Senior Trauma Patients

An Integrated Approach

Hans-Christoph Pape
Stephen L. Kates
Christian Hierholzer
Heike A. Bischoff-Ferrari
Editors

Springer

Senior Trauma Patients

Hans-Christoph Pape
Stephen L. Kates
Christian Hierholzer
Heike A. Bischoff-Ferrari
Editors

Senior Trauma Patients

An Integrated Approach

Springer

Editors
Hans-Christoph Pape
Department of Trauma Surgery
University Hospital Zurich
Zürich, Switzerland

Stephen L. Kates
Department of Orthopaedic Surgery
Virginia Commonwealth University
Richmond, VA, USA

Christian Hierholzer
Department of Trauma Surgery
University Hospital Zurich
Zürich, Switzerland

Heike A. Bischoff-Ferrari
Department of Aging Medicine
and Aging Research
City Hospital Zurich-Waid
Zurich University
Zürich, Switzerland

ISBN 978-3-030-91482-0 ISBN 978-3-030-91483-7 (eBook)
https://doi.org/10.1007/978-3-030-91483-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

We would like to dedicate this book to Prof. Dr. Hans-Peter Simmen, Prof. emeritus, Department of Trauma, University of Zurich, Switzerland, for his accomplishments in regard to orchestrating the first certified Geriatric Trauma Center in Switzerland.

Foreword

It is well known that people are getting older in all industrialized countries offering good quality of life as well as modern medical treatment. For instance, statistical mean age is as high as 86 years for women and 82 years for men in Switzerland, respectively. Similar figures are reported from other European nations. To provide optimal treatment for aged persons, many hospitals established specialized geriatric departments in the last years. Even congresses with tailored programs are held to fit the scientific needs for treating elderly people.

A femur fracture in 80-year-old person may not only be a broken bone. In the presence of comorbidities, it is an "attack on the entire organism." Identical surgical principles are applied. However, impaired bone quality and comorbidities make the healing process much more complicated. The follow-up care requires the advice of many specialists; the rehabilitation procedures have to be adapted.

The people 70+ suffer more severe injuries. According to publicly available data from the "German Trauma Registry," 25% of the polytraumatized patients are over 70 years old. These injuries include not only high velocity trauma such as road traffic accidents but rather low impact trauma resulting from a fall on stairs. It is not unusual that frail patients present with head injury (intracerebral hematoma), serial rib fractures with lung contusions in addition to a hip fracture. Many persons 70+ are on anticoagulant or antiplatelet agents which aggravate their condition.

How to go on if you are called to an aged patient suffering from fractures in addition to many comorbidities such as an insulin-dependent diabetes and bleeding disorders due to antiplatelet agents following stent implantation ? Please, consult this textbook.

This textbook *Senior Trauma Patients: An Integrated Approach* is designed to improve diagnostics and treatments of patients 70+, who belong to the most difficult ones, a doctor has to deal with. The editors are to be congratulated: They realized a comprehensive overview on geriatric trauma. I am sure that this reference work will help to better understand and treat the sickest patients.

Hans-Peter Simmen
Professor Emeritus of Surgery, Former Chairman
of the Department of Traumatology
University Hospital Zurich
Zurich, Switzerland

Preface

The world's aging population is rapidly growing, and many older adults will suffer low energy trauma due to falls or accidents. Over the past decade, many initiatives have been developed to improve the management of older adults with such injuries.

The two most popular approaches include efforts to improve the aftercare provided by orthopedic trauma surgeons and the interdisciplinary comanagement approach that involves both geriatricians and surgeons. The latter approach has been adopted widely and involves care in the hospital, including medication management, peri-surgical care, and prevention of secondary fractures by standardized protocols.

Among these initiatives are Orthogeriatric Management with the Fragility Fracture Network (FFN) and the AO, the Geriatric Trauma Center certification initiative by the German Trauma Association and the German Geriatric Association, and the "Own the Bone" by the American Orthopaedic Association (AOA).

This book covers the essential aspects of geriatric fracture management, perioperative care, postoperative ICU management, and follow-up care. Because the number of geriatric (poly-) trauma cases will rise significantly, it includes a new standard operating procedure (SOP) for these and other patients. Outcome differences (compared with younger patients) are explained for major fracture types along with physiological compensation mechanisms, frailty, and nutrition. We hope that this comprehensive text will add to the general knowledge of this important topic.

Zürich, Switzerland — Hans-Christoph Pape
Richmond, VA, USA — Stephen L. Kates
Zürich, Switzerland — Christian Hierholzer
Zürich, Switzerland — Heike A. Bischoff-Ferrari

Contents

Part VIII Rehabilitation and Outcomes

Part I

Introduction: Physiology of Ageing

1 Epidemiology

Marianne Comeau-Gauthier, Daniel Axelrod, and Mohit Bhandari

1.1 Introduction

Geriatric patients may pose unique and significant challenges in the trauma setting with regard to injury severity assessment, resuscitation, and treatment, when compared to patients under the age of 65 years. Apart from the substantially higher morbidity and mortality [8, 9], one must recognize the critical and unique psychosocial components in the care of the elderly [10]. While special considerations should be made for the geriatric polytraumatized patient, current evidence-based recommendations are founded primarily on retrospective studies including a significant portion of registry-based cohort studies and a limited number of prospective studies [7, 11, 12]. To date, no randomized controlled trials have been performed to guide best practice and improve outcomes.

The geriatric trauma population is commonly defined as patients aged 65 and older [12], although trauma mortality increases significantly from the age of 55 [13–19], independently from the degree of injury. Additionally, some authors have reported specific predictive factors that may apply for patients aged 80 years and older only [14, 20]. The National Trauma Data Bank (NTDB) reports the first peak in the number of trauma-related injuries leading to admission to a trauma center between ages of 14–29 years old, primarily from motor vehicle-related accidents, and reports a second peak starting after the age of 50 years, when falls begin to increase [1]. Males account for 70% of all incidents up to age 70, while after 71 years, most patients are female [1].

1.2 Clinical Significance of the Aging Process on the Polytraumatized Patient

1.2.1 Age-Related Physiologic Decline

Despite defining the elderly as aged above 65 years, the impact of aging on trauma has been found to be as early as 40 years [21]. The combination of age-related immunosenescence and trauma-related immune dysregulation likely contributes to a higher mortality and morbidity rate in older adults [22]. It was found that elderly victims had increased tissue inhibitor of metalloproteinases-2 (TIMP-2) levels [23], an indicator of

M. Comeau-Gauthier · D. Axelrod (✉)
Division of Orthopedic Surgery, McMaster University, Hamilton, ON, Canada
e-mail: marianne.comeaugauthier@medportal.ca; daniel.axelrod@medportal.ca

M. Bhandari
Division of Orthopedic Surgery, McMaster University, Hamilton, ON, Canada

Department of Health Research Methods, Evidence and Impact (HEI), McMaster University, Hamilton, ON, Canada
e-mail: bhandam@mcmaster.ca

H.-C. Pape et al. (eds.), *Senior Trauma Patients*, https://doi.org/10.1007/978-3-030-91483-7_1

the severity of pathologic immune activation, and polytraumatized geriatric patients more often develop SIRS compared with younger patients [24].

Decreased myocardial pumping efficacy [25–27], decline in myocardial conducting system responsiveness to demands on the cardiovascular system [28, 29], hypertension [30], and accumulation of atherosclerotic plaque [26] lead to a narrower range of end diastolic volumes required to preserve and optimize cardiac function/output. These changes in the cardiovascular system translate into a reduced ability to respond to hypovolemia and shock and challenges during resuscitation, as both under-resuscitation and over-resuscitation are harmful [31], which is why some authors advocate for a lower threshold in implementing invasive monitoring in this population [12, 32, 33]. The loss of functional respiratory reserve, decreased lung compliance, loss of alveolar surface, and increased ventilation/perfusion mismatch [34] added with higher rates of multiple rib fractures with a seemingly lower transfer of energy [35–37] could partially account for a higher number of days on ventilators [3] and a higher risk of pulmonary infection [37] associated with elderly victims. Increased prevalence of osteoporosis in this population [38] leads to higher severity fractures compared to younger patients with a similar mechanism of injury. Increased intracranial space due to brain atrophy and greater stretching of intracranial vessels directly increase the rate of intracranial bleedings [18, 39].

1.2.2 Effect on Triage

In a 10-year retrospective review (1994–2004) of the Maryland Ambulance Information System by Chang et al. [40], elderly victims were three times more likely to be under-triaged compared with younger patients, which remained significant on multivariate analysis (controlling for year, sex, injury, mechanism, transport reasons, emergency medical service provider level training, jurisdictional region). These results were corroborated by two subsequent large registry-based cohort studies [41, 42]. These findings are highly significant as under-triage of an elderly victim leads to fourfold the mortality and discharge disability rate as compared to their younger counterparts [43].

Several factors have been reported to impair adequate triage of elderly patients, including healthcare provider bias, unrecognized comorbidities, communication impairment, inaccuracy of Glasgow Coma Scale (GCS) scoring in geriatric patients, and lack of reliable parameters indicator of injury severity and sufficient resuscitation. Elderly victims are found to be less likely to trigger a trauma team activation, despite a similar percentage of ISS above 15 and the higher need for urgent craniotomy and orthopedic procedures [43]. A noisy and chaotic trauma bay is certainly not favorable to doctor-patient communication and history taking in a “hard of hearing” elderly, which is often assumed as intellectual impairment [10]. Mental status examinations and GCS scoring can be particularly difficult in geriatric patients with preexisting cognitive decline, hearing impairment, or sequelae of previous strokes [44]. Furthermore, heart rate and blood pressure were not found to be predictive of severe impending mortality and inadequate resuscitation in patients aged above 65 years old [43]. Increased mortality has been reported among the elderly with heart rates greater than 90 beats per minute and systolic blood pressure less than 110 mmHg, while the same increase in mortality is not seen in younger patients [45].

Current guidelines from the America Trauma Life Support (ATLS) recommend transporting any patient older than 55 years old to a trauma center [46], while the Eastern Association from the Surgery of Trauma (EAST) guidelines recommend geriatric-specific care for any patient older than 65 years old [12]. Recent evidence-based review from EAST has shown decreased mortality in severely injured geriatric patients treated in trauma care centers as compared to non-trauma centers, and therefore, recommend initial assessment and care in a certified trauma center [7].

1.3 Mechanisms of Injury

While trauma is the fifth cause of death in the elderly, blunt trauma secondary to a fall from any height is the leading cause of high-energy injuries in the geriatric patient [1, 3, 47–50], representing nearly three-quarters of all traumas in this population [3], followed by traffic-related accidents, either as the driver or as a pedestrian hit by a car [1, 49, 50]. Penetrating trauma, firearm injuries, assault, and burns are much less common. Adults aged over 65 are almost two to three times more likely to die of their injuries, even after controlling for race, sex, injury mechanism, and ISS [3, 50, 51] Geriatric status was found to be one of the main independent factors for mortality across all mechanisms of injury [49].

A 10-year retrospective review found that nearly 60% of trauma admission in the geriatric population are secondary to high-energy mechanism [3]. However, elderly presented following low or high-energy injury mechanism are nearly seven times more likely to have higher Abbreviated Injury Score (AIS) to any body region [2] and usually present with a higher ISS [3] as compared with younger patients.

Traumatic brain injuries (TBI) are the leading cause of trauma-related mortality and morbidity in the elderly, with falls as the leading causative mechanism (51%), followed by motor vehicle traffic crashes (9%) [4]. Independently of the mechanism of injury, subdural hematomas are three times more likely in the elderly population [3, 5]. Extensive guidelines on primary assessment, imaging indications, and normalization of the lowering of the International Normalized Radio (INR) have been published in an attempt to prevent the disastrous outcomes associated with severe TBIs [52–54].

A 6-year retrospective chart review (2004–2010) from a level I trauma center reported the frequency of fracture location in high-energy (ISS ≥ 16) geriatric traumas. Elderly most often sustained a fracture to the spine (74%), followed by the pelvis (35%), femur (31%), forearm (24%), clavicle (23%), scapula (21%), tibia/fibula (19%), ankle (17%), acetabulum (10%), humerus shaft (7%), hand (7%), proximal humerus (5%), and foot (4%) [55]. Of all the spine injuries, only 13% required surgery [55]. Injuries to the odontoid and the C1–C2 level are the most frequent spinal injuries [5, 6] and can result from a seemingly trivial mechanism of injuries such as a fall from standing or seating height. Around 95% of the pelvis fractures did not require surgical management from which lateral compression injury types are most frequently encountered [56], whereas 10% of the acetabulum fracture were treated operatively [55]. Long bones, pelvic, rib, and sternal fractures are most commonly seen due to osteoporosis. These fractures are usually more complex secondary to bone osteoporosis, making it more fragile or the presence of prosthesis/implants. Adults aged 70 years old are less likely to have solid organ injuries compared with younger patients [57]. Although abdominal traumas are rare, they, much like other injuries, have four times higher mortality compared to the younger trauma patients [5, 58] and are significantly more frequent in the non-survivors [59].

1.3.1 Falls

In the largest aggregation of U.S./Canadian trauma registry data, NTDB reports falls as the leading cause of admission in a trauma center, while the largest number of deaths are caused by fall-related injuries [1]. Elderly patients presented with an ISS ≥ 16 were more likely to have sustained a fall from any height [48, 60] and less likely to have sustained a firearm injury [60]. When comparing younger and older groups, same-level falls resulted in serious injury 30% of the time in the elderly group compared with 4% in the younger patients [48]. In the same study, falls from standing height were also responsible for an ISS above 15, approximately 30-fold more in the elderly group [48].

Low energy falls are responsible for more than 50% of traumatic-related deaths in patients over 65 years old, while they account for only 9–11% of injury-related deaths in younger individuals [61, 62]. Additionally, the elderly are up to 4 times more likely to die from a fall compared with patients under the age of 65 years old [3, 49]. Traumatic brain injury [4, 63, 64] and long bone fractures [4] are the leading cause of mortality and morbidity following a fall. Other injuries that commonly occur to the elderly following ground-level falls are cervical spine fractures, rib fractures, and pelvis fractures, which are most frequently lateral compression injuries, while abdominal injuries are rare [64]. Death-related falls from a low height (≤3 m) are most commonly associated with fractures of the skull, cervical spine, and thoracic injuries and are more likely to occur as the height of the fall increases, whereas fracturing of the lower extremities is more likely to occur as the height of the fall decreases [65]. In the same study, postmortem skeletal analysis reports only a rare incidence of upper extremity fractures in cases of fatal low free falls [65]. Growing evidence supports the promotion of ground-level falls as high-energy mechanism of injury in geriatric trauma.

1.3.2 Traffic-Related Injuries

Traffic-related injuries account for 10–25% of trauma admission in the elderly population [3]. Although this particular population does not necessarily have a higher incidence of traffic-related accidents [35], they have twice the mortality rate as compared to their younger counterpart [3, 35–37, 66, 67], either as a driver, a passenger, or a pedestrian. Patients aged more than 55 years old are more likely to sustain severe (ISS ≥ 16) or critical injuries (ISS ≥25) with a higher rate of severe head injuries (AIS head/neck score ≥ 3) [18, 36], spinal injuries [18], pelvis fractures [18], and chest injuries [18, 35–37], from which the three most common include rib fractures [35–37], flail chest [35], and sternum fractures [35]. While younger patients have a higher rate of abdominal, solid organ (spleen, liver, kidney), and facial injuries [18, 35], operative rates for chest, abdomen, and musculoskeletal injuries are similar for both group ages [35]. Moreover, the number of rib fractures has been correlated with increased mortality and risk of pneumonia [37]. As such, healthcare providers should maintain a high suspicion index for chest injuries in this population and scrutinize radiographs for chest wall fractures that are easily missed on plain, low-quality, radiographs taken in the trauma bay [35].

1.3.3 Pedestrian Injuries

In regard to pedestrian injuries, tibia and combined tibia and femur fractures are more common in adults and the elderly, whereas femur fractures are more common in children [15, 17]. This propensity for femur fracture is likely related to the patient's height and location of the first impact. In general, patients older than 55 years will have more intracranial injuries [15, 17, 68], upper [68] and lower extremity fractures [15, 17, 68], and more pelvic fracture [15, 68], but similar rate of solid organ injury [17, 68], abdomen [17, 68], and GI injuries [17, 68]. The seriousness of the injuries also showed a significant linear increase with increasing age [15, 17] along with mortality rate [3, 15, 17, 68]. While spinal injuries are uncommon in children and young adults, the risk of spinal injuries increases significantly with age [15, 17], demonstrating the importance to have a high index of suspicion when evaluating the spine in elderly patients.

1.3.4 Other Mechanism of Injuries

Other mechanisms of injuries include penetrating trauma, abuse and assaults, and burns. They are less frequent in the elderly compared with their younger counterparts; nevertheless, they are associated with higher mortality, longer ICU stay [69], higher morbidity [69], more complications [69], and longer length of hospital stay [69] and less likely to be discharged home [69]. Geriatric patients have the highest suicide risk among all age group [70] and constitute the third leading cause of injury in this population [71]. Patients older than 75 years were significantly more likely than patients 55–74 years old to suffer self-inflicted injuries [72]. The most common methods used are firearms and jumping from height [73, 74], both of which are associated with the highest case-fatality rate [1].

1.4 Outcomes

1.4.1 Comorbidities and Mortality

The in-hospital death rate in geriatric trauma victims has been estimated from 15% to 30%, whereas mortality in younger patients has been estimated at 4–8% [8, 75–78]. One explanation is the higher comorbidity rate compared with younger patients [49, 50, 79], longer Intensive Care Unit (ICU) stay [3, 35], and higher rate of overall complications [3, 80, 81], which increase the likelihood of death or severe disability [50]. In a meta-analysis by Hashmi et al. [8], combined odds of dying in those older than 74 years was 1.67 (96% CI, 1.34–2.08) compared with patients aged 65–74 years old, while no significant difference was observed between those aged 75–84 years old compared with those older than 84 years old. However, registry-based cohort reported a linear relationship between age and mortality rate [47, 82, 83]. Among all injuries, head traumas, spinal cord, and extremity injuries have the highest risk of in-hospital mortality, with severe head injury correlating with mortality the most [4].

Geriatric status [80, 81, 84], ISS (≥9 and ≥16) [47, 63, 76, 80–85], GCS (≤8) [20, 47, 63, 76, 81–83, 85], intubation [20, 47], coagulopathy and blood thinners [20, 63], anemia [63, 85], fluid requirements [76, 82, 84], dementia [86], and pre-existing pulmonary conditions [86], cardiovascular [80, 81, 86] or liver disease [80, 81, 86], and chronic renal failure [20, 81, 86] have been shown to be predictors of mortality. Similarly, the development of cardiovascular complications [76, 80], ARDS [76], renal failure [80] or infections [47, 76, 80], and geriatric status [80, 81, 84] also contribute to a higher mortality rate. A retrospective review comparing mortality and outcomes in the early decade vs late decade could not report a significant decrease in hospital mortality or ICU length of stay [87]. Others have reported a slight, but barely significant, improvement in mortality rates over the past 10 years [83, 88].

1.4.2 Discharge Status

Elderly trauma patients are more likely to be discharged into a care facility compared with younger patients with similar injuries [36]. Grossman et al. [78] examined long-term survival and functional status in geriatric trauma patients 5 years after previous study completion; nearly half of the patients were still alive, with 22% of geriatric patients still living at home. The authors report that although it was not possible to determine the true cost-effectiveness of this outcome, it is likely considered as a desirable outcome following trauma and appreciable long-term survival with a reasonable functional status can be anticipated for some [78]. In another study, recorded discharge disposition demonstrated that 45% of patients were ultimately discharged home, and 76% returned to baseline independence with activities of daily living or returned to the baseline level of activity [89].

The ISS and comorbidities appear to play a role in predicting mortality, but not necessarily functional outcome and discharge status [11, 32, 89]. Geriatric patients older than 80 years have poorer functional outcomes than those aged 65–80 years [90]. Furthermore, geriatric patients who do not respond to aggressive resuscitation efforts within a timely fashion are more likely to have poorer outcomes [11]. The EAST guidelines propose to consider less aggressive resuscitation measures in "non-responders" or without improvement within 72 h in patients with initial GCS score less than 8 [11, 12]. Although elderly victims are at higher risk of mortality and morbidity than younger patients, we are not able to accurately predict functional outcomes based on initial presentation, with the exception of severe head injury [11]. This requires prompt and aggressive treatment program to allow geriatric patients to regain their preinjury functional level.

1.4.3 Palliative Care and Withdrawal of Care

A recent evidence-based review by EAST has not shown a definitive and solid evidence to justify the use of routine palliative care in the geriatric population, while no studies have effectively assessed the impact on discharge disposition, quality of life, pain, and long-term functional status [7]. The argument for routine palliative care in geriatric trauma patients is driven by the decreased length of stay [91–93] and hospital costs [91] without negatively impacting mortality in the ICU [94, 95]. However, Kupensky et al. [93] compared geriatric trauma patients who had received a palliative medicine consultation compared with those who had not; patients receiving palliative care were significantly older, had higher mean ISS, and higher mortality rate than patients who did not receive palliative care.

Withdrawal of support remains more common in the very old patient. There remains a paucity of documentation in regard to advance directives and code status [96, 97]. Patients receiving palliative medicine care were significantly more likely to discuss advanced directives and resulted in consensus around goals of care [93].

1.5 Conclusion

The geriatric population is expected to live longer, with more comorbidities, while having more active lives much more later in life, thereby engaging in activities that increase the risk of high-energy trauma [3]. One must recognize one's own bias regarding treatment of the geriatric patient as well as the increased mortality rate associated with this specific population even in instances of low energy traumas. Evidence suggests very little, if any, improvement in incidence rates of fall-related injuries and death and the need for much-needed investment in preventive measures. No specific factors have been found to be predictive of functional outcomes, and aggressive management is warranted as there remains a substantial potential to retain the elderly as active and productive members of society, even after a significant trauma [50].

References

1. (COT) ACoSACoT. National Trauma Data Bank Annual Report 2016. 2016 [cited 2020 August 21]; Available from: https://www.facs.org/quality-programs/trauma/tqp/center-programs/ntdb/docpub.
2. Henary BY, Ivarsson J, Crandall JR. The influence of age on the morbidity and mortality of pedestrian victims. Traffic Inj Prev. 2006;7(2):182–90.
3. Lowe JA, Pearson J, Leslie M, Griffin R. Ten-year incidence of high-energy geriatric trauma at a level 1 trauma center. J Orthop Trauma. 2018;32(3):129–33.
4. Thompson HJ, McCormick WC, Kagan SH. Traumatic brain injury in older adults: epidemiology, outcomes, and future implications. J Am Geriatr Soc. 2006;54(10):1590–5.
5. Mandavia D, Newton K. Geriatric trauma. Emerg Med Clin North Am. 1998;16(1):257–74.
6. Lomoschitz FM, Blackmore CC, Mirza SK, Mann FA. Cervical spine injuries in patients 65 years old and older: epidemiologic analysis regarding the effects of age and injury mechanism on distribution, type, and stability of injuries. Am J Roentgenol. 2002;178(3):573–7.
7. Aziz HA, Lunde J, Barraco R, Como JJ, Cooper Z, Hayward Iii T, et al. Evidence-based review of trauma center care and routine palliative care processes for geriatric trauma patients; A collaboration from the American Association for the Surgery of Trauma Patient Assessment Committee, the American Association for the Surgery of Trauma Geriatric Trauma Committee, and the Eastern Association for the Surgery of Trauma Guidelines Committee. J Trauma Acute Care Surg. 2019;86(4):737–43.
8. Hashmi A, Ibrahim-Zada I, Rhee P, Aziz H, Fain MJ, Friese RS, et al. Predictors of mortality in geriatric trauma patients: a systematic review and meta-analysis. J Trauma Acute Care Surg. 2014;76(3):894–901.
9. McCoy GF, Johnstone RA, Duthie RB. Injury to the elderly in road traffic accidents. J Trauma Acute Care Surg. 1989;29(4):494–7.
10. Marciani RD. Critical systemic and psychosocial considerations in management of trauma in the elderly. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol. 1999;87(3):272–80.
11. Jacobs DG, Plaisier BR, Barie PS, Hammond JS, Holevar MR, Sinclair KE, et al. Practice management guidelines for geriatric trauma: the EAST Practice Management Guidelines Work Group. J Trauma Acute Care Surg. 2003;54(2):391–416.
12. Calland JF, Ingraham AM, Martin N, Marshall GT, Schulman CI, Stapleton T, et al. Evaluation and management of geriatric trauma: an Eastern

Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73(5):S345–S50.
13. Kuhne CA, Ruchholtz S, Kaiser GM, Nast-Kolb D. Mortality in severely injured elderly trauma patients—when does age become a risk factor? World J Surg. 2005;29(11):1476–82.
14. Campbell-Furtick M, Moore BJ, Overton TL, Phillips JL, Simon KJ, Gandhi RR, et al. Post-trauma mortality increase at age 60: a cutoff for defining elderly? Am J Surg. 2016;212(4):781–5.
15. Demetriades D, Murray J, Martin M, Velmahos G, Salim A, Alo K, et al. Pedestrians injured by automobiles: relationship of age to injury type and severity. J Am Coll Surg. 2004;199(3):382–7.
16. Davis JW, Kaups KL. Base deficit in the elderly: a marker of severe injury and death. J Trauma Acute Care Surg. 1998;45(5):873–7.
17. Hannon M, Hadjizacharia P, Chan L, Plurad D, Demetriades D. Prognostic significance of lower extremity long bone fractures after automobile versus pedestrian injuries. J Trauma Acute Care Surg. 2009;67(6):1384–8.
18. Talving P, Teixeira PGR, Barmparas G, DuBose J, Preston C, Inaba K, et al. Motorcycle-related injuries: effect of age on type and severity of injuries and mortality. J Trauma Acute Care Surg. 2010;68(2):441–6.
19. Vollmer DG, Torner JC, Jane JA, Sadovnic B, Charlebois D, Eisenberg HM, et al. Age and outcome following traumatic coma: why do older patients fare worse? J Neurosurg. 1991;75(Supplement):S37–49.
20. Bala M, Willner D, Klauzni D, Bdolah-Abram T, Rivkind AI, Gazala MA, et al. Pre-hospital and admission parameters predict in-hospital mortality among patients 60 years and older following severe trauma. Scand J Trauma Resusc Emerg Med. 2013;21(1):91.
21. Morris JA, Mackenzie EJ, Damiano AM, Bass SM. Mortality in trauma patients: the interaction between host factors and severity. J Trauma Acute Care Surg. 1990;30(12):1476–82.
22. Lineberry C, Stein DE. Infection, sepsis, and immune function in the older adult receiving critical care. Crit Care Nurs Clin. 2014;26(1):47–60.
23. Braunstein M, Kusmenkov T, Mutschler W, Kammerlander C, Böcker W, Bogner-Flatz V. Polytrauma in older adults leads to significantly increased TIMP-1 levels in the early posttraumatic period. J Immunol Res. 2020;2020
24. Baltazar GA, Bassett P, Pate AJ, Chendrasekhar A. Older patients have increased risk of poor outcomes after low-velocity pedestrian–motor vehicle collisions. Pragmatic Observ Res. 2017;8:43.
25. Boss GR, Seegmiller JE. Age-related physiological changes and their clinical significance. West J Med. 1981;135(6):434.
26. Weisfeldt M. Aging, changes in the cardiovascular system, and responses to stress. Am J Hypertens. 1998;11(S2):41S–5S.
27. Hossack KF, Bruce RA. Maximal cardiac function in sedentary normal men and women: comparison of age-related changes. J Appl Physiol. 1982;53(4):799–804.
28. Davies MJ, Lye M. Pathology of the aging heart. In: Textbook of geriatric medicine and gerontology. Edinburgh: Churchill Livingstone; 1992. p. 181–5.
29. Feldman RD, editor. Physiological and molecular correlates of age-related changes in the human beta-adrenergic receptor system; 1986.
30. Rommens PM, Kuhn S. Principles of damage control in the elderly. In: Damage control management in the polytrauma patient. Springer; 2017. p. 249–61.
31. Demarest GB, Osler TM, Clevenger FW. Injuries in the elderly: evaluation and initial response. Geriatrics. 1990;45(8)
32. McMahon DJ, Shapiro MB, Kauder DR. The injured elderly in the trauma intensive care unit. Surg Clin. 2000;80(3):1005–19.
33. Sartorelli KH, Rogers FB, Osler TM, Shackford SR, Cohen M, Vane DW. Financial aspects of providing trauma care at the extremes of life. J Trauma Acute Care Surg. 1999;46(3):483–7.
34. Fairman R, Rombeau JL, Miller TA. Physiologic problems in the elderly surgical patient. Physiologic basis of modern surgical care. St Louis: CV Mosby; 1988. p. 1108–17.
35. Yee WY, Cameron PA, Bailey MJ. Road traffic injuries in the elderly. Emerg Med J. 2006;23(1):42–6.
36. Bauzá G, LaMorte WW, Burke PA, Hirsch EF. High mortality in elderly drivers is associated with distinct injury patterns: analysis of 187,869 injured drivers. J Trauma Acute Care Surg. 2008;64(2):304–10.
37. Bulger EM, Arneson MA, Mock CN, Jurkovich GJ. Rib fractures in the elderly. J Trauma Acute Care Surg. 2000;48(6):1040–7.
38. Lyles KW. Osteoporosis: pathophysiology, clinical presentation, and management. Textb Internal Med. 1997:2536–41.
39. Gowing R, Jain MK. Injury patterns and outcomes associated with elderly trauma victims in Kingston, Ontario. Can J Surg. 2007;50(6):437.
40. Chang DC, Bass RR, Cornwell EE, MacKenzie EJ. Undertriage of elderly trauma patients to state-designated trauma centers. Arch Surg. 2008;143(8):776–81.
41. Xiang H, Wheeler KK, Groner JI, Shi J, Haley KJ. Undertriage of major trauma patients in the US emergency departments. Am J Emerg Med. 2014;32(9):997–1004.
42. Garwe T, Stewart K, Stoner J, Newgard CD, Scott M, Zhang Y, et al. Out-of-hospital and inter-hospital under-triage to designated tertiary trauma centers among injured older adults: a 10-year statewide geospatial-adjusted analysis. Prehosp Emerg Care. 2017;21(6):734–43.
43. Lehmann R, Beekley A, Casey L, Salim A, Martin M. The impact of advanced age on trauma triage decisions and outcomes: a statewide analysis. Am J Surg. 2009;197(5):571–5.

44. Zuercher M, Ummenhofer W, Baltussen A, Walder B. The use of Glasgow Coma Scale in injury assessment: a critical review. Brain Inj. 2009;23(5):371–84.
45. Heffernan DS, Thakkar RK, Monaghan SF, Ravindran R, Adams CA Jr, Kozloff MS, et al. Normal presenting vital signs are unreliable in geriatric blunt trauma victims. J Trauma Acute Care Surg. 2010;69(4):813–20.
46. Chapleau W, Haskin D, LeBlanc P, Cardenas G, Borum S, Torres N, et al. Advanced trauma life support (ATLS®): the ninth editio; 2013.
47. Labib N, Nouh T, Winocour S, Deckelbaum D, Banici L, Fata P, et al. Severely injured geriatric population: morbidity, mortality, and risk factors. J Trauma Acute Care Surg. 2011;71(6):1908–14.
48. Sterling DA, O'connor JA, Bonadies J. Geriatric falls: injury severity is high and disproportionate to mechanism. J Trauma Acute Care Surg. 2001;50(1):116–9.
49. Brown CVR, Rix K, Klein AL, Ford B, Teixeira PGR, Aydelotte J, et al. A comprehensive investigation of comorbidities, mechanisms, injury patterns, and outcomes in geriatric blunt trauma patients. Am Surg. 2016;82(11):1055–62.
50. Keller JM, Sciadini MF, Sinclair E, O'Toole RV. Geriatric trauma: demographics, injuries, and mortality. J Orthop Trauma. 2012;26(9):e161–e5.
51. Shifflette VK, Lorenzo M, Mangram AJ, Truitt MS, Amos JD, Dunn EL. Should age be a factor to change from a level II to a level I trauma activation? J Trauma Acute Care Surg. 2010;69(1):88–92.
52. Docimo S Jr, Demin A, Vinces F. Patients with blunt head trauma on anticoagulation and antiplatelet medications: can they be safely discharged after a normal initial cranial computed tomography scan? Am Surg. 2014;80(6):610–3. Epub 2014/06/03
53. Ivascu FA, Howells GA, Junn FS, Bair HA, Bendick PJ, Janczyk RJ. Rapid warfarin reversal in anticoagulated patients with traumatic intracranial hemorrhage reduces hemorrhage progression and mortality. J Trauma Acute Care Surg. 2005;59(5):1131–9.
54. Ivascu FA, Janczyk RJ, Junn FS, Bair HA, Bendick PJ, Howells GA. Treatment of trauma patients with intracranial hemorrhage on preinjury warfarin. J Trauma Acute Care Surg. 2006;61(2):318–21.
55. Abdelfattah A, Core MD, Cannada LK, Watson JT. Geriatric high-energy polytrauma with orthopedic injuries: clinical predictors of mortality. Geriatr Orthop Surg Rehab. 2014;5(4):173–7.
56. Henry SM, Pollak AN, Jones AL, Boswell S, Scalea TM. Pelvic fracture in geriatric patients: a distinct clinical entity. J Trauma Acute Care Surg. 2002;53(1):15–20.
57. Peterson BE, Jiwanlal A, Della Rocca GJ, Crist BD. Orthopedic trauma and aging: it isn't just about mortality. Geriatr Orthop Surg Rehab. 2015;6(1):33–6.
58. Young L, Ahmad H. Trauma in the elderly: a new epidemic? Aust N Z J Surg. 1999;69(8):584–6.
59. Akköse Aydýn Þ, Bulut M, Fedakar R, Özgürer A, Özdemir F. Trauma in the elderly patients in Bursa. Turkish J Trauma Emerg Surg. 2006;12(3):230–4.
60. Reich MS, Dolenc AJ, Moore TA, Vallier HA. Is early appropriate care of axial and femoral fractures appropriate in multiply-injured elderly trauma patients? J Orthop Surg Res 2016;11(1):1–6.
61. Baker SP, Harvey AH. Fall injuries in the elderly. Clin Geriatr Med. 1985;1(3):501–12.
62. Hogue CC. Injury in late life: Part I. Epidemiology. J Am Geriatr Soc. 1982;30(3):183–90.
63. Schoeneberg C, Probst T, Schilling M, Wegner A, Hussmann B, Lendemans S. Mortality in severely injured elderly patients: a retrospective analysis of a German level 1 trauma center (2002–2011). Scand J Trauma Resusc Emerg Med. 2014;22(1):45.
64. Bhattacharya B, Maung A, Schuster K, Davis KA. The older they are the harder they fall: injury patterns and outcomes by age after ground level falls. Injury. 2016;47(9):1955–9.
65. Rowbotham SK, Blau S, Hislop-Jambrich J, Francis V. Skeletal trauma resulting from fatal low (≤3 m) free falls: an analysis of fracture patterns and morphologies. J Forensic Sci. 2018;63(4):1010–20.
66. Azami-Aghdash S, Aghaei MH, Sadeghi-Bazarghani H. Epidemiology of road traffic injuries among elderly people; a systematic review and meta-analysis. Bull Emerg Trauma. 2018;6(4):279.
67. Etehad H, Yousefzadeh-Chabok SH, Davoudi-Kiakalaye A, Moghadam DA, Hemati H, Mohtasham-Amiri Z. Impact of road traffic accidents on the elderly. Arch Gerontol Geriatr. 2015;61(3):489–93.
68. Siram SM, Sonaike V, Bolorunduro OB, Greene WR, Gerald SZ, Chang DC, et al. Does the pattern of injury in elderly pedestrian trauma mirror that of the younger pedestrian? J Surg Res. 2011;167(1):14–8.
69. Nagy KK, Smith RF, Roberts RR, Joseph KT, An GC, Bokhari F, et al. Prognosis of penetrating trauma in elderly patients: a comparison with younger patients. J Trauma. 2000;49(2):190–3.
70. Baker S, Baker SP, Ginsburg MJ, Li GG, O'Neill B. The injury fact book. USA: Oxford University Press; 1992.
71. Binder S. Injuries among older adults: the challenge of optimizing safety and minimizing unintended consequences. Injury Prev. 2002;8(Suppl. 4):iv2–4.
72. Lustenberger T, Inaba K, Schnüriger B, Barmparas G, Eberle BM, Lam L, et al. Gunshot injuries in the elderly: patterns and outcomes. A national trauma databank analysis. World J Surg. 2011;35(3):528–34.
73. Stevens JA, Hasbrouck LM, Durant TM, Dellinger AM, Batabyal PK, Crosby AE, et al. Surveillance for injuries and violence among older adults. Morb Mortal Wkly Rep: CDC Surveillance Summaries. 1999:27–50.
74. Abrams RC, Marzuk PM, Tardiff K, Leon AC. Preference for fall from height as a method of suicide by elderly residents of New York City. Am J Public Health. 2005;95(6):1000–2.
75. MacKenzie EJ, Rivara FP, Jurkovich GJ, Nathens AB, Frey KP, Egleston BL, et al. A national evaluation of the effect of trauma-center care on mortality. N Engl J Med. 2006;354(4):366–78.

76. Tornetta P, Mostafavi H, Riina J, Turen C, Reimer B, Levine R, et al. Morbidity and mortality in elderly trauma patients. J Trauma Acute Care Surg. 1999;46(4):702–6.
77. Dimitriou R, Calori GM, Giannoudis PV. Polytrauma in the elderly: specific considerations and current concepts of management. Eur J Trauma Emerg Surg. 2011;37(6):539–48.
78. Grossman MD, Ofurum U, Stehly CD, Stoltzfus J. Long-term survival after major trauma in geriatric trauma patients: the glass is half full. J Trauma Acute Care Surg. 2012;72(5):1181–5.
79. Bergeron E, Clement J, Lavoie A, Ratte S, Bamvita J-M, Aumont F, et al. A simple fall in the elderly: not so simple. J Trauma Acute Care Surg. 2006;60(2):268–73.
80. Perdue PW, Watts DD, Kaufmann CR, Trask AL. Differences in mortality between elderly and younger adult trauma patients: geriatric status increases risk of delayed death. J Trauma Acute Care Surg. 1998;45(4):805–10.
81. Grossman MD, Miller D, Scaff DW, Arcona S. When is an elder old? Effect of preexisting conditions on mortality in geriatric trauma. J Trauma Acute Care Surg. 2002;52(2):242–6.
82. Ley EJ, Clond MA, Srour MK, Barnajian M, Mirocha J, Margulies DR, et al. Emergency department crystalloid resuscitation of 1.5 L or more is associated with increased mortality in elderly and non-elderly trauma patients. J Trauma Acute Care Surg. 2011;70(2):398–400.
83. Ringen AH, Gaski IA, Rustad H, Skaga NO, Gaarder C, Naess PA. Improvement in geriatric trauma outcomes in an evolving trauma system. Trauma Surg Acute Care Open. 2019;4(1):e000282.
84. Hammer PM, Storey AC, Bell T, Bayt D, Hockaday MS, Zarzaur BL Jr, et al. Improving geriatric trauma outcomes: a small step toward a big problem. J Trauma Acute Care Surg. 2016;81(1):162–7.
85. Ross SW, Adeyemi FM, Zhou M, Minhajuddin AT, Porembka MR, Cripps MW, et al. One-year mortality in geriatric trauma patients: improving upon the geriatric trauma outcomes score utilizing the social security death index. J Trauma Acute Care Surg. 2019;87(5):1148–55.
86. Camilloni L, Farchi S, Rossi PG, Chini F, Borgia P. Mortality in elderly injured patients: the role of comorbidities. Int J Injury Control Safety Promotion. 2008;15(1):25–31.
87. Samayoa AX, Vu T, Olszewski T, Bova M, Yan Q, Kirton O. Have outcomes improved in trauma patients age 90 years and older over the past decade: experience at a level II trauma center. Am J Surg. 2018;215(6):1000–3.
88. Maxwell CA, Miller RS, Dietrich MS, Mion LC, Minnick A. The aging of America: a comprehensive look at over 25,000 geriatric trauma admissions to United States hospitals. Am Surg. 2015;81(6):630–6.
89. Ferrera PC, Bartfield JM, D'Andrea CC. Outcomes of admitted geriatric trauma. Am J Emerg Med. 2000;18(5):575–80.
90. Grossman M, Scaff DW, Miller D, Reed Iii J, Hoey B, Anderson Iii HL. Functional outcomes in octogenarian trauma. J Trauma Acute Care Surg. 2003;55(1):26–32.
91. Khandelwal N, Benkeser D, Coe NB, Engelberg RA, Teno JM, Curtis JR. Patterns of cost for patients dying in the intensive care unit and implications for cost savings of palliative care interventions. J Palliat Med. 2016;19(11):1171–8.
92. Katrancha ED, Zipf J. Evaluation of a virtual geriatric trauma institute. J Trauma Nurs. 2014;21(6):278–81.
93. Kupensky D, Hileman BM, Emerick ES, Chance EA. Palliative medicine consultation reduces length of stay, improves symptom management, and clarifies advance directives in the geriatric trauma population. J Trauma Nurs. 2015;22(5):261–5.
94. Mosenthal AC, Murphy PA, Barker LK, Lavery R, Retano A, Livingston DH. Changing the culture around end-of-life care in the trauma intensive care unit. J Trauma Acute Care Surg. 2008;64(6):1587–93.
95. Matsushima K, Schaefer EW, Won EJ, Armen SB. The outcome of trauma patients with do-not-resuscitate orders. J Surg Res. 2016;200(2):631–6.
96. McBrien ME, Kavanagh A, Heyburn G, Elliott JRM. ‘Do Not Attempt Resuscitation’(DNAR) decisions in patients with femoral fractures: modification, clinical management and outcome. Age Ageing. 2013;42(2):246–9.
97. Trunkey DD, Cahn RM, Lenfesty B, Mullins R. Management of the geriatric trauma patient at risk of death: therapy withdrawal decision making. Arch Surg. 2000;135(1):34–8.

2 Cardiovascular Ageing

Marco Luciani, Frank Ruschitzka, and Giovanni G. Camici

2.1 Epidemiology

According to the World Health Organization, cardiovascular diseases (CVD) are the leading causes of morbidity and mortality in industrialized nations, and they are expected to become the first cause of mortality also in low- and middle-income countries in the near future.

Incidence of CVD has reached pandemic proportions in light of combined social changes and medical improvements occurred in the last decades, resulting in a significant demographic shift that will lead by 2040 to a 22% prevalence of subjects older than 65 [1]. Owing to numerous preventive, diagnostic, and therapeutic means implemented on a global scale, life expectancy has dramatically increased over the course of the last 50 years, resulting in a 16.5 year gain in life expectancy within this timeframe and reaching a life expectancy of 71.9 years worldwide.

M. Luciani (✉)
Department of Internal Medicine, Cantonal Hospital of Baden, Baden, Switzerland

F. Ruschitzka
Department of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland
e-mail: frank.ruschitzka@usz.ch

G. G. Camici
Department of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland

Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland
e-mail: giovanni.camici@uzh.ch

Increased life expectancy has, particularly in high-income areas, expanded the terminal phase of life which is characterized by a series of different disabilities affecting the quality of life itself where non-mutually exclusive CVD lead to a final stage of cardiac impairment called heart failure [2]. Concomitantly, the clinical picture and therefore the general population outlook is heterogeneous with non-cardiovascular diseases also playing a role. Together with intrinsic risk factors, environmental ones such as nutrition [3], alcohol abuse [4], lack of physical exercise [5], and pollution [6] can determine the morphofunctional phenotype of cardiac impairment.

A recent population study in the UK showed that, despite a reduction in the annual incidence of heart failure diagnosis (−7%), its prevalence increased (+12%) in light of adequate public health policies and effective therapeutic strategies [7].

These numbers are translated into a public healthcare system challenge with an annual expenditure of nearly $125,000 per heart failure patient, a sum that is doomed to increase in the near future [8].

2.2 Features

With ageing, the cardiovascular system undergoes a series of structural and functional changes dictated by molecular and cellular mechanisms affecting different anatomical structures such as

H.-C. Pape et al. (eds.), *Senior Trauma Patients*, https://doi.org/10.1007/978-3-030-91483-7_2

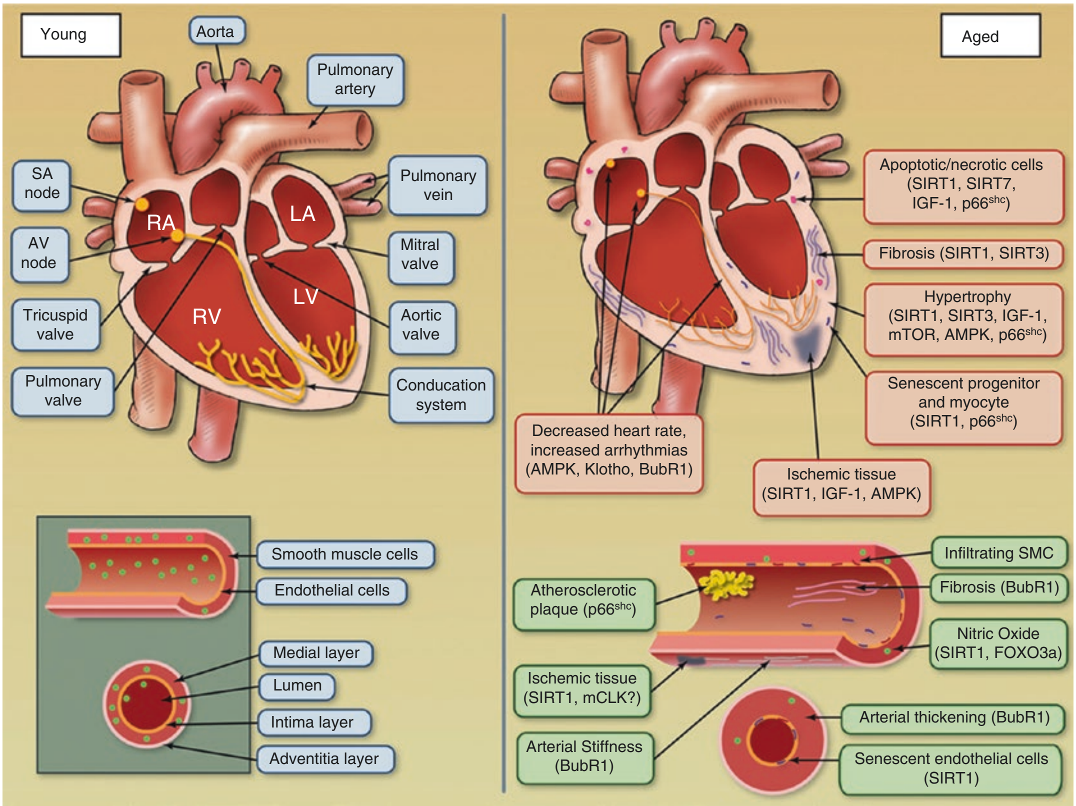

Fig. 2.1 Age-dependent changes to cardiovascular tissues. Molecular, cellular, and tissue changes occurring with time ultimately altering morphology and function of the heart and vessels. (North BJ, Sinclair DA, *The Intersection between Aging and Cardiovascular Disease,* Circulation Research 2012;110:1097–1108)

the myocardium, the valve apparatus, the conduction system, and the vasculature as shown in Fig. 2.1.

The indisputable evidence connecting CVD with age notwithstanding, it still remains elusive whether ageing per se should be considered as an independent risk factor, a process, or rather an epiphenomenon of accumulated stochastic molecular events exhausting compensatory defensive response and ultimately yielding to reduced homeostasis and therefore morbid conditions.

2.3 Arterial Ageing

Over time, significant peripheral and coronary vascular changes occur leading to the two most common forms of CVD observed in the elderly: arterial hypertension and coronary artery disease (CAD). A key early step in the development of these diseases is represented by endothelial dysfunction where the bioavailability of nitric oxide (NO)—a key protective factor with vasodilatory, anti-adhesion, and anti-aggregation properties—is drastically reduced.

2.3.1 Arterial Ageing: Arterial Hypertension

Starting from the age of 50, arterial hypertension in elderly patients is principally characterized by isolated, elevated systolic pressure with a progressive decline in diastolic pressure, intuitively leading to widened pulse pressure and an increased pulse wave velocity (PWV). Such condition is primarily driven by concomitant endothelial dysfunction and central arterial stiffness, which are intimately interconnected within a self-sustaining vicious cycle of hemodynamic load, endothelial activation, inflammation, and persistent damage. Endothelial dysfunction includes reduced vasodilatatory capability determined by reduced NO bioavailability [9], impaired endothelial-dependent responsiveness to prostaglandins [10], increased levels of the vasoconstrictor endothelin-1, and systemic molecular signature changes towards pro-inflammatory molecules, i.e. TNF-alpha, IL-6. Such changes are associated with altered vascular homeostasis, favouring a prooxidant and pro-inflammatory milieu with a tendency to cardiovascular adverse events [11]. On the other hand, arterial stiffness is due to altered proteolytic activities by metalloproteinases (MMPs), cathepsins, and neutrophil elastase as well as an age-related increased production of TGF-β favouring abnormal elastin fragmentation, fibers calcification, augmented collagen deposition, endothelial senescence, and tissue invasion by inflammatory cells and smooth muscle cells overgrowth [12]. This process is macroscopically translated into luminal enlargement and wall thickening as well as wall stiffening with reduced arterial distensibility yielding an increased PWV.

In order to compensate these changes and preserve sufficient peripheral perfusion, the myocardium undergoes a series of cellular, structural, and functional ploys which in the long run predispose to irreversible chronic cardiac dysfunction. As shown in Fig. 2.2, increased aortic impedance and ventricular loading are counteracted by increased wall tension featuring augmented wall thickness and prolonged systole.

A longer systolic interval is possible when time from diastole is borrowed. In order to preserve contractile activity, this physiological compromise causes an incomplete relaxation and thus forces the heart to increase its cavities as well as filling pressures.

2.3.2 Arterial Ageing: Coronary Artery Disease

Among CVD, CAD is the most common cause of morbidity and mortality in elderly patients responsible for nearly one-fifth of death cases and representing the first aetiology of heart failure [13] as illustrated in Fig. 2.3.

In comparison to the general population, elderly patients are usually more difficult to diagnose in light of the concomitant comorbidities and of atypical clinical presentation; this still holds true despite this subpopulation being more frequently affected and with extended involvement of the coronary tree.

Pathogenesis of *CAD* is based on a plethora of interconnected factors determining atherosclerosis. Despite being initially considered solely as a cholesterol storage disease, it is now accepted that inflammation plays a central role in atherosclerotic plaque formation, progression, and rupture. Initiation sites are usually localized in peculiar sectors where laminar blood flow is disturbed (branches); lack of luminal elastin coupled with proteoglycans exposure favours subendothelial low-density lipoproteins' (LDL) deposition. In the presence of inflammatory cells, LDLs are a vulnerable substrate to a number of posttranslational modifications as well as to oxidative stress caused by myeloperoxidase or lypoxygenases release. LDL oxidation triggers endothelial adhesion molecules overexpression (CCL5, CXCR3, CCL2, CCR5, CCR2, CXCR1), promoting further cellular invasion. Over time, plaques evolve from fatty streaks where T-cells and monocytes-derived foam cells load are predominant towards more complex histological lesions [14–16].

The natural history of CAD is strongly affected by age: in fact, CAD is more commonly diagnosed in aged individuals and a positive direct correlation between age and number and size of lesions is present. As later discussed, compensatory myocardial hypertrophy represents an additional metabolic challenge for coronary cir-

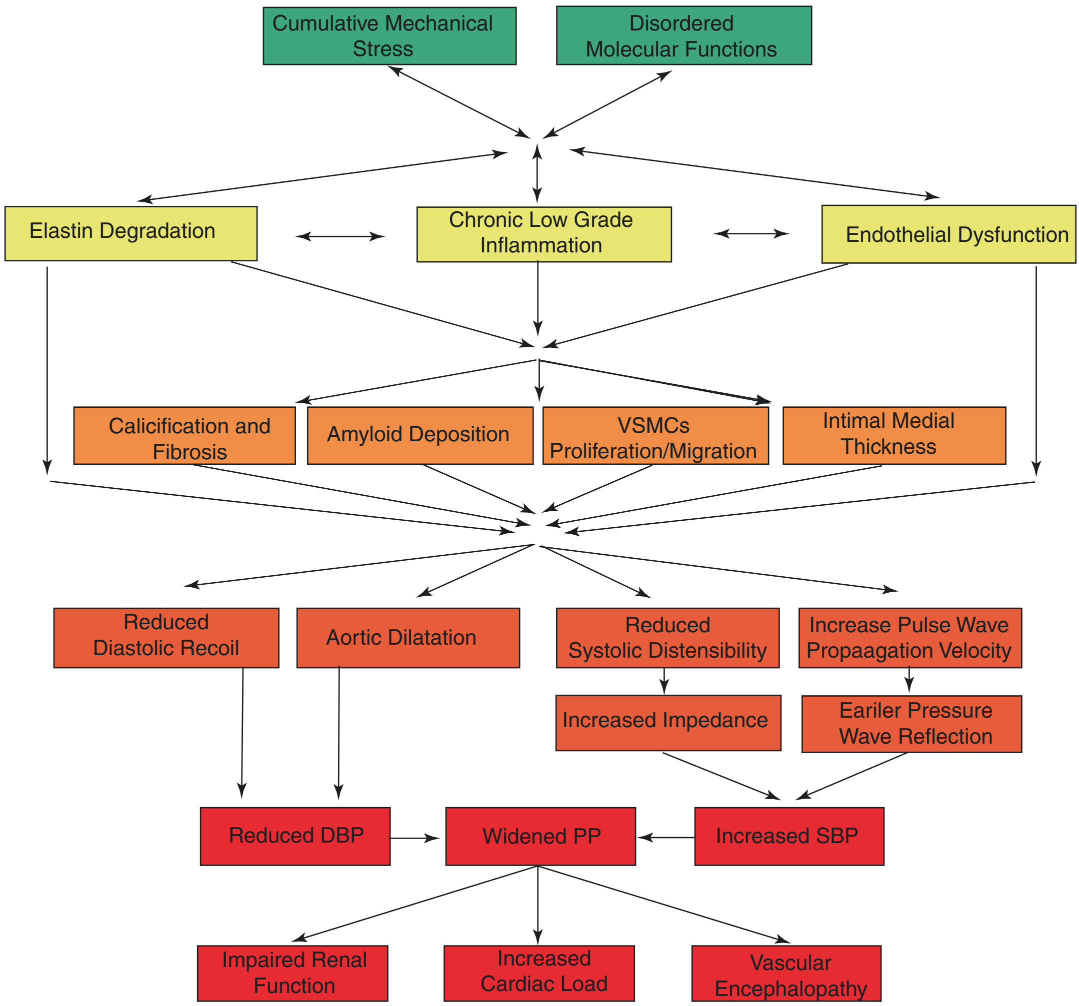

Fig. 2.2 Conceptual model of arterial ageing and arterial decline. Herein are reported the intertwined, compensating mechanisms which will eventually lead to the well-characterized vascular dysfunction of the elderly (Lakatta EG. So! What's Ageing? Is Cardiovascular Ageing a Disease? Journal of Molecular and Cellular Cardiology;83:1–13)

culation. With prolonged systolic time, reduced luminal diameter, and decreased vascular density, chronic and/or acute ischemic damage can occur more frequently.

Specific histological features distinguish atherosclerotic lesions that are more prone to rupture and thus cause acute coronary syndromes. Such lesions are usually larger, presenting a bigger necrotic core (cell debris and cholesterol crystals) and a protective fibrous cap invaded by pro-inflammatory cells and less smooth muscle cells [17].

2.3.3 Arterial Ageing: Cardiac Microvascular Disease

Microcirculation is defined as blood vessels with a diameter inferior to 100 mm and its role is particularly important in regulating tissue perfusion and cell function in response to the release of a multitude of dilating and constricting factors [18].

Even in the absence of image-detectable and clinically significant coronary lesions, dysfunc-

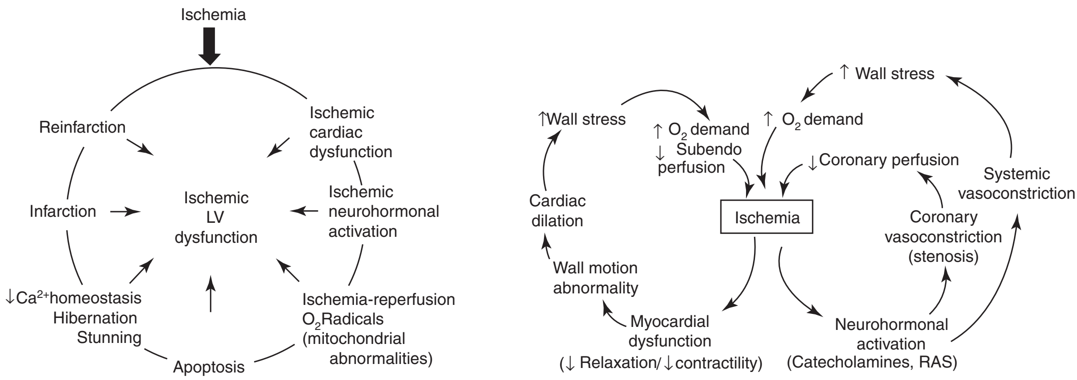

Fig. 2.3 The vicious cycle of myocardial ischemia—Ischemic damage, independently of magnitude and extension, leads to ventricular dysfunction which is temporarily compensated by a number of physiological ploys (autonomic, neurohormonal, etc.) preserving myocardial function. Over time, these ploys exhaust their compensatory capabilities yielding to a decompensated myocardium. (Remme WJ, *Overview of the relationship between ischemia and congestive heart failure*, Clinical Cardiology 2000;23 (Suppl. IV):1–13)

tional microcirculation can dramatically change patients' prognosis. Microcirculation can be affected in a wide range of chronic and acute conditions (ischemia, hypertension, diabetes, obesity, tobacco use, renal impairment, and with age per se). As previously mentioned, senescent endothelium as well as smooth muscle cells, in low calibre arterioles, tend to lose their capability to regulate vascular resistance and match energy request with blood flow, ultimately affecting cardiac performance itself and increasing the chances of myocardial ischemia. In fact, myocardial oxygen extraction tends already to maximal capabilities in resting conditions, and therefore its delivery heavily relies on blood flow. In case of increased oxygen demand, a proportional increase in coronary blood flow must be matched with metabolic requests [19, 20].

2.4 Myocardial Hypertrophy

Pathological myocardial hypertrophy as frequently observed in the elderly is an irreversible process governed by different yet intertwined molecular pathways in contrast to the physiological reversible hypertrophy observed in other conditions such as in athletes. Hypertrophy in the failing ageing heart is characterized by cellular loss, partially compensated with survived hypertrophic cardiomyocytes, and due to the aforementioned ischemic burden, progressively replaced with nonfunctional fibroblasts.

Such structural changes can be regarded as a maladaptation of cardiomyocytes to mechanical and chemical stress events, reactivating the so-called "fetal gene program" by promoting chromatin remodelling, transcriptional, and posttranscriptional upregulation for specific genes transcription factors such as the myocyte enhancer factor 2 (MEF2A-C), erythroid transcription factor (GATA4).

Upon reactivation, a series of common fetal isoforms genes are accessed for transcription such as muscle creatine kinase (Ckm), alpha myosin chain (Myh-6), myosin light chain (Myl1), and Troponins C and I (Tnnc1, Tnni3). It is now widely accepted that the aberrant expression of fetal genes in the postnatal heart involved in contractility, calcium handling, and myocardial energetics has only a temporary beneficial effect as it bears a negative prognostic significance [21].

2.5 Amyloidosis

An additional, yet underestimated, cause of myocardial hypertrophy is represented by amyloidosis caused by the extracellular deposition of insoluble fibrils. This is an autoptic finding; in nearly 20% of subjects older than 80, it is the amyloid deposition within the myocardium.

Amyloid plaques are stable, extracellular aggregates derived from proteinaceous by-products yielding to histological changes and organ dysfunction. All amyloidoses have a common pathogenic mechanism consisting of erroneous protein folding. In fact, each protein sequence undergoes a number of quality control systems in order to acquire a correct tridimensional structure and therefore fulfil the physiological function, localization, and interactions. In the unfortunate, yet not uncommon, case of combined adverse events (genetic mutation, protein overproduction, age per se, concomitant comorbidities, iatrogenic factors), proteins can acquire aberrant conformations. Once a single protein is abnormally arranged (monomer) and has overwhelmed additional cellular control systems, it aggregates into larger and more complex structures called oligomers, and further on into fibers and finally deposit into stable and pathognomonic structures called amyloid plaques [22].

With the term cardiac amyloidosis, we engulf a heterogenous group of medical conditions affecting the heart muscle which can have variable degrees of severity, prevalence, and evolution.

Light chain immunoglobulins can affect the heart in 50% of cases depending on the type of cell dyscrasia and median age of presentation can vary for the same reason. Of note, heart failure represents the worst prognostic factor in these patients [23].

Transthyretin, whether wild-type or mutated, is the biological precursor of systemic senile and systemic familial amyloidosis, respectively. In the absence of mutations, the mean age of presentation is around 75 years and cardiac involvement prevalence increases with age. Nowadays, nearly 100 different transthyretin mutations have been reported, each with their peculiar physicochemical properties determining their noxious properties and natural progression. Cardiac involvement greatly varies in terms of age presentation and concomitant nervous involvement based on the type of mutation [24].

Other proteins of cardiac and noncardiac origins can deposit within the myocardium such as Atrial Natriuretic Peptide giving rise to isolated atrial amyloidosis, serum amyloid A to amyloid A amyloidosis, and β_2-microglobulin which tends to deposit in patients with long-standing dialytic treatment [25].

At early stages when typical signs of prominent cardiac involvement such as thickened myocardial walls with reduced electrical voltages on ECG tracings are not apparent yet, cardiac amyloidosis can represent a challenging diagnosis. While endomyocardial biopsy represents the definitive mean for confirming the diagnostic hypothesis [26, 27], Technetium 99 m pyrophosphate (Tc 99 m PYP) cardiac imaging has emerged as a highly sensitive and specific technique for detecting ATTR cardiac amyloidosis and capable of distinguishing it from AL cardiac amyloidosis [28].

2.6 Atrial Fibrillation

AF is already the most commonly occurring dysrhythmia with a lifetime risk for AF of around 25%, indicating that one out of four women or men over age 40 will experience AF.

The estimated global prevalence of AF of 33 million in 2010 is expected to double by 2050 because of population ageing, the rising prevalence of cardiometabolic risk factors, and the improved survival from cardiovascular events [29, 30]. Importantly, prevalence, both of the global incidence and the age-adjusted mortality rates, is also rising [29]. The most important modifiable risk factors, particularly elevated blood pressure and obesity, explain about 50% of the population's attributable risk for AF development.

While AF is associated with a five-fold increase in the risk of ischemic stroke and up to 20% of all strokes are attributable to AF, the lack of temporal relationship between arrhythmia episodes and adverse outcomes has questioned the causal role of AF in the development of stroke.

Characterized by the presence of rapid, irregular, and fibrillatory waves that vary in magnitude, shape, and timing, possibly affecting hemodynamic cardiac performance itself [31], atrial fibrillation usually develops in the context of a diseased left atrium due to the hemodynamical challenges of high filling pressures, as in hypertension and/or heart failure with preserved or reduced ejection and fraction, and altered histological substrates that predispose to arrhythmic event or increased vulnerability. Indeed, on top of structural abnormalities, AF normally requires a trigger event of cardiac or noncardiac origin such as autonomic tone change, neurohormonal activation, inflammation, or other stimuli.

2.7 Valvular Diseases

Cardiac valve diseases are of remarkable importance in the general population; over the last decades, they have changed aetiology and demographic patterns transitioning from prevalent rheumatologic sequelae of the adult to a typical degenerative process of the elderly with increasing prevalence starting from the sixth and seventh decade of life.

As shown in Fig. 2.4, heart valve diseases of any severity rapidly increase from 0.5% before the age of 55 and they reach at least a 12% prevalence in subjects older than 75, with mitral regurgitation being the most common (from 10.9% to 7.1%) form followed by aortic stenosis (4.6–2.8%), aortic regurgitation (2–1.7%), and mitral stenosis (0.2%) [32].

Each type of valve disease challenges the myocardium with peculiar combinations of pressure and/or volume overload determining temporary compensatory responses, ultimately exhausting the morphofunctional reserve of the heart itself and becoming a significant determinant of mortality.

Mitral regurgitation provokes left ventricular cavities enlargement without compensatory wall hypertrophy; on the other hand, aortic insufficiency predisposes to ventricular enlargement coupled to hypertrophy. Patients with aortic stenosis have hypertrophic hearts without cavities dilatation, whereas mitral stenosis presents with significant left atrial enlargement leaving the left ventricle unaffected.

Mitral insufficiency can be divided into two distinct nosocomial entities: a primary degeneration of the valve called organic and a function regurgitation due to altered surrounding structures. Organic mitral valve degeneration can have two major pathogenic mechanisms: myxomatous degeneration or fibroelastic deficiency. The former is believed to be driven by myofibroblast activation secreting MMPs and altering extracellular matrix turnover as well as TGF-β sustaining

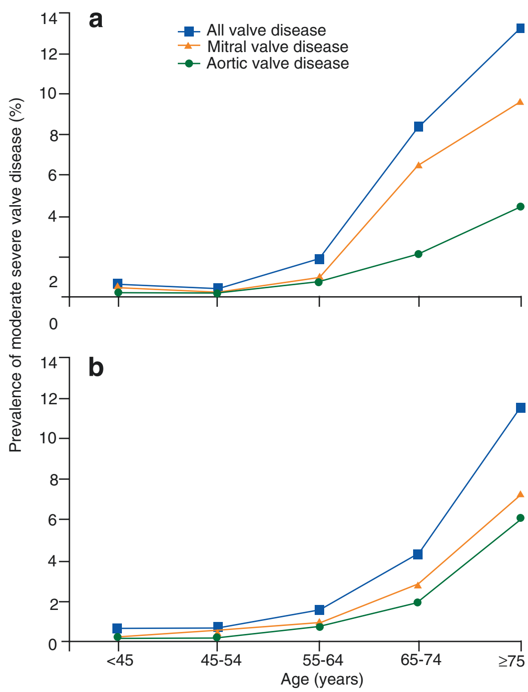

Fig. 2.4 Prevalence of valve heart disease per age**.** Both aortic and mitral valves undergo a series of herein described histological changes that are clinically translated into stenosis and insufficiency. Prevalence increases over the course of three decades from nearly 1% (45–54 years of age) to 12% (>75 years of age) representing a common finding in this population. (Nkomo VT, Gardin JM, Skelton TN, Gottidiner JC, Scott GC, Enrriquez-Sarano M. *Burden of valvular heart diseases: a population-based study*, Lancet. 2006;368: 1005–1011)

myofibroblast proliferation and differentiation. The latter is still not well-understood, but it is characterized by an age-dependent impairment of connective tissue fiber synthesis. Myxomatous mitral valves feature redundant prolapsing tissue, leaflet, and annulus calcification as well as annular dilatation in contrast to the other form which usually tends to tether chordae and eventually rupture them [33, 34]. Patients may remain symptomatic over the vast majority of the natural history of the disease until an irreversible stage characterized by preserved systolic function with pulmonary hypertension or atrial fibrillation begins.

Concerning aortic stenosis, the sclerotic process (with or without stenosis) represents a classic echocardiographic finding of the elderly being detectable in nearly half of subjects older than 85 [35]. Aortic valve calcification is believed to progress with the same cellular and molecular mechanisms of atherosclerosis; nevertheless, such hypothesis remains *open* in light of the lack of benefit from statin therapy.

After a long asymptomatic phase where the myocardium can counteract flow obstruction with compensatory hypertrophy, patients with severe aortic stenosis rapidly complain of angina, syncope, and fatigue and mortality rate abruptly rises to 25% per year [36].

2.8 Therapy

Medical therapeutic mainstays of the various cardiovascular conditions rely on judicious evaluation in the setting of polymorbic patients who most likely require multidrug therapy. In addition, renal function should be regularly monitored in order to correctly provide dose medication and to avoid expectable, adverse, and overdosing effects. Unfortunately, the elderly population is underrepresented in the vast majority of clinical trials in spite of the unmet need for tailored medical therapy for this subpopulation. The above-mentioned complex clinical scenario poses an additional challenge in the decision making process since classic, clinical hard endpoints should be coupled with the quality of life and frailty scoring systems. In fact, life expectancy might not be perceived as a pivotal determinant by senior patients who are more concerned in preserving their daily activity independence.

Conflict of Interest *Prof. Ruschitzka has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years (remuneration for the time spent in activities, such as participation as steering committee member of clinical trials and member of the Pfizer Research Award selection committee in Switzerland, were made directly to the University of Zurich). The Department of Cardiology (University Hospital of Zurich/University of Zurich) reports research-, educational-, and/or travel grants from Abbott, Amgen, Astra Zeneca, Bayer, Berlin Heart, B. Braun, Biosense Webster, Biosensors Europe AG, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Bracco, Cardinal Health Switzerland, Corteria, Daiichi, Diatools AG, Edwards Lifesciences, Guidant Europe NV (BS), Hamilton Health Sciences, Kaneka Corporation, Kantar, Labormedizinisches Zentrum, Medtronic, MSD, Mundipharma Medical Company, Novartis, Novo Nordisk, Orion, Pfizer, Quintiles Switzerland Sarl, Sahajanand IN, Sanofi, Sarstedt AG, Servier, SIS Medical, SSS International Clinical Research, Terumo Deutschland, Trama Solutions, V-Wave, Vascular Medical, Vifor, Wissens Plus, and ZOLL. The research and educational grants do not impact on Prof. Ruschitzka's personal remuneration.*

References

1. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123:933–44.
2. Braunwald E. Heart failure. JACC Heart Fail. 2013;1:1–20.
3. Miller V, Mente A, Dehghan M, et al. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. Lancet. 2017;390:2037–49.
4. Whitman IR, Agarwal V, Nah G, et al. Alcohol abuse and cardiac disease. J Am Coll Cardiol. 2017;69:13–24.
5. Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130,000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017;390:2643–54.
6. Aung N, Sanghvi MM, Zemrak F, et al. Association between ambient air pollution and cardiac morpho-functional phenotypes: insights from the UK Biobank Population Imaging Study. Circulation. 2018;138:2175–86.
7. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-

based study of 4 million individuals. Lancet. 2018;391:572–80.
8. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. BMC Cardiovasc Disord. 2018;18:74.
9. Donato AJ, Eskurza I, Silver AE, et al. Direct evidence of endothelial oxidative stress with aging in humans: relation to impaired endothelium-dependent dilation and upregulation of nuclear factor-kappaB. Circ Res. 2007;100:1659–66.
10. Singh N, Prasad S, Singer DR, MacAllister RJ. Ageing is associated with impairment of nitric oxide and prostanoid dilator pathways in the human forearm. Clin Sci (Lond). 2002;102:595–600.
11. Camici GG, Sudano I, Noll G, Tanner FC, Luscher TF. Molecular pathways of aging and hypertension. Curr Opin Nephrol Hypertens. 2009;18:134–7.
12. Chung HY, Sung B, Jung KJ, Zou Y, Yu BP. The molecular inflammatory process in aging. Antioxid Redox Signal. 2006;8:572–81.
13. Remme WJ. Overview of the relationship between ischemia and congestive heart failure. Clin Cardiol. 2000;23:IV4–8.
14. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111:3481–8.
15. Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868–74.
16. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med. 2011;17:1410–22.
17. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol. 2006;47:C13–8.
18. Gutterman DD, Chabowski DS, Kadlec AO, et al. The human microcirculation: regulation of flow and beyond. Circ Res. 2016;118:157–72.
19. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72:2625–41.
20. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med. 2007;356:830–40.
21. Dirkx E, da Costa Martins PA, De Windt LJ. Regulation of fetal gene expression in heart failure. Biochim Biophys Acta. 2013;1832:2414–24.
22. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349:583–96.
23. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol. 2016;68:1323–41.
24. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and treatment of cardiac amyloidosis. Nat Rev Cardiol. 2015;12:91–102.
25. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: a review. J Am Heart Assoc. 2012;1:e000364.
26. Rapezzi C, Lorenzini M, Longhi S, et al. Cardiac amyloidosis: the great pretender. Heart Fail Rev. 2015;20:117–24.
27. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation. 2009;120:1203–12.
28. Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. JAMA Cardiol. 2016;1:880–9.
29. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129:837–47.
30. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet. 2015;386:154–62.
31. Falk RH. Atrial fibrillation. N Engl J Med. 2001;344:1067–78.
32. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368:1005–11.
33. Levine RA, Hagege AA, Judge DP, et al. Mitral valve disease--morphology and mechanisms. Nat Rev Cardiol. 2015;12:689–710.
34. Anyanwu AC, Adams DH. Etiologic classification of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency. Semin Thorac Cardiovasc Surg. 2007;19:90–6.
35. Supino PG, Borer JS, Preibisz J, Bornstein A. The epidemiology of valvular heart disease: a growing public health problem. Heart Fail Clin. 2006;2:379–93.
36. Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968;38:61–7.