Fibrolytic markers

Matrix metalloproteinases (MMPs) are a group of extracellular matrix enzymes involved in the remodeling of the aorta, which have also been shown to be elevated and activated in acute dissection. Matrix metalloproteinases are released into the interstitial space and also into the circulation. This may result in collapse of medial layer collagen and elastin fibers, eventually leading to aortic remodeling and dissection.

Plasma concentrations of the MMP-9 subunit have been reported to be increased within 1 hour after onset of symptoms in patients with AAD ($P < .03$, types A and B, respectively, 29.3 ± 16.1 and 16.7 ± 2.1 ng/mL [n = 13] vs control 7.74 ± 1.6 ng/mL [n = 10]) with increased MMP-9 concentrations continuing until 2 months of follow-up.[27] Studies suggest that plasma MMP levels might be used not only in rapid diagnosis of AAD but also in long-term follow-up to monitor aortic remodeling. Inhibition of MMP-2 and MMP-9 synthesis by administration of doxycycline effectively prevented thoracic aortic aneurysm formation in a mouse model of MFS, thus indicating that inhibiting the activities of MMPs might be a potential therapeutic target for aortic aneurysm and dissection.[28]

Transforming growth factor β

Circulating TGF-β is another notable biomarker that has received recent attention because it may serve in therapeutic monitoring of aortic remodeling in patients with MFS.[29] Circulating TGF-β concentrations have been shown to be elevated in patients with MFS as compared with control individuals ($P < .001$, 15 ± 1.7 ng/mL [n = 53] vs 2.5 ± 0.4 ng/mL [n = 74]). Patients with MFS treated with angiotensin II receptor blocker (n = 55) or β-blocker (n = 80) showed significantly lower total TGF-β concentrations compared with untreated patients with MFS ($P < .05$). Circulating TGF-β levels have also recently been shown to be markedly elevated in patients with AAD, especially in Stanford type A dissections ($P < .01$, 28.5 ± 14.7 ng/mL, n = 20) compared with type B (14.4 ± 481 ng/mL, n = 8), thus suggesting that TGF-β may potentially serve as an aortic biomarker beyond its potential role for monitoring aortic size in MFS.[30]

Thrombotic markers

D-dimer

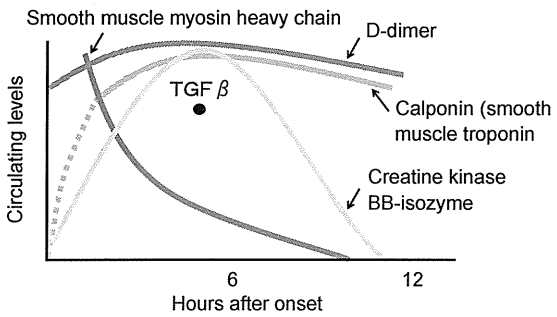
The most promising biomarker for use in suspected acute dissection at the present time is D-dimer. The initial discovery that D-dimer showed increased levels in aortic dissection might have been by chance, but further studies have shown that it can be used both to rule in the disease in the early hours after onset and to use as a rule-out marker and, thus, is the only biomarker at present that is closest to golden standard status. Importantly, it is already widely available for clinical use including point-of-care rapid tests.

D-dimer is a fibrin fragment seen in coagulopathic disorders, and measurements are routinely used in the diagnosis of PE.[31] Classic AAD also shows elevated levels of this biomarker.[15,31-33] A cutoff level of 500 ng/mL, which is presently used for PE, has been confirmed in multiple studies to also be applicable to rule out AAD. The largest study on the use of D-dimer in aortic dissection[34] showed marked elevations of this biomarker in the early hours after onset (<6 hours) of acute dissection (aortic dissection, type A 3213 ± 1465 ng/mL and type B 3574 ± 1430 ng/mL [n = 87] vs controls of myocardial infarction 1459 ± 1650 ng/mL, angina 760 ± 974 ng/mL, PE 2452 ± 1891 ng/mL, and other uncertain diagnosis 1399 ± 1511 ng/mL [n = 133]; sensitivity 95.7% and specificity 61.3% at a cutoff level of 500 ng/mL within the first 6 hours) and that the disease could also be ruled in using a cutoff of 1600 ng/mL in the initial 6 hours.

Studies including those mentioned previously have suggested that plasma D-dimer may be a useful screening tool to rule out AAD, but most of these studies were inconclusive because of limited sample size and different cutoff values as well as lack of a control group. Recent meta-analyses using systematically searched clinical studies in EMBASE, MEDLINE, CINAHL, and BIOSIS have been performed to access the missed diagnostic test measurements such as PPV or NPV and likelihood ratios (LRs).[35] One study included AAD cases confirmed by standard imaging techniques and autopsy or pathological examination, with D-dimer measured by standard plasma assays, and included control groups in which absolute numbers of true positive, false positive, true negative, and false negative were obvious or could be derived. D-Dimer testing showed a high sensitivity of 0.97 (95% CI 0.94-0.98, $I^2 = 0.47$) and a negative LR of 0.06 (95% CI 0.02-0.13, $I^2 = 0.0\%$) with narrow confidence intervals. Receiver operating characteristic curve analysis yielded a high certainty for excluding AAD on the basis of negative results (AUC 0.94). A pooled specificity of 0.59 (95% CI 0.53-0.64, $I^2 = 0.0\%$) and a positive LR of 2.58 (95% CI 1.76-3.78, $I^2 = 0.0\%$) did not increase the certainty of diagnosis for AAD. The diagnostic odds ratio was 21.27 (95% CI 11.64-38.88, $I^2 = 0.0\%$).[35] D-Dimer was collectively shown to be a favorable rule-out tool.

A more recent meta-analysis that added results of newer studies, notably the IRAD-Bio study, as done by some of the authors,[34] showed essentially similar results that D-dimer has a high sensitivity and a low negative LR as suited for a rule-out marker but showed only marginal specificity and positive LRs. Overall pooled data estimated a high sensitivity of 0.97(95% CI 0.94-0.99) and a high NPV of 0.96 (95% CI 0.93-0.98), with little statistical heterogeneity ($Q = 1.77$ [$I^2 < 0.001$, $P = .94$] and $Q = 1.45$ [$I^2 < 0.01$, $P = .96$], respectively). By contrast, specificity

Figure 2



Time course of biomarkers in aortic dissection. Modified from Suzuki et al[38].

was low at 0.56 (95% CI 0.51-0.60) and PPV at 0.60 (95% CI 0.55-0.66), with significant heterogeneity (Q = 33.8 [I^2 = 0.82, P < .001] and Q = 8.2 [I^2 = 0.39, P = .22], respectively). Negative LR showed an excellent discriminative ability of 0.06 (95% CI 0.03-0.12, I^2 < 0.001); on the other hand, positive LR showed a poor discriminative ability of 2.43 (95% CI 1.89-3.12, I^2 = 0.78).[36] On the latter, some of the authors reported in the IRAD-Bio study that high D-dimer levels in the early hours (<6 hours) after symptom onset would allow for rule-in diagnosis of AAD, but the meta-analysis did not address time-dependent effects likely because other studies examining D-dimer have not pursued time course.

Therefore, the accumulated evidence suggests that D-dimer testing might be helpful in risk stratifying patients with suspected AAD. Importantly, because the same cutoff level used to rule-out PE can be applied to aortic dissection, this single blood test can be used to rule-out both diseases, which is advantageous from the standpoint of simplicity and cost-effectiveness.[31] With the appropriate understanding in use and interpretation (eg, possible lack of elevations in intramural hematoma and thrombosed false lumen[37]), D-dimer testing may be a potential biomarker solution for sorting out chest pain syndromes where very high levels will lead clinicians to look for AAD or PE as opposed to acute coronary syndromes (see Figure 1 for diagnostic algorithm and Figure 2 for time course of diagnostic biomarkers).

On the potential use of D-dimer in the subacute and chronic phases, sustained elevation up to 20 days after thoracic endovascular aortic repair and increasing maximum D-dimer values postoperatively have been shown to be associated with decreased survival after the procedure, thus suggesting potential use as a prognostic marker, as well.[39] On the platform for D-dimer use, the Tina-quant (Roche Diagnostics, Mannheim, Germany) and Innovance (Siemens, Erlangen, Germany) tests are also in recent use, in addition to the common STA-Liatest (Diagnostica Stago, Asnieres, France), mainly for Europe. Although there is a lack of data for aortic dissection, a better sensitivity (96%-100%) and specificity (37.5%-38.2%) for venous thrombosis has been reported with the latter platform.[40] This assay also maintains a standard cutoff level at 500 ng/mL, with the 90th percentile of a normal collective at 550 ng/mL.

Abdominal aortic aneurysms

Aortic aneurysms of the abdomen (AAA) are frequent in elderly patients (eg, >5% prevalence according to an Australian study[41]). Increasing use of ultrasound screening and incidental diagnosis with other imaging modalities such as CT will increase recognition of aneurysms in early stages, but use of biomarkers for this disease focuses more on their use in monitoring progression/expansion rather than acute diagnosis at presentation (eg, rupture).

Risk of rupture increases when aortic growth exceeds expected expansion,[42] and investigations to identify surrogate biomarkers that correlate with expansion rate have been a topic of interest. Several circulating markers have shown association with AAA expansion, symptom onset, and rupture. Serum elastin peptide (SEP) levels have been shown to be modestly associated with AAA expansion rate within the first year of observation and risk of later rupture.[43,44] Correlation between SEP and AAA diameter with contained rupture (r = 0.809, P < .001) but not with elective AAA repair (r = 0.034, P = .825) has also been described.[45] Tumor necrosis factor α and interleukin (IL)-8 levels have also been reported to be significantly lower in large AAAs and in symptomatic AAAs (P < .05).[46] Not surprisingly, markers such as procollagen, MMP-9, fibrinogen, D-dimer, tissue plasminogen activator, and IL-6 have been pursued but with varying results.[41] Although a single biomarker may not be sufficient, multiple biomarkers in combination might be of benefit. Initial AAA dimensions, SEP, serum peptide of type III collagen, and expansion rate show significant independent associations, and a multivariate formula using these parameters has been shown to predict cases reaching 5 cm in diameter within 5 years, with a sensitivity of 91% and specificity of 87% by receiver operating characteristic analysis.[47] Newer proteomic methods have also identified proteins involved in the kallikrein-kinin system (eg, kallistatin, carboxypeptidase B2, and protein AMBP) to be potential biomarkers of the disease.[48]

Thoracic aortic aneurysms

Thoracic aortic aneurysm has a strong genetic basis. Marfan syndrome is a representative genetic disorder complicated by aortic aneurysmal formation often of the thoracic aorta. This syndrome is diagnosed on the basis

Table I. Biomarkers of aortic diseases

	Biomarker	Characteristics	Time course	Reference, tested samples, diagnostic performance
Aortic dissection	SM-MHC	- Found in the aortic media layer - Performance appropriate for a rule-in marker	- Elevation limit in the initial 3-6 h[14,19,20] - Very short time window	Suzuki et al,[14] n = 27, sensitivity 90%, specificity 97%
	BB isoenzyme of creatine kinase	- Consists of M and B isozymes - BB isozyme is selective for neurologic and smooth muscle	- Elevated in aortic dissection with peak approximately 6 h after onset of symptoms[21]	Suzuki et al[21], n = 30, AAD group vs control group 3.4 ± 1.0 SE vs 0.2 ± 0.1 SE IU/L
	Calponin	- A troponin counterpart of smooth muscle	- Has a longer time course than the BB isozymes of creatine kinase - Remains elevated within the initial 24 h[22]	Suzuki et al[22], n = 150, AUC acidic calponin 0.63, AUC basic calponin 0.67
	Elastin	- A structural protein in the vessel wall	- <2-Fold increase over healthy controls depending on age[23]	Shinohara et al[23], n = 175, sensitivity 64.0%, specificity 94.8%
	CRP	- May help monitoring evolution of false lumen thrombosis[24] - Lack of specificity[25]	- Peak level during admission maybe a predictor for adverse long-term events[25]	Sakura et al[25], n = 233, CRP high group vs low group, hazard ratio 6.02, $P = .0001$
	MMP	- In particular, the subunit MMP-9 is elevated in aortic dissection[27]	- Increases within 1 h from onset of symptoms[27]	Sangiorgi et al[27], n = 23, AAD group vs control group 29.3 vs 7.74 ng/mL, $P < .03$
	Circulating TGF-β	- Therapeutic monitoring of aortic remodeling in patients with MFS[29]	- Elevated in AAD[30]	Suzuki et al[30], n = 28, type A AAD vs type B AAD 28.5 vs 14.4 ng/mL, $P < .01$
	D-dimer	- A fibrin fragment seen in coagulopathic disorders	- Elevated in AAD[15,31-34]	Suzuki et al[34], n = 200, at cutoff level 500 ng/mL, sensitivity 96.6%, specificity 46.6%
		- A rule-in and rule-out marker	- Cutoff level of 500 ng/mL used already for PE is also applicable to rule out aortic dissection	Shimony et al[36], meta-analysis, 7 studies, n = 734, sensitivity 97%, NPV 0.96, specificity 56%, PPV 0.60
		- The only biomarker close to golden standard status	- Acute dissection can be ruled in using a cutoff of 1600 ng/mL in the initial 6 h[34]	
		- Widely available for clinical use, including rapid tests due to its value for diagnosing acute PE[31]	- Increasing maximum D-dimer values post–thoracic endovascular aortic repair are associated with decreased survival.[39]	
		- Possibly lack of elevations in intramural hematoma and thrombosed false lumen[37]		
Abdominal aortic aneurysm	SEP	- Associates with AAA expansion and later rupture[43,44]	- Use of biomarkers for this disease focuses more on their use in monitoring progression/ expansion rather than acute diagnosis.	Lindholt et al[43], 112 patients with AAA from 4404 men screened, prospective study, correlation: $r = 0.4$
	Procollagen, MMP-9, fibrinogen, D-dimer, tissue plasminogen activator, and IL-6	- These markers show varying results,[41]		These markers show varying results.[41]
	(Proteins involved in the kallikrein-kinin system)	- For example, kallistatin, carboxypeptidase B2, and protein AMBP could be potential biomarkers of the disease.[42]		
Thoracic aortic aneurysm	MMP-9, TIMP-1 circulating TGF-β	- Ratio of MMP-9 to TIMP-1 increased in TAA and dissection[49] - Therapeutic monitoring of aortic remodeling in patients with MFS[52]	- TAA has a strong genetic basis and is often less inflammatory.	Koullias et al[49], n = 47, increased MMP-9/TIMP-1 ratio to control group, $P < .05$ Ahimastos et al[52], n = 17, for 24 weeks, ACEI vs placebo, 59.6 vs 45.3 ng/mL, $P = .01$

(*continued on next page*)

Table I. (*continued*)

	Biomarker	Characteristics	Time course	Reference, tested samples, diagnostic performance
Aortitis	PTX-3	- A vascular-selective CRP - Selective produced by vascular endothelial cells, macrophages, and neutrophils	- May be a potential biomarker for Takayasu arteritis - Reflects pathogenetic activity of Takayasu arteritis regardless of therapeutic steroid use[58]	Ishihara et al[58], aortitis n = 41, sensitivity 82.6%, specificity 77.8%

of clinical features; genetic testing for clinical use is still controversial because of a lack of a genotype-phenotype correlation. Unlike abdominal aortic aneurysm formation, the pathogenesis of thoracic aortic aneurysm is mainly caused by silent medial layer degradation and is often less inflammatory, thus making use of conventional inflammatory biomarkers less informative. Several markers have been pursued, including MMPs, which are known to be involved in the pathogenesis of thoracic aortic aneurysm. A relative index of the ratio of MMP-9 to tissue inhibitor of metalloproteinase-1 (TIMP-1) has been shown to be increased in both patients with thoracic aortic aneurysm and patients with dissection compared with control patients, thus suggesting that imbalance of MMP-TIMP might be important for the development and progression of aortic disease.[49] Elevated MMP levels have also been shown to be associated with recurrent blood flow in aneurysms after endovascular therapy.[50,51]

Transforming growth factor β signaling also contributes to aortic degeneration in MFS. Angiotensin-converting inhibitor (ACEI) treatment reduces TGF-β blood concentrations in both latent (59.6-45.3 ng/mL in ACEI group, $P = .01$ vs placebo) and active (46.2-42.1 ng/mL in ACEI group, $P = .02$ vs placebo) forms.[52] Recent studies have also shown that mutations in smooth muscle cell isoforms of α- and β-myosin heavy chain (SM-MHC) cause familial thoracic aortic aneurysm leading to AADs.[53] The protein levels of SM-MHC are elevated in patients with aneurysmal rupture and may also be a potential candidate biomarker for this condition (T. Suzuki et al, unpublished observation). Another proposed strategy for identifying thoracic aortic aneurysms is investigation of the gene expression signature in peripheral blood.[54] A preliminary study has identified 41 gene signatures in peripheral blood cells that distinguish patients with aneurysm from control subjects, with an accuracy of 78% to 80%.[55] The ribonucleic acid signature also provides additional information to detect impending rupture or dissection.

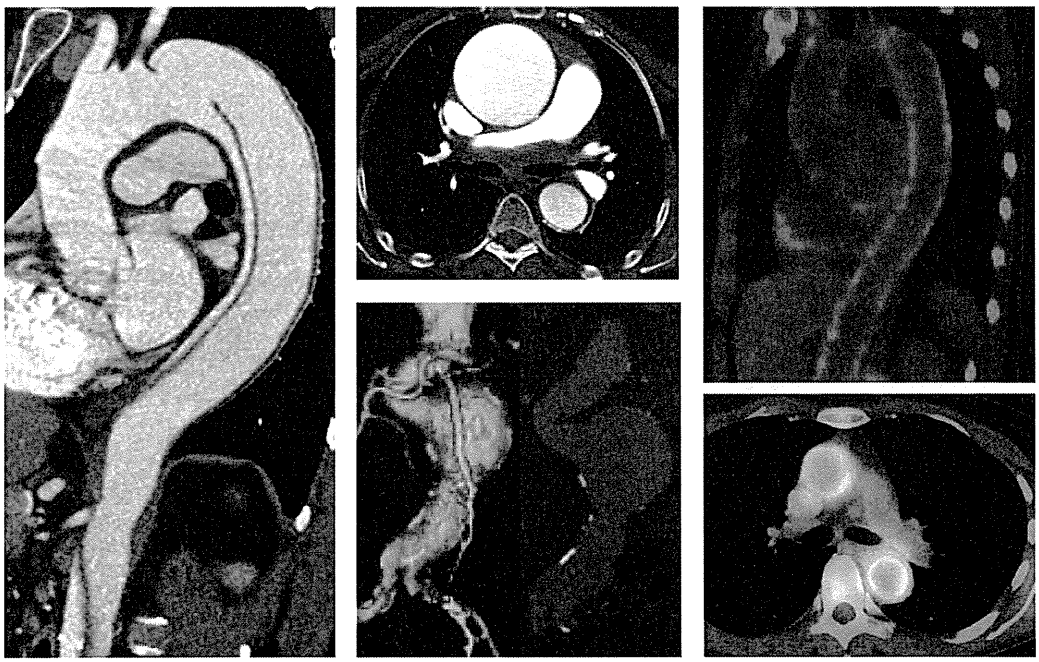
Aortitis

Aortitis (Takayasu arteritis) is an uncommon chronic vasculitis mainly involving the aorta and main branches. Biochemical monitoring of the pathogenic state is a viable target for aortic biomarkers. The erythrocyte sedimentation rate and CRP level have been used as markers of disease activity.[56,57] Although preliminary tests did now show smooth muscle proteins to demonstrate a sufficient dynamic range for diagnostic use (T. Suzuki et al, unpublished observation), a recent vascular inflammatory biomarker, pentraxin-3 (PTX-3), has shown promise as a potential biomarker for Takayasu arteritis. Pentraxin-3 is a "vascular-selective CRP," with both PTX-3 and CRP belonging to the pentraxin family with CRP harboring a short pentraxin domain, whereas PTX-3 harbors a long pentraxin domain and, importantly, is selectively produced by vascular endothelial cells, macrophages, and neutrophils. A study comparing the usefulness of highly sensitive CRP and PTX3 showed that PTX3 is more specific for arterial inflammation than CRP (highly sensitive CRP, sensitivity 65.2%, specificity 94.4%, AUC 0.905; PTX3, sensitivity 82.6%, specificity 77.8%, AUC 0.914). Plasma MMP-3 levels showed a positive correlation with predonisolone dose as used for treatment, whereas PTX3 levels were not correlated with its dose (MMP-3: $R = 0.649$, PTX3: $R = 0.432$), which suggests that this biomarker reflects pathogenic activity of Takayasu aortitis regardless of therapeutic steroid use.[58]

Future perspectives

Biomarkers for aortic diseases in general remain few. Increasing awareness to the importance of aortic and vascular diseases owing to an aging society with increasing atherosclerotic disease is a prerequisite condition for further advancement of this field. Noninvasive, relatively inexpensive, and nontechnical methods of early diagnosis and/or progression of disease using biomarkers would be ideal to meet this need.[38] Table I and Figure 3 summarize our present knowledge. Emerging technologies such as proteomic methods may also help in identifying new and translatable biomarkers. Society guidelines recognize the need for the development of aortic biomarkers. The European Society of Cardiology (ESC) guidelines on aortic dissection, published in 2001,[11] mention the potential of using SM-MHC. The latest guidelines from the United States (American College of Cardiology/American Heart Association) in 2010 recog-

Figure 3



Aortic dissection	Aortic aneurysm	Aortitis
Smooth muscle myosin heavy chain, BB-isoenzyme of creatine kinase, calponin, elastin, C-reactive protein (CRP), matrix metallo-proteinases (MMP), circulating transforming growth factor α (TGF-α), D-dimer	Pro-collagen, MMP-9, fibrinogen, D-dimer, tissue plasminogen activator, interleukin-6	Pentraxin-3 (PTX-3) High sensitive CRP (hsCRP) Erhythrocyte sedimentation rate (ESR)

Biomarkers categorized according to aortic disease with representative images.

nize that several biomarkers have been investigated for their use in the evaluation of AAD such as SM-MHC, D-dimer, and high-sensitivity CRP.[8] The American guidelines further state that these markers show diagnostic promise and that biomarker development is an important future research direction.

As we look to the future, aortic diseases should be recognized as conditions that will benefit from a noninvasive blood test and therefore are a target of biomarker development. To develop the golden standard, which is necessary and sufficient to both rule in and rule out disease, will be of utmost importance. D-Dimer in aortic dissection is promising for the present, but more "vascular-specific" biomarkers need to be developed in the future. Clinical studies that not only address diagnostic performance in a certain disease but also build confidence in using the biomarker under wider and general circumstances need to be addressed to confidently use these biomarkers in the emergency room and when triaging patients with certain symptoms/signs (eg, chest pain). For acute diseases, point-of-care tests would be most useful, but these are technically challenging and will require more work after the initial assays are developed.

In the end, how diagnostic biomarkers are helpful in the clinic will depend on their additive usefulness in light of current clinical diagnostic algorithms and imaging modalities. This will hold not only for acute disease but also for chronic monitoring of aortic pathologies in relevance to timing and indication of treatment and outcome.

Disclosures

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慢性炎症を基盤とする心血管病態モニタリングマーカーの開発と臨床導入の実現－慢性炎症の制御に着目した創薬のための新たなバイオマーカー開発－研究班

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