CARDIOVASCULAR

Short-acting $P_2Y_{12}$ blockade to reduce platelet dysfunction and coagulopathy during experimental extracorporeal circulation and hypothermia

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Editor’s key points

- Extracorporeal circulation and hypothermia can induce platelet activation and dysfunction in cardiac surgery.
- Cangrelor, a short-acting platelet adenosinediphosphate receptor blocker, was used to prevent platelet activation in ex vivo and in vivo models of extracorporeal circulation.
- Cangrelor reversibly reduced platelet activation, providing a potential pharmacological strategy to reduce bleeding complications.

Background. Extracorporeal circulation (ECC) and hypothermia are routinely used in cardiac surgery to maintain stable circulatory parameters and to increase the ischaemic tolerance of the patient. However, ECC and hypothermia cause platelet activation and dysfunction possibly followed by a devastating coagulopathy. Stimulation of the adenosinediphosphate (ADP) receptor $P_2Y_{12}$ plays a pivotal role in platelet activation. This experimental study tested $P_2Y_{12}$ receptor blockade as an approach to protect platelets during ECC.

Methods. Human blood was treated with the short-acting $P_2Y_{12}$ blocker cangrelor (1 μM, $t_{1/2}$, 5 min) or the $P_2Y_{12}$ inhibitor 2-MeSAMP (100 μM) and circulated in an ex vivo ECC model at normothermia (37°C) and hypothermia (28°C). Before and after circulation, markers of platelet activation and of coagulation (thrombin–antithrombin complex generation) were analysed. During hypothermic ECC in pigs, the effect of reversible $P_2Y_{12}$ blockade on platelet function was evaluated by cangrelor infusion (0.075 μg kg$^{-2}$ 1 min$^{-2}$).

Results. During ex vivo hypothermic ECC, $P_2Y_{12}$ blockade inhibited platelet granule release ($P<0.01$), platelet–granulocyte binding ($P<0.05$), and platelet loss ($P<0.001$), whereas no effects on platelet–ECC binding, platelet CD42b$^a$ expression, glycoprotein IIb/IIIa activation, or thrombin–antithrombin complex generation were observed. During hypothermic ECC in pigs, cangrelor inhibited platelet–fibrinogen binding ($P<0.05$) and ADP-induced platelet aggregation ($P<0.001$). Platelet function was rapidly restored after termination of cangrelor infusion.

Conclusions. $P_2Y_{12}$ blockade by cangrelor prevents platelet activation during ECC and hypothermia. Owing to its short half-life, platelet inhibition can be well controlled, thus potentially reducing bleeding complications. This novel pharmacological strategy has the potential to reduce complications associated with ECC and hypothermia.

Keywords: cardiopulmonary bypass; extracorporeal circulation; hypothermia; platelets

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Extracorporeal circulation (ECC) is used in many cardiac surgical procedures, and hypothermia ranging between 28 and 32°C is also widely used as an adjunct to ECC to increase ischaemic tolerance. However, shear stress within extracorporeal circuits and hypothermia result in platelet activation. Contact of blood with artificial ECC surfaces leads to deposition of plasma proteins including fibrinogen at the interface. Fibrinogen is the main ligand of the platelet receptor glycoprotein IIb/IIIa (GPIIb/IIIa; CD41/CD61) and mediates binding of platelets in aggregates. As a consequence of contact with ECC, platelets release their granule contents, form aggregates, adhere to the ECC surface, and are therefore unavailable for adequate blood coagulation. This dysfunction of platelets plays an important role in severe bleeding\(^1\) and thromboembolic complications associated with ECC.\(^2-5\)

Pharmacological inhibition of GPIIb/IIIa has been proposed to protect platelet function temporarily during ECC.\(^6,7\)
This approach, termed 'platelet anaesthesia', has not become established in clinical routine because the half-lives of commercially available GPIIb/IIIa blockers are on the order of 2 h and might therefore promote bleeding complications. The optimal agent for platelet protection would therefore be short-acting to achieve safe therapy during ECC and hypothermia with rapid recovery.

Shear stress within the ECC circuit results in substantial release of the platelet agonist adenosine diphosphate (ADP) from platelets and erythrocytes in amounts sufficient to induce platelet aggregation. Released ADP recruits additional circulating platelets and amplifies the platelet activation cascade (the ADP augmentation pathway). ADP-mediated platelet activation is therefore of particular importance during ECC. In addition, the platelet agonist ADP also plays a central role in hypothermia-induced platelet activation, and pharmacological blockade of the platelet ADP receptor \( P_2Y_{12} \) inhibits hypothermia-induced platelet activation.

The aim of this study was to establish a pharmacological strategy suitable for platelet protection during ECC and hypothermia under clinical conditions. Using an ex vivo ECC model, we analysed the role of \( P_2Y_{12} \) blockade on platelet activation at normothermia (37 °C) and hypothermia (28 °C). Furthermore, we used the short-acting \( P_2Y_{12} \) blocker cangrelor (1/2 h) for temporary platelet inhibition during in vivo hypothermic ECC in a pig model.

**Methods**

**Ex vivo Chandler loop model**

Blood sampling procedures were approved by the ethics committee of the University of Tübingen, Germany. Blood from non-medicated male subjects, who gave signed informed consent, was collected by venipuncture. Blood was anticoagulated with heparin (final concentration 3 IU ml\(^{-1} \)) and amounts sufficient to induce platelet aggregation. Released ADP recruits additional circulating platelets and amplifies the platelet activation cascade (the ADP augmentation pathway). ADP-mediated platelet activation is therefore of particular importance during ECC. In addition, the platelet agonist ADP also plays a central role in hypothermia-induced platelet activation, and pharmacological blockade of the platelet ADP receptor \( P_2Y_{12} \) inhibits hypothermia-induced platelet activation.

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**Cardiopulmonary bypass**

An arterial catheter (Leader-Cath, 4.5 Fr, Vygon GmbH & Co. KG, Aachen, Germany) and a central venous catheter (7 Fr, Arrow International Inc., PA, USA) were inserted in the left carotid artery and the left internal jugular vein, respectively. To prepare connection of the heart–lung machine (HLM), median sternotomy was performed. An aortic cannula (16 Fr, Jostra) was inserted into the ascending aorta and a venous cannula (MECC-Set, 32/40 Fr, Jostra) was inserted into the right atrium according to standard procedures. Heparin (Ratiopharm GmbH) was administered in a dose of 500 IU kg\(^{-1} \) to prevent blood clotting inside the HLM and to achieve an activated clotting time (ACT) of >400 s. ACT measurements were performed using the Hemochrom Jr. II system (Life Systems, Hamburg, Germany) and were repeated at least each 30 min. If necessary, additional heparin was administered. Cardiopulmonary bypass (CPB) was established using an HLM (53 System Slimline; Stöckert, Munich, Germany) containing the following elements: 3/8 in. tubing (Bioline coating, Jostra), bag reservoir (Medistat, Medemblik, The Netherlands), and oxygenator (Quadrox, Bioline coating, Jostra). Blood flow within the CPB circuit was maintained by a roller pump (Stöckert). A suction device served to return any blood from the pericardial cavity to the circulation. The oxygenator was connected to a heat exchanger to establish desired blood temperatures in the range of 37–28 °C. The priming volume (1 litre) consisted of one-third of isotonic saline (Fresenius Kabi) and two-thirds of 6% hydroxyethyl starch (Fresenius Kabi) and was heparinized (heparin concentration: 5 IU ml\(^{-1} \)).

CPB was performed with an average flow of 3–3.5 litre min\(^{-1} \) to establish a mean arterial pressure of 60 mm Hg. Aortic clamping was not performed and the heart was left beating throughout the whole procedure. After connection of the HLM, the animal was cooled to 28 °C using the CPB circuit. After rewarmin to 37 °C, weaning from CPB was...
performed by administration of norepinephrine (maximum of 0.1 µg kg⁻¹ min⁻¹) to establish a mean arterial pressure of >60 mm Hg. After weaning from CPB, protamine was administered (400 IU kg⁻¹).

**Administration of study medication and blood sampling**

Cangrelor (The Medicines Company) was dissolved in water to achieve a final concentration of 0.05 mg ml⁻¹. Continuous infusion of cangrelor (0.075 µg kg⁻¹ min⁻¹; cangrelor-treated group) or placebo (0.0015 ml kg⁻¹ min⁻¹ solvent at an equivalent volume; placebo group) was started 10 min before initiation of CPB and was terminated upon weaning from CPB.

Blood was sampled at skin incision before sternotomy (T1), 10 min after initiation of cangrelor or placebo infusion and heparin application directly before the start of CPB (T2), 45 min after the start of CPB (T3), directly before the end of CPB (T4), 10 min after the end of CPB (T5), and 60 min after the end of CPB (T6).

**Flow cytometry**

Human platelets were analysed directly after blood sampling (baseline) and after 30 min of *ex vivo* ECC in baseline and circulated samples. Expression of P-selectin, CD42b, and activated GPIIb/IIIa on human platelets was analysed according to previously described methods. For detection of platelet–granulocyte binding, 45 µl of whole blood was incubated for 20 min with 10 µl of an anti-CD41-FITC monoclonal antibody (mAb, Beckman Coulter, Marseille, France) and 10 µl of an anti-CD15-PE mAb (Beckman Coulter). Afterwards, samples were treated with FACS Lysing Solution (BD Biosciences). Flow cytometry was performed by administration of norepinephrine (maximum of 0.1 µg kg⁻¹ min⁻¹) to establish a mean arterial pressure of >60 mm Hg. After weaning from CPB, protamine was administered (400 IU kg⁻¹).

**Measurement of plasma β-thromboglobulin and thrombin–antithrombin complex concentrations**

Analyses of β-thromboglobulin (β-TG) and thrombin–antithrombin (TAT) complex concentrations were performed as previously described using ELISA kits from Diagnostica Stago (Asnières, France, for β-TG levels) and Enzygnost TAT micro (Siemens, Marburg, Germany), respectively. Ex vivo platelet aggregation was measured as previously described in porcine platelet-rich plasma at the indicated sampling time points. In short, platelet-rich plasma was prepared and aggregation was induced by ADP (f.c.: 20 µM) and measured using a four-channel aggregometer (PAP-4, Biodata Corp., Horsham, PA, USA).

**Whole-blood count analysis**

Human or porcine whole blood was anticoagulated using EDTA (EDTA-Monovette®, Sarstedt, Nümbrecht, Germany) and blood count analysis was performed using an ABX Micros 60 blood analyser (Axon Lab AG, Baden-Dättwil, Switzerland).

**Statistical analysis**

Data are depicted as means with standard error of the mean (SEM). For experiments in the *ex vivo* ECC model, mean baseline values were transformed to 100% to compare ECC-related effects between the two temperature groups. Data measured after ECC are given in relation to the adjusted baseline values.

To adjust for haemodilution caused by the ECC priming volume, a haematocrit correction was performed for porcine platelet counts, which were sampled during and after porcine CPB. The haematocrit correction factor was calculated by dividing the baseline haematocrit (T1) by haematocrit values measured during and after CPB (T2–T6). Values measured at T2–T6 were multiplied by the respective haematocrit correction factor.

The mean baseline (T1) values of both treatment groups were adjusted to 100%, if indicated. In each group, data measured at time points T2–T6 are given in relation to these adjusted baseline values.

To analyse differences between data sets, repeated-measures ANOVA with Bonferroni’s multiple comparison test was performed. A *P*-value of < 0.05 was defined as statistically significant.
Results

To analyse the effect of P₂Y₁₂ blockade during ECC and hypothermia on platelets, we used a Chandler loop model to mimic ECC at 37 and 28 °C.

P₂Y₁₂ receptor blockade inhibits platelet granule release, platelet–granulocyte binding, and platelet loss during ex vivo hypothermic ECC

The release of platelet α-granules during normothermic and hypothermic ex vivo ECC was determined by evaluating surface expression of P-selectin and plasma β-TG concentrations. Investigation of these markers is a reliable method for the detection of platelet degranulation and therefore platelet activation.

Hypothermic ECC increased levels of the platelet activation markers P-selectin 5.9-fold and β-TG 44-fold (P<0.0001; Fig. 1a and b). Normothermic ECC caused a 16-fold increase in β-TG plasma levels (P<0.01), whereas no significant increase in P-selectin expression was observed. In the hypothermic group, treatment with the P₂Y₁₂ antagonists cangrelor or 2-MeSAMP significantly decreased levels of the platelet activation markers P-selectin and β-TG, respectively (P<0.0001; Fig. 1a and b). P₂Y₁₂ blockade decreased β-TG release during normothermic ECC, however, without reaching statistical significance.

To investigate platelet dense granule release during normothermic and hypothermic ECC, plasma ADP concentrations were determined after 30 min of ex vivo ECC at 37 and 28 °C. Only hypothermic ECC resulted in a significant 1.5-fold increase (P<0.05) of ADP levels. Cangrelor and 2-MeSAMP significantly decreased (P<0.01) ADP concentrations close to values observed at baseline (Fig. 1c).

Platelet–granulocyte aggregate formation was significantly increased during hypothermic ECC (P<0.01; Fig. 1a). Treatment with the P₂Y₁₂ antagonists cangrelor significantly reduced this effect (P<0.05).

Moreover, ECC resulted in a significant loss of circulating platelets (Fig. 1e; P<0.0001) in vehicle (PBS)-treated blood (control), which was further increased by hypothermia (P<0.001). This effect was significantly reduced by both cangrelor (P<0.001) and 2-MeSAMP (P<0.0001).

Effects of ex vivo ECC and P₂Y₁₂ blockade on platelet–ECC binding, CD42bα expression, and GPIIb/IIIa activation

Hypothermic ECC resulted in a significant increase in platelet adherence to the artificial ECC surface (P<0.05; Fig. 2a). P₂Y₁₂ blockers (cangrelor or 2-MeSAMP) had no effect on platelet–ECC interaction. Neither ECC at 37 or 28 °C nor P₂Y₁₂ blockade had a significant effect on expression of the platelet von Willebrand factor receptor CD42bα (Fig. 2a). Hypothermic ECC resulted in activation of the platelet–fibrinogen receptor GPIIb/IIIa (P<0.001). This effect was decreased by P₂Y₁₂ blockade, however, without reaching statistical significance (data not shown).

P₂Y₁₂ blockade has no effect on TAT complex formation during ECC

As an index for thrombin generation indicating activation of the plasma coagulation cascade, we measured TAT complex formation before and after ECC in all groups. Normothermic and hypothermic ECC induced mild increases in TAT levels. Treatment with P₂Y₁₂ blockers had no effect on this phenomenon (n=4; data not shown).

Effects of short-acting P₂Y₁₂ blockade during hypothermic CPB in vivo

Components and duration of CPB

Next, we asked whether the inhibitory effects of P₂Y₁₂ blockade on ex vivo ECC- and hypothermia-induced platelet activation would also be valid for the in vivo setting. Therefore, we evaluated the effect of cangrelor during hypothermic CPB in pigs. We used an HLM consisting of heparin-coated components (Bioline) which are used in adult cardiac surgery. CPB was performed with a median duration of 85 min [inter-quartile range (IQR): 22.5 min] in the placebo group and 75 min (IQR: 15 min) in the cangrelor-treated group (P=0.1443 derived from paired t-test). The cangrelor dose used during hypothermic CPB was determined in preliminary experiments using cangrelor from 0.025 to 2 μg kg⁻¹ min⁻¹ (data not shown). A dose of 0.075 μg kg⁻¹ min⁻¹ was found to sufficiently inhibit platelet function and allow rapid reversibility of P₂Y₁₂ blockade at the same time.

A timeline indicating CPB procedures and blood sampling time points is shown in Figure 3.

Effects of CPB on haematocrit values, haemoglobin concentrations, and platelet counts

The CPB priming volume causes haemodilution and hence decreased haematocrit values (Fig. 4a). Therefore, 45 min after the start of CPB, haematocrit values were significantly lower in both treatment groups in comparison with pre-CPB values. Notably, at each time point, no differences in haematocrit (Fig. 4a) and haemoglobin values (Fig. 4b) between both groups were observed. Furthermore, no significant differences in platelet counts (Fig. 4c) were measured between control- and cangrelor-treated animals during and after hypothermic CPB.

Effects on platelet aggregation

A major concern in the setting of pharmacological platelet inhibition during CPB is the potential induction of platelet dysfunction and bleeding. Therefore, we first evaluated the duration of platelet inhibition during CPB using the short-acting platelet P₂Y₁₂ inhibitor cangrelor. ADP-induced platelet aggregation was investigated at different time points before, during, and after CPB (Fig. 5). Cangrelor infusion significantly inhibited ADP-induced platelet aggregation directly after the start of infusion before CPB (T2, P<0.01), after 45 min of CPB (T3, P<0.0001), and before the end of CPB (T4, P<0.05). Notably, 10 min after cangrelor infusion was
terminated, platelet function returned to values observed in placebo-treated controls.

**Effects of P$_{2}Y_{12}$ blockade on fibrinogen binding to porcine platelets**

Platelet activation is associated with a conformational switch of the GPIIb/IIIa receptor allowing fibrinogen binding that can be detected in flow cytometry. In order to evaluate the potential activating effects of CPB in vivo, binding of fibrinogen to platelets was determined (Fig. 6). In placebo-treated animals, an increase in platelet–fibrinogen binding was observed during hypothermic CPB reaching statistical significance (P<0.05) 60 min after CPB. This phenomenon was inhibited by cangrelor treatment (P<0.05).

**Discussion**

This study investigates the ex vivo and in vivo effects of P$_{2}Y_{12}$ blockade during ECC at normothermia and hypothermia on
platelets. Our results highlight the major role of the platelet receptor P₂Y₁₂ and its agonist ADP in ECC- and hypothermia-induced platelet activation. During ex vivo ECC, P₂Y₁₂ blockade inhibits hypothermia and ECC-induced platelet granule release, platelet–granulocyte aggregate formation, and platelet loss. In order to investigate the pharmacological strategy of platelet protection during ECC and hypothermia under realistic in vivo conditions, we used a porcine hypothermic CPB model. Under in vivo conditions, CPB-induced platelet–fibrinogen binding as an indicator for platelet activation and platelet aggregation is inhibited by i.v. infusion of the short-acting P₂Y₁₂ blocker cangrelor. After the termination of CPB and end of cangrelor infusion, platelet aggregation and therefore platelet haemostatic function rapidly return to values measured before CPB. These results indicate that short-acting P₂Y₁₂ blockade during CPB provides fully functional platelets after CPB.

Exposure of blood to artificial ECC surfaces results in platelet dysfunction, which can be followed by deleterious bleeding complications, thromboembolic events, myocardial
infarction, and increased mortality. Therefore, a routine strategy to protect platelet function during ECC would be very beneficial for clinical procedures. After ECC, the action of the respective platelet blocker should reverse to provide fully functional platelets for haemostasis at the end of surgery. Therefore, the practicality of this approach is highly dependent on the half-life of the platelet inhibitor. Previous reports described a protective effect using GPIIb/IIIa blockers during ECC and hypothermia. However, the most short-acting GPIIb/IIIa blockers that are commercially available (tirofiban and eptifibatide) are not ideal agents for platelet protection during ECC because of high postoperative bleeding risks due to their long half-lives of 1.5–2 h. Furthermore, GPIIb/IIIa blockade can be associated with a paradoxical platelet-activating effect possibly resulting in thrombotic events. Therefore, the establishment of new anti-platelet strategies for platelet protection during ECC is of major importance.

ECC induces release of the platelet agonist ADP, and ADP metabolism is decreased by hypothermia. Thus, the platelet ADP receptor P2Y12 is an important pharmacological target for platelet protection during hypothermic ECC. Despite several proven advantages of the currently used P2Y12 blockers clopidogrel and prasugrel, clinical studies reveal that these agents can cause severe bleeding complications. This can be explained by the fact that clopidogrel and prasugrel cause irreversible P2Y12 blockade resulting in prolonged inhibition of platelet function. A new family of direct P2Y12 inhibitors including cangrelor, ticagrelor, and elinogrel are under clinical testing. Among these, cangrelor, which can be administered i.v., has the shortest half-life which allows rapid reversal of platelet inhibition. Two Phase III clinical trials (CHAMPION-PCI and CHAMPION-PLATFORM) compared cangrelor with clopidogrel or placebo in patients undergoing percutaneous coronary intervention. No significant differences in clinical effectiveness or outcome compared with clopidogrel treatment were found. However, our current findings and other studies verify both the effectiveness of cangrelor in preventing platelet activation and its fast reversibility to regain full platelet function. As observed in our present study, the rapid on-set and off-set of this agent allows targeted and short-term platelet protection in the setting of ECC. Regarding potential bleeding complications, our data showed no influence.

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**Fig 4** Haematocrit and haemoglobin values and platelet counts. Before, during, and following hypothermic CPB in vehicle-treated (placebo) and cangrelor-treated (0.075 μg kg⁻¹ min⁻¹) pigs, changes in haematocrit (a) and haemoglobin concentration (b) were measured. Data are given as mean and SEM. In both groups, baseline values (T1) were compared with T2–T6 of the respective group using RM-ANOVA with Bonferroni’s multiple comparison test (**P<0.01; ***P<0.001; ****P<0.0001; n=5). Platelet counts (c) were measured at all time points (T1–T6). Data are given as mean and SEM. For platelet counts, a haematocrit correction was performed for values measured after the start of CPB (T2–T6) to adjust for haemodilution caused by the priming volume of the HLM. The mean baseline values were adjusted to 100% and data measured during and after CPB are given in relation to the adjusted baseline value in each treatment group; groups were compared using RM-ANOVA with Bonferroni’s multiple comparison test. T1, skin incision before median sternotomy; T2, 10 min after initiation of cangrelor or placebo infusion and heparin application directly before the start of CPB; T3, 45 min after the start of CPB; T4, directly before the end of CPB; T5, 10 min after the end of CPB; T6, 60 min after the end of CPB.
of cangrelor on haemoglobin values as an indicator for blood loss. These findings indicate that short-acting P2Y12 blockade might be safely performed during hypothermic ECC.

During ECC, fibrinogen is deposited at the ECC surface and can mediate platelet−ECC binding.14 In our ex vivo experiments, platelet−ECC adhesion was not prevented by P2Y12 blockade. This indicates that platelet−ECC binding occurs independently of ADP. This can be explained by the fact that even unstimulated platelets adhere to immobilized fibrinogen via their non-activated GPIIb/IIIa receptor.35 P2Y12 blockade also did not significantly reduce GPIIb/IIIa activation during ex vivo hypothermic ECC. Furthermore, P2Y12 blockade had no effect on TAT complex formation. These findings confirm findings of other authors that further ADP-independent events regarding the activation of platelets and plasma coagulation occur during ECC.2 3 7

However, P2Y12 blockade effectively decreased platelet granule release, platelet−granulocyte aggregate formation, and platelet loss during ECC. The reason why platelet loss was decreased, but not completely abolished, might be explained by the fact that P2Y12 blockade inhibits platelet−granulocyte binding and thereby loss of platelets in cell aggregates, but does not prevent adhesion of platelets to the ECC surface.

Our finding that ADP plasma concentrations decreased in the presence of P2Y12 blockers can be explained by the fact that P2Y12 blockade inhibits platelet dense granule release, which consequently results in lower ADP plasma concentrations. As previously shown, ADP is continuously metabolized in plasma and whole blood.13 36 This phenomenon contributes to the tendency for lower ADP levels in P2Y12 blocker-treated samples compared with baseline values observed in our experiments.

In our ex vivo experiments, cangrelor was administered as a single bolus (final concentration of 1 μM) just before the start of circulation. This cangrelor concentration approximately doubles concentrations that have been continuously infused to patients in clinical studies.37–39 However, because continuous infusion into our closed-loop ECC model is not possible due to technical limitations, the cangrelor concentration possibly decreased during ECC due to metabolism in blood. Nevertheless, the used cangrelor dosage was obviously adequate to test the principal effects of P2Y12 inhibition on platelet activation during ECC.

In our in vivo experiments, cangrelor was infused in a dose of 0.075 μg kg⁻¹ min⁻¹, which is lower than that used in clinical studies. We therefore expect that cangrelor plasma concentrations in our in vivo experiments are below the cangrelor plasma concentration of 426 ± 102 ng ml⁻¹ measured after infusing cangrelor in a dose of 4 μg kg⁻¹ min⁻¹ in patients.34 Nevertheless, platelet−fibrinogen binding indicating GPIIb/IIIa activation and platelet aggregation were still effectively inhibited by the cangrelor concentration used in our porcine hypothermic CPB model. In our in vivo
experiments, significant GPIIb/IIIa activation was not detected until 1 h after hypothermic CPB. Furthermore, minimal loss of platelets occurred during hypothermic CPB in vivo. These results can be explained by the fact that the haemocompatibility of the ECC circuit in our in vivo experiments was optimized by a heparin–polypeptide coating, which is also widely used in cardiac surgery. Heparin coating of ECC surfaces exerts less activating effects on blood components, but platelet activation is still observed and might still contribute to coagulopathy. Hence, pharmacological platelet protection is still desirable and beneficial in heparin-coated ECC circuits. Other mechanisms, like haemodilution caused by the ECC priming volume, might also contribute to the observed phenomena.

In conclusion, infusion of short-acting P2Y12 receptor antagonists has the potential to inhibit life-threatening platelet-mediated prothrombotic events and postoperative bleeding complications in the setting of ECC and hypothermia. This innovative pharmacological strategy could significantly improve the safety of CPB procedures, thus warranting further studies to evaluate the benefits of this approach under clinical conditions.

Declaration of interest
None declared.

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