Computational Biomechanics in Thoracic Aortic Dissection:

Today’s Approaches and Tomorrow’s Opportunities

Barry J. Doyle^{1,2} and Paul E. Norman^{1,3}

- 1. Vascular Engineering, Intelligent Systems for Medicine Laboratory, School of Mechanical and Chemical Engineering, The University of Western Australia, Perth, Australia.
- 2. Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh, UK.
- 3. School of Surgery, The University of Western Australia, Perth, Australia.

ABSTRACT

Dissection of an artery is characterised by the separation of the layers of the arterial wall causing blood to flow within the wall. The incidence rates of thoracic aortic dissection (AoD) are increasing, despite falls in virtually all other manifestations of cardiovascular disease, including abdominal aortic aneurysm (AAA). Dissections involving the ascending aorta (Type A) are a medical emergency and require urgent surgical repair. However, dissections of the descending aorta (Type B) are less lethal and require different clinical management whereby the patient may not be offered surgery unless complicating factors are present. But how do we tell if a patient will develop a complication later on? Currently, there is no consensus and the evidence

base is limited. There is an opportunity for computational biomechanics to help clinicians decide as to which cases to repair and which to manage with blood pressure control. In this review article, we look at AoD from both the clinical and biomechanical perspective and discuss some of the recent computational studies of both Type A and B AoD. We then focus more on Type B where the real opportunity for patient-specific modelling exists. Finally, we look ahead at some of the promising areas of research that may help clinicians improve the decision-making process surrounding Type B AoD.

Keywords: aortic dissection; computational biomechanics; patient-specific modelling

INTRODUCTION

Dissection of an artery is characterised by the separation of the layers of the arterial wall causing blood to flow within the wall. A tear in the wall allows blood to pass into a new cavity called the 'false lumen'. Dissection can occur in any major artery but it is most common in the thoracic aorta. The management of Aortic Dissection (AoD) is challenging with uncertainty around which patients should receive surgery and which should be managed conservatively. Despite numerous publications we still do not know (a) precisely what triggers a dissection, (b) how to predict progression of AoD, or (c) how best to treat those diagnosed with certain types of AoD. Furthermore, it can be very challenging to accurately diagnose the disease and in the case of dissections of the ascending aorta, the mortality rate increases by 1% for every hour left untreated. The most recent clinical guidelines³¹ offer many recommendations to clinicians but also identify several critical issues that must be resolved.

In this review article, we will begin by describing the clinical aspects of the disease, before focussing on the computational biomechanics and the potential role of patient-specific modelling in the diagnosis, prognosis and treatment stages of this often fatal condition. We will then look ahead to what may be on the horizon for computational biomechanics of AoD.

THE CLINICAL PERSPECTIVE

The aorta is the body's main conduit. It has a wall comprised of three-layers: the innermost layer (intima) is a smooth surface lined with a single layer of endothelial cells (endothelium) that are in direct contact with the flowing blood. The endothelium

1 is metabolically highly active and helps regulate haemostasis. Besides being a main
2 conduit, the aorta also has a key role in systemic vascular resistance and heart rate
3 via pressure-responsive receptors located in the ascending aorta and aortic arch.
4
5 When the normal structure of the aorta becomes compromised, aortic disease
6 occurs, with AoD now representing an increasingly common cause of aortic
7 emergencies requiring surgical intervention.^{29, 45}

14 *Pathogenesis and natural history*

15
16 The cause of AoD is poorly understood and is complicated further by its relationship
17 with aortic ulceration, intramural haematoma and aneurysmal dilation.⁷⁶ Although
18 cases of AoD are seen in congenital conditions such as Marfan syndrome, the
19 majority of cases are not due to any demonstrable connective tissue disorder and
20 are associated with hypertension, older age and, to a variable extent,
21 atherosclerosis. The role of inflammation, tissue necrosis and calcification in the
22 initiation and progression of AoD is unknown. The initiation of the intimal tear is
23 influenced by the systolic blood pressure and its location probably relates to focal
24 structural weakness. Subsequent propagation of the dissection is thought to be
25 influenced by pulse pressure and cycle frequency.⁷⁰ The most common symptom of
26 AoD is severe acute chest and thoracic back pain. This may be associated with
27 either hypertension, or in the event of aortic rupture, hypotension. The dissection
28 may spread into, and sometimes occlude, any of the major branches or the aorta.
29 This complication can give rise to very complex patterns of symptoms due to end-
30 organ ischaemia – including stroke, myocardial infarction, visceral and limb
31 ischaemia.⁸⁸ The natural history of AoD depends on the classification (see Figure 1).
32
33 In this review we will use the Stanford classification system. Type A is more lethal
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

than Type B, and approximately half of patients with Type A will die within 48 hours of the onset of symptoms.²²

[Possible location of Figure 1]

As Type A dissections can involve the coronary arteries, additional complications can occur such as myocardial infarction and the aortic valves can become disrupted, leading to acute heart failure. Type A dissection is a medical emergency and surgery should be performed immediately if the patient is medically fit,²² however, perioperative mortality rates and neurological complications are extremely high at 25% and 18%, respectively.^{13, 84} Therefore, as most patients with Type A AoD need surgery, the question becomes how can we improve the pre-surgical planning and post-surgery outcome? Type B dissections are less lethal and patients can often be stabilised with best medical treatment (BMT) to control pain and blood pressure. However, complicating factors present an additional challenge: how can we tell if a patient will develop a complication? Unlike Type A, these patients may not be offered surgery based on clinical factors. Patient-specific modelling may be able to elucidate factors unbeknownst to the clinician to help in the decision process.

Data from the International Registry of Aortic Dissection (IRAD) shows that about 30% of Type B cases develop a complication.⁶ Complications include occlusion of branch arteries (visceral, renal or lower limb) and aortic rupture. The risk factors for adverse events and death include: poor blood pressure control, aortic diameter >4cm on admission, large entry tear size and a patent or partially thrombosed false lumen.^{81, 85} Progressive aortic expansion is influenced by intraluminal pressure and in vivo haemodynamics, and is likely to be exacerbated by a lack of false lumen

outflow.¹² Ex-vivo pressure studies suggest that false lumen pressures are highest with small proximal tears and lack of distal outflow tears.

There are no known biomarkers of Type B AoD and a new method of non-invasively predicting the haemodynamic load on the aortic wall would have real benefits. The long-term prognosis also appears to be variable. Chronic aneurysmal dilation and cumulative mortality is reported in 25-50% of cases within 5 years.⁷ There is some evidence that false lumen diameter $\geq 22\text{mm}$ is a stronger predictor of late dilation than initial aortic diameter,⁷⁹ however, prediction of late adverse events is as uncertain as it is for early complications – again reflecting the need for new approaches.

Management Options

Diagnosis of AoD is usually via medical imaging; beginning with chest radiography and CT, often followed by MRI and/or transoesophageal echocardiography (TOE). Once diagnosed, as mentioned earlier, the management options for Type A AoD is typically urgent repair. With Type B AoDs, a decision must be made as to the severity of the symptoms and the chance of complications; with those considered to be uncomplicated are managed with best medical treatment (BMT), with surgical intervention, usually thoracic endovascular aortic repair (TEVAR), the preferred choice in complicated cases.²³ However, the evidence base for this approach is limited.

THE BIOMECHANICAL PERSPECTIVE

Layer-specific strength

There are a plethora of studies on the strength and behaviour of healthy aortic tissue,^{33, 90, 91} AAA wall tissue and thrombus^{62-64, 83, 90} and thoracic aortic aneurysm (TAA) tissue,^{1, 25, 66} however, the data is scarce on tissue excised from AoD cases. Holzapfel et al.³³ performed layer-specific tests of healthy aorta and showed that each layer behaves differently, whereas, Sokolis et al.⁷⁸ performed layer-specific uniaxial tensile tests and reported that the intima is much weaker than the media and adventitia. Weisbecker et al.⁹¹ performed layer-specific uniaxial tensile experiments on the thoracic and abdominal aorta. However, although they show that the intimal layer is the stiffest layer; they did not report failure strengths. Pasta et al.⁶⁶ performed delamination tests on thoracic aorta tissue samples excised from patients undergoing ATAA repair. They manually created an initial delamination plane (i.e. an intimal tear) and showed a difference in dissection strength between the circumferential and longitudinal directions and effectively measured the separation forces.

Computational Assessment

Computational biomechanical modelling has proven successful in many aortic applications, in particular, AAA. We can compute the stress in the aortic wall using direct^{15, 17, 18, 20, 28, 49, 54} and inverse methods^{51, 52} or more recently, without any knowledge of material properties.³⁵ We can also determine the haemodynamics within healthy⁹² or diseased aortas.^{4, 5, 16, 47} The use of computational modelling in AoD is gaining momentum. In PubMed alone, there are 40 reports since 2005, of which 35 are within the last five years (search terms: 'computational', 'aortic', 'dissection'). What is interesting about AoD is that patients are diagnosed using a range of medical imaging modalities from CT to MRI to TOE. This provides a wealth

of imaging data for computational studies, often with longitudinal data that is ideal for follow-up patient-specific modelling (see Figure 2).

[Possible location of Figure 2]

When modelling is used to investigate either Type A or B AoD, the primary quantities of interest is intramural wall stress (e.g. von Mises stress) or wall shear stress (WSS). From a biomechanical perspective, the intramural stress is relevant as it is this stress that may overcome the strength of the intimal layer to cause the initial entry tear. On the other hand, WSS is of critical importance as it is abnormal WSS that triggers endothelial dysfunction which is then responsible for a host of biological processes.

COMPUTATIONAL BIOMECHANICS OF TYPE A AoD

In Type A cases, the forces acting on the ascending aorta are entirely different to those of the descending aorta (i.e. Type B). The cyclic longitudinal stretching of the aortic root results in large stresses on the ascending aorta and proximal arch region, and computational efforts have focussed on predicting these stresses.

Tissue Stress in Type A AoD

A material will fail will the stress exceeds the strength. One of the earlier studies⁸² using an idealised geometry, suggested that the longitudinal stress in the wall could be a key cause of circumferentially-orientated tears, which have been reported to be the more common orientation, albeit from a review of autopsies many decades ago.³² Several studies have used finite element analysis (FEA) to compute the wall stress in the ascending aorta in both idealised² and patient-specific geometries.^{19, 57,}

⁵⁸ Beller et al.² proposed that aortic root motion, which can be as much as 22 mm,³ increases the longitudinal stress acting on the ascending aorta, thus increasing the risk of a circumferential tear. Although this was a relatively simple geometric model, the work highlighted a potentially important finding as aortic root motion can be measured noninvasively with angiography. However, this is yet to be demonstrated using patient-specific cases. Whereas there are numerous reports on the wall stress in patient-specific ATAA,^{58, 67, 75} there are few studies that assess the wall stress in non-aneurysmal thoracic aortas.^{19, 57} Nathan et al.⁵⁷ examined the thoracic aorta of 47 patients and showed that the wall stress was at a maximum in the ascending aorta near the sinotubular junction and distal to the left subclavian artery, which is where the majority of intimal tears occur. Later, Doyle et al.¹⁹ assessed the wall stress in the thoracic aorta of 50 patients and found that the maximum stresses also occurred in the ascending aorta or aortic arch, which agrees with tear locations reported previously.³⁴ However, what both studies lack is data on dissected cases or retrospective validation using pre-dissection geometries.

COMPUTATIONAL BIOMECHANICS OF TYPE B AoD

Like in Type A, the tissue stresses in cases of Type B are important and in Figure 3 we present data showing the wall stress of two different sufferers at different time points.

[Possible location of Figure 3]

However, the computational focus in Type B AoD primarily investigates the haemodynamics. Using computational fluid dynamics (CFD), we can estimate the

1 haemodynamic pressure, time averaged WSS (TAWSS), the development of vortical
2 structures⁵ or the attachment of monocytes to the endothelium³⁰ and particle
3 residence time (PRT).⁴⁶ The earlier investigations of AoD^{26, 27, 69} were limited to
4 idealised geometries and it was not until 2008 and the work of Karmonik et al.⁴¹ that
5 patient-specific geometries were analysed.⁴¹ Figure 4 shows some of our on-going
6 work exploring if low TAWSS can predict complication in Type B AoD.
7
8
9
10
11
12
13
14
15
16

17 *[Possible location of Figure 4]*

18 *True-False Lumen Blood Exchange*

19
20
21 In AoD there can be a single tear into the false lumen, or often, several (see Figure
22 5). In Cheng et al.¹² they determined that approximately 80% of the aortic flow
23 entered the false lumen. However, the geometry used had a particularly large false
24 lumen volume extending from the aortic arch to the iliac arteries. They also report on
25 turbulence intensity and found it to peak at 70% in the tear region. In a similar study
26 by Cheng et al.,¹¹ they investigated four cases, each with false lumens extending
27 from the arch to the distal aorta. They show the impact of tear size on flow entering
28 the false lumen and the percentages of flow into the false lumen ranged from 40-
29 96% depending on the geometry.¹¹ Similarly, Chen et al.⁹ report that approximately
30 40% of blood flow passes through the false lumen during each heart beat and
31 estimated the pressure drop at systole in their patient to be 75 mmHg, compared to
32 less than 23 mmHg in healthy thoracic aortas.⁶⁵ Using an experimental setup, Tsai et
33 al.⁸⁷ showed that in the absence of a distal tear allowing blood to pass from the false
34 lumen back into the true lumen, the systolic pressure was higher in the true lumen
35 (111 v 106 mmHg) and diastolic pressure was higher in the false lumen (60 v 55
36 mmHg). Without a distal tear, the waveform of the false lumen pressure was
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 dampened compared with true lumen pressure, with higher diastolic pressure but
2 lower systolic pressure.⁸⁷ This implies that in the case of small proximal tears and a
3
4 lack of distal tear, the inflow and outflow conditions may give rise to lumen expansion
5
6 and potential rupture.
7
8
9

10
11 *[Possible location of Figure 5]*
12

13 *Thrombosis of the False Lumen*

14
15
16
17 Intuitively, one may think it is desirable for the false lumen to thrombose and exclude
18
19 the false lumen from the blood flow. However, partial false lumen thrombosis is a
20
21 significant predictor of postdischarge mortality as it promotes inflammation and wall
22
23 weakening.⁸⁶ Partial thrombosis of the false lumen while the true lumen geometry
24
25 remains unchanged results in large increases in false lumen pressure, thus
26
27 potentially causing further progression and even rupture. Therefore, predicting cases
28
29 that will thrombose is an important challenge. In Cheng et al.,¹¹ they use PRT in a
30
31 patient followed over 28 months and demonstrated that the regions of high PRT
32
33 correspond with the regions of thrombosis.
34
35
36
37
38
39

40 *Pre- and Post-Treatment*

41
42
43 Whereas several papers have investigated the haemodynamics in patient-specific
44
45 pre- and post-treatment ATAA, few have focused on AoD. Karmonik et al.³⁸ used a
46
47 reconstruction from MRI and virtually created different scenarios. First they modelled
48
49 the case as presented, with entry/exit tears into the false lumen. They then
50
51 manipulated the geometry to (a) simulate blockage of the exit tear due to thrombosis,
52
53
54 (b) cover the entry tear to simulate TEVAR and (c) completely remove the
55
56 intraluminal septum to represent complete aortic repair. By blocking the entry tear,
57
58
59
60
61
62
63
64
65

1 the pressure in the false lumen essentially diminished, however, due to the restricted
2 true lumen geometry, the blood velocities are high and in this configuration the long
3 term outcomes may not be favourable as the endothelial layer will be subjected to
4 excessive WSS. In the third scenario, which represents expansion of the true lumen
5 due to the placement of a stent-graft, the results show favourable haemodynamics.
6
7
8
9
10

11
12 Chen et al.⁸ investigated management via BMT. In this study, the authors compare
13 the haemodynamics in a patient-specific case at initial presentation and after four
14 years. They show that over the four years the geometry is relatively unchanged and
15 that BMT has lowered pressures and WSS in the geometry. Furthermore, it flattens
16 the large pressure gradient seen initially on the outer wall of the false lumen (which
17 is where most dissections rupture), thus reducing the chance of progression or
18 further complication.
19
20
21
22
23
24
25
26
27
28

29 *Variations in Modelling Approach*

30
31 As with many computational biomechanics studies, the approaches vary
32 significantly.¹⁵ For instance, the inlet boundary conditions differ across studies; in
33 Chen et al.⁸ they apply an inlet velocity to the ascending aorta extracted from Morris
34 et al.⁵⁶ which was originally from Di Martino et al.¹⁴ Interestingly, this velocity profile
35 was measured in AAA and presumably at the infrarenal location. The same authors
36 then investigate what appears to be the same geometry⁹ using a velocity profile
37 measured in 13 healthy cases.²⁴ It is interesting to note that they find little difference
38 in the peak WSS in each patient (96 Pa and 98 Pa, respectively) despite using very
39 different inlet velocities. In Cheng et al.^{11, 12} they apply a flow rate measured in the
40 ascending aorta of three patients undergoing repair for atrial septal defect.⁶⁸
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

On the other hand Karmonik et al.³⁸⁻⁴³ use patient-specific phase contrast MRI (pcMRI) measurements as input which in theory enables the calculation of patient-specific data. However, the computational mesh used in all these reports does not have a refined boundary layer mesh and uses very low numbers of tetrahedral elements throughout the computational domain (~264,000–388,000 elements). Likewise, the work of Tse et al.⁸⁹ who investigated a pre and post-aneurysmal dissection case also employ a coarse mesh (84,209 and 114,148 elements) without a refined boundary layer. Refinement of the mesh in the boundary layer is critical and was shown to change the resulting velocity, pressure and WSS by 9%, 30% and 24%, respectively.⁹ More recently, Cheng et al.¹⁰ also used pcMRI data while using a highly refined computational mesh with adequate boundary layer. This work perhaps represents the state of the art in computational simulation of Type B AoD. Besides the variations in input boundary conditions, other modelling assumptions impact the resulting data. The application of a pressure wave boundary condition or Windkessel model at the branching outlets compared to the assumption of zero pressure can slightly change results in the same geometry, albeit a change in peak WSS of only 2 Pa in one geometry.^{8, 9} Other assumptions such as the Newtonian properties of the blood, the potential effects of turbulent flow and the rigidity of the vessel wall, all have varying effects on simulations and ideally should be investigated in each patient-specific geometry.

THE FUTURE PERSPECTIVE

Patient-Specific Modelling in the Clinic

1 Patient-specific modelling has the potential to transform the way we diagnose and
2 treat patients, not just in AoD, but across a wide range of clinical problems from
3 orthopaedics⁷⁷ to whole body image registration⁴⁸ to tumour growth.⁵⁰ As mentioned
4 earlier, many cases AoD patients are imaged using several different modalities, thus
5 providing an excellent platform for patient-specific modelling. In the most recent
6 clinical guidelines on AoD,³¹ the committee acknowledge that the collaboration of
7 multiple medical specialities is needed. However, there appears to be a role for
8 patient-specific modelling here. Using a variety of different workflows, we can
9 estimate the structural stresses and the blood flow (and therefore, many additional
10 quantities such as WSS, vortices and PRT) in the dissected region. We can also
11 provide estimates of the pressure within the false lumen region and potentially
12 indicate whether or not expansion and/or rupture are likely. Along with more
13 biomechanical experiments to determine the layer-specific failure and delamination
14 strength of the aorta, we can begin to develop risk assessment methods that may
15 help further indicate those likely to develop complications in Type B AoD. Patient-
16 specific modelling also enables device testing prior to surgery, where the clinician
17 can not only size the most appropriate stent-graft based on detailed 3D
18 measurements, but now determine the optimum device based on the resulting
19 haemodynamics also. This is precisely the level of information that clinicians require
20 to inform their management decisions. Furthermore, patient-specific modelling may
21 be useful to indicate those susceptible to AoD by predicting abnormalities in flow or
22 structural stresses early on when the aorta is still relatively healthy.¹⁹

23 *Real Time and Large Scale Simulations*

24 In the clinic, it is desirable to have data available almost immediately, especially in
25 the case of emergencies like Type A AoD and in certain cases of Type B AoD. There

1 have been major advances in real time simulations of deformable soft tissues⁹⁴ and
2 brain deformation.^{36, 37} The trade-off between computational time and accuracy is a
3 major challenge, although recently a method of computing fractional flow reserve
4 (FFR) has reduced the computational time from 5 days to a matter of seconds.⁷⁴
5
6
7
8
9

10 Perhaps the biggest challenge is to provide enough evidence that patient-specific
11 modelling can benefit patients of AoD. The PREDICTION Study⁸⁰ showed that low
12 WSS in the coronary arteries predicts plaque enlargement and lumen narrowing.
13 They performed CFD on over 500 patients at baseline and follow-up, which
14 represents a tremendous effort. We need to learn from this study and design trials
15 with enough power to show that modelling predicts patients that will have a
16 complication and thus should be surgically repaired, rather than managed with
17 medication.
18
19
20
21
22
23
24
25
26
27
28
29

30 *Functional Imaging and Computational Biomechanics*

31 PET-CT is fast becoming a viable tool to image vascular diseases and predict cases
32 at risk of a clinical event. Uptake of the radiotracer 18F-fluorodeoxyglucose (18F-
33 FDG) is an established surrogate for inflammation and major advancements have
34 been made since the early work of Sakalihasan et al.⁷³ In Type B AoD, 18F-FDG
35 was shown to differentiate acute from chronic dissection in clinically unclear cases,⁷¹
36 be significantly associated with rupture or progression⁴⁴ and shown to be a useful
37 imaging marker of complications (see Figure 6).⁷²
38
39
40
41
42
43
44
45
46
47
48
49
50
51

52 *[Possible location of Figure 6]*

53 One of the first reports correlating 18F-FDG uptake and wall stress in five cases of
54 AAA⁹³ suggested a possible co-localisation of uptake and high wall stress. This was
55
56
57
58
59
60
61
62
63
64
65

1 followed by Maier et al.⁵³ who showed a positive correlation between uptake and wall
2 stress in 18 patients. More recently, Nchimi et al.⁵⁹ demonstrated modest positive
3 correlation between uptake and wall stress in 53 patients. Following a different
4 approach, Hardman et al.³⁰ used CFD and PRT to predict the regions of increased
5 monocyte deposition with a view to linking the data to regions of high uptake. If
6 monocyte deposition correlated with regions of high uptake, and as 18F-FDG uptake
7 has been shown to be useful in Type B AoD^{44, 72} computational modelling could
8 potentially eliminate the requirement for expensive PET-CT in the future. We have
9 begun investigating this relationship in patients with various forms of aortic valve
10 disease²¹ (see Figure 7).
11
12
13
14
15
16
17
18
19
20
21
22
23
24

25 *[Possible location of Figure 7]*
26
27
28
29
30
31

32 **CONCLUSIONS**

33
34

35 When compared to AAA, the literature on computational biomechanics of AoD is
36 scarce. The few reports that are available, highlight the potential of computational
37 modelling, but also reveal many shortcomings. Firstly, the sample sizes need to be
38 increased and we need to devise strategies that continue reducing the computational
39 time so that it is feasible to analyse many cases within a reasonable time frame.
40 Furthermore, we need to plan our studies to ensure we have follow up data to relate
41 computational predictions to clinical events. The future is certainly bright for the use
42 of computational biomechanics in AoD and hopefully the same impact can be made
43 on this disease as was seen in AAA over the past few decades. Efforts are underway
44 to show the true potential of patient-specific modelling in AoD and perhaps over the
45 coming years we may see some changes to the diagnosis and management of the
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

disease, but until then, computational biomechanics will remain but a promising research tool in aortic dissection.

Acknowledgements

The authors would like to thank Eileen Wiryadinata and Adam Byass from The University of Western Australia, and Peter Hoskins, David Newby, Marc Dweck and Scott Semple from The University of Edinburgh. We would also like to thank our funding sources; The University of Western Australia and the National Health and Medical Research Council (Grants: APP1063986, APP1083572).

Conflict of Interest

The authors have nothing to declare.

References

1. Azadani, A. N., S. Chitsaz, A. Mannion, A. Mookhoek, A. Wisneski, J. M. Guccione, M. D. Hope, L. Ge, and E. E. Tseng. Biomechanical Properties of Human Ascending Thoracic Aortic Aneurysms. *Ann Thorac Surg.* 96: 50-58, 2013.
2. Beller, C. J., M. R. Labrosse, M. J. Thubrikar, and F. Robicsek. Role of Aortic Root Motion in the Pathogenesis of Aortic Dissection. *Circulation.* 109: 763-769, 2004.

3. Beller, C. J., M. R. Labrosse, M. J. Thubrikar, G. Szabo, F. Robicsek, and S. Hagl. Increased Aortic Wall Stress in Aortic Insufficiency: Clinical Data and Computer Model. *Eur J Cardiothorac Surg.* 27: 270-275, 2005.
4. Biasetti, J., T. Gasser, M. Auer, U. Hedin, and F. Labruto. Hemodynamics of the Normal Aorta Compared to Fusiform and Saccular Abdominal Aortic Aneurysms with Emphasis on a Potential Thrombus Formation Mechanism. *Ann Biomed Eng.* 38: 380-390, 2010.
5. Biasetti, J., F. Hussain, and T. C. Gasser. Blood Flow and Coherent Vortices in the Normal and Aneurysmatic Aortas: A Fluid Dynamical Approach to Intra-Luminal Thrombus Formation. *J R Soc Interface.* 8: 1449-1461, 2011.
6. Boher, A. M., E. M. Isselbacher, C. A. Nienaber, S. Trimarchi, A. Evangelista, D. G. Montgomery, J. B. Froehlich, M. P. Ehrlich, J. K. Oh, J. L. Januzzi, P. O'Gara, T. M. Sundt, K. M. Harris, E. Bossone, R. E. Pyeritz, K. A. Eagle, and IRAD Investigators. The Irad Classification System for Characterizing Survival after Aortic Dissection. *Am J Med.* 126: 730.e719-730.e724, 2013.
7. Brunkwall, J., and T. Lubke. Part One: For the Motion. We Do Not Need Level 1 Evidence Comparing Best Medical Treatment with Tevar in Patients with Uncomplicated Type B Aortic Dissection. *Eur J Vasc Endovasc Surg.* 46: 274-277, 2013.
8. Chen, D., M. Muller-Eschner, D. Kotelis, D. Bockler, Y. Ventikos, and H. von Tengg-Kobligh. A Longitudinal Study of Type-B Aortic Dissection and Endovascular Repair Scenarios: Computational Analyses. *Med Eng Phys.* 35: 1321-1330, 2013.

9. Chen, D., M. Muller-Eschner, H. von Tengg-Kobligk, D. Barber, D. Bockler, R. Hose, and Y. Ventikos. A Patient-Specific Study of Type-B Aortic Dissection: Evaluation of True-False Lumen Blood Exchange. *Biomed Eng Online*. 12: 65, 2013.
10. Cheng, Z., C. Juli, N. B. Wood, R. G. Gibbs, and X. Y. Xu. Predicting Flow in Aortic Dissection: Comparison of Computational Model with Pc-Mri Velocity Measurements. *Med Eng Phys*. 36: 1176-1184, 2014.
11. Cheng, Z., C. Riga, J. Chan, M. Hamady, N. B. Wood, N. J. Cheshire, Y. Xu, and R. G. Gibbs. Initial Findings and Potential Applicability of Computational Simulation of the Aorta in Acute Type B Dissection. *J Vasc Surg*. 57: 35S-43S, 2013.
12. Cheng, Z., F. P. Tan, C. V. Riga, C. D. Bicknell, M. S. Hamady, R. G. Gibbs, N. B. Wood, and X. Y. Xu. Analysis of Flow Patterns in a Patient-Specific Aortic Dissection Model. *J Biomech Eng*. 132: 051007. doi: 051010.051115/051001.4000964, 2010.
13. Chiappini, B., M. Schepens, E. Tan, A. Dell' Amore, W. Morshuis, K. Dossche, M. Bergonzini, N. Camurri, L. B. Reggiani, G. Marinelli, and R. Di Bartolomeo. Early and Late Outcomes of Acute Type a Aortic Dissection: Analysis of Risk Factors in 487 Consecutive Patients. *Eur Heart J*. 26: 180-186, 2005.
14. Di Martino, E., G. Guadagni, A. Fumero, G. Ballerini, R. Spirito, P. Biglioli, and A. Redaelli. Fluid-Structure Interaction within Realistic Three-Dimensional Models of the Aneurysmatic Aorta as a Guidance to Assess the Risk of Rupture of the Aneurysm. *Med Eng Phys*. 23: 647 - 655, 2001.

15. Doyle, B., A. Callanan, and T. McGloughlin. A Comparison of Modelling Techniques for Computing Wall Stress in Abdominal Aortic Aneurysms. *Biomed Eng Online*. 6: 38, 2007.
16. Doyle, B., T. McGloughlin, E. Kavanagh, and P. Hoskins, 'From Detection to Rupture: A Serial Computational Fluid Dynamics Case Study of a Rapidly Expanding, Patient-Specific, Ruptured Abdominal Aortic Aneurysm', in *Computational Biomechanics for Medicine*, ed. by Barry Doyle, Karol Miller, Adam Wittek and Poul M. F. Nielsen (Springer New York, 2014), pp. 53-68.
17. Doyle, B. J., A. Callanan, P. E. Burke, P. A. Grace, M. T. Walsh, D. A. Vorp, and T. M. McGloughlin. Vessel Asymmetry as an Additional Diagnostic Tool in the Assessment of Abdominal Aortic Aneurysms. *J Vasc Surg*. 49: 443-454, 2009.
18. Doyle, B. J., A. Callanan, P. A. Grace, and E. G. Kavanagh. On the Influence of Patient-Specific Material Properties in Computational Simulations: A Case Study of a Large Ruptured Abdominal Aortic Aneurysm. *Int J Numer Meth Biomed Eng*. 29: 150-164, 2013.
19. Doyle, B. J., P. R. Hoskins, K. Miller, D. E. Newby, and M. R. Dweck, 'Biomechanical Analysis of the Thoracic Aorta: Could Wall Stress and 3d Geometry Help Identify Patients at Risk of Acute Aortic Dissection? ', in *3rd International Conference on Mathematical and Computational Biomedical Engineering – CMBE2013*, ed. by P. Nithiarasu and R. Löhner (Hong Kong: 2013).
20. Doyle, B. J., T. M. McGloughlin, K. Miller, J. T. Powell, and P. E. Norman. Regions of High Wall Stress Can Predict the Future Location of Rupture of Abdominal Aortic Aneurysm. *Cardiovasc Intervent Radiol*. 37: 815-818, 2014.

21. Dweck, M. R., C. Jones, N. V. Joshi, A. M. Fletcher, H. Richardson, A. White, M. Marsden, R. Pessotto, J. C. Clark, W. A. Wallace, D. M. Salter, G. McKillop, E. J. R. van Beek, N. A. Boon, J. H. F. Rudd, and D. E. Newby. Assessment of Valvular Calcification and Inflammation by Positron Emission Tomography in Patients with Aortic Stenosis. *Circulation*. 125: 76-U424, 2012.
22. Erbel, R., V. Aboyans, C. Boileau, E. Bossone, R. D. Bartolomeo, H. Eggebrecht, A. Evangelista, V. Falk, H. Frank, O. Gaemperli, M. Grabenwöger, A. Haverich, B. Iung, A. J. Manolis, F. Meijboom, C. A. Nienaber, M. Roffi, H. Rousseau, U. Sechtem, P. A. Sirnes, R. S. v. Allmen, C. J. M. Vrints, J. L. Zamorano, S. Achenbach, H. Baumgartner, J. J. Bax, H. Bueno, V. Dean, C. Deaton, Ç. Erol, R. Fagard, R. Ferrari, D. Hasdai, A. Hoes, P. Kirchhof, J. Knuuti, P. Kolh, P. Lancellotti, A. Linhart, P. Nihoyannopoulos, M. F. Piepoli, P. Ponikowski, P. A. Sirnes, J. L. Tamargo, M. Tendera, A. Torbicki, W. Wijns, S. Windecker, P. Nihoyannopoulos, M. Tendera, M. Czerny, J. Deanfield, C. D. Mario, M. Pepi, M. J. S. Taboada, M. R. v. Sambeek, C. Vlachopoulos, and J. L. Zamorano, *2014 ESC Guidelines on the Diagnosis and Treatment of Aortic Diseases*. Vol. 35, *Document Covering Acute and Chronic Aortic Diseases of the Thoracic and Abdominal Aorta of the Adult* the Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC) (2014), pp. 2873-2926.
23. Fattori, R., P. Cao, P. De Rango, M. Czerny, A. Evangelista, C. Nienaber, H. Rousseau, and M. Schepens. Interdisciplinary Expert Consensus Document on Management of Type B Aortic Dissection. *J Am Coll Cardiol*. 61: 1661-1678, 2013.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
24. Fielden, S. W., B. K. Fornwalt, M. Jerosch-Herold, R. L. Eisner, A. E. Stillman, and J. N. Oshinski. A New Method for the Determination of Aortic Pulse Wave Velocity Using Cross-Correlation on 2d Pcmr Velocity Data. *J Magn Reson Imaging*. 27: 1382-1387, 2008.
 25. Fukui, T., T. Matsumoto, T. Tanaka, T. Ohashi, K. Kumagai, H. Akimoto, K. Tabayashi, and M. Sato. In Vivo Mechanical Properties of Thoracic Aortic Aneurysmal Wall Estimated from in Vitro Biaxial Tensile Test. *Biomed Mater Eng*. 15: 295-305, 2005.
 26. Gao, F., Z. Guo, M. Sakamoto, and T. Matsuzawa. Fluid-Structure Interaction within a Layered Aortic Arch Model. *J Biol Phys*. 32: 435-454, 2006.
 27. Gao, F., M. Watanabe, and T. Matsuzawa. Stress Analysis in a Layered Aortic Arch Model under Pulsatile Blood Flow. *Biomed Eng Online*. 5: 25, 2006.
 28. Gasser, T. C., M. Auer, F. Labruto, J. Swedenborg, and J. Roy. Biomechanical Rupture Risk Assessment of Abdominal Aortic Aneurysms: Model Complexity Versus Predictability of Finite Element Simulations. *Eur J Vasc Endovasc Surg*. 40: 176-185, 2010.
 29. Hagan, P. G., C. A. Nienaber, E. M. Isselbacher, D. Bruckman, D. J. Karavite, P. L. Russman, A. Evangelista, R. Fattori, T. Suzuki, J. K. Oh, A. G. Moore, J. F. Malouf, L. A. Pape, C. Gaca, U. Sechtem, S. Lenferink, H. J. Deutsch, H. Diedrichs, J. Marcos y Robles, A. Llovet, D. Gilon, S. K. Das, W. F. Armstrong, G. M. Deeb, and K. A. Eagle. The International Registry of Acute Aortic Dissection (Irad): New Insights into an Old Disease. *JAMA*. 283: 897-903, 2000.
 30. Hardman, D., B. J. Doyle, S. I. Semple, J. M. Richards, D. E. Newby, W. J. Easson, and P. R. Hoskins. On the Prediction of Monocyte Deposition in

Abdominal Aortic Aneurysms Using Computational Fluid Dynamics. Proc Inst
Mech Eng H. 227: 1114-1124, 2013.

31. Hiratzka, L. F., G. L. Bakris, J. A. Beckman, R. M. Berson, V. F. Carr, D. E. Casey Jr, K. A. Eagle, L. K. Herman, E. M. Isselbacher, E. A. Kazerooni, N. T. Kouchoukos, B. W. Lytle, D. M. Milewicz, D. L. Reich, S. Sen, J. A. Shinn, L. G. Svensson, D. M. Williams. ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 121: e266-369, 2010.
32. Hirst, A. E., Jr., V. J. Johns, Jr., and S. W. Kime, Jr. Dissecting Aneurysm of the Aorta: A Review of 505 Cases. Medicine (Baltimore). 37: 217-279, 1958.
33. Holzapfel, G. A., G. Sommer, M. Auer, P. Regitnig, and R. W. Ogden. Layer-Specific 3d Residual Deformations of Human Aortas with Non-Atherosclerotic Intimal Thickening. Ann Biomed Eng. 35: 530-545, 2007.
34. Jaussaud, N., S. Chitsaz, A. Meadows, M. Wintermark, N. Cambronero, A. N. Azadani, D. A. Saloner, T. A. Chuter, and E. E. Tseng. Acute Type a Aortic Dissection Intimal Tears by 64-Slice Computed Tomography: A Role for Endovascular Stent-Grafting? J Cardiovasc Surg (Torino). 2012.

35. Joldes, G., K. Miller, A. Wittek, and B. Doyle. A Simplified and Effective Method of Computing Wall Stress in Abdominal Aortic Aneurysms J Mech Behav Biomed Mater. Submitted, 2015.
36. Joldes, G., A. Wittek, M. Couton, S. Warfield, and K. Miller. Real-Time Prediction of Brain Shift Using Nonlinear Finite Element Algorithms. Med Image Comput Comput Assist Interv. 5762: 300-307, 2009.
37. Joldes, G. R., A. Wittek, and K. Miller. Real-Time Nonlinear Finite Element Computations on Gpu - Application to Neurosurgical Simulation. Comput Methods Appl Mech Eng. 199: 3305-3314, 2010.
38. Karmonik, C., J. Bismuth, M. G. Davies, D. J. Shah, H. K. Younes, and A. B. Lumsden. A Computational Fluid Dynamics Study Pre- and Post-Stent Graft Placement in an Acute Type B Aortic Dissection. Vasc Endovascular Surg. 45: 157-164, 2011.
39. Karmonik, C., J. Bismuth, T. Redel, J. E. Anaya-Ayala, M. G. Davies, D. J. Shah, and A. B. Lumsden. Impact of Tear Location on Hemodynamics in a Type B Aortic Dissection Investigated with Computational Fluid Dynamics. Conf Proc IEEE Eng Med Biol Soc. 2010: 3138-3141, 2010.
40. Karmonik, C., J. Bismuth, D. J. Shah, M. G. Davies, D. Purdy, and L. A. B. Computational Study of Haemodynamic Effects of Entry- and Exit-Tear Coverage in a DeBakey Type Iii Aortic Dissection: Technical Report. Eur J Vas Endovasc Surg. 42: 172-177, 2011.
41. Karmonik, C., J. X. Bismuth, M. G. Davies, and A. B. Lumsden. Computational Hemodynamics in the Human Aorta: A Computational Fluid Dynamics Study of Three Cases with Patient-Specific Geometries and Inflow Rates. Technol Health Care. 16: 343-354, 2008.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
42. Karmonik, C., M. Muller-Eschner, S. Partovi, P. Geisbusch, M. K. Ganten, J. Bismuth, M. G. Davies, D. Bockler, M. Loebe, A. B. Lumsden, and H. von Tengg-Kobligk. Computational Fluid Dynamics Investigation of Chronic Aortic Dissection Hemodynamics Versus Normal Aorta. *Vasc Endovascular Surg.* 47: 625-631, 2013.
 43. Karmonik, C., S. Partovi, M. Muller-Eschner, J. Bismuth, M. G. Davies, D. J. Shah, M. Loebe, D. Bockler, A. B. Lumsden, and H. von Tengg-Kobligk. Longitudinal Computational Fluid Dynamics Study of Aneurysmal Dilatation in a Chronic Debakey Type Iii Aortic Dissection. *J Vasc Surg.* 56: 260-263 e261, 2012.
 44. Kato, K., A. Nishio, N. Kato, H. Usami, T. Fujimaki, and T. Murohara. Uptake of 18f-Fdg in Acute Aortic Dissection: A Determinant of Unfavorable Outcome. *J Nucl Med.* 51: 674-681, 2010.
 45. Khandheria, B. K. Aortic Dissection. The Last Frontier. *Circulation.* 87: 1765-1768, 1993.
 46. Kunov, M. J., D. A. Steinman, and C. R. Ethier. Particle Volumetric Residence Time Calculations in Arterial Geometries. *J Biomech Eng.* 118: 158-164, 1996.
 47. Les, A. S., S. C. Shadden, C. A. Figueroa, J. M. Park, M. M. Tedesco, R. J. Herfkens, R. L. Dalman, and C. A. Taylor. Quantification of Hemodynamics in Abdominal Aortic Aneurysms During Rest and Exercise Using Magnetic Resonance Imaging and Computational Fluid Dynamics. *Ann Biomed Eng.* 38: 1288-1313, 2010.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
48. Li, M., K. Miller, G. R. Joldes, B. Doyle, R. R. Garlapati, R. Kikinis, and A. Wittek. Patient-Specific Biomechanical Model as Whole-Body Ct Image Registration Tool. *Med Image Anal.* 22: 22-34, 2015.
 49. Li, Z. Y., U. Sadat, U. K.-I. J, T. Y. Tang, D. J. Bowden, P. D. Hayes, and J. H. Gillard. Association between Aneurysm Shoulder Stress and Abdominal Aortic Aneurysm Expansion: A Longitudinal Follow-up Study. *Circulation.* 122: 1815-1822, 2010.
 50. Liu, Y., S. M. Sadowski, A. B. Weisbrod, E. Kebebew, R. M. Summers, and J. Yao. Patient Specific Tumor Growth Prediction Using Multimodal Images. *Med Image Anal.* 18: 555-566, 2014.
 51. Lu, J., X. Zhou, and M. L. Raghavan. Inverse Elastostatic Stress Analysis in Pre-Deformed Biological Structures: Demonstration Using Abdominal Aortic Aneurysms. *J Biomech.* 40: 693-696, 2007.
 52. Lu, J., X. Zhou, and M. L. Raghavan. Inverse Method of Stress Analysis for Cerebral Aneurysms. *Biomech Model Mechanobiol.* 7: 477-486, 2008.
 53. Maier, A., M. Essler, M. W. Gee, H.-H. Eckstein, W. A. Wall, and C. Reeps. Correlation of Biomechanics to Tissue Reaction in Aortic Aneurysms Assessed by Finite Elements and [18f]–Fluorodeoxyglucose–PET/CT. *Int J Numer Meth Biomed Eng.* 28: 456-471, 2012.
 54. Maier, A., M. W. Gee, C. Reeps, J. Pongratz, H. H. Eckstein, and W. A. Wall. A Comparison of Diameter, Wall Stress, and Rupture Potential Index for Abdominal Aortic Aneurysm Rupture Risk Prediction. *Ann Biomed Eng.* 38: 3124-3134, 2010.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
55. Morris, L., P. Delassus, A. Callanan, M. Walsh, F. Wallis, P. Grace, and T. McGloughlin. 3d Numerical Simulation of Blood Flow through Models of the Human Aorta. *J Biomech Eng.* 127: 767 - 775, 2005.
 56. Morris, L., P. Delassus, M. Walsh, and T. McGloughlin. A Mathematical Model to Predict the in Vivo Pulsatile Drag Forces Acting on Bifurcated Stent Grafts Used in Endovascular Treatment of Abdominal Aortic Aneurysms (AAA). *J Biomech.* 37: 1087-1095, 2004.
 57. Nathan, D. P., C. Xu, J. H. Gorman, 3rd, R. M. Fairman, J. E. Bavaria, R. C. Gorman, K. B. Chandran, and B. M. Jackson. Pathogenesis of Acute Aortic Dissection: A Finite Element Stress Analysis. *Ann Thorac Surg.* 91: 458-463, 2011.
 58. Nathan, D. P., C. Xu, T. Plappert, B. Desjardins, J. H. Gorman, 3rd, J. E. Bavaria, R. C. Gorman, K. B. Chandran, and B. M. Jackson. Increased Ascending Aortic Wall Stress in Patients with Bicuspid Aortic Valves. *Ann Thorac Surg.* 92: 1384-1389, 2011.
 59. Nchimi, A., J. P. Cheramy-Bien, T. C. Gasser, G. Namur, P. Gomez, L. Seidel, A. Albert, J. O. Defraigne, N. Labropoulos, and N. Sakalihasan. Multifactorial Relationship between 18f-Fluoro-Deoxy-Glucose Positron Emission Tomography Signaling and Biomechanical Properties in Unruptured Aortic Aneurysms. *Circ Cardiovasc Imaging.* 7: 82-91, 2014.
 60. Nicholls, W. W., and M. F. O'Rourke, *Mcdonald's Blood Flow in Arteries.* 4th edn (New York: Oxfröd University Press, 1998).
 61. Nienaber, C. A., and J. T. Powell, Management of Acute Aortic Syndromes. *Eur Heart J.* 33: 26-35, 2012.

62. O'Leary, S. A., D. A. Healey, E. G. Kavanagh, M. T. Walsh, T. M. McGloughlin, and B. J. Doyle. The Biaxial Biomechanical Behavior of Abdominal Aortic Aneurysm Tissue. *Ann Biomed Eng.* 42: 2440-2450, 2014.
63. O'Leary, S. A., J. J. Mulvihill, H. E. Barrett, E. G. Kavanagh, M. T. Walsh, T. M. McGloughlin, and B. J. Doyle. Determining the Influence of Calcification on the Failure Properties of Abdominal Aortic Aneurysm (AAA) Tissue. *J Mech Behav Biomed Mater.* 42: 154-167, 2015.
64. O'Leary, S. A., E. G. Kavanagh, P. A. Grace, T. M. McGloughlin, and B. J. Doyle. The Biaxial Mechanical Behaviour of Abdominal Aortic Aneurysm Intraluminal Thrombus: Classification of Morphology and the Determination of Layer and Region Specific Properties. *J Biomech.* 47: 1430-1437, 2014.
65. Olufsen, M. S., C. S. Peskin, W. Y. Kim, E. M. Pedersen, A. Nadim, and J. Larsen. Numerical Simulation and Experimental Validation of Blood Flow in Arteries with Structured-Tree Outflow Conditions. *Ann Biomed Eng.* 28: 1281-1299, 2000.
66. Pasta, S., J. A. Phillippi, T. G. Gleason, and D. A. Vorp. Effect of Aneurysm on the Mechanical Dissection Properties of the Human Ascending Thoracic Aorta. *J Thorac Cardiovasc Surg.* 143: 460-467, 2012.
67. Pasta, S., A. Rinaudo, A. Luca, M. Pilato, C. Scardulla, T. G. Gleason, and D. A. Vorp. Difference in Hemodynamic and Wall Stress of Ascending Thoracic Aortic Aneurysms with Bicuspid and Tricuspid Aortic Valve. *J Biomech.* 46: 1729-1738, 2013.
68. Patel, D. J., J. C. Greenfield, Jr., W. G. Austen, A. G. Morrow, and D. L. Fry. Pressure-Flow Relationships in the Ascending Aorta and Femoral Artery of Man. *J Appl Physiol.* 20: 459-463, 1965.

69. Qiao, A., and Y. Liu. Medical Application Oriented Blood Flow Simulation. Clin Biomech. 23, Supplement 1: S130-S136, 2008.
70. Rajagopal, K., C. Bridges, and K. R. Rajagopal. Towards an Understanding of the Mechanics Underlying Aortic Dissection. Biomech Model Mechanobiol. 6: 345-359, 2007.
71. Reeps, C., J. Pelisek, R. A. Bundschuh, M. Gurdan, A. Zimmermann, S. Ockert, M. Dobritz, H. H. Eckstein, and M. Essler. Imaging of Acute and Chronic Aortic Dissection by 18f-FDG PET/CT. J Nucl Med. 51: 686-691, 2010.
72. Sakalihasan, N., C. A. Nienaber, R. Hustinx, P. Lovinfosse, M. El Hachemi, J. P. Cheramy-Bien, L. Seidel, J. P. Lavigne, J. Quaniers, M. A. Kerstenne, A. Courtois, A. Ooms, A. Albert, J. O. Defraigne, and J. B. Michel. (Tissue Pet) Vascular Metabolic Imaging and Peripheral Plasma Biomarkers in the Evolution of Chronic Aortic Dissections. Eur Heart J Cardiovasc Imaging. 2015.
73. Sakalihasan, N., H. Van Damme, P. Gomez, P. Rigo, C. M. Lapiere, B. Nussgens, and R. Limet. Positron Emission Tomography (Pet) Evaluation of Abdominal Aortic Aneurysm (AAA). Eur J Vasc Endovasc Surg. 23: 431-436, 2002.
74. Sankaran, S., L. J. Grady, and C. A. Taylor. Real-Time Sensitivity Analysis of Blood Flow Simulations to Lumen Segmentation Uncertainty. Med Image Comput Comput Assist Interv. 8674: 1-8, 2014.
75. Shang, E. K., D. P. Nathan, S. R. Sprinkle, R. M. Fairman, J. E. Bavaria, R. C. Gorman, J. H. Gorman, and B. M. Jackson. Impact of Wall Thickness and

- Saccular Geometry on the Computational Wall Stress of Descending Thoracic Aortic Aneurysms. *Circulation*. 128: S157-S162, 2013.
76. Sheikh, A. S., K. Ali, and S. Mazhar. Acute Aortic Syndrome. *Circulation*. 128: 1122-1127, 2013.
 77. Shim, V. B., R. P. Pitto, R. M. Streicher, P. J. Hunter, and I. A. Anderson. Development and Validation of Patient-Specific Finite Element Models of the Hemipelvis Generated from a Sparse Ct Data Set. *J Biomech Eng*. 130: 051010, 2008.
 78. Sokolis, D. P., E. P. Kritharis, and D. C. Iliopoulos. Effect of Layer Heterogeneity on the Biomechanical Properties of Ascending Thoracic Aortic Aneurysms. *Med Biol Eng Comput*. 50: 1227-1237, 2012.
 79. Song, H. K., M. Kindem, J. E. Bavaria, H. C. Dietz, D. M. Milewicz, R. B. Devereux, K. A. Eagle, C. L. Maslen, B. L. Kroner, R. E. Pyeritz, K. W. Holmes, J. W. Weinsaft, V. Menashe, W. Ravekes, and S. A. LeMaire. Long-Term Implications of Emergency Versus Elective Proximal Aortic Surgery in Patients with Marfan Syndrome in the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Consortium Registry. *J Thorac Cardiovasc Surg*. 143: 282-286, 2012.
 80. Stone, P. H., S. Saito, S. Takahashi, Y. Makita, S. Nakamura, T. Kawasaki, A. Takahashi, T. Katsuki, S. Nakamura, A. Namiki, A. Hirohata, T. Matsumura, S. Yamazaki, H. Yokoi, S. Tanaka, S. Otsuji, F. Yoshimachi, J. Honye, D. Harwood, M. Reitman, A. U. Coskun, M. I. Papafaklis, and C. L. Feldman. Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Endothelial Shear Stress and Arterial Plaque Characteristics: The Prediction Study. *Circulation*. 126: 172-181, 2012.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
81. Sueyoshi, E., I. Sakamoto, K. Hayashi, T. Yamaguchi, and T. Imada. Growth Rate of Aortic Diameter in Patients with Type B Aortic Dissection During the Chronic Phase. *Circulation*. 110 (Suppl 1): II256-261, 2004.
 82. Thubrikar, M. J., P. Agali, and F. Robicsek. Wall Stress as a Possible Mechanism for the Development of Transverse Intimal Tears in Aortic Dissections. *J Med Eng Technol*. 23: 127-134, 1999.
 83. Tong, J., T. Cohnert, P. Regitnig, and G. A. Holzapfel. Effects of Age on the Elastic Properties of the Intraluminal Thrombus and the Thrombus-Covered Wall in Abdominal Aortic Aneurysms: Biaxial Extension Behaviour and Material Modelling. *Eur J Vasc Endovasc Surg*. 42: 207-219, 2011.
 84. Trimarchi, S., C. A. Nienaber, V. Rampoldi, T. Myrmel, T. Suzuki, R. H. Mehta, E. Bossone, J. V. Cooper, D. E. Smith, L. Menicanti, A. Frigiola, J. K. Oh, M. G. Deeb, E. M. Isselbacher, and K. A. Eagle. Contemporary Results of Surgery in Acute Type a Aortic Dissection: The International Registry of Acute Aortic Dissection Experience. *J Thorac Cardiovasc Surg*. 129: 112-122, 2005.
 85. Trimarchi, S., J. L. Tolenaar, F. H. Jonker, B. Murray, T. T. Tsai, K. A. Eagle, V. Rampoldi, H. J. Verhagen, J. A. van Herwaarden, F. L. Moll, B. E. Muhs, and J. A. Elefteriades. Importance of False Lumen Thrombosis in Type B Aortic Dissection Prognosis. *J Thorac Cardiovasc Surg*. 2012.
 86. Tsai, T. T., A. Evangelista, C. A. Nienaber, T. Myrmel, G. Meinhardt, J. V. Cooper, D. E. Smith, T. Suzuki, R. Fattori, A. Llovet, J. Froehlich, S. Hutchison, A. Distant, T. Sundt, J. Beckman, J. L. Januzzi, Jr., E. M. Isselbacher, and K. A. Eagle. Partial Thrombosis of the False Lumen in Patients with Acute Type B Aortic Dissection. *N Engl J Med*. 357: 349-359, 2007.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
87. Tsai, T. T., M. S. Schlicht, K. Khanafer, J. L. Bull, D. T. Valassis, D. M. Williams, R. Berguer, and E. K. A. Tear Size and Location Impacts False Lumen Pressure in an Ex Vivo Model of Chronic Type B Aortic Dissection. *J Vasc Surg.* 47: 844-851, 2008.
 88. Tsai, T. T., S. Trimarchi, and C. A. Nienaber. Acute Aortic Dissection: Perspectives from the International Registry of Acute Aortic Dissection (Irad). *Eur J Vas Endovasc Surg.* 37: 149-159, 2009.
 89. Tse, K. M., P. Chiu, H. P. Lee, and P. Ho. Investigation of Hemodynamics in the Development of Dissecting Aneurysm within Patient-Specific Dissecting Aneurismal Aortas Using Computational Fluid Dynamics (CFD) Simulations. *J Biomech.* 44: 827-836, 2011.
 90. Vande Geest, J. P., M. S. Sacks, and D. A. Vorp. The Effects of Aneurysm on the Biaxial Mechanical Behavior of Human Abdominal Aorta. *J Biomech.* 39: 1324-1334, 2006.
 91. Weisbecker, H., D. M. Pierce, P. Regitnig, and G. A. Holzapfel. Layer-Specific Damage Experiments and Modeling of Human Thoracic and Abdominal Aortas with Non-Atherosclerotic Intimal Thickening. *J Mech Behav Biomed Mater.* 12: 93-106, 2012.
 92. Wen, C. Y., A. S. Yang, L. Y. Tseng, and J. W. Chai. Investigation of Pulsatile Flowfield in Healthy Thoracic Aorta Models. *Ann Biomed Eng.* 38: 391-402, 2010.
 93. Xu, X. Y., A. Borghi, A. Nchimi, J. Leung, P. Gomez, Z. Cheng, J. O. Defraigne, and N. Sakalihasan. High Levels of ^{18}F -Fdg Uptake in Aortic Aneurysm Wall Are Associated with High Wall Stress. *Eur J Vasc Endovasc Surg.* 39: 295-301, 2010.

94. Zhang, S., L. Gu, W. Liang, P. Huang, J. Boehm, and J. Xu, 'The Framework for Real-Time Simulation Of deformable Soft-Tissue Using a Hybrid Elastic Model', in *Biomedical Simulation*, ed. by Matthias Harders and Gábor Székely (Springer Berlin Heidelberg, 2006), pp. 75-83.

FIGURE LEGENDS

Figure 1: Stanford and DeBakey classifications of aortic dissection. Figure from ⁶¹. Aortic dissection is classified based on the anatomy of the problem and typically follows a Stanford and/or DeBakey system (see Figure 1). Stanford Type A affects the ascending aorta and arch, and Type B begins beyond the left subclavian artery. Whereas, DeBakey Type I involves the ascending and descending aorta (Stanford Type A); DeBakey Type II involves the ascending aorta only (Stanford Type A); and DeBakey Type III involves the descending aorta only (Stanford Type B).

Figure 2: Example 3D reconstructions of a complicated case of Type B AoD (with intramural haematoma) from baseline to three months. In this patient, the dissected wall was thrombosed and there is no obvious sign of an entry tear. Also shown is an example finite element mesh for both the lumen and thrombosed region used for wall stress calculations.

Figure 3: Wall stress distributions on the intimal surface of two different cases of aortic disease. These results were obtained using our new computational approach that does not rely on any knowledge of patient-specific material properties.³⁵ *Top row*: A case of Type B AoD with intramural haematoma at baseline and 3 months later. The regions of elevated wall stress at baseline expanded rapidly. *Bottom row*:

1 A typical case of Type B AoD with true and false lumens showing the wall stress at
2 baseline prior to any form of aortic dissection and then 7 years later when the
3 descending aorta had dissected resulting in several tears on the intima (see also
4 Figure 5). Note that the geometries are shown not to scale and different magnitudes
5 of stress are used in the bottom row. The actual geometry used in each analysis is
6 shown alongside. In the top row, the peak wall stress at baseline was ~0.3 MPa and
7 ~0.9 MPa at follow-up. In the bottom row, the wall stress was significantly higher
8 around the tear locations due to the irregular geometry and high curvature. At
9 baseline, the peak wall stress was ~0.4 MPa and >1.5 MPa at follow-up. According
10 to ⁷⁸ the ultimate tensile strength (UTS) of the intimal layer is ~0.86 MPa. Also, the
11 wall stress was high in the ascending aorta which also witnessed significant
12 expansion over the 7 years.

13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30 Figure 4: Preliminary computational modelling data. Here we show that the regions
31 of low TAWSS (< 0.4 Pa) predicted at baseline are where the aorta expanded rapidly
32 over the next few months. It has been shown that WSS < 0.4 Pa promotes monocyte
33 deposition ³⁰ and regions of local expansion ¹⁶ in AAA. Case shown is the same as
34 Figures 2 and 3. The WSS was computed using a core of tetrahedral elements and
35 six layers of prisms elements where each layer gets progressively smaller towards
36 the wall. The inlet boundary condition was the velocity profile used in Morris et al.⁵⁵
37 which is originally from Nicholls and O'Rourke.⁶⁰

38
39
40
41
42
43
44
45
46
47
48
49
50 Figure 5: Example 3D reconstruction of Type B AoD (*left*) with multiple channels
51 to/from false lumen. In this particular case the 3D reconstruction revealed five
52 channels (*right*). Case shown is the same as Figure 3.

Figure 6: 18F-FDG data of Type B AoD showing a favourable outcome (top) and a complicated case with rapid progression of the dissection 3 months after initial presentation (bottom). The arrows show the dissected regions in the descending aorta.⁴⁴

Figure 7: Preliminary data correlating 18F-FDG uptake to regions of WSS in a non-dissected thoracic aorta. (A) Coronal CT; (B) corresponding coronal 18F-FDG PET-CT; (C) 3D reconstruction from CT; (D) 18F-FDG uptake mapped to 3D reconstruction; (E) WSS distributions computed with CFD. The WSS data was computed using a mesh with a similar meshing and modelling approach to that of Figure 4.

Figure 1
[Click here to download Figure: Doyle_Fig1.tif](#)

DeBakey I and II
Stanford A

Stanford B

DeBakey IIIa and IIIb
Stanford B

Figure 2
Click here to download Figure: Doyle_Fig2.tif

Figure 3
[Click here to download Figure: Doyle_Fig3.tif](#)

Figure 4
[Click here to download Figure: Doyle_Fig4.tif](#)

Figure 5
[Click here to download Figure: Doyle_Fig5.tif](#)

Figure 6
[Click here to download Figure: Doyle_Fig6.tif](#)

Figure 7
[Click here to download Figure: Doyle_Fig7.tif](#)

Form for Disclosure of Potential Conflicts of Interest
[Click here to download Form for Disclosure of Potential Conflicts of Interest: Doyle_coi_disclosure.pdf](#)