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Heparin Induced Thrombocytopenia: Its Significance in Cardiac Surgical Patient

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1. Introduction

Intravenous heparin remains main stem therapy during cardiac and vascular surgical procedures. Heparin therapy is often continued after surgery as part of prophylactic treatment (deep venous thrombosis) or bridging therapy (for atrial fibrillation, prosthetic valve(s) or Dacron grafts implanted in the heart) until INR levels reach therapeutic levels with warfarin therapy.

Complications resulting from the use of heparin are relatively rare. Among the most common are bleeding initiated by excessive inhibition of thrombin and other clotting factors and thrombosis caused by inadequate anticoagulation. Heparin Induced Thrombocytopenia (HIT) is a rare but potentially life-threatening complication. The literature, which is describing HIT is still somewhat confusing since it uses a variety for terms for HIT. Type I HIT, sometimes called non-immune heparin-associated thrombocytopenia, is a benign process and presents as a mild thrombocytopenia with the platelet count rarely decreasing below 100.000/ml. Type I HIT develops early after heparin exposure, typically within 2-3 days. It probably results from a direct effect of heparin on platelets and occurs in about 10%–30% of patients receiving heparin (1).

In contrast, and of greater clinical concern, is type II HIT - and immune mediated syndrome associated with platelet activation, increased thrombin production and thrombogenesis leading to thrombo-embolic complications.

The following chapter will briefly discuss the epidemiology, pathogenesis and management options for ICU and cardiac surgical patients diagnosed with true HIT.

2. Epidemiology and pathogenesis

HIT is a rare complication of heparin therapy primarily affecting the surgical population. It occurs in 1-2% of cardiovascular surgery patients, 3%-10% of orthopaedic surgery patients and in less than 1% of obstetrical patients. It is higher in the orthopaedic population since they usually require prolonged treatment with heparin for DVT prophylaxis following surgery. Within the cardiac surgical population, patients who require implantation of a left ventricular assist device are at very high risk of developing HIT (> 10%). The incidence of HIT in patients treated in medical wards is usually very low (< 0.25%).

HIT develops primarily in patients treated with unfractionated heparin (UFH) but it can also develop in patients treated with low molecular weight heparins (LMWH) however the probability is significantly lower. The classical presentation of HIT might be confusing since the thrombocytopenia is usually not severe (a drop of 50-60% when compared to pre-op values) and the dominating clinical symptoms are usually related to thrombo-embolic complications. The final diagnosis can be confirmed only by additional, relatively complicated laboratory tests, which usually take several days to complete. In the meantime, if HIT is suspected, treatment should be initiated based on strong clinical indications.

HIT is an immune reaction associated with the formation of antibodies directed against heparin-Platelet Factor 4 (PF-4) complexes. Once heparin is administered to a patient, platelets release PF-4, which binds heparin. The heparin-PF-4 complex is highly immunogenic and initiates formation of antibodies, which belong to many subgroups (IgG, IgM and IgA). Among these classes of immunoglobulins, only IgG is capable of triggering the reaction responsible for HIT. The immune system of the patient develops sensitivity (memory) to complexes of heparin-PF-4. When a second dose of heparin is given (even a small amount) it causes platelet degranulation and release of PF-4. Antibodies then bind to the complexes (Fab fragment) and to the surface of platelets (Fc fragment) initiating a cascade of events that result in further platelet activation and release of large amounts of PF-4 along with further platelet aggregation and thrombin generation. Strong activation of thrombin leads to clot formation and subsequent thrombo-embolic events. PF-4 can also bind to other substances, which are chemicaly similar to heparin. They belong to a group of molecules called glycosaminoglycans (GAGs). Many GAGs are present on the surface of the endothelial cells. This interaction amplifies the reaction leading to further platelet activation and aggregation, inflammation and propagates clot formation. The above described sequence of events presents clinically as thrombocytopenia accompanied by thrombotic complications. 80% of embolic events take place in the venous system while the remaining 20% occur in the arterial system. Rarely, HIT presents as a systemic reaction, for example disseminated intravascular coagulation (DIC). Therefore, HIT should be considered as a pro-thrombotic disorder leading to venous or major arterial thrombosis with potentially life-threatening consequences.

Antibodies against heparin-PF-4 are usually detectable for up to 3 months after the last heparin exposure. After the antibodies disappear the patient can be safely treated with heparin again.

3. Diagnosis

Usually the first clinical suspicion of HIT occurs when the platelet count drops in a patient being treated with heparin. Thrombocytopenia is usually not severe (40-60,000) or more than 50% of baseline value and it very rarely reaches a level that would cause spontaneous bleeding. The incidence of thrombocytopenia usually has a predictable time pattern. There are 3 possible clinical scenarios.

1. Thrombocytopenia occurring 5-10 days after initiating therapy with heparin. This is the most common clinical scenario.
2. Thrombocytopenia occurring within 24 h after initiating heparin therapy (so-called acute or rapid-onset HIT). This scenario usually occurs in patients who received heparin before surgery, for example as a treatment of unstable angina
3. Thrombocytopenia with delayed onset. In this scenario the platelet drop occurs many days after discontinuing the heparin therapy, usually after the patient is being

discharged from hospital. There are some cases of super-acute HIT, which occurs almost immediately after a second dose of heparin and presents in the form systemic syndrome with dramatic picture of disseminated intravascular coagulation (DIC).

Among patients who develop thrombocytopenia caused by HIT, 30-50 % have thrombotic complications (Table 1). For many clinicians this is a paradoxical phenomenon since heparin is supposed to prevent thrombosis. Venous thrombosis commonly occurs in the lower extremities frequently leading to pulmonary embolism (PE) or venous gangrene with distal necrosis of the limb.

Vasculature	Venous	Arterial
Lower extremities	DVT	Ischemia
Upper extremities	Often with venous catheters	
Adrenal veins	Adrenal insufficiency	
Mesenteric or portal	Liver dysfunction	Bowel or renal
Cerebral venous sinus	Neurological impairment	Stroke
Coronary artery/graft		Ischemia or MI

Table 1. Thrombosis occurring in HIT.

HIT may also present as a systemic reaction. With the injection of the second dose of heparin (i.e. subcutaneous heparin used for DVT prophylaxis), the patient can develop several systemic symptoms, for example skin necrosis, seizures, shivering, hypo- or hypertension and tachycardia, or an anaphylactic reaction. As mentioned before the most severe form of HIT with systemic presentation is DIC. These symptoms are most likely related to a massive release of platelet contents including PF-4 but also histamine, serotonin and other vasoactive substances. Additionally, it has been suggested that systemic presentation of HIT includes extensive endothelial involvement (PF4 binds to GAGs). Various skin lesions at injection sites (erythema induratum, localized or diffuse urticaria, diffuse exanthema) can be also suggestive of HIT in 20% of cases. Livedo reticularis is observed in some patients and is associated with microangiopathy and microvascular thrombosis of the dermis. Lesions are painful, spread centrifugally, and may appear like necrotic purpura with a hemorrhagic bullous course, and central necrosis. 75% of patients showing cutaneous symptoms do not have any notable thrombocytopenia.

Basic laboratory tests reveal thrombocytopenia, and sometimes the blood film can show fragmentation of destroyed erythrocytes. Severe thrombocytopenia (< 20,000) usually indicates that diagnosis of HIT is unlikely. At the same time we need to rule out the most common causes of thrombocytopenia in patients being treated in the ICU (massive blood loss, sepsis, other drug-induced thrombocytopenia, i.e. vancomycin,). Among other less common syndromes causing thrombocytopenia, which should be included in differential diagnosis are: antiphospholipid syndrome, disseminated intravascular coagulation caused by other precipitating factor, thrombotic thrombocytopenic purpura and post-transfusion purpura.

One of the most popular schemes of assessment and clinical diagnosis of HIT was developed by Warkentin and called 'four T' (Table 2). T stands for **t**hrombocytopenia, **t**iming, **t**hrombosis and o**t**her causes. For each category the patient receives 0, 1 or 2 points. For a score of 0-3 points, the diagnosis of HIT is unlikely, 4-5 points requires laboratory testing to confirm the diagnosis but in most cases does not require treatment, however, if patients receive a score of ≥ 6 points treatment should be initiated immediately.

Criteria	2 points	1 point	0 points
Timing (of thrombo-cytopenia)	5-10 days after heparin or during 1st day of therapy if heparin within previous 30 days	> 10 days after heparin or during 1st days of therapy if heparin used before (31-100 days)	No previous use of heparin
Thrombocytopenia (Platelet count)	< 50% of baseline value or > 20,000	30-50% of baseline value or 10-20,000	< 30% of baseline value or < 10,000
Thrombosis	New incident of thrombosis or skin necrosis in injection site or systemic reaction during dosing of heparin	Progressing or recurrent thrombosis or suspicion of thrombosis without proven diagnosis	No thrombo-embolic complications
Other explanations of thrombocytopenia	No other causes	Potential causes	Confirmed other causes
≥ 6 points mandates initiation of HIT therapy prior to receiving laboratory results confirming the diagnosis.			

Table 2. Table describes scoring system used for clinical diagnosis of HIT.

As mentioned before HIT can be only confirmed by a specific laboratory tests. First, a screening test is performed to detect HIT antibodies. This screening test detects all classes of immunoglobulins but as mentioned earlier, only IgG can trigger HIT. For example, in the case of cardiac surgical patients 20-40% of them develop antibodies, but only 1-2% are truly HIT-positive. On the other hand, if the screening test does not detect any immunoglobulins the presence of HIT can be ruled out. In the case of a positive HIT screen we need further confirmation to be able to show that these (detected) antibodies can trigger platelet activation. The most popular assay used is the Serotonin Release Assay (SRA), which uses plasma obtained from the patient, heparin and specially prepared, radio-labeled platelets. If the patient's plasma activates platelets (ie: causes release of serotonin) the patient can be diagnosed as having HIT (positive). Unfortunately, SRA is performed in only a few centers and thus the results of the test are usually not available for several days. An alternative to the SRA performed by some laboratories is the heparin-induced platelet aggregation assay (HIPA), which also demonstrates the presence of a clinically relevant antibody. In the meantime, the medical team needs to initiate treatment based on the clinical symptoms and probability of a positive diagnosis of HIT (>6 points in scale proposed by Warkentin).

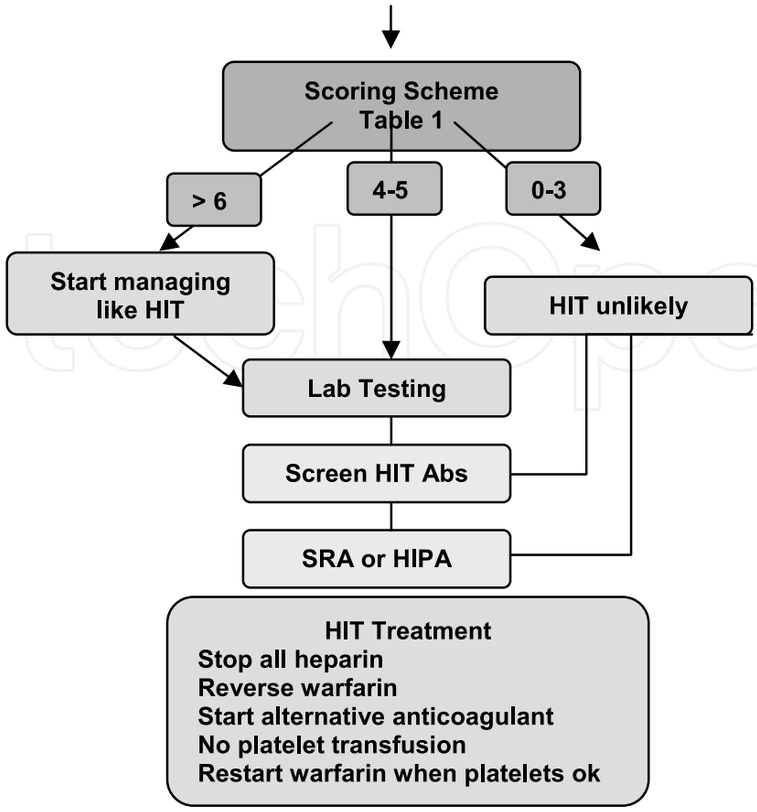

Fig. 1.

4. Management

Principles of treatment for patient diagnosed with HIT can be outlined in the following points.

1. Discontinue all forms of heparin including line flushes, LMWH or lines coated with heparin (i.e. heparin-bound Swan-Ganz catheter). Even tiny amounts of heparin can precipitate HIT.
2. Do not transfuse platelets to treat thrombocytopenia. Transfusion may precipitate further thrombotic events because HIT antibodies will activate transfused platelets.
3. Initiate treatment with heparin alternatives, the most commonly used drugs belong to 2 classes of anticoagulants: long acting, antithrombin III (ATIII) dependent factor Xa inhibiting oligosaccahrides or direct thrombin inhibitors (DTI).
4. If patient is already receiving warfarin it should be reversed with vitamin K. During the early stages of warfarin therapy, levels of protein C (a natural anticoagulant) will drop before the rest of the coagulation factors are inhibited and this can make the patient even more pro-thrombotic at the initial stages of warfarin therapy.
5. Warfarin therapy may be re-instituted when the platelets recover back to the baseline level. Warfarin derivatives must overlap for 4-5 days with anti Xa inhibitors or DTI therapy.

It should be stressed that stopping heparin without initiating anti- Xa inhibitors or DTI therapy is not sufficient for prevention of thrombotic complications.

The fundamental difference between heparin and Xa inhibitors or DTIs lies in the mechanism of their action. Heparin requires a cofactor, which is called antithrombin- III (ATIII), additionally it can not bind to thrombin, which is already attached to a fibrin network. A long half-life and a stable level of anticoagulation characterize indirect factor Xa inhibitors, similar to heparin since they also require ATIII. The pharmacokinetic profile of anti-Xa inhibitors makes them favorable to use in the ICU setting (one dose a day). On the other hand, the fact that they do not have antidote may complicate clinical management in case patient requires surgical intervention. Specific assays are available to measure drug levels.

The second group of medications DTIs bind and inhibit thrombin directly by connecting to 2 active exosites. They have a short half-life and may interfere with the thrombin-induced protein C pathway. Similar to indirect Xa inhibitors, DTIs do not have an antidote, therefore their action cannot be reversed. All these agents can be safely used in patients with thrombocytopenia.

Currently there are five main drugs used for HIT therapy: danaparoid, fondaparinux, bivalirudin, argatroban and hirudins. Danaparoid and fondaparinux belong to ATIII-dependent anti-Xa inhibitors, lepirudin, bavalirudin and argatroban belong to group of DTI. Danaparoid, lepirudin and argatroban are approved for treatment of HIT, bivalirudin and fondaparinux are not but have high rationale to be used for HIT therapy. Those five agents will be discussed below; additionally their brief characteristics are presented in Table 3.

Non-thrombin Inhibitors			
	Danaparoid		Ancrod
T1/2 Elimination	7-25 hrs		3-5 hrs, >24 hr
Monitoring	Anti Xa levels		Fibrinogen
Reversal	incomplete with protamine		FFP, cryo
Direct Thrombin Inhibitors			
	r-hirudin	Argatroban	Bivalirudin
Thrombin binding	Irreversible	Reversible	Reversible
Metabolism	Renal	Hepatic	Plasma, renal
T1/2 Elimination	40-120 min	25-50 min	25 min
Monitoring	aPTT, ECT	aPTT, ACT	ECT, kACT

Table 3. Short description of pharmacokinetic properties of alternative anticoagulants used in treatment of HIT

Danaparoid. Danaparoid is a mixture of several glycoaminoglycans, mainly haparan sufate. It has both anti-thrombin and anti- Xa properties but later predominates. It can be given as subcutaneous or intravenous injection and has long half-life (25h). Danaparoid has a unique property; in therapeutic concentration it can inhibit platelet activation caused by HIT antibodies, stopping vicious circle of thrombotic complications. It is usually administered once a day and first dose should be given intravenously to rapidly achieve therapeutic concentration. Similar to other agents used for treatment of HIT Danaparoid has no antidote.

Fondaparinux. Fondaparinux also belongs to group of indirect anti-Xa inhibitors but when compared to Danaparoid it does not have anti-thrombin properties. Half-life of Fondaparinux is 17 h. Paradoxically, Fondaparinux can trigger formation of HIT antibodies but its use is still considered to be very effective treatment of HIT.

R-Hirudins. Currently, there are two formulations of r-Hirudins available on the market: lepirudin and desirudin. Hirudins belong to DTI and have very high affinity to thrombin including molecules bonded to fibrin. This high affinity makes binding practically irreversible. Half-life of R-Hirudins is 80 min., they are eliminated almost exclusively by kidneys. In patients with kidney dysfunction half-life of r-Hirudins is totally unpredictable. R-hirudins are highly efficacious but treatment is complicated by high incidence of hemorrhagic complications (15%). Literature reports on several cases of lethal anaphylactic reactions complicating re-exposure to Hirudins.

Argatroban. When compared to Hirudins, Argatroban bindings to thrombin are reversible. Drug is primarily metabolized and excreted by liver therefore is recommended for use in patients with kidney dysfunction or failure. Frequency of major bleeding complicating argatroban therapy is 8%, more over patients treated with Argatroban have high incidence of limb amputation. Most likely it is related to difficulties in achieving therapeutic level and fact that Argatroban artificially elevates values of INR. It may compromise safe overlap and transition from Argatroban therapy to Coumadin. Experience with Argatroban used for cardiac surgical procedures is highly unfavorable.

Bivalirudin. Bivalirudin belongs to reversible DTI and among all agents used for HIT therapy presents most favorable pharmacokinetic profile. It has short half-life (25 min) and is primarily metabolized by plasma enzymatic degradation. It makes it drug of choice in patients with kidney and/or liver dysfunction (i.e. ICU patients). On the other hand due to plasma enzymatic degradation of bivalirudin any blood anticoagulated with this agent, which in stagnation will eventually clot. This property requires alternative approaches during CPB: the pump suckers must be replaced with cell saver and cardioplegia pump must be continuously flushed. Additionally, presence of clots in pericardium (stagnated blood) does not indicate that patient is not adequately anticoagulated. Therapy with Bivalirudin should be monitored with Ecarin Clotting Time (ECT), which is not available in many institutions. As an alternative one can use direct DTI assay or aPTT or plasma modified ACT if Bivalirudin is to be used for CPB purposes. Properties of Bivalirudin make it agent of choice for cardiac surgical procedures in HIT-positive patients who cannot be re-scheduled beyond time when HIT antibodies disappear.

5. HIT patient for CPB

One of the most challenging situations facing cardiac anaesthesiologists is intra-operative management of the patient who requires a cardiac surgical procedure who is HIT positive. Whenever possible it is recommended to delay surgery until the HIT antibodies have cleared (on average 100 days). Unfortunately, in some clinical situations it is not possible; for example: left main stenoses with symptoms of unstable angina, rapidly progressing endocarditis or heart transplantation are among the most common clinical scenarios. Among all of the presented agents (see **Table 3**), none of them is approved for anticoagulation during cardiopulmonary bypass (CPB). Therefore therapy with DTIs or indirect anti Xa inhibitors during cardiac surgery with use of CPB should be considered as an "off-label" application for these drugs. All of them have been used in different doses with varying

protocols and outcomes were not always favorable. Their recommended doses and protocols for clinical use are presented in **Table 4.** When comparing all of these agents, Bivalirudin appears to offer that most favorable outcome with respect to control of anticoagulation during extracorporeal circulation. The features of Bivalirudin, which makes it a favorable agent for use with CPB are: a short half-life and metabolism that is independent from kidney and liver function. A protocol based on data from the literature and our own experience is presented in the **Appendix 1.**

Anticoagulant	Dosages for CPB
Danaparoid	Bolus 125 units kg^{-1} iv, post thoracotomy CPB prime 3 units ml^{-1} Infusion 7 units kg^{-1} h^{-1} iv on CPB If clotting noted additional bolus 1250 units Stop infusion 45 minutes before end of CPB
Ancrod	Infusion 8.4 units h^{-1} x 12hrs preoperatively check fibrinogen levels q 4hrs Stop infusion preoperatively once the target fibrinogen level of 0.4-0.8 gm L^{-1} is reached If fibrinogen > 0.8 gm L^{-1} restart the infusion at 2.1 units h^{-1}
Hirudin	Bolus 0.25 mg kg^{-1}, pre cannulation CPB prime 0.25 mg kg^{-1} Infusion 0.5 mg min^{-1} iv, maintain ECT > 400s Additional bolus to maintain ECT Stop infusion before end of CPB
Argatroban	Bolus 0.1 mg kg^{-1} iv, 20 minutes pre cannulation Infusion 5-10 ug kg^{-1} min^{-1} iv, maintain ACT > 400s CPB prime 0.05 mg kg^{-1} Additional 2 mg iv boluses to maintain ACT Stop infusion before end of CPB
Bivalirudin	Bolus 1.5 mg kg^{-1} iv, pre cannulation CPB prime 50mg Infusion 2.5 mg kg^{-1} h^{-1} iv, maintain ECT > 400s Stop infusion before end of CPB

Table 4. Dosages of alternative anticoagulants used for patients who are HIT positive and require cardiac surgery with the use of cardiopulmonary bypass

It should be mentioned that there are some reports in the literature recommending the use of strategies other than using a DTI or indirect Xa inhibitor for anticoagulation during CPB. The most encouraging of those are: use of plasmapheresis prior to CPB to clear all HIT antibodies followed by use of regular doses of heparin or to use a prostacyclin infusion combined with antiplatelet therapy with GPIIb/GPIIIa inhibitors.

Appendix 1 Scheme of CPB approach with bivalirudin anticoagulation for HIT positive patients			
Requirements	For Anesthesiologist	For Surgeon	For Perfusionists
Staffing	2 anesthesiologist required, one responsible for anticoagulation, one for anesthesia	Regular setup	2 perfusionists required
Anticoagulation	Separate line for bivalirudin Bolus 1-1.5 mg/kg Followed by infusion 2.5mg/kg/h Discontinue infusion 15 min. prior to decannulation	Stagnant blood will clot (pericardium, pleura)-do not panic Suction-only from cell saver Consider continuous cardioplegia Consider flushing grafts with bivalirudin solution (0.1 mg/ml)	50 mg of bivalirudin into pump prime Monitor anticoagulation with Ecarin Clotting time (>400 sec) or ACT> 370 sec Additional bolus of 0.25mg/kg if ECT/ACT values below recommended, consider increasing infusion after bolus Cannot use suction units of CPB machine- only cell saver Have second circuit as a back-up solution
Hemostasis	Maintain normothermia after CPB Maximum dose of antifibrinolitic Be prepared for massive transfusion protocol No antidote for bivalirudin	Meticulous haemostasis Bleeding might continue for up to 45 min. after commencing CPB	Cell saver use to continue after CPB Be prepared to perform ultrafiltration after CPB to speed up elimination of bivalirudin. Extra pump blood must be stored in citrated bags
Other important points	Reduce doses in patients with kidney dysfunction	Flush you mammary every 10 min	Divede duties between 2 perfusionists prior to procedure
Equipment	Everything heparin free (lines, line flushed, PA catheters)	Lots of additional equipment in the room	Cell saver, additional pump as backup, ECT machine if available in your institution

Appendix 1.

6. Summary

HIT represents a rare but potentially life threatening complication of heparin therapy. Its pathogenesis is based on an immunological reaction specifically the formation of antibodies directed against a complex of heparin and PF-4. Secondary exposure to heparin triggers a reaction leading to activation of platelets, their aggregation and adhesion to endothelium leading to formation of clots (80% in the venous system and 20% in arteries) and subsequent thrombotic events.

The definitive diagnosis of HIT requires sophisticated laboratory tests that may take a while to get results from. Therefore treatment should be initiated before final results are obtained

based on high clinical suspicion. The most important principles of therapy include: discontinuation of any form of heparin therapy, treatment with indirect inhibitors of factor Xa or direct thrombin inhibitors and reversal of vitamin K antagonists if they were used previously. Additionally, transfusion of platelets should be avoided since it will only precipitate their activation and aggravate the clinical symptoms.

7. Key points

- Heparin -induced thrombocytopenia (HIT) is a rare highly under-diagnosed but life threatening complication of heparin therapy.
- HIT is a clinico-pathological syndrome requiring multiple laboratory tests to make the final diagnosis. Most often treatment must be initiated before final diagnosis is established
- The most important principles of therapy include: discontinuation of any form of heparin, avoidance of platelet transfusion, treatment with indirect inhibitors of factor Xa or direct thrombin inhibitors and reversal of vitamin K antagonists if they were used previously.
- Management of a HIT-positive patient undergoing cardiac surgery with the use of CPB presents a challenge for the anesthesiologist.

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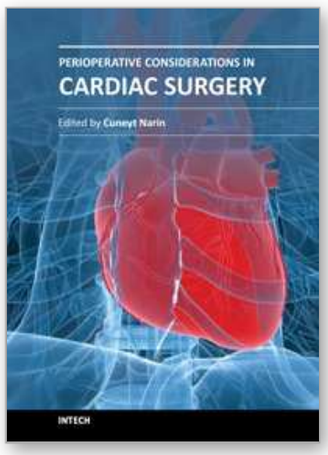

Perioperative Considerations in Cardiac Surgery

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This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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