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ORIGINAL ARTICLE

High mortality associated with intracardiac and intrapulmonary thromboses after cardiopulmonary bypass

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Abstract
Purpose Intrapulmonary or intracardiac thrombosis is a rare but catastrophic event following complex cardiothoracic surgery. Although there have been multiple cases reported in the literature, the causes of these events are largely unknown. In this retrospective review, we attempt to identify risk factors and propose possible mechanisms of thromboses after cardiopulmonary bypass (CPB).
Methods A literature search was conducted using the MEDLINE and EMBASE with these keywords: (intra)-pulmonary thrombosis, pulmonary embolism, pulmonary infarction, lung embolism, (intra)cardiac thrombosis, cardiac thrombi, in combination with CPB, extracorporeal membrane oxygenation, deep hypothermic circulatory arrest, or cardiac surgery. Putative risk factors were compiled from reported cases.
Results We identified 34 cases of massive intrapulmonary and/or intracardiac thromboses. All but 2 cases (94.1%) were fatal. Clinical presentations were systemic hypotension and/or pulmonary hypertension, right ventricular failure, and cardiogenic shock in 32 (94.1%) cases. The timing was immediate (<10 min) following hemostatic intervention in 16 cases (47.1%), within 45 min in 8 cases (23.5%), and not reported in the rest. Putative risk factors included antifibrinolytic use (88.2%), congestive heart failure (55.9%), prolonged CPB use (>2 h) (41.1%), and low activated clotting time (<400 s) after initial heparinization (20.6%). The administration of tissue plasminogen activator in 5 cases was ineffective.
Conclusions Massive thrombosis following cardiac surgery is a highly lethal event with limited treatment options. Particular attention should be paid to the status of thrombin regulatory proteins before protamine and other hemostatic interventions in patients undergoing complex cardiac surgery with antifibrinolytic agents.

Keywords Intrapulmonary thrombosis · Intracardiac thrombosis · Antithrombin · Cardiopulmonary bypass · Transfusion

Introduction

The predisposing conditions for thrombosis as originally put forth by Rudolf Virchow are frequently found in patients undergoing cardiac surgery (Fig. 1). In addition to preexisting cardiovascular abnormalities in blood flow, vascular integrity, and blood coagulability [1], the triad of thrombotic stimuli is further potentiated by surgical interventions using cardiopulmonary bypass (CPB). Bleeding tendency is a predominant phenotype of coagulopathy after a complex cardiothoracic surgery, but intrapulmonary and intracardiac thromboses have been reported as rare but devastating complications that follow protamine or other hemostatic interventions. After prolonged CPB and deep hypothermic circulatory arrest (DHCA), many patients

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develop coagulopathy as a consequence of consumptive and dilutional losses of platelets, fibrinogen, and other coagulation factors [2–4]. To reduce postoperative bleeding and transfusion requirements, antifibrinolytic agents are prophylactically administered during surgery [5]. Postoperatively, patients with profuse bleeding are transfused with platelet concentrate (PLT), fresh frozen plasma (FFP), and cryoprecipitate [6, 7]. In some situations, plasma-derived or recombinant factor concentrates such as prothrombin complex concentrate (PCC) [8], recombinant factor VIIa (rFVIIa) [7], or fibrinogen concentrate [9] are also administered. In contrast to bleeding complications that are evident immediately after CPB, disseminated intravascular coagulation (DIC) is seldom recognized because activated clotting time (ACT) remains well above the threshold of 400–500 s regardless of heparin and antithrombin (AT) levels during a prolonged CPB [2]. It is often difficult to delineate the etiology of thromboses because of preoperative patient risks, complexity of procedures, and high transfusion requirements after CPB. Therefore, we conducted a thorough review of rare post-CPB thrombotic complications to devise potential preventive measures.

Materials and methods

Identification of reported thrombotic events and putative risk factors in cardiothoracic surgery

Relevant thrombotic events in cardiothoracic surgery were searched using the Ovid MEDLINE from 1968 to 2011 (last entry, 11 May 2011) and the EMBASE from 1968 to 2011 (last entry, 11 May 2011), with no language restrictions [10]. The keywords for search were as follows: (intra)pulmonary thrombosis, pulmonary embolism, pulmonary infarction, lung embolism, (intra)cardiac thrombosis, cardiac thrombi, in combination with CPB, extracorporeal membrane oxygenation (ECMO), DHCA, or cardiac surgery.

Putative risk factors of thrombosis were identified from the literature relating to abnormalities in blood flow, vascular integrity, and blood coagulability (Fig. 1) [1]. These factors include age, DHCA, CPB duration, antifibrinolytic usage, reduced heparin sensitivity, warfarin usage, hereditary thrombophilia, endocarditis, and transfusion of hemostatic components [11–13].

Patients

A total of 34 thrombotic complications related to CPB and/or ECMO were identified in the literature (20 articles). Isolated coronary thrombotic events were excluded [14–16]. The first case series of intravascular thromboses after DHCA was reported in 1993, and pulmonary thrombi were confirmed by post mortem in two cases (only one case was individually identifiable) [17, 18]. For every identified (individual) case, demographics (age, gender, body weight, and indication for surgery), putative risk factors, clinical presentation (symptoms, and timing), treatment (reinstitution of CPB, ventricular assist device, and/or thrombolysis), and outcome (mortality) were collected.

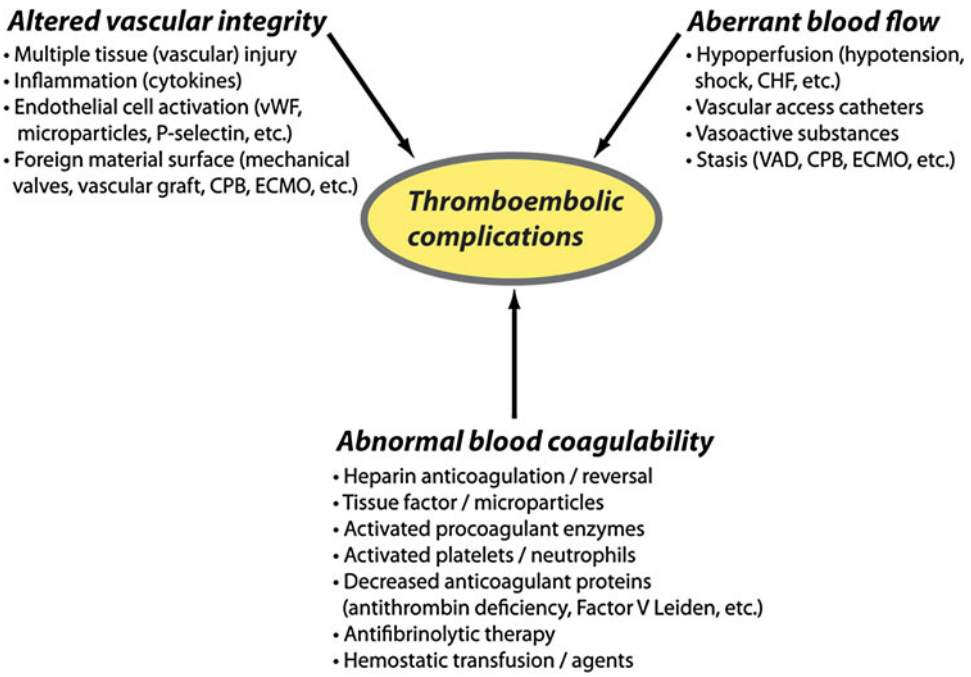

Fig. 1 Virchow's triad. Virchow's triad depicts three key conditions (altered vascular integrity, aberrant blood flow, abnormal blood coagulability) that predispose patients to thrombosis. Preexisting diseases and surgical interventions in cardiac surgical patients strongly affect the risk of thrombosis. *vWF* von Willebrand factor, *CPB* cardiopulmonary bypass, *ECMO* extracorporeal membrane oxygenator, *CHF* congestive heart failure, *VAD* ventricular assist device

Data presentations

Continuous variables are presented as median with ranges, and categorical variables are presented as numbers with percentages. Putative risk factors are compiled in arbitrary categories and presented as numbers with percentages.

Results

Patient demographics

Of 34 patients identified with intrapulmonary or intracardiac thrombi, 12 (35.3%) were older than 65 years, 17 (50.0%) were between 40 and 65 years of age, and 5 (14.7%) were 40 years or younger. The median age was 56 years (11 months to 79 years). Seventeen (50.0%) were male and 14 (41.2%) were female; in 3 cases, the gender was not recorded. The body weight was reported in 19 patients with median value of 68 kg (range, 8.3–101 kg). The indications for cardiothoracic surgery are summarized in Table 1.

Clinical presentations

In 32 of 34 cases (94.1%), cardinal signs of intrapulmonary or intracardiac thrombosis were systemic hypotension or pulmonary hypertension leading to cardiogenic shock, right ventricular failure, biventricular failure, or cardiac arrest. Two patients presented with clot in an ECMO circuit [19, 20]. Hemodynamic instability was not responsive to intravenous inotropic support, and rescue attempts were made by administering heparin, reinstitution of CPB, and/or ventricular assist device (VAD) placement. Most thrombotic events seemed to have occurred within 10 min of protamine or hemostatic product administration. The thrombotic event occurred in 6 patients during protamine administration, in 6 patients during platelet transfusion, in 1 patient during FFP transfusion, and in 1 patient during cryoprecipitate administration. Immediate thrombosis also occurred in 1 patient who received activated PCC [19], in another who received PCC [21], and in 2 patients who received rFVIIa (80–90 μg/kg) [20, 22]. In other cases, thrombotic events occurred within 45 min of the hemostatic intervention: 15 and 45 min after PCC in 2 patients [8], and 31 min after rFVIIa (87 μg/kg) in 1 patient [23].

Putative thrombosis risk factors

Various putative risk factors for the development of intrapulmonary thrombosis or intracardiac thrombosis during cardiac surgery have been compiled from the literature (Table 2). The most frequently described risk factors are CPB duration, DHCA, and the use of antifibrinolytic medication. The total CPB duration was reported as less than 2 h in 8 patients (23.5%), longer than 2 h in 14 patients (41.1%), and unspecified in 12 patients (35.3%). DHCA was used in 9 cases (26.5%). The use of antifibrinolytic agents was reported in 30 patients (88.2%). The use of aprotinin was more common than that of ε-aminocaproic acid (25 patients, 73.5% vs. 5 patients, 14.7%).

As a surrogate marker of low AT activity, lowest ACT values below 400 s during CPB were found in 7 cases (20.6%). In 20 patients (58.8%), the lowest ACT values were more than 400 s. A number of patients had preoperative diagnosis of congestive heart failure (19 cases, 55.9%), and 7 patients were treated with oral anticoagulation (20.6%). Two patients (5.9%) were found to carry heterozygous factor V Leiden mutation. Endocarditis was found in 4 patients (11.8%).

Although not necessarily considered as a direct trigger of thrombotic complications, platelet concentrate and FFP were frequently administered (35.3% and 26.5%, respectively) to treat bleeding before the occurrence of thrombotic complications. Cryoprecipitate, PCCs, and rFVIIa were transfused in some cases, but they were usually given after transfusion of platelets and FFP.

Use of transesophageal echocardiography for diagnosis

Intraoperative thrombosis was empirically diagnosed by symptoms [high pulmonary artery (PA) pressure, right ventricular (RV) failure, etc.], and later confirmed during the attempted thrombectomy or post mortem in case reports from the 1990s [8, 18, 24, 25]. The autopsy typically revealed extensive thrombi in the small pulmonary arteries.

Intraoperative transesophageal echocardiography (TEE) was used to document the location of thrombus in 19 cases described in 16 publications from 2001 to 2008 [20–23, 26–37]. In 3 (15.8%) of 19 cases, thrombus formation was observed in right cardiac chambers and/or pulmonary arteries, leading to acute right ventricular failure. Disseminated thrombi in left chambers and/or aorta were observed in 7 (36.8%) of 19 cases. Thrombus formation was found in both right and left cardiac chambers in 9 (47.4%) of 19 cases.

Treatment and outcome

In most cases, the reinstitution of CPB was attempted to stabilize hemodynamic status and to remove thrombi. However, 32 of 34 cases resulted in death (mortality, 94.1%). Two patients survived; 1 patient died after several weeks in a chronic care facility [35], but the other patient who received bivalirudin anticoagulation had a full functional recovery [22].

Table 1 Systemic thrombotic events after cardiopulmonary bypass

No.	Age (years)	Sex	Weight (kg)	Procedure	Coexisting conditions	Anti-lytic	Low ACT	CPB time	Intraoperative event	Possible trigger	Thrombus sites	Diagnosis	Rescue attempt	References
1	65	F	NR	Asc Ao repl, DHCA	Thoracic aortic aneurysm	AP	750	NR	↑PAP, RV failure	Protamine	Lung capillaries	PM	–	Saffitz et al. [18]
2	64	F	78	HT/BIVAD	CHF	AP	600	105+	Ao cannula clot	Protamine	Ao cannula, Asc Ao	Visual	Repeat CPB	Gitter et al. [24]
3	69	F	65	TAA repl, DHCA	Thoracic aortic aneurysm	AP	732	240	RV failure	Protamine	RV, PA	PM	RVAD	Alvarez et al. [25]
4	37	F	NR	HT	CHF	AP	NR	NR	V fib arrest	PCC 1,500 U	Lung capillaries	PM	Repeat CPB, HT	Kohler et al. [8]
5	55	M	NR	HT	VKA, CHF	NR	NR	NR	↑PAP, hypotension	PCC 2,000 U	Pulmonary arteries	PM	Repeat CPB, HT	Kohler et al. [8]
6	70	M	NR	Asc Ao repl, AVR, DHCA	Endocarditis, Ao root abscess, Leiden ±	EA	500	311	Hypotension	Protamine	LA, LV, Ao	TEE	–	Franshawe et al. [27]
7	76	F	NR	Asc Ao repl, DHCA	Aortic aneurysm	EA	500	233	Hypotension	FFP	RA, PA, Desc Ao	TEE	–	Franshawe et al. [27]
8	0.9	NR	8.3	Hemi-Fontan	Single ventricle, tricuspid atresia	AP	408	NR	Intracardiac thrombi	Protamine	LA, LV, Abd Ao	TEE	ECMO, tPA	Heindel et al. [26]
9	56	M	87	LT	Previous LT	NR	NR	NR	Hypotension, bradycardia	APCC	ECMO	Visual	ECMO	Bui et al. [19]
10	56	F	39	MVR, AVR	Rheumatic heart dz, A fib, CHF, LA clot	AP	999	213	Hypotension, BV failure	Protamine	LA, Ao, PA	TEE	–	Ramsey et al. [28]
11	50	F	43	HLT	Eisenmenger syndrome	AP	999	NR	↑PAP, hypotension	Protamine	RV, PA, RVAD	TEE	RVAD	Ramsey et al. [28]
12	73	M	NR	CABG	V fib, CHF, CRF, heparin for 13 days, HIT+	NR	450	345	Biventricular failure	–	RA, LA, RV, LV	TEE	–	Lagare et al. [29]
13	78	F	NR	TAA repl, DHCA	Ruptured TA aneurysm	AP	600	212	Cardiac arrest	PLT	Ao	TEE	–	Augoustides et al. [30]
14	69	F	NR	MVR	MVR	AP	400	NR	Cardiogenic shock	Cryo, PLT	LA, Desc Ao	TEE	–	Augoustides et al. [31]
15	53	M	66	HT	CHF	AP	430	106	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
16	42	M	71	HT	CHF	AP	400	125	↑PAP	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
17	19	M	68	LVR, MVP	V fib, CPR	EA	294	167	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
18	60	M	82	LVAD	CHF	AP	338	74	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
19	55	M	62	LVR, MVR	CHF	AP	362	136	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
20	47	F	101	LVAD	CHF	AP	536	177	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
21	56	M	80	LVAD	CHF, CPR	AP	387	90	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]

Table 1 continued

No.	Age (years)	Sex	Weight (kg)	Procedure	Coexisting conditions	Anti-lytic	Low ACT	CPB time	Intraoperative event	Possible trigger	Thrombus sites	Diagnosis	Rescue attempt	References
22	56	F	70	LVAD	CHF, hepatic failure	AP	999	71	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
23	20	M	100	LVAD	CHF, hepatic failure	AP	306	84	↑PAP, RV failure	Protamine	Lung capillaries	PM	RVAD	Cooper et al. [38]
24	46	F	50	AVR	DVT, endocarditis, prolonged heparin	AP	472	60+	↑PAP, hypotension	FFP	RA, LA, RV, LV, SVC	TEE	tPA	Kottenberg-Assenmacher et al. [33]
25	75	NR	NR	TAA repl	Thoracic aortic aneurysm	AP	NR	NR	Hypotension	ProtamineAP, PLT	RA, LA, Ao	TEE	tPA	Schmitz and Hartmann [34]
26	60	NR	NR	TAA repl	Thoracic aortic aneurysm	AP	NR	NR	Hypotension	ProtamineAP, PLT	RA, RV, AV, Ao	TEE	tPA	Schmitz and Hartmann [34]
27	61	M	NR	AVR, DHCA	Previous CABG, Leiden ±	AP	500	NR	Hypotension	Protamine	IVC	TEE	Repeat CPB	Shore-Lesserson et al. [32]
28	78	F	NR	Redo AVR, MVR, TVR, CABG	CHF	AP	500	240	Hypotension, RV failure	ProtaminePLT	LA, Ao	TEE	Repeat CPB, BIVAD	Stone et al. [37]
29	40	F	60	CPR	CHF, IACD, tamponade	EA	450	>300	Cardiac arrest, ECMO clot	FVIIa 80 μg/kg	ECMO, all chambers	TEE	–	Swaminathan et al. [20]
30	59	M	80	LVAD	AMI, BIVAD, HIT+	AP	500	120	NR	FVIIa 90 μg/kg	LA, PV, IVC	TEE	–	Apostolidou et al. [22]
31	79	F	NR	Asc Ao repl, AVR, DHCA	Type A dissection, endocarditis	AP	500	202	Hypotension, RV failure	FVIIa 87 μg/kg	RA, LA, RV, LV	TEE	tPA	Lichtman et al. [23]
32	67	F	53	Redo MVR, AVR, TVR	MV prosthesis, CHF, hepatic congestion	AP	464	179	↑PAP, hypotension	ProtaminePLT	RA, RV, PA	TEE	–	Neira et al. [35]
33	48	M	NR	Des Ao, LVAD	CHF	NR	NR	NR	Hypotension	Cryo	LV, Ao	TEE	–	Trigo et al. [36]
34	69	M	NR	MVR, redo arch repl, DHCA	Marfan syndrome	EA	NR	>420	LV failure	PCC 1,600 U	LA, LV, Ao	TEE	Repeat CPB	Lukauskis and Banks [21]

ACT lowest activated clotting time reported (in seconds), *AMI* acute myocardial infarction, *anti-lytic* antifibrinolytic used, *AP* aprotinin, *APCC* activated prothrombin complex concentrate, *Asc Ao* ascending aorta, *AVR* aortic valve replacement, *BIVAD* biventricular assist device, *BV* RV and LV, *CABG* coronary artery bypass grafting, *CHF* congestive heart failure, *CPB* time duration of cardiopulmonary bypass (in minutes), *CPR* cardiopulmonary resuscitation, *Cryo* cryoprecipitate, *Desc Ao* descending aorta, *DHCA* deep hypothermic circulatory arrest, *EA* ε-aminocaproic acid, *ECMO* extracorporeal membrane oxygenator, *FFP* fresh frozen plasma, *FVIIa* recombinant activated factor VII, *HIT+* positive antibody for heparin-induced thrombocytopenia, *HLT* heart-lung transplantation, *HT* heart transplant, *IABP* intraaortic balloon pump, *IACD* implantable automatic cardioverter defibrillator, *IVC* inferior vena cava, *LA* left atrium, *Leiden ±* heterozygous Leiden V mutation, *LT* lung transplantation, *LV* left ventricle, *LVAD* left ventricular assist device, *LVR* left ventricular reconstruction, *MVP* mitral valvuloplasty, *MVR* mitral valve replacement, *NR* not reported, *PAP* pulmonary arterial pressure, *PCC* prothrombin complex concentrate, *PM* postmortem, *PLT* platelet concentrate, *RA* right atrium, *repl* replacement, *RV* right ventricle, *SVC* superior vena cava, *TAA* thoracoabdominal aneurysm, *TEE* (intraoperative) transesophageal echocardiography, *tPA* tissue plasminogen activator, *V fib* ventricular fibrillation, *visual* visually confirmed in the field

Table 2 Putative risk factors of thrombosis

Variable	Number(s)	Percentage(s) (%)
Age (years)		
≤40	5	14.7
>40 and ≤65	17	50.0
>65	12	35.3
DHCA		
Used	9	26.5
Not used	25	73.5
CPB duration		
≤2 h	8	23.5
>2 h	14	41.1
Not specified	12	35.3
Antifibrinolytic agent		
Aprotinin	25	73.5
ε-aminocaproic acid	5	14.7
Not specified	4	11.8
Lowest ACT after heparin		
≤400 s	7	20.6
>400 s	20	58.8
Not specified	7	20.6
Congestive heart failure	19	55.9
Warfarin	7	20.6
Endocarditis	4	11.8
Transfusion		
Platelet concentrate	12	35.3
Fresh frozen plasma	9	26.5
Cryoprecipitate	7	20.6
Prothrombin complex concentrate[a]	4	11.8
Recombinant FVIIa	3	8.8

Eight additional cases from Cooper et al. [38] also received platelets and FFP

[a] One case in prothrombin complex concentrates was activated prothrombin complex concentrate

Right heart failure associated with pulmonary thrombi is extremely difficult to treat. Rescue attempts with inhaled nitric oxide (NO, 5–40 ppm) to reduce high pulmonary artery pressures [20, 32, 35], and implantation of right VADs [25, 28, 38] were performed, but both failed to improve the outcome. Tissue plasminogen activator (tPA) was used intravenously (10–100 mg) in 4 cases [26, 33, 34], and by intrapulmonary injection (250 μg) [35], but all cases resulted in death.

Discussion

Thirty-four cases of post-CPB thrombotic complications were identified from our review of the literature in cardiothoracic surgery. The coagulation management in CPB procedures is unique for the high-intensity anticoagulation followed by its rapid reversal. Thrombin generation is resumed at the sites of vascular injury (Fig. 2a, b) and graft anastomosis as anticoagulant activities of tissue factor pathway inhibitor [39] and AT [40] rapidly decrease after protamine administration (Fig. 3). The rapid onset (<10 min) of intravascular thrombus formation after protamine administration underlies the critical imbalance between procoagulant stimuli and endogenous anticoagulant activities. Even in the presence of heparin anticoagulation, potent procoagulant stimuli and proinflammatory state cannot be fully suppressed during CPB. Increased tissue factor expression on stimulated monocytes and activated endothelia contributes to the systemic procoagulant tendency [41, 42]. The onset of thrombin generation using tissue factor stimulation is within 10 min after heparin neutralization with protamine [43, 44], which may explain the rapid onset of thrombus formation. Further, the inability to regulate thrombin activity can be explained by several important changes in coagulation. Critical fibrinogen deficiency (<100 mg/dl) leads to the formation of unstable platelet aggregates [45, 46] and to the release of active proteases including FXa and thrombin [47, 48] (Fig. 2c). Platelet–platelet interactions via von Willebrand factors are transient compared to those mediated by fibrinogen [45, 46]. Half-lives of FXa and thrombin are prolonged in the presence of low natural anticoagulant inhibitors [49]. Endothelium-bound thrombomodulin is downregulated by inflammation (e.g., infection) [50], and its capacity to activate protein C can be depressed as plasma protein C level becomes low [51]. Plasma AT activity is also decreased to about 40% in most CPB cases [43, 52], and to below 20% after extreme CPB runs [7, 26]. The length of CPB was more than 2 h in 14 (41.1%) of 34 cases (Table 2). Taken together, it is speculated that nonlocalized thrombus formation could result from severe deficiencies of fibrinogen and endogenous coagulation inhibitors, which play pivotal roles in regulating thrombin (Fig. 2c).

The numbers of intraoperative thrombotic events during cardiac surgery and liver transplantation have been increasing since 2001 [10, 52], which is likely the result of the more widespread use of intraoperative TEE, permitting a prompt diagnosis of systemic thrombosis. Thrombotic events might have been previously considered as a "protamine reaction" and thus underreported before the TEE era. A rapid confirmation of thrombus formation helps to establish a definitive diagnosis so that a life-saving measure can be quickly implemented, as discussed below. It is also important to rule out preexisting thrombi in vena cava, atrium, ventricle, cardiac valves, and pulmonary vasculatures during the baseline TEE examination [53].

Therapeutic interventions for acute RV or LV failure caused by thromboses are rather limited. In

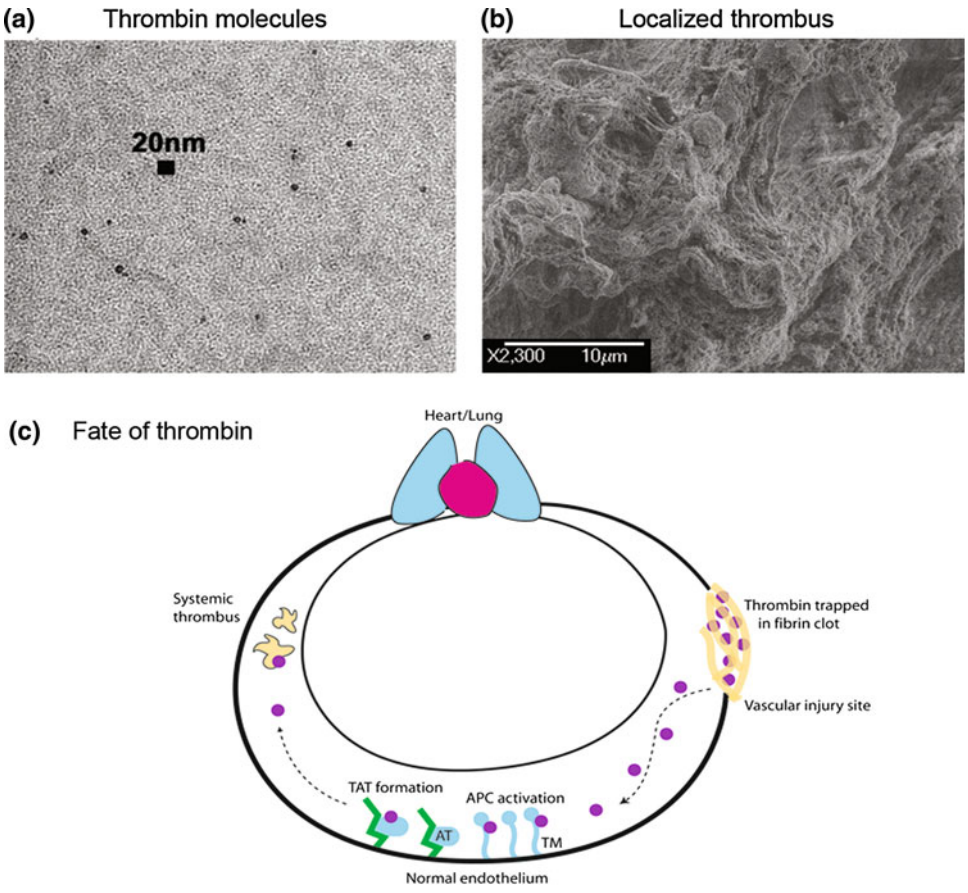

Fig. 2 The systemic control of thrombin and systemic thrombus. Activities of activated protein C (*APC*) and antithrombin (*AT*) play the pivotal role in inhibiting systemic prothrombotic activities. **a** Thrombin generated on the surface of an activated platelet is mostly contained (localized) within polymerized fibrin (**b**). **c** If thrombin (*filled circles*) is released from the vascular injury site, it is rapidly captured by endothelium-bound thrombomodulin (*TM*). TM-bound thrombin activates protein C, which neutralizes activated FV and FVIII. Thrombin is eventually neutralized by AT, forming the thrombin–antithrombin complex (*TAT*). In case of severe loss of fibrinogen, AT, TM, and proteins C and S, thrombin activity cannot be regulated (prolonged plasma half-life), increasing the risk of systemic thrombosis

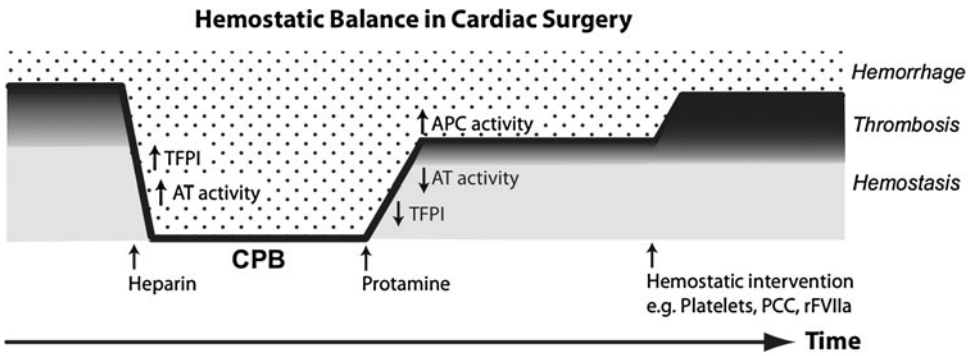

Fig. 3 Hemostatic balance in cardiac surgery. Potential risks for hemorrhage (*dots*) and thrombosis (*dark shading*) change dynamically according to anticoagulation and hemostatic management during cardiac surgery. The administration of heparin rapidly increases the activity of tissue factor pathway inhibitor (*TFPI*) and antithrombin (*AT*). The reversal of anticoagulation with protamine decreases the risk of bleeding, but there is a small risk of thrombosis. In response to thrombin generation, activated protein C (*APC*) activity increases. In case of severe bleeding, additional interventions including platelets, cryoprecipitates, recombinant factor VIIa (*rFVIIa*), or prothrombin complex concentrate (*PCC*) can improve hemostasis, but with a potential risk of thrombosis. *CPB* cardiopulmonary bypass

hemodynamically compromised patients, reinstituting CPB may be the only option to evacuate thrombi and to restore cardiovascular function. Unfortunately, a successful weaning from the repeat CPB is far less likely in case of severe right ventricular dysfunction secondary to pulmonary thrombi. Intraaortic balloon pump and VAD placement have been used to support myocardial function without success [25, 28, 38]. During liver transplantation, tPA has been successfully used to dissolve pulmonary thrombi [54, 55], but several such attempts failed in post-CPB cases [26, 33–35]. The inefficacy of fibrinolytic therapy in post-CPB situations may be explained by several mechanisms. First, antifibrinolytic agents such as lysine analogues and aprotinin have been routinely used in complex cardiac cases.

Table 3 Risks for low antithrombin activity in cardiothoracic surgical patients

Preoperative heparin >4 days
Prolonged CPB >3 h
Deep hypothermic circulatory arrest
Extensive cell saver use
Sepsis/disseminated intravascular coagulation
Heparin-induced thrombocytopenia
Small body size (petite female)
Pediatric heart surgery
Liver failure
Nephrotic syndrome
Asparaginase therapy
Congenital AT deficiency

These agents antagonize endogenous and tPA-induced fibrinolysis [56, 57]. Second, intravenously injected tPA cannot be transported to thrombi for its action when blood flow is limited by the low perfusion [58]. Last, plasminogen can be depleted after severe hemodilution after a prolonged CPB [4].

Preventive strategies for post-CPB thromboses are very important because the mortality rate from intravascular coagulation is extremely high. First, adequate heparin anticoagulation during prolonged CPB plays a key role in preventing consumptive losses of coagulation proteins and in reducing the need for hemostatic interventions [59]. Anticoagulant activities of heparin are mediated by AT, and therefore its supplementation may be necessary in suspected hereditary or acquired AT deficiency (Table 3). AT concentrates at 500–1,000 IU can be administered intravenously to increase plasma AT activity by approximately 17–33% in a 70-kg person. FFP is not as effective as AT concentrates as a treatment for heparin insensitivity [52, 60], but critically low AT activity (<30%) invariably coexists with low procoagulant levels at the end of CPB [4, 52]. Indeed, ACT values were reasonable (>400 s) in most cases (58.8%; Table 2), but high ACT values (>700 s) may merely reflect depletions of procoagulant proteins, fibrinogen, and platelets during prolonged CPB [59, 61]. If FFP could be administered in sufficient amounts (5–8 ml/kg/h) during CPB (e.g., after the 2nd hour) in conjunction with ultrafiltration, it might be feasible to maintain adequate AT activity during CPB lasting more than 3 h. The use of FFP in this clinical context is distinct from the prophylactic use of FFP in routine CPB cases (1–2 h) to improve hemostasis. The latter FFP usage was shown to be hemostatically ineffective [62, 63] and is now discouraged [64].

Antifibrinolytic therapy is routinely used during CPB to improve hemostatic function. Indeed, the use of antifibrinolytic agents was documented in 30 (88.2%) of 34 cases; 25 cases were associated with aprotinin, but it is possible that aprotinin might have been selectively for higher risk cases compared to those in which lysine analogues were used (Table 2). Some have expressed concerns about antifibrinolytic agents during DHCA cases for factor V Leiden mutation, which is associated with increased risk of venous thrombosis [27, 32]. However, DHCA was used in only 9 (26.5%) of 34 thrombosis cases (Table 2). The evidence for increased postsurgical thrombotic risks associated with factor V Leiden mutation is insufficient [10, 65–67]. Once systemic thrombi are formed in the presence of any antifibrinolytic agent, it would be difficult to break them down because they are more resistant to fibrinolysis. It is therefore very important to avoid nonlocalized thrombus formation by optimizing the balance of coagulation, especially when antifibrinolytics are in use.

The risk of thrombosis generally increases with age [13, 68, 69], but no such relationship was found in small case series of post-CPB thrombosis. Preexisting ventricular dysfunction may predispose patients to thrombosis because of venous congestion and blood stasis [1]. Of 34 patients, 19 (55.9%) had congestive heart failure (Table 2). Various hemostatic interventions were administered to treat bleeding after CPB. It is impossible to compare the relative risk of thrombosis among components because sample sizes are small. The administration of rFVIIa or PCCs is aimed to improve local thrombin generation for hemostasis, but with an increased risk of systemic thrombin release. Thrombin circulates longer in plasma when AT and other inhibitors are depressed [46], and circulating platelets can form a thrombus after thrombin stimulation. Interestingly, one of the few survivors of intracardiac thrombosis received bivalirudin anticoagulation for heparin-induced thrombocytopenia [22]. It is conceivable that systemic extension of thrombus formation might have been prevented by bivalirudin-mediated thrombin inhibition. A potential use of direct thrombin inhibitors in cases of intravascular thromboses in AT deficiency is yet to be evaluated [22, 70, 71].

The present study has important limitations. Because of the small sample size and retrospective nature, we cannot ascertain the risk of systemic thromboses associated with certain conditions. For example, tranexamic acid is increasingly used to replace aprotinin, which had been taken off the market, but there is a paucity of information on its safety in prolonged CPB cases [4, 72, 73]. All post-CPB thrombosis cases in Table 1 originated from North America and Europe. It is uncertain if perioperative thrombosis risks would be different among different ethnicities, although the Asian population seems to be at lower risk for venous thrombosis than Caucasians and African Americans [74]. Lethal complications of cardiac surgery are likely underreported, and thus it is not feasible to estimate the overall prevalence of intrapulmonary and/or intracardiac thromboses.

As depicted in Virchow's triad, preexisting abnormalities in blood flow, disruptions of vascular integrity, and rapid changes in blood coagulability can potentially cause major thrombus formation in high-risk cardiac surgical patients (Fig. 1). Further clinical trials and data collection (clinical registry) are warranted to develop safe and efficient strategies to achieve hemostatic balances in complex cardiac surgical patients using conventional blood products (e.g., platelets, FFP, and cryoprecipitate) as well as plasma-derived concentrates (e.g., AT, PCC, fibrinogen concentrate).

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