minimum atmospheric pressure values were similarly shown to be lower on and preceding days with vs. days without acute aortic dissection irrespective of Stanford type. Results were mostly statistically significant, with p-values of 0.053, 0.050, 0.046, 0.047, 0.045 and 0.136 being returned by the Wilcoxon test for days with vs. days without acute aortic dissection irrespective of Stanford type and days 1, 2 and 3 and the weeks and months preceding them (Tables 31, 32).

This trend towards lower atmospheric pressure levels during periods preceding acute aortic dissection was confirmed by the evaluation of area-wide maximum pressure levels, which were similarly found to be lower on days with occurrence of acute aortic dissection irrespective of Stanford type than on days when no acute aortic dissection occurred. Lower maximum atmospheric pressures also prevailed during all periods other than the 30-day interval preceding days with vs. days without occurrence of acute aortic dissection irrespective of Stanford type. Statistical significance was not reached by any of the results (Tables 33, 34).

6.5.1.2 Association between atmospheric pressure and acute type A dissection

The findings for acute aortic dissections irrespective of type outlined above were mostly confirmed by the results obtained for acute Stanford type A dissections. Area-wide mean atmospheric pressure values were lower on and preceding days when acute type A dissection occurred than on and preceding days when acute type A dissection did not occur. Results were not statistically significant for any of the intervals evaluated (Tables 29, 30).

Area-wide minimum atmospheric pressure values (Tables 31, 32) further confirmed the general trend, being similarly lower on and preceding days with vs. without acute type A dissection.

Area-wide maximum atmospheric pressure values showed a similar tendency towards lower levels on days with vs. days without acute type A dissection as well as on days 1, 2 and 3 preceding them, but were higher during the 7-day and 30-day intervals preceding acute aortic type A dissections than during the reference intervals (Tables 33, 34).

The results for minimum and maximum values, however, were not statistically significant.

6.5.1.3 Association between atmospheric pressure and acute type B dissection

The results obtained for acute aortic dissections irrespective of Stanford type and acute type A dissection are further confirmed by the results returned by the Wilcoxon test for atmospheric pressure levels prevailing on and preceding days with vs. days without acute type B dissection.

Like for the other categories of dissections evaluated, area-wide mean atmospheric pressure values were lower on days on which acute Stanford type B dissection occurred than on days on which acute Stanford type B dissection did not occur (Tables 29, 30). The same applies to minimum atmospheric pressure levels (Tables 31, 32) and maximum atmospheric pressure levels (Tables 33, 34) on and preceding days with vs. days without acute type B dissection. Statistical significance was not reached by any of the results obtained for acute type B dissection.

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Mean atmospheric pressure on each day with vs. without dissection	No	2038	1103.60	2249136.00	No	2072	1101.99	2283329.50	No	2160	1098.95	2373721.50
	Yes	156	1017.81	158779.00	Yes	122	1021.19	124585.50	Yes	34	1005.69	34193.50
	Total	2194			Total	2194			Total	2194		
Mean atmospheric pressure on day 1 preceding each day	No	2038	1103.56	2249061.50	No	2072	1102.04	2283432.50	No	2160	1098.86	2373544.00
	Yes	156	1018.29	158853.50	Yes	122	1020.35	124482.50	Yes	34	1010.91	34371.00
	Total	2194			Total	2194			Total	2194		
Mean atmospheric pressure on day 2 preceding each day	No	2038	1103.49	2248907.00	No	2072	1102.06	2283461.00	No	2160	1098.78	2373361.00
	Yes	156	1019.28	159008.00	Yes	122	1020.11	124454.00	Yes	34	1016.29	34554.00
	Total	2194			Total	2194			Total	2194		
Mean atmospheric pressure on day 3 preceding each day	No	2038	1103.36	2248655.50	No	2072	1102.01	2283365.50	No	2160	1098.71	2373205.00
	Yes	156	1020.89	159259.50	Yes	122	1020.90	124549.50	Yes	34	1020.88	34710.00
	Total	2194			Total	2194			Total	2194		
Mean atmospheric pressure during week preceding each day	No	2038	1102.03	2245934.00	No	2072	1098.72	2276542.50	No	2160	1100.60	2377306.50
	Yes	156	1038.34	161981.00	Yes	122	1076.82	131372.50	Yes	34	900.25	30608.50
	Total	2194			Total	2194			Total	2194		
Mean atmospheric pressure during month preceding each day	No	2038	1105.39	2252782.50	No	2072	1101.87	2283069.00	No	2160	1100.75	2377628.50
	Yes	156	994.44	155132.50	Yes	122	1023.33	124846.00	Yes	34	890.78	30286.50
	Total	2194			Total	2194			Total	2194		

Table 29. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean atmospheric pressure values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Mean atmospheric pressure on each day with vs. without dissection	Mean atmospheric pressure on day 1 preceding each day	Mean atmospheric pressure on day 2 preceding each day	Mean atmospheric pressure on day 3 preceding each day	Mean atmospheric pressure during week preceding each day	Mean atmospheric pressure during month preceding each day
Mann-Whitney U	146533.000	146607.500	146762.000	147013.500	149735.000	142886.500
Wilcoxon W	158779.000	158853.500	159008.000	159259.500	161981.000	155132.500
Z	-1.630	-1.620	-1.600	-1.567	-1.210	-2.108
Asymp. Sig. (2-tailed)	.103	.105	.110	.117	.226	.035

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	117082.500	116979.500	116951.000	117046.500	123869.500	117343.000
Wilcoxon W	124585.500	124482.500	124454.000	124549.500	131372.500	124846.000
Z	-1.369	-1.384	-1.388	-1.374	-.371	-1.331
Asymp. Sig. (2-tailed)	.171	.166	.165	.169	.711	.183

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	33598.500	33776.000	33959.000	34115.000	30013.500	29691.500
Wilcoxon W	34193.500	34371.000	34554.000	34710.000	30608.500	30286.500
Z	-.852	-.803	-.753	-.711	-1.830	-1.918
Asymp. Sig. (2-tailed)	.394	.422	.451	.477	.067	.055

Table 30. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean atmospheric pressure values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Minimum atmospheric pressure on each day with vs. without dissection	No	2038	1104.74	2251450.00	No	2072	1102.86	2285123.00	No	2160	1099.19	2374242.00
	Yes	156	1002.98	156465.00	Yes	122	1006.49	122792.00	Yes	34	990.38	33673.00
	Total	2194			Total	2194			Total	2194		
Minimum atmospheric pressure on day 1 preceding each day	No	2038	1104.85	2251675.00	No	2072	1102.91	2285238.00	No	2160	1099.24	2374352.00
	Yes	156	1001.54	156240.00	Yes	122	1005.55	122677.00	Yes	34	987.15	33563.00
	Total	2194			Total	2194			Total	2194		
Minimum atmospheric pressure on day 2 preceding each day	No	2038	1104.96	2251908.00	No	2072	1103.06	2285535.50	No	2160	1099.21	2374287.50
	Yes	156	1000.04	156007.00	Yes	122	1003.11	122379.50	Yes	34	989.04	33627.50
	Total	2194			Total	2194			Total	2194		
Minimum atmospheric pressure on day 3 preceding each day	No	2038	1104.92	2251828.50	No	2072	1103.04	2285496.50	No	2160	1099.19	2374247.00
	Yes	156	1000.55	156086.50	Yes	122	1003.43	122418.50	Yes	34	990.24	33668.00
	Total	2194			Total	2194			Total	2194		
Minimum atmospheric pressure during week preceding each day	No	2038	1104.99	2251964.00	No	2072	1102.60	2284582.50	No	2160	1099.67	2375296.50
	Yes	156	999.69	155951.00	Yes	122	1010.92	123332.50	Yes	34	959.37	32618.50
	Total	2194			Total	2194			Total	2194		
Minimum atmospheric pressure during month preceding each day	No	2038	1103.07	2248063.50	No	2072	1101.81	2282956.50	No	2160	1098.62	2373022.00
	Yes	156	1024.69	159851.50	Yes	122	1024.25	124958.50	Yes	34	1026.26	34893.00
	Total	2194			Total	2194			Total	2194		

Table 31. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide minimum atmospheric pressure values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Minimum atmospheric pressure on each day with vs. without dissection	Minimum atmospheric pressure on day 1 preceding each day	Minimum atmospheric pressure on day 2 preceding each day	Minimum atmospheric pressure on day 3 preceding each day	Minimum atmospheric pressure during week preceding each day	Minimum atmospheric pressure during month preceding each day
Mann-Whitney U	144219.000	143994.000	143761.000	143840.500	143705.000	147605.500
Wilcoxon W	156465.000	156240.000	156007.000	156086.500	155951.000	159851.500
Z	-1.934	-1.963	-1.994	-1.983	-2.001	-1.490
Asymp. Sig. (2-tailed)	.053	.050	.046	.047	.045	.136

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	115289.000	115174.000	114876.500	114915.500	115829.500	117455.500
Wilcoxon W	122792.000	122677.000	122379.500	122418.500	123332.500	124958.500
Z	-1.633	-1.650	-1.694	-1.688	-1.553	-1.314
Asymp. Sig. (2-tailed)	.103	.099	.090	.091	.120	.189

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	33078.000	32968.000	33032.500	33073.000	32023.500	34298.000
Wilcoxon W	33673.000	33563.000	33627.500	33668.000	32618.500	34893.000
Z	-.994	-1.024	-1.006	-.995	-1.281	-.661
Asymp. Sig. (2-tailed)	.320	.306	.314	.320	.200	.509

Table 32. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide minimum atmospheric pressure values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Maximum atmospheric pressure on each day with vs. without dissection	No	2038	1102.05	2245979.00	No	2072	1099.78	2278748.50	No	2160	1099.60	2375145.50
	Yes	156	1038.05	161936.00	Yes	122	1058.74	129166.50	Yes	34	963.81	32769.50
	Total	2194			Total	2194			Total	2194		
Maximum atmospheric pressure on day 1 preceding each day	No	2038	1101.98	2245845.00	No	2072	1099.80	2278786.50	No	2160	1099.52	2374973.50
	Yes	156	1038.91	162070.00	Yes	122	1058.43	129128.50	Yes	34	968.87	32941.50
	Total	2194			Total	2194			Total	2194		
Maximum atmospheric pressure on day 2 preceding each day	No	2038	1101.91	2245699.50	No	2072	1099.78	2278754.00	No	2160	1099.47	2374860.50
	Yes	156	1039.84	162215.50	Yes	122	1058.70	129161.00	Yes	34	972.19	33054.50
	Total	2194			Total	2194			Total	2194		
Maximum atmospheric pressure on day 3 preceding each day	No	2038	1101.89	2245661.00	No	2072	1099.85	2278879.50	No	2160	1099.40	2374696.50
	Yes	156	1040.09	162254.00	Yes	122	1057.67	129035.50	Yes	34	977.01	33218.50
	Total	2194			Total	2194			Total	2194		
Maximum atmospheric pressure during week preceding each day	No	2038	1098.24	2238213.00	No	2072	1094.96	2268761.00	No	2160	1100.63	2377367.00
	Yes	156	1087.83	169702.00	Yes	122	1140.61	139154.00	Yes	34	898.47	30548.00
	Total	2194			Total	2194			Total	2194		
Maximum atmospheric pressure during month preceding each day	No	2038	1094.59	2230778.50	No	2072	1092.27	2263190.50	No	2160	1099.77	2375503.00
	Yes	156	1135.49	177136.50	Yes	122	1186.27	144724.50	Yes	34	953.29	32412.00
	Total	2194			Total	2194			Total	2194		

Table 33. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide maximum atmospheric pressure values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Maximum atmospheric pressure on each day with vs. without dissection	Maximum atmospheric pressure on day 1 preceding each day	Maximum atmospheric pressure on day 2 preceding each day	Maximum atmospheric pressure on day 3 preceding each day	Maximum atmospheric pressure during week preceding each day	Maximum atmospheric pressure during month preceding each day
Mann-Whitney U	149690.000	149824.000	149969.500	150008.000	157456.000	153037.500
Wilcoxon W	161936.000	162070.000	162215.500	162254.000	169702.000	2230778.500
Z	-1.216	-1.199	-1.179	-1.174	-.198	-.777
Asymp. Sig. (2-tailed)	.224	.231	.238	.240	.843	.437

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	121663.500	121625.500	121658.000	121532.500	121133.000	115562.500
Wilcoxon W	129166.500	129128.500	129161.000	129035.500	2268761.000	2263190.500
Z	-.695	-.701	-.696	-.715	-.773	-1.593
Asymp. Sig. (2-tailed)	.487	.483	.486	.475	.439	.111

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	32174.500	32346.500	32459.500	32623.500	29953.000	31817.000
Wilcoxon W	32769.500	32941.500	33054.500	33218.500	30548.000	32412.000
Z	-1.240	-1.193	-1.162	-1.118	-1.846	-1.338
Asymp. Sig. (2-tailed)	.215	.233	.245	.264	.065	.181

Table 34. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide maximum atmospheric pressure values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.5.2 Fluctuations in atmospheric pressure during periods preceding acute aortic dissection

6.5.2.1 Maximum atmospheric pressure amplitudes on and preceding days with vs. days without acute aortic dissection

Evaluation of the area-wide amplitudes between the maximum and minimum atmospheric pressure levels prevailing during each of the intervals evaluated was performed to test the hypothesis that acute aortic dissection may be triggered by significant fluctuations in atmospheric pressure.

This hypothesis was confirmed in that the area-wide amplitudes between the maximum and minimum atmospheric pressure values during the intervals evaluated were higher for days with and periods preceding acute aortic dissections irrespective of Stanford type and type A dissections than for the reference periods. The results reached statistical significance to a considerable extent, with p-values of 0.094, 0.067, 0.047, 0.041, 0.139 and 0.243 for acute aortic dissections irrespective of Stanford type and p-values of 0.043, 0.031, 0.019, 0.015, 0.090 and 0.162 for acute type A dissections being returned by the Wilcoxon test for days with vs. days without dissection and days 1, 2 3 and the weeks and months preceding them, respectively (Tables 36, 37).

The results obtained for type B dissections significantly differ from the results for total dissections irrespective of Stanford type and acute type A dissections in that the area-wide atmospheric pressure amplitudes were lower during all periods evaluated. These results, however, did not reach statistical significance (Tables 36, 37).

6.5.2.2 Local atmospheric pressure development during the 4-day interval preceding and including the date of dissection

As it was hypothesized that acute aortic dissection may not only tend to be preceded by drops in temperature but also in atmospheric pressure, local mean atmospheric pressure levels prevailing on and preceding the dates of onset were compared, ranking the days leading up to the onset of dissection from lowest to highest atmospheric pressure.

Similar to the findings reported for temperature development above, differences between local mean atmospheric pressure values between the days preceding acute aortic dissection were too small to be of practical relevance (Table 35).

	Type A+B	Min.	Max.	Mean	Std. Deviation
Local mean atm. pres. on day 2 preceding onset	156	8861.50	10066.42	9512.34	292.05
Local mean atm. pres. on day 3 preceding onset	156	8860.58	10066.88	9512.36	292.33
Local mean atm. pres. on day 1 preceding onset	156	8863.00	10065.88	9512.36	291.77
Local mean atm. pres. on day of onset	156	8865.13	10065.21	9512.40	291.50
	Type A				
Local mean atm. pres. on day 3 preceding onset	122	8860.58	10050.50	9495.16	297.48
Local mean atm. pres. on day 2 preceding onset	122	8861.50	10051.46	9495.17	297.03
Local mean atm. pres. on day 1 preceding onset	122	8863.00	10052.29	9495.22	296.59
Local mean atm. pres. on day of onset	122	8865.13	10053.00	9495.32	296.15
	Type B				
Local mean atm. pres. on day of onset	34	9033.13	10065.21	9573.69	269.41
Local mean atm. pres. on day 1 preceding onset	34	9034.13	10065.88	9573.84	268.96
Local mean atm. pres. on day 2 preceding onset	34	9035.08	10066.42	9573.96	268.54
Local mean atm. pres. on day 3 preceding onset	34	9036.00	10066.88	9574.06	268.11

Table 35. Study area 01 Jul 2004 through 30 Jun 2010: Mean local atmospheric pressure levels preceding onset of dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections. Days ranked by atmospheric pressure from lowest to highest. Atmospheric pressure indicated in 0.1 hPa

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Area–wide atmospheric pressure amplitude on each day with vs. without dissection	No	2038	1091.24	2223937.50	No	2072	1090.85	2260249.50	No	2160	1097.96	2371603.00
	Yes	156	1179.34	183977.50	Yes	122	1210.37	147665.50	Yes	34	1068.00	36312.00
	Total	2194			Total	2194			Total	2194		
Area–wide atmospheric pressure amplitude on day 1 preceding each day	No	2038	1090.65	2222753.50	No	2072	1090.42	2259349.50	No	2160	1097.83	2371319.00
	Yes	156	1186.93	185161.50	Yes	122	1217.75	148565.50	Yes	34	1076.35	36596.00
	Total	2194			Total	2194			Total	2194		
Area–wide atmospheric pressure amplitude on day 2 preceding each day	No	2038	1090.08	2221574.50	No	2072	1089.77	2258006.50	No	2160	1097.91	2371483.00
	Yes	156	1194.49	186340.50	Yes	122	1228.76	149908.50	Yes	34	1071.53	36432.00
	Total	2194			Total	2194			Total	2194		
Area–wide atmospheric pressure amplituude on day 3 preceding each day	No	2038	1089.86	2221129.50	No	2072	1089.52	2257487.00	No	2160	1097.94	2371557.50
	Yes	156	1197.34	186785.50	Yes	122	1233.02	150428.00	Yes	34	1069.34	36357.50
	Total	2194			Total	2194			Total	2194		
Area–wide atmospheric pressure amplitude during week preceding each day	No	2038	1091.97	2225434.50	No	2072	1091.93	2262485.00	No	2160	1097.62	2370864.50
	Yes	156	1169.75	182480.50	Yes	122	1192.05	145430.00	Yes	34	1089.72	37050.50
	Total	2194			Total	2194			Total	2194		
Area–wide atmospheric pressure amplitude during month preceding each day	No	2038	1093.13	2227801.00	No	2072	1092.91	2264519.50	No	2160	1097.78	2371196.50
	Yes	156	1154.58	180114.00	Yes	122	1175.37	143395.50	Yes	34	1079.96	36718.50
	Total	2194			Total	2194			Total	2194		

Table 36. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide atmospheric pressure amplitzdes on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Area–wide atmospheric pressure amplitude on each day with vs. without dissection	Area–wide atmospheric pressure amplitude on day 1 preceding each day	Area–wide atmospheric pressure amplitude on day 2 preceding each day	Area–wide atmospheric pressure amplitude on day 3 preceding each day	Area–wide atmospheric pressure amplitude during week preceding each day	Area–wide atmospheric pressure amplitude during month preceding each day
Mann-Whitney U	146196.500	145012.500	143833.500	143388.500	147693.500	150060.000
Wilcoxon W	2223937.500	2222753.500	2221574.500	2221129.500	2225434.500	2227801.000
Z	-1.674	-1.830	-1.984	-2.043	-1.478	-1.168
Asymp. Sig. (2-tailed)	.094	.067	.047	.041	.139	.243

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	112621.500	111721.500	110378.500	109859.000	114857.000	116891.500
Wilcoxon W	2260249.500	2259349.500	2258006.500	2257487.000	2262485.000	2264519.500
Z	-2.025	-2.158	-2.355	-2.431	-1.696	-1.397
Asymp. Sig. (2-tailed)	.043	.031	.019	.015	.090	.162

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	35717.000	36001.000	35837.000	35762.500	36455.500	36123.500
Wilcoxon W	36312.000	36596.000	36432.000	36357.500	37050.500	36718.500
Z	-.274	-.196	-.241	-.261	-.072	-.163
Asymp. Sig. (2-tailed)	.784	.844	.810	.794	.942	.871

Table 37. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide atmospheric pressure amplitudes on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.5.3 Summary of results

The results regarding atmospheric pressure levels prevailing on and preceding days with vs. days without occurrence of acute aortic dissection are summarized in Tables 38 and 39 below. The medians of the area-wide mean atmospheric pressure values are shown in Table 40 to provide an impression of the actual magnitude of the atmospheric pressure differences observed.

Area-wide mean atmospheric pressure values were lower on and preceding days when acute aortic dissection irrespective of Stanford type, acute type A dissection and acute type B dissection occurred than on days when acute aortic dissection did not occur. Similarly, area-wide minimum atmospheric pressure levels were consistently lower on and preceding days with vs. days without acute aortic dissection for all categories of dissections evaluated. Area-wide maximum atmospheric pressure levels were similarly lower, a differing result only being reported for the 30-day interval for acute aortic dissections irrespective of Stanford type and for the 7 and 30-day intervals for acute type A dissections. Overall, a largely uniform result demonstrating lower atmospheric pressures on and preceding days with vs. without aortic dissection was obtained.

Evaluation of the area-wide amplitudes between maximum and minimum atmospheric pressure levels for the various periods and categories of dissections similarly showed an impressively consistent result for acute aortic dissections irrespective of type and type A dissections with greater amlitudes on and preceding days with dissection than during the reference intervals. In contrast, atmospheric pressure amplitudes on and preceding days with acute type B dissection were lower than on and preceding days without.

Evaluation of atmospheric pressure development during the days leading up to the onset of acute aortic dissection yielded no significant results for any of the categories of dissections.

	Day with vs. without dissection			Day 1 preceding each day			Day 2 preceding each day			Day 3 preceding each day			Week preceding each day			Month preceding each day		
	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B
Area–wide mean atmospheric pressure	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	↓	(↓)	(↓)
Area-wide minimum atmospheric pressure	(↓)	(↓)	(↓)	↓	(↓)	(↓)	↓	(↓)	(↓)	↓	(↓)	(↓)	↓	(↓)	(↓)	(↓)	(↓)	(↓)
Area-wide maximum atmospheric pressure	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↓)	(↑)	(↓)	(↓)	(↑)	(↓)	(↑)	(↑)	(↓)

Table 38. Study area 01 Jul 2004 through 30 Jun 2010: Summary of results for atmospheric pressure prevailing on and preceding days with vs.days without acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

	Day with vs. without dissection			Day 1 preceding each day			Day 2 preceding each day			Day 3 preceding each day			Week preceding each day			Month preceding each day		
	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B
Area-wide atmospheric pressure amplitude	(↑)	↑	(↓)	(↑)	↑	(↓)	↑	↑	(↓)	↑	↑	(↓)	(↑)	(↑)	(↓)	(↑)	(↑)	(↓)

Table 39. Study area 01 Jul 2004 through 30 Jun 2010: Summary of results for area–wide atmospheric pressure amplitudes on and preceding days with vs. days without acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Tables 38, 39. Summary of results:

↑ = higher, statistically significant
↓ = lower, statistically significant
(↑) = higher, not statistically significant
(↓) = lower, not statistically significant

☐ = result confirming hypothesis
■ = result deviating from hypothesis

	A+B	N	Median	A	N	Median	B	N	Median
Median of area–wide mean atmospheric pressure on each day with vs. without dissection	No	2038	9613.30	No	2072	9613.25	No	2160	9612.79
	Yes	156	9599.78	Yes	122	9599.31	Yes	34	9611.63
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean atmospheric pressure on day 1 preceding each day	No	2038	9613.19	No	2072	9613.19	No	2160	9612.35
	Yes	156	9600.94	Yes	122	9600.55	Yes	34	9613.40
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean atmospheric pressure on day 2 preceding each day	No	2038	9613.36	No	2072	9613.40	No	2160	9612.94
	Yes	156	9602.73	Yes	122	9602.51	Yes	34	9615.13
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean atmospheric pressure on day 3 preceding each day	No	2038	9613.55	No	2072	9613.56	No	2160	9613.15
	Yes	156	9605.34	Yes	122	9604.22	Yes	34	9616.75
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean atmospheric pressure during week preceding each day	No	2038	9611.75	No	2072	9611.30	No	2160	9611.75
	Yes	156	9605.33	Yes	122	9611.12	Yes	34	9595.07
	Total	2194		Total	2194		Total	2194	
Median of area–wide mean atmospheric pressure during month preceding each day	No	2038	9610.09	No	2072	9609.94	No	2160	9609.98
	Yes	156	9602.35	Yes	122	9603.19	Yes	34	9601.18
	Total	2194		Total	2194		Total	2194	

Table 39. Study area 01 Jul 2004 through 30 Jun 2010: Medians of area–wide mean atmospheric pressure values on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.6 RELATIVE AIR HUMIDITY

The following area-wide mean relative air humidity values, calculated from the hourly readings obtained from the meteorological stations, were used for statistical evaluation purposes:

- mean relative air humidity on each day of the study period
- mean relative air humidity on day 1 preceding each day
- mean relative air humidity on day 2 preceding each day
- mean relative air humidity on day 3 preceding each day
- mean relative air humidity during the week preceding each day
- mean relative air humidity during the month preceding each day

6.6.1 Association between relative air humidity and acute aortic dissection irrespective of Stanford type

Apart from day 2 preceding days with vs. days without acute aortic dissection irrespective of Stanford type, area-wide mean relative air humidity was higher on and preceding days with acute aortic dissection. The results obtained did not reach statistical significance (Tables 40, 41).

6.6.2 Association between relative air humidity and acute type A dissection

The result for acute type A dissections was the same as for acute aortic dissections irrespective of Stanford type, with higher relative air humidity shown by application of the Wilcoxon test for all intervals apart from day 2 preceding days with vs. without acute type A dissection. Again, results did not reach statistical significance (Tables 40, 41).

6.6.3 Association between relative air humidity and acute type B dissection

The result obtained for acute type B dissections differs from those above in that relative air humidity was lower during all periods apart from day 3 preceding days with vs. days without acute type B dissection (Tables 40, 41).

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Mean relative air humidity on each day with vs. without dissection	No	2038	1096.81	2235290.50	No	2072	1094.17	2267126.00	No	2160	1100.04	2376079.50
	Yes	156	1106.57	172624.50	Yes	122	1154.01	140789.00	Yes	34	936.34	31835.50
	Total	2194			Total	2194			Total	2194		
Mean relative air humidity on day 1 preceding each day	No	2038	1096.05	2233748.00	No	2072	1094.31	2267404.50	No	2160	1099.19	2374258.50
	Yes	156	1116.46	174167.00	Yes	122	1151.73	140510.50	Yes	34	989.90	33656.50
	Total	2194			Total	2194			Total	2194		
Mean relative air humidity on day 2 preceding each day	No	2038	1099.05	2239858.00	No	2072	1098.22	2275510.50	No	2160	1098.27	2372262.50
	Yes	156	1077.29	168057.00	Yes	122	1085.28	132404.50	Yes	34	1048.60	35652.50
	Total	2194			Total	2194			Total	2194		
Mean relative air humidity on day 3 preceding each day	No	2038	1094.87	2231344.00	No	2072	1094.94	2268726.00	No	2160	1097.47	2370533.00
	Yes	156	1131.87	176571.00	Yes	122	1140.89	139189.00	Yes	34	1099.47	37382.00
	Total	2194			Total	2194			Total	2194		
Mean relative air humidity during week preceding each day	No	2038	1095.12	2231863.00	No	2072	1094.37	2267530.00	No	2160	1098.26	2372248.00
	Yes	156	1128.54	176052.00	Yes	122	1150.70	140385.00	Yes	34	1049.03	35667.00
	Total	2194			Total	2194			Total	2194		
Mean relative air humidity during month preceding each day	No	2038	1093.23	2228005.00	No	2072	1091.10	2260762.00	No	2160	1099.61	2375158.00
	Yes	156	1153.27	179910.00	Yes	122	1206.17	147153.00	Yes	34	963.44	32757.00
	Total	2194			Total	2194			Total	2194		

Table 40. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean relative air humidity on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Mean relative air humidity on each day with vs. without dissection	Mean relative air humidity on day 1 preceding each day	Mean relative air humidity on day 2 preceding each day	Mean relative air humidity on day 3 preceding each day	Mean relative air humidity during week preceding each day	Mean relative air humidity during month preceding each day
Mann-Whitney U	157549.500	156007.000	155811.000	153603.000	154122.000	150264.000
Wilcoxon W	2235290.500	2233748.000	168057.000	2231344.000	2231863.000	2228005.000
Z	-.185	-.388	-.413	-.703	-.635	-1.141
Asymp. Sig. (2-tailed)	.853	.698	.679	.482	.525	.254

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	119498.000	119776.500	124901.500	121098.000	119902.000	113134.000
Wilcoxon W	2267126.000	2267404.500	132404.500	2268726.000	2267530.000	2260762.000
Z	-1.014	-.973	-.219	-.779	-.954	-1.950
Asymp. Sig. (2-tailed)	.311	.331	.826	.436	.340	.051

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	31240.500	33061.500	35057.500	36653.000	35072.000	32162.000
Wilcoxon W	31835.500	33656.500	35652.500	2370533.000	35667.000	32757.000
Z	-1.495	-.998	-.454	-.018	-.450	-1.244
Asymp. Sig. (2-tailed)	.135	.318	.650	.985	.653	.214

Table 41. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean relative air humidity on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.7 PRECIPITATION

Precipitation values were provided in the form of hourly readings indicated in 0.1 mm/h by the nine meteorological stations. The hourly totals were added up to obtain local 24-hour totals, which were subsequently used to calculate the area-wide mean values used for statistical evaluation purposes:

- mean precipitation on each day of the study period
- mean precipitation on day 1 preceding each day
- mean precipitation on day 2 preceding each day
- mean precipitation on day 3 preceding each day
- mean precipitation during the week preceding each day
- mean precipitation during the month preceding each day

6.7.1 Association between precipitation and acute aortic dissection irrespective of Stanford type

Evaluation of area-wide mean total precipitation showed no clear trend, area-wide mean total amounts of precipitation being partly higher and partly being lower on and preceding days with aortic dissection than during the reference periods (Tables 42, 43).

6.7.2 Association between precipitation and acute type A dissection

The same result was obtained for acute type A dissections, i.e. no positive or negative correlation between area-wide mean precipitation and occurrence of acute type A dissection was discernible (Tables 42, 43).

6.7.3 Association between precipitation and acute type B dissection

Like for acute aortic dissections irrespective of Stanford type and acute type A dissections, no clear trend towards higher or lower area-wide mean precipitation was identifiable on and preceding days with vs. days without acute aortic type B dissection (Tables 42, 43).

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Mean precipitation on each day with vs. without dissection	No	2038	1100.03	2241868.00	No	2072	1097.92	2274896.00	No	2160	1099.48	2374887.00
	Yes	156	1064.40	166047.00	Yes	122	1090.32	133019.00	Yes	34	971.41	33028.00
	Total	2194			Total	2194			Total	2194		
Mean precipitation on day 1 preceding each day	No	2038	1097.21	2236115.00	No	2072	1093.98	2266732.00	No	2160	1100.60	2377298.00
	Yes	156	1101.28	171800.00	Yes	122	1157.24	141183.00	Yes	34	900.50	30617.00
	Total	2194			Total	2194			Total	2194		
Mean precipitation on day 2 preceding each day	No	2038	1097.90	2237513.00	No	2072	1098.55	2276203.00	No	2160	1096.86	2369225.00
	Yes	156	1092.32	170402.00	Yes	122	1079.61	131712.00	Yes	34	1137.94	38690.00
	Total	2194			Total	2194			Total	2194		
Mean precipitation on day 3 preceding each day	No	2038	1096.34	2234331.50	No	2072	1099.55	2278264.00	No	2160	1094.44	2363982.50
	Yes	156	1112.71	173583.50	Yes	122	1062.71	129651.00	Yes	34	1292.13	43932.50
	Total	2194			Total	2194			Total	2194		
Mean precipitation during week preceding each day	No	2038	1095.73	2233102.00	No	2072	1097.00	2272988.00	No	2160	1096.31	2368029.00
	Yes	156	1120.60	174813.00	Yes	122	1105.96	134927.00	Yes	34	1173.12	39886.00
	Total	2194			Total	2194			Total	2194		
Mean precipitation during month preceding each day	No	2038	1100.54	2242903.50	No	2072	1100.82	2280906.50	No	2160	1097.18	2369912.00
	Yes	156	1057.77	165011.50	Yes	122	1041.05	127008.50	Yes	34	1117.74	38003.00
	Total	2194			Total	2194			Total	2194		

Table 42. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean precipitation on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Mean precipitation on each day with vs. without dissection	Mean precipitation on day 1 preceding each day	Mean precipitation on day 2 preceding each day	Mean precipitation on day 3 preceding each day	Mean precipitation during week preceding each day	Mean precipitation during month preceding each day
Mann-Whitney U	153801.000	158374.000	158156.000	156590.500	155361.000	152765.500
Wilcoxon W	166047.000	2236115.000	170402.000	2234331.500	2233102.000	165011.500
Z	-.685	-.078	-.107	-.315	-.472	-.813
Asymp. Sig. (2-tailed)	.493	.938	.915	.753	.637	.416

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	125516.000	119104.000	124209.000	122148.000	125360.000	119505.500
Wilcoxon W	133019.000	2266732.000	131712.000	129651.000	2272988.000	127008.500
Z	-.130	-1.085	-.325	-.632	-.152	-1.013
Asymp. Sig. (2-tailed)	.896	.278	.745	.527	.879	.311

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	32433.000	30022.000	35345.000	30102.500	34149.000	36032.000
Wilcoxon W	33028.000	30617.000	2369225.000	2363982.500	2368029.000	2369912.000
Z	-1.184	-1.850	-.380	-1.828	-.701	-.188
Asymp. Sig. (2-tailed)	.236	.064	.704	.068	.483	.851

Table 43. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean precipitation on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.8 WIND SPEED

The following area-wide mean wind speed values, determined on the basis of the 24-hour values derived from the hourly readings provided by the nine meteorological stations, were used for statistical evaluation purposes:

- mean wind speed on each day of the study period
- mean wind speed on day 1 preceding each day
- mean wind speed on day 2 preceding each day
- mean wind speed on day 3 preceding each day
- mean wind speed during the week preceding each day
- mean wind speed during the month preceding each day

6.8.1 Association between wind speed and acute aortic dissection irrespective of Stanford type

Evaluation of area-wide mean wind speed on and preceding days with vs. days without occurrence of acute aortic dissection irrespective of Stanford type showed higher wind speeds for all periods evaluated other than the 30-day interval. The p-values returned by the Wilcoxon test were 0.034, 0.010, 0.030, 0.360, 0.015 and 0.977 (Tables 44, 45).

6.8.2 Association between wind speed and acute type A dissection

Wind speeds were similarly higher on and preceding days with occurrence of acute type A dissection than on and preceding days without, lower wind speeds being shown only for the 30-day intervals, the Wilcoxon test returing p-values of 0.035, 0.014, 0.085, 0.307, 0.033 and 0.719 (Tables 44, 45).

6.8.3 Association between wind speed and acute type B dissection

Wind speeds were higher on and preceding days with vs. days without occurrence of acute type B dissection for all intervals evaluated. Once again, results for acute type B dissection differed from those for acute aortic dissection irrespective of type and acute type A dissections in that they did not reach statistical significance at all (Tables 44, 45).

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Mean wind speed on each day with vs. without dissection	No	2038	1089.57	2220535.00	No	2072	1090.57	2259657.00	No	2160	1096.66	2368793.00
	Yes	156	1201.15	187380.00	Yes	122	1215.23	148258.00	Yes	34	1150.65	39122.00
	Total	2194			Total	2194			Total	2194		
Mean wind speed on day 1 preceding each day	No	2038	1087.86	2217062.50	No	2072	1089.46	2257371.00	No	2160	1096.11	2367606.50
	Yes	156	1223.41	190852.50	Yes	122	1233.97	150544.00	Yes	34	1185.54	40308.50
	Total	2194			Total	2194			Total	2194		
Mean wind speed on day 2 preceding each day	No	2038	1089.39	2220185.50	No	2072	1091.85	2262306.50	No	2160	1095.28	2365794.00
	Yes	156	1203.39	187729.50	Yes	122	1193.51	145608.50	Yes	34	1238.85	42121.00
	Total	2194			Total	2194			Total	2194		
Mean wind speed on day 3 preceding each day	No	2038	1094.08	2229727.50	No	2072	1094.15	2267076.50	No	2160	1097.48	2370566.00
	Yes	156	1142.23	178187.50	Yes	122	1154.41	140838.50	Yes	34	1098.50	37349.00
	Total	2194			Total	2194			Total	2194		
Mean wind speed during week preceding each day	No	2038	1088.36	2218077.00	No	2072	1090.51	2259533.00	No	2160	1095.58	2366459.00
	Yes	156	1216.91	189838.00	Yes	122	1216.25	148382.00	Yes	34	1219.29	41456.00
	Total	2194			Total	2194			Total	2194		
Mean wind speed during month preceding each day	No	2038	1097.61	2236928.00	No	2072	1098.68	2276467.00	No	2160	1096.47	2368376.00
	Yes	156	1096.07	170987.00	Yes	122	1077.44	131448.00	Yes	34	1162.91	39539.00
	Total	2194			Total	2194			Total	2194		

Table 44. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean speed of wind on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Area-wide mean wind speed on each day with vs. without dissection	Area-wide mean wind speed on day 1 preceding each day	Area-wide mean wind speed on day 2 preceding each day	Area-wide mean wind speed on day 3 preceding each day	Area-wide mean wind speed during week preceding each day	Area-wide mean wind speed during month preceding each day
Mann-Whitney U	142794.000	139321.500	142444.500	151986.500	140336.000	158741.000
Wilcoxon W	2220535.000	2217062.500	2220185.500	2229727.500	2218077.000	170987.000
Z	-2.120	-2.576	-2.166	-.915	-2.443	-.029
Asymp. Sig. (2-tailed)	.034	.010	.030	.360	.015	.977

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	112029.000	109743.000	114678.500	119448.500	111905.000	123945.000
Wilcoxon W	2259657.000	2257371.000	2262306.500	2267076.500	2259533.000	131448.000
Z	-2.112	-2.448	-1.723	-1.021	-2.130	-.360
Asymp. Sig. (2-tailed)	.035	.014	.085	.307	.033	.719

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	34913.000	33726.500	31914.000	36686.000	32579.000	34496.000
Wilcoxon W	2368793.000	2367606.500	2365794.000	2370566.000	2366459.000	2368376.000
Z	-.493	-.817	-1.311	-.009	-1.130	-.607
Asymp. Sig. (2-tailed)	.622	.414	.190	.993	.259	.544

Table 45. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean speed of wind on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

6.9 WIND DIRECTION

The following wind direction values, determined on the basis of the 24-hour values derived from the hourly readings provided by the nine meteorological stations, were used for statistical evaluation purposes:

- mean wind direction on each day of the study period
- mean wind direction on day 1 preceding each day
- mean wind direction on day 2 preceding each day
- mean wind direction on day 3 preceding each day
- mean wind direction during the week preceding each day
- mean wind direction during the month preceding each day

Application of the Wilcoxon test yielded statistically significant results for neither of the categories of acute aortic dissections.

6.9.1 Association between wind direction and acute aortic dissection irrespective of Stanford type

Evaluation of area-wide mean wind direction values showed no discernible trend, area-wide mean values being partly higher and partly being lower on and preceding days with vs. days without dissection irrespective of Stanford type (Tables 46, 47).

6.9.2 Association between wind direction and acute type A dissection

A similar result was obtained for acute type A dissections, i.e. no positive or negative association between area-wide mean wind direction values and occurrence of acute type A dissection was shown (Tables 46, 47).

6.9.3 Association between wind direction and acute type B dissection

Like for acute aortic dissections irrespective of Stanford type and acute type A dissections, no clear trend regarding wind direction was identifiable on and preceding days with vs. with acute aortic type B dissection (Tables 46, 47).

	A+B	N	Mean rank	Sum of ranks	A	N	Mean rank	Sum of ranks	B	N	Mean rank	Sum of ranks
Mean direction of wind on each day with vs. without dissection	No	2038	1094.26	2230112.00	No	2072	1091.79	2262196.50	No	2160	1099.92	2375830.50
	Yes	156	1139.76	177803.00	Yes	122	1194.41	145718.50	Yes	34	943.66	32084.50
	Total	2194			Total	2194			Total	2194		
Mean direction of wind on day 1 preceding each day	No	2038	1095.55	2232723.50	No	2072	1096.43	2271809.00	No	2160	1096.68	2368829.50
	Yes	156	1123.02	175191.50	Yes	122	1115.62	136106.00	Yes	34	1149.57	39085.50
	Total	2194			Total	2194			Total	2194		
Mean direction of wind on day 2 preceding each day	No	2038	1097.36	2236416.00	No	2072	1098.14	2275348.50	No	2160	1096.75	2368982.50
	Yes	156	1099.35	171499.00	Yes	122	1086.61	132566.50	Yes	34	1145.07	38932.50
	Total	2194			Total	2194			Total	2194		
Mean direction of wind on day 3 preceding each day	No	2038	1103.46	2248857.50	No	2072	1103.11	2285651.50	No	2160	1097.74	2371121.00
	Yes	156	1019.60	159057.50	Yes	122	1002.16	122263.50	Yes	34	1082.18	36794.00
	Total	2194			Total	2194			Total	2194		
Mean direction of wind during week preceding each day	No	2038	1099.83	2241447.00	No	2072	1100.13	2279468.50	No	2160	1097.17	2369893.50
	Yes	156	1067.10	166468.00	Yes	122	1052.84	128446.50	Yes	34	1118.28	38021.50
	Total	2194			Total	2194			Total	2194		
Mean direction of wind during month preceding each day	No	2038	1099.22	2240216.50	No	2072	1099.40	2277962.50	No	2160	1097.30	2370169.00
	Yes	156	1074.99	167698.50	Yes	122	1065.18	129952.50	Yes	34	1110.18	37746.00
	Total	2194			Total	2194			Total	2194		

Table 46. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean direction of wind on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

Test Statistics: Grouping variable: Occurrence of dissection

	Mean direction of wind on each day with vs. without dissection	Mean direction of wind on day 1 preceding each day	Mean direction of wind on day 2 preceding each day	Mean direction of wind on day 3 preceding each day	Mean direction of wind during week preceding each day	Mean direction of wind during month preceding each day
Mann-Whitney U	152371.000	154982.500	158675.000	146811.500	154222.000	155452.500
Wilcoxon W	2230112.000	2232723.500	2236416.000	159057.500	166468.000	167698.500
Z	-.865	-.522	-.038	-1.594	-.622	-.460
Asymp. Sig. (2-tailed)	.387	.602	.970	.111	.534	.645

Test Statistics: Grouping variable: Occurrence of type A dissection

Mann-Whitney U	114568.500	124181.000	125063.500	114760.500	120943.500	122449.500
Wilcoxon W	2262196.500	2271809.000	132566.500	122263.500	128446.500	129952.500
Z	-1.739	-.325	-.195	-1.711	-.801	-.580
Asymp. Sig. (2-tailed)	.082	.745	.845	.087	.423	.562

Test Statistics: Grouping variable: Occurrence of type B dissection

Mann-Whitney U	31489.500	34949.500	35102.500	36199.000	36013.500	36289.000
Wilcoxon W	32084.500	2368829.500	2368982.500	36794.000	2369893.500	2370169.000
Z	-1.427	-.483	-.441	-.142	-.193	-.118
Asymp. Sig. (2-tailed)	.154	.629	.659	.887	.847	.906

Table 47. Study area 01 Jul 2004 through 30 Jun 2010: Wilcoxon test comparing area-wide mean direction of wind on and preceding days with vs. days without occurrence of acute aortic dissection, shown for acute aortic dissections irrespective of Stanford type, acute type A and acute type B dissections

7 DISCUSSION

7.1 DEMOGRAPHIC ASPECTS

Our study population comprising 156 patients fairly reflects the characteristics of the patient groups described by other investigators as far as its demographic composition is concerned. With a mean age of 61.48±12.33 years and a share of 69.2% male vs. 30.8% female patients, it does not differ relevantly, for example, from a population of 464 patients described by the IRAD investigators in 2000 [15], where the mean age was reported to be 63 years, and the share of male patients 65.3%. Similar characteristics were also indicated for some of the larger study populations included in studies investigating chronobiological rhythmicity or seasonal fluctuations in the frequency of aortic dissections such as a population of 389 subjects described by Kobza et al. [135] in 2002, where 75.58% of the patients were male and 24.42% female, or a population of 204 subjects described by Lasica et al. [129] in 2006, where the shares of male and female patients were 66.5% and 33.5%, respectively.

7.2 SHARES OF ACUTE TYPE A AND TYPE B DISSECTIONS

The share of acute type A dissections in our study population was 78.3%, while only 21.7% were diagnosed with type B dissection. Our share of type A dissections is therefore considerably higher than the figures published for type A dissections, for example, by the IRAD investigators in 2006 [66], who reported shares of 62.2% and 37.8% for type A and type B dissections, respectively, for a study population of 1256 patients, or by Lasica et al. [129], whose study population comprised 65.7% of type A and 34.3% of type B dissections. Percentages differing even more from ours were published by Sumiyoshi et al. [128] in 2002, who investigated weekly and seasonal variation in the occurrence of acute aortic dissection in a population of 387 patients and reported untypically reversed shares of 47.5% and 52.5% for type A and type B dissections, respectively. Figures fairly resembling ours were published by Kobza et al. [135] in 2002, who reported a share of 72.50% of their study population of 389 patients being diagnosed with acute type A dissection, while 27.50% were found to suffer from acute type B dissection.

These varying shares of type A and type B dissections may be explained by differences in organization of patient care and different levels of diagnostic and therapeutic options available at peripheral hospitals in different countries. Patients with acute type B dissection need not necessarily be transferred to a tertiary care facility, provided that medical care is organized in such a way that cases of type B dissection can be efficiently diagnosed and managed at peripheral hospitals, whereas practically all acute type A dissections will be transferred to the nearest tertiary referral center capable of providing emergent cardiovascular surgery.

This may account for the fact that acute type B dissections seem to be underrepresented in the present study. It may also explain why the results for type B dissections differ from those obtained for the entire study population or the subgroup of the type A dissections and why most of the results for the type B dissections failed to reach statistical significance.

7.3 CIRCANNUAL DISTRIBUTION OF AND VARIATIONS IN FREQUENCY OF ACUTE AORTIC DISSECTION

Analysis of our study population demonstrated a variation in the frequency of occurrence of acute aortic dissections throughout the year. It shows a clear winter peak with a trough during the warmer seasons for acute aortic dissections irrespective of Stanford type and acute type A dissections, while acute type B dissections follow a different pattern with a peak in spring and a fairly even distribution over the remaining seasons of the year.

A similar winter peak in the occurrence of acute aortic dissections was found by most other authors investigating the subject. [123] [124] [128] [129] Kobza et al., investigating differences in seasonal rhythmicity between acute type A and type B dissections in a population of 389 patients over a period of 11 years, reported not only a winter peak for type A dissections but also a delayed peak in spring for type B dissections that coincides with the seasonal distribution identified in our study population. [135]

Several groups of investigators moreover reported circannual variation to be more pronounced in women as opposed to men, in patients with type B dissection as opposed to patients with type A dissection, in younger as opposed to older individuals, and in patients with as opposed to patients without a history of diabetes or arterial hypertension. The explanations suggested to explain these findings include speculations that type A dissection may require a higher triggering shear stress than type B dissection, that the elderly may be protected by a higher degree of autonomic dysfunction resulting in smaller variation in sympathetic nervous system activity, and that antihypertensive medication may blunt response to seasonal changes. [124] [129]

Overall, the winter peak in acute aortic dissections thus identified by most authors coincides not only with the seasonal fluctuation reported for other major adverse cardiovascular events, but also with the winter peak reported for systemic blood pressure, which is not only the major risk factor of acute aortic dissection but also known to change with temperature.

7.4 ASSOCIATION BETWEEN METEOROLOGICAL CONDITIONS AND ACUTE AORTIC DISSECTION

7.4.1 Association between temperature and acute aortic dissection

Statistical evaluation has confirmed the hypothesis that lower temperatures prevailed on and preceding days with occurrence of acute aortic dissection than on and preceding days on which acute aortic dissection did not occur. Temperature has been reported, as a matter of fact, to be the most important meteorological parameter exerting an influence on frequencies of occurrence from the earliest investigations of the association between weather and cardiovascular mortality onward, with almost all authors reporting an inverse relationship between temperature and cardiovascular mortality. [176] [177] [[178].

Additionally, it was observed that annual cardiovascular mortality in Europe increases from south to north, i.e. from the Mediterranean countries to Scandinavia, which may be attributable to more than lifestyle and dietary factors. Instead, a correlation may also be seen between increasing cardiovascular death rates, on the one hand, and increasing latitudes and decreasing temperatures, on the other, blood pressure once again being suggested as a major risk factor fluctuating with temperature. [179] Similarly focusing on climate, a group of investigators in the framework of the International Registry of Aortic Dissections investigated the influence exerted by meteorological conditions on the occurrence of acute aortic dissection in two different climate settings, i.e. a cold and a temperate zone. Reporting a winter peak for both climates, they came to the conclusion that temperature changes and/or endogenous circannual rhythms are probably more relevant than absolute temperature values as far as the frequency of occurrence of acute aortic dissection is concerned. [180]

V. Benouaich et al., studying 206 cases of acute type A dissection in south–western France to investigate differences in the monthly and seasonal incidence of acute aortic dissection, similarly found that cold weather as well as drops in temperature irrespective of the season are associated with the incidence of acute aortic dissection. Like most other investigators, they suggest that an increase in sympathetic activity causing an increase in blood pressure may be the causative factor. [143] C. Repanos et al., in contrast, reviewed a small group of 26 patients who underwent emergency surgery following aortic dissection in the period between 1996 and 2002 but were not able to establish a statistically significant correlation between temperature and the incidence of acute aortic dissection, nor did they succeed in providing evidence of any kind of seasonal variation at all. [141] This may, however, be due to the small size of their study population as well as to the fact that the weather data for a study area covering 50 miles in diameter was obtained from one central weather station only so that weather variations within the study area may not have been properly reflected.

7.4.2 Association between atmospheric pressure and acute aortic dissection

An association between atmospheric pressure and acute aortic dissection has not been conclusively proven yet. Repanos et al. [141] investigated a possible impact of atmospheric pressure on acute aortic dissection but found no relevant correlation.

The statistical evaluation of our data, in contrast, has shown a relevant trend towards lower atmospheric pressure levels prevailing on and preceding days with vs. days without acute aortic dissection. Additionally, the amplitudes between maximum and minimum atmospheric pressure on and preceding days with vs. days without acute aortic dissection irrespective of Stanford type and acute type A dissection were higher than on and preceding days on which aortic dissection did not occur.

These findings are in keeping with the results of a number of investigators who studied possible correlations between atmospheric pressure and acute aortic pathologies but focused on ruptured aortic aneurysms rather than aortic dissection. Harkin et al. [138], for example, acquired data on 144 cases of ruptured abdominal aortic aneurysms and found that low atmospheric pressure is associated with high abdominal aneurysm rupture rates in Northern Ireland. They demonstrated significantly lower atmospheric pressure values on days when ruptures occurred than on days without rupture, the association being especially marked in patients with a known history of hypertension. Similar findings were published by Bown et al. [137] in 2002, who reviewed 223 confirmed cases of ruptured abdominal aortic aneurysm during a 10 year period and demonstrated a significant relationship between atmospheric pressure and rupture of abdominal aortic aneurysms. Their results show that mean monthly atmospheric pressure was significantly lower in calendar months preceding months in which high numbers of cases of ruptured abdominal aortic aneurysm were admitted. Killeen et al. [139] reviewed a total of 201 cases presenting with ruptured abdominal aortic aneurysms over a 15 year period at two hospitals in Ireland and also found a negative correlation between the number of patients admitted per month and the mean atmospheric pressure during the previous month. Additionally, they reported significantly greater daily atmospheric pressure variability on days when patients with ruptured abdominal aortic aneurysms were admitted than during the reference periods.

A significant effect of changes in atmospheric pressure on the frequency of vascular incidents was also demonstrated by Landers et al. [181], who observed that patients with rupture of intracranial aneurysms tended to present in groups, and particularly so after abrupt changes in weather. Their results are in keeping with those of a number of further authors such as Jehle et al. [182] or Chyatte et al. [183], who were able to show that the incidence of subarachnoid hemorrhage increased on days with marked fluctuations in atmospheric pressure.

All these findings are also relevant with a view to acute aortic dissection, as it may be assumed that the mechanisms leading to non-iatrogenic, non-traumatic acute injury of arterial vessels such as rupture of abdominal or intracranial aneurysms are at least partly the same as those contributing to aortic dissection.

7.4.3 Relevance of relative air humidity, precipitation and wind

Relative air humidity, precipitation and wind were not considered to be of primary importance as factors contributing to increased incidence of acute aortic dissection. Mean wind speed was, in fact, the only meteorological influence that was shown to be of some relevance, being higher on and during most of the periods preceding days with vs. days without acute aortic dissection.

Overall, they may probably be considered as secondary influences contributing to cold stress by additionally drawing heat from the body, the degree of coldness perceived by the human body and answered by physiological responses known to be increased by humidity, precipitation or wind chill.

7.5 DIFFERENCES BETWEEN TYPE A AND TYPE B DISSECTIONS

Acute type A dissections and, as acute type A dissections account for 78.2% of all acute aortic dissections included in the present study, acute aortic dissections irrespective of Stanford type show a marked winter peak and a trough during the warm season, while type B dissections show a peak in spring but otherwise little seasonal variability. In this respect, Mehta et al. argue that, compared with type B dissection, type A dissection may require a higher triggering shear stress than type B dissections. [124] Correspondingly, it may be assumed that acute type B dissections tend to occur at fairly the same rate throughout the year and lack particular peaks unless very significant and abrupt changes in meteorological conditions occur while the sections of the aorta involved in type A dissections are more susceptible to meteorological influences.

In addition to the different shares of patients with acute type A and type B dissections referred to our clinic as a consequence of the difference in treatment algorithms for acute type A and type B dissections, this may help explaining the different findings reported for type A and type B dissections.

8 CONCLUSIONS

This study confirms the monthly and seasonal variability in the occurrence of acute aortic dissection described previously as well as the differing peaks for acute type A and type B dissections suggested by a number of authors. Additionally, a relevant trend towards lower temperatures and lower atmospheric pressure levels prevailing on and preceding days with vs. days without acute aortic dissection has been identified. Acute aortic dissections were associated with higher fluctuations in atmospheric pressure and higher wind speeds. Type A and type B dissections have been shown to differ as far as the association between their incidence and the meteorological conditions prevailing at and preceding the date of onset is concerned.

Overall, and in particular taking the results published by previous authors in terms of the correlation between meteorological conditions and the likelihood of occurrence of acute aortic pathologies into account, further investigation of the implications of the susceptibility of aortic disease to meteorological conditions seems to be warranted.

With modern imaging methods available on a decentralized basis and increasing numbers of patients covered by monitoring programs after incidental diagnosis of aortic aneurysms, second thought may be given to the association between meteorological conditions, on the one hand, and the likelihood of acute aortic dissection or rupture of aortic aneurysms, on the other, with a view to adequate timing of elective aortic aneurysm repair, avoidance of exposure of predisposed patients to acute temperature changes such as may result from travelling or pressure changes occurring, for example, from air travel, etc. Physicians should be aware of the additional protection that can be afforded to predisposed individuals by adjusting ß-blocking or anti-hypertensive medication on a seasonal basis to optimize protection against blood pressure surges caused by cold stress, while future implications may arise from ongoing climatic change in combination with aging populations and increasing cardiovascular morbidity.

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