Platelet function analyzer (PFA)-100® closure time in the evaluation of platelet disorders and platelet function


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Summary. Background: Closure time (CT), measured by platelet function analyzer (PFA-100®) device, is now available to the clinical laboratory as a possible alternative or supplement to the bleeding time test. Aim: On behalf of the Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH-SSC), a working group was formed to review and make recommendations on the use of the PFA-100 CT in the evaluation of platelet function within the clinical laboratory. Methods: The Medline database was searched to review the published information on the PFA-100 CT in the evaluation of platelet disorders and platelet function. This information, and expert opinion, was used to prepare a report and generate consensus recommendations. Results: Although the PFA-100 CT is abnormal in some forms of platelet disorders, the test does not have sufficient sensitivity or specificity to be used as a screening tool for platelet disorders. A role of the PFA-100 CT in therapeutic monitoring of platelet function remains to be established. Conclusions: The PFA-100 closure time should be considered optional in the evaluation of platelet disorders and function, and its use in therapeutic monitoring of platelet function is currently best restricted to research studies and prospective clinical trials.

Introduction

Closure time (CT), measured by platelet function analyzer (PFA-100®) device, is now available to the clinical laboratory as a possible alternative or supplement to the bleeding time test [1–4]. On behalf of the Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH-SSC), this document reviews recent literature and provides consensus recommendations on using PFA-100 CT in the evaluation of platelet function within the clinical laboratory.

Methodology

A working group of the Platelet Physiology Subcommittee of the ISTH-SSC on the PFA-100 CT was established to review information on the test and to make recommendations on the use of the PFA-100 CT in the evaluation of platelet function by clinical laboratories. Relevant articles were identified by searching the MEDLINE database for English papers on the PFA-100 CT, published before June 2005. Members of the working group reviewed and summarized the published literature, and provided expert opinions to establish consensus recommendations.

Results and discussion

Principles of the CT measured by the PFA-100 device

The PFA-100 CT was introduced to provide a simple, rapid assessment of high shear-dependent platelet function by a procedure that uses small amounts of citrated blood (0.8 mL/cartridge; maximal CT results: 300 s) [1,2,4,5]. Blood samples are aspirated at high shear rates (5000–6000 s⁻¹) through a capillary in the instrument cartridge and encounter a membrane coated with collagen and epinephrine (CEPI) or collagen and ADP (CADP) [1]. The membrane triggers platelet adhesion, activation and aggregate formation, leading to occlusion of the 150 µm central aperture and cessation of blood flow [1]. Results are reported as the CT in seconds for the
CEPI and CADP cartridges, with values > 300 s reported as non-closure [1].

**Variables influencing PFA-100 CT results**

The PFA-100 CT is highly dependent on von Willebrand factor (VWF) binding to the platelet membrane glycoprotein (GP) receptors Ib/IX/V and integrin αIIbβ3 (IIb/IIIa) under high shear [1,2,5–9]. CT has higher sensitivity for von Willebrand disease (VWD) compared with the bleeding time, and CT is abnormal in some congenital and acquired platelet function defects, but is not prolonged by coagulation factor deficiencies (reviewed in Harrison [5]) [4,7,10–19]. This review is primarily focused on the use of PFA-100 CT for evaluating platelet disorders and platelet function.

The manufacturer advises that each laboratory should establish its own PFA-100 CT reference ranges, using buffered 0.109 M (3.2%) or 0.129 M (3.8%) citrate anticoagulated blood [5,20,21]. Quality control procedures are important for test performance, but because the test requires whole blood, there are no provided quality control materials [5]. Coefficients of variation range between 6% and 13% for CT with normal samples [8,22,23]. CT are significantly higher for samples collected in 3.8% compared with 3.2% citrate, and 3.8% citrate increases the CEPI CT sensitivity to aspirin [23,24]. Samples anticoagulated with thrombin inhibitors (e.g. PPACK) have similar CT to 3.2% or 3.8% citrate anticoagulated samples [25]. CT should be determined within 4 h of sampling [8,23], and to avoid artefactual results, pneumatic tubes should not be used for sample transport [26]. Small diurnal variations in CT results have been noted, with morning samples showing shorter CT, particularly with the CEPI cartridge [27]. CT reference ranges for males and females are similar although older males may have slightly shorter CT [28,29]. Children and adults have similar CT values whereas neonates have shorter CT because of higher hematocrit and VWF levels [30–32].

Like the bleeding time, the PFA-100 CT is prolonged by significant reductions in the platelet count or hematocrit [2,3,8,22,33]. For blood samples containing < 100 × 10^9 platelets L^-1, there is an inverse relationship between the CT and platelet count [2]. Although CT can be normal in some macrothrombocytopenic disorders (Table 1) [16,34,35], CT is usually abnormal with platelet counts below 50 × 10^9 L^-1, and is often prolonged to non-closure with severe thrombocytopenia (e.g. 10 × 10^9 platelets L^-1) [8]. CT is usually abnormal when the blood hematocrit is below 25%, and there is non-closure with hematocrits adjusted to below 10% [2,8].

The PFA-100 CT shows an inversely proportional relationship to plasma VWF levels in healthy controls and individuals with VWF deficiency [7,36–40]. PFA-100 CT are approximately 10–20% longer in individuals with group O, probably because of their lower plasma VWF [37,41–43]. There is evidence that platelet VWF, and the profile of VWF multimers in plasma, influences the PFA-100 CT, based on observations of prolonged CT in type 1 ‘platelet

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**Table 1** PFA-100® closure times (CT) findings in congenital and acquired, non-drug-induced platelet disorders

<table>
<thead>
<tr>
<th>Disorders with normal platelet counts</th>
<th>Total number of subjects reported (numbers per study)</th>
<th>CADP CT</th>
<th>CEPI CT</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>23 (2,6,1,8,5,1)</td>
<td>P</td>
<td>P</td>
<td>[7,8,16,34,49,50]</td>
</tr>
<tr>
<td>Aspirin-like defect</td>
<td>6</td>
<td>N</td>
<td>P</td>
<td>[7]</td>
</tr>
<tr>
<td>P2Y12 deficiency</td>
<td>4 (1*,2,1)</td>
<td>N or P</td>
<td>N or P</td>
<td>[16] (M. Cattaneo, unpublished; P. Nurden, unpublished)</td>
</tr>
<tr>
<td>Dense granule deficiency</td>
<td>30 (4,6,7,1,12)</td>
<td>N or P</td>
<td>N or P</td>
<td>[7,8,14,16,34]</td>
</tr>
<tr>
<td>Hermansky–Pudlak syndrome</td>
<td>44 (7,13,5,19)</td>
<td>N or P</td>
<td>N or P</td>
<td>[8,34,50,53]</td>
</tr>
<tr>
<td>Primary secretion defects</td>
<td>30 (10,10,10)</td>
<td>N</td>
<td>N or P</td>
<td>[14,34,52]</td>
</tr>
<tr>
<td>Platelet procoagulant defect</td>
<td>1</td>
<td>N</td>
<td>N</td>
<td>[16]</td>
</tr>
<tr>
<td>Disorders with reduced or normal platelet counts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernard–Soulier syndrome</td>
<td>8 (2,6)</td>
<td>P</td>
<td>P</td>
<td>[8,34]</td>
</tr>
<tr>
<td>Platelet-type von Willebrand disease</td>
<td>3</td>
<td>P</td>
<td>P</td>
<td>[7]</td>
</tr>
<tr>
<td>Grey platelet syndrome</td>
<td>3 (1,2)</td>
<td>P</td>
<td>P</td>
<td>[16,34]</td>
</tr>
<tr>
<td>Wiskott–Aldrich syndrome</td>
<td>5</td>
<td>N or P</td>
<td>N or P</td>
<td>[34]</td>
</tr>
<tr>
<td>Hereditary macrothrombocytopenia</td>
<td>5 (3,2)</td>
<td>N</td>
<td>N or P</td>
<td>[16,35]</td>
</tr>
<tr>
<td>Hereditary macrothrombocytopenia</td>
<td>11</td>
<td>N or P</td>
<td>N or P</td>
<td>[34]</td>
</tr>
<tr>
<td>Undefined autosomal dominant thrombocytopenia</td>
<td>1</td>
<td>N</td>
<td>N</td>
<td>[16]</td>
</tr>
<tr>
<td>Primary bone marrow disorders</td>
<td>69 (7,62)</td>
<td>N or P</td>
<td>N or P</td>
<td>[16,92]</td>
</tr>
</tbody>
</table>

Note, the data reported with CADP and CEPI cartridges, indicated as normal (N) or prolonged (P), are based on small numbers of reported cases.

*Indicates a patient with an ADP receptor/signal transduction defect [16] that was later found to be P2Y12 deficient (W. L. Nichols, pers. comm.). M. Cattaneo, Università di Milano, Milan, Italy; P. Nurden, Hopital Cardiologique, UMR 5533 CNRS, Pessac, France; W. L. Nichols, Mayo Clinic, Rochester, MN, USA.

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low’, type 1 ‘platelet discordant’, type 2A and type 3 VWD, and their failure to correct with VWF replacement [13,44,45]. In patients with severe aortic stenosis and an acquired VWD characterized by the loss of the largest multimers, the PFA-100 CT is prolonged and shortens rapidly after surgery, along with the recovery of the largest multimers [46]. There is also evidence that higher platelet collagen receptor density (α2β1 and to some extent GP VI) is associated with shorter PFA-100 CT, especially in type 1 VWD [9,36,37,47].

Consumption of flavonoid rich foods (e.g. red wine, cocoa and chocolate) can prolong the CEPI CT [48]. Other dietary effects (e.g. fish oil consumption) on the PFA-100 CT have not been characterized.

**PFA-100 CT in congenital platelet disorders**

In congenital platelet disorders, the PFA-100 CT varies with the severity and nature of the platelet defect (Table 1). The relatively severe function defects associated with deficiencies or dysfunction of the platelet membrane GP receptors (αIIbβ3, GP IIB/IIIa; Glanzmann thrombasthenia) or GP Ib/IX/V (Bernard–Soulier syndrome or platelet-type VWD) result in markedly prolonged PFA-100 CT and typically non-closure with CEPI and CADP cartridges [7,8,16,34,49,50]. Platelet membrane density of α2β1, and GP VI influences PFA-100 CT [9,36,47], but there is currently no information on CT in platelet α2β1 or GP VI deficiency or dysfunction, because of the paucity of well-characterized patients with defects in these proteins. Among the more common congenital platelet function disorders (including dense granule deficiency and conditions with defective secretion), PFA-100 CT findings are variable and they are more frequently detected with the CEPI cartridge than the CADP cartridge (which is often normal) (Table 1) [4,5,7,8,14,16,34,50–52].

There is a need for more information on the PFA-100 CT in congenital platelet disorders as reported studies (summarized in Table 1) have evaluated relatively small numbers of individuals (<50/study) with varying mixes of characterized disorders [8,14,16,19,34,49,50,52,53]. The estimated PFA-100 CT sensitivity to platelet disorders has ranged from 24% [52], for a recent prospective study of previously undiagnosed patients identified to have platelet secretion defects, to values of 80% and higher, for studies that included previously diagnosed cases and more severe platelet disorders [8,16,34,50,53] or that had a more limited sample size [19]. Differences in study designs (prospective or retrospective case identification and selection, variable inclusion of drug-induced platelet dysfunction) are likely reasons for the differences in sensitivity. Reduced platelet counts of some congenital platelet disorders make abnormal PFA-100 CT results difficult to interpret [54], although non-closure CT is the typical finding for Bernard–Soulier syndrome [8,34], and normal to near normal CT is typical of some other macrothrombocytopenias [16] (Table 1).

Further prospective studies on PFA-100 CT are needed to better characterize the findings in different congenital platelet disorders and their relationship to severity of bleeding symptoms. In a recent study of 5649 patients undergoing preoperative assessment, CEPI CT were abnormal 40% of the individuals with positive-bleeding histories; however, the value of the CT in detecting platelet disorders was not determined as diagnostic platelet function testing was not performed [55].

Based on the parameters known to influence the PFA-100 CT, and results for different platelet disorders (Table 1), prolonged results cannot distinguish severe platelet disorders from VWD, and as such, have limited specificity [5,51,56]. When the clinical suspicion of a platelet disorder is high, a full range of platelet function tests need to be performed irrespective of whether the PFA-100 CT is normal or abnormal, as the test does not detect all platelet disorders, particularly milder function defects (Table 1 and references; reviewed in [5,51,52]). Despite its limitations, the PFA-100 CT can provide rapid results and an early indication of the potential bleeding problem. A combined analysis of PFA-100 CT with both cartridges may help distinguish some platelet function disorders (e.g. dense granule deficiency or secretion defects, Table 1) from disorders with prolonged CEPI and CADP CT (e.g. moderate-to-severe VWD, platelet-type VWD, Bernard–Soulier syndrome, and Glanzmann thrombasthenia) [5,7,8,14,16,34,50–52].

**PFA-100 CT and acquired platelet dysfunction because of antiplatelet drugs**

Reported effects of antiplatelet drugs on PFA-100 CT are summarized in Table 2. Therapeutic agents that target the platelet receptor (αIIbβ3 (abciximab, eptifibatide, and tirofiban) prolong PFA-100 CT with both cartridges (Table 2) [25,57–62], consistent with the very prolonged CT in Glanzmann thrombasthenia (Table 1) [7,8,16,34,49,50]. After αIIbβ3 inhibitor therapy is discontinued, the PFA-100 CT can remain abnormal for up to 12 h after abciximab [61,62], and for up to 4–6 h after eptifibatide [62].

### Table 2 Effects of antiplatelet therapies on the PFA-100 CT

<table>
<thead>
<tr>
<th>Drug</th>
<th>CADP CT</th>
<th>CEPI CT</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitors of ligand binding to αIIbβ3: abciximab, tirofiban, or eptifibatide</td>
<td>P</td>
<td>P</td>
<td>[25,57–62]</td>
</tr>
<tr>
<td>COX-1 inhibitors: ASA and other NSAIDs</td>
<td>N</td>
<td>N or P</td>
<td>[10,15,24,48,67–69,76,93]</td>
</tr>
<tr>
<td>Thienopyridines:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticlopidine or clopidogrel</td>
<td>N or P</td>
<td>N or P</td>
<td></td>
</tr>
<tr>
<td>Ticlopidine or clopidogrel and aspirin</td>
<td>N or P</td>
<td>P</td>
<td>[25,72–76]</td>
</tr>
</tbody>
</table>

Findings reported with CADP and CEPI cartridges are indicated as normal (N) or prolonged (P).
Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit platelet function by blocking cyclooxygenase 1 (COX-1) and thereby thromboxane generation prolong the CEPI CT in about 95% of healthy individuals, but have little to no effect on CADP CT [10,49,63] (reviewed in [5,64]). Studies of patients on aspirin therapy for coronary or peripheral vascular arterial disease indicate that only 20–50% have a prolonged CEPI CT [65–68]. Differences in reported CEPI CT sensitivity for aspirin may reflect differences in populations studied (e.g. healthy controls compared with patients with higher VWF levels), aspirin dosage and formulation effects [67], and pretest variables, such as the citrate concentration used for sample collection [24,69]. It is important to recognize that the aspirin/NSAID pattern of PFA-100 CT abnormalities (CEPI prolonged, CADP normal) is not specific for drug-induced platelet dysfunction as similar abnormalities occur with congenital platelet disorders (Table 1) [4,8,14,34,50,51,53] and with consumption of flavonoid-rich foods [48]. When NSAIDs are discontinued, PFA-100 CT abnormalities revert by 6 days with aspirin [70] and by 24 h with ibuprofen [71].

The PFA-100 CT is relatively insensitive to therapy with ticlopidine and clopidogrel, with detection of effects showing time and dose dependence [20,25,57,72–76]. CADP and CEPI CT detect synergism in the antiplatelet effects of clopidogrel and aspirin [73,74]. It has not yet been established if the PFA-100 CT is useful for monitoring therapy with antiplatelet agents in patients with, or at risk for, coronary, cerebral, or peripheral vascular arterial disease [64]. Multiple studies have reported individuals who appear to be ‘resistant’ to aspirin on the basis of normal CEPI CT on therapy [10,49,65–67,69,73]. These studies indicate that CEPI CT can be normal even when COX-1 is adequately blocked. A significant inverse association exists between plasma VWF and CEPI CT during aspirin therapy [15], and as many patients with arterial disease have high plasma VWF levels, and short baseline CT, it is not surprising that a relatively high proportion have normal CEPI CT on aspirin [66,77–80]. Higher doses of aspirin have been reported to increase the proportions of individuals with prolonged CEPI CT in some studies [67] but not in others [68,81] and uncoated aspirin prolongs the CT more than enteric-coated aspirin [67]. Although some studies have suggested adverse events are more prevalent among individuals with normal CEPI CT on aspirin therapy, the majority of studies are too small to draw firm conclusions and differences reported have not reached statistical significance [64,65,78]. Large, prospective, randomized-clinical trials are needed to determine if the PFA-100 CT is useful to predict adverse events or make therapeutic decisions on aspirin therapy. Evidence is required to support making clinical recommendations based on a normal CEPI CT in patients on aspirin therapy. It has been recommended that the term ‘aspirin resistance’ not be applied to these patients and that PFA-100 CT not be measured on patients on aspirin therapy outside of research studies (reviewed in [64,78]).

There is limited information on the effects of many other drugs on the PFA-100 CT. The PFA-100 CT is prolonged approximately 30% above baseline in subjects taking the serotonin-reuptake inhibitor paroxetine [82].

PFA-100 CT and acquired platelet dysfunction during cardiopulmonary bypass

Acquired qualitative defects in platelet function can cause bleeding after cardiac and cardiopulmonary bypass surgery. CADP CT is significantly prolonged after heparinization for bypass procedures, probably because of interference of high heparin concentrations on VWF binding to platelet GP Ib/IX/V [42]. CADP CT was reported to be further prolonged during extracorporeal circulation, with rapid reversal of the abnormality after surgery [42]. In this study, preoperative CEPI CT was abnormal because of aspirin therapy, and the magnitude of CT prolongation was not predictive of postoperative bleeding [42].

PFA-100 CT and coronary syndromes

One study of patients, with acute chest pain and suspected acute coronary syndromes, reported shorter CADP CT and increased plasma VWF levels in the subset with myocardial infarction [83]. Shorter CADP and CEPI CT, and higher VWF levels, at presentation were also correlated with biochemical evidence of greater myocardial necrosis [83]. One study of PFA-100 CT, before and after exercise, in patients with stable angina who underwent coronary angiography reported that reductions in CT (10 or more seconds from baseline) were associated with vessel stenoses whereas increases in CT (10 or more second from baseline) were not [84]. Further prospective studies are needed to determine if the PFA-100 CT is useful for management of coronary syndromes.

PFA-100 CT in uremia and liver disease

CEPI CT and CADP CT tend to be prolonged in patients with uremia or liver cirrhosis [85,86], possibly from associated anemia, as the abnormalities correct with in vitro elevation of the hematocrit [85].

PFA-100 CT in monitoring therapies for bleeding

While PFA-100 CT can detect hemostatic effects of some therapies given to treat or prevent bleeding, there have been no studies designed to determine if improved CT predicts improved clinical outcomes with regard to hemorrhage and few studies of its utility in monitoring therapy for qualitative platelet defects. Correction of a prolonged CEPI CT with desmopressin (DDAVP) therapy has been reported in small studies of patients with storage pool disease and primary secretion defects associated with increased plasma VWF [14]. DDAVP also significantly shortens the CADP and CEPI CT of healthy individuals [58]. In type 1 VWD, prolonged CEPI and/or CADP CT show correction after DDAVP-induced
increases in plasma VWF but not in patients with discordant or low levels of platelet VWF [11,13,44,87]. In severe VWD, PFA-100 CT often does not correct with VWF replacement, possibly because of abnormalities in concentrate multimer profile and/or lack of intraplatelet VWF [11,13,44,45].

No studies have investigated PFA-100 CT in patients given DDAVP for bleeding secondary to antiplatelet therapy, although CT shortening occurs in healthy individuals given DDAVP after antiplatelet agents [17,58]. One study of 30 healthy volunteers, given 500 mg of aspirin for 3 days (which prolonged CEPI CT in ~90% of volunteers), reported normalization of PFA-100 CT by 30 min in all subjects given intravenous DDAVP, and in 93% given nasal DDAVP [17]. Another study of 10 healthy volunteers, treated with DDAVP after aspirin and eptifibatide, reported accelerated normalization of CEPI and CADP CT that was most evident several hours after DDAVP was given [88].

It must be emphasized that none of the studies reporting normalized PFA-100 CT during DDAVP therapy for certain congenital or acquired qualitative platelet defects (in lieu or in addition to the bleeding time) or type 1 VWD were designed to evaluate if normalized CT correlated with improved clinical outcomes.

Few studies have evaluated the utility of the PFA-100 CT in monitoring other therapies. With platelet transfusion therapy, shortening of the PFA-100 CT by more than 40 s, or its normalization, has been reported to correlate better with cessation of bleeding than corrected platelet count increments [88]. Data are lacking on the utility of the PFA-100 CT to monitor hemostasis in other clinical situations (e.g. uremia).

Changes in PFA-100 CT with other therapies

Although the clinical significance is unknown, PFA-100 CT can be prolonged by perioperative colloid or crystalloid administration [89] and by plasmapheresis [90]. In vitro, the PFA-100 CT is prolonged by low-molecular weight dextran sulfate [91].

Recommendations

The PFA-100 CT is now an optional test for clinical laboratories to consider as part of their diagnostic evaluation of platelet disorders and platelet function. To date, the evidence on the PFA-100 CT in different congenital platelet disorders indicates that the test does not have sufficient sensitivity or specificity to be used as a screening tool in determining which individuals need further testing for platelet disorders. However, data are available only on a limited number of patients with defined disorders. Prolonged CT can reflect other abnormalities (e.g. VWD), and as such, abnormal results require further diagnostic evaluations. Normal CT can help exclude some severe platelet defects (e.g. Glanzmann thrombasthenia and Bernard-Soulier syndrome) and moderate-to-severe VWD, but if clinical suspicion is strong, further testing should be performed. A role for the PFA-100 CT in therapeutic monitoring remains to be established, and therefore its use in such monitoring is currently best restricted to research studies and prospective clinical trials. Based on the current knowledge, adequately powered clinical studies that compare results to meaningful clinical outcomes are required to establish a role for the PFA-100 CT in predicting clinical outcomes and/or monitoring therapy.

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