Review

Laboratory Tests for Markers of Activation of Coagulation and Fibrinolysis

Labortests für Marker der Gerinnungs- und Fibrinolyseaktivierung

F. Dati[1,2], H. Pelzer[1], Carola Wagner[1]

Summary: Molecular markers of activation of coagulation and fibrinolysis have become measurable by common laboratory techniques, e.g. solid phase enzyme immunoassay. Thrombin-antithrombin III complex (TAT), prothrombin fragment 1+2 (F1+2) and fibrin monomer (FM) reflect thrombin generation or activity, while D-Dimer and plasmin-α_2-antiplasmin complex (PAP) indicate secondary fibrinolysis and plasmin generation. Extensive clinical studies have shown the specific usefulness of the different activation markers in thromboembolic diseases, inherited thrombophilia, disseminated intravascular coagulation as well as in anticoagulant or thrombolytic therapy. The review presented summarizes important actual developements in this field of laboratory diagnostics.

Keywords: Blood Coagulation Disorders; Disseminated Intravascular Coagulation; Fibrinolysis; Peptide Fragments; Fibrin-Fibrinogen Degradation Products; Thrombin/metabolism; Plasmin/metabolism

Zusammenfassung: Die molekularen Marker der Gerinnungs- und Fibrinolyseaktivierung sind heute mit üblichen Labormethoden wie dem Festphasen-Enzymimmunoassay meßbar. Thrombin-Antithrombin III-Komplex (TAT), Prothrombinfragment 1+2 (F1+2) und Fibrinmonomer (FM) repräsentieren die Bildung bzw. Aktivität von Thrombin, während D-Dimer und Plasmin-α_2-Antiplasmin-Komplex (PAP) sekundäre Fibinolyse und Plasminbildung anzeigen. Ausgedehnte klinische Studien haben den diagnostischen Nutzen der verschiedenen Aktivierungsmarker bei thromboembolischen Erkrankungen, angeborener Thrombophilie, disseminierter intravasaler Gerinnung sowie bei der antikoagulatorischen oder thrombolytischen Therapie aufgezeigt. Die vorliegende Übersicht faßt wichtige aktuelle Entwicklungen und Erkenntnisse auf diesem Gebiet der Laboratoriumsdiagnostik zusammen.

Schlüsselwörter: Blutgerinnungsstörungen; Disseminierte intravasale Gerinnung; Fibrinolyse; Peptidfragmente; Fibrin-Fibrinogenspaltprodukte; Thrombin/Stoffwechsel; Plasmin/Stoffwechsel.

[1]Behring Diagnostics GmbH, Marburg, Germany
[2]Author for correspondence: Dr. Francesco Dati, Behring Diagnostics GmbH, P.O. Box 1149, D-35001 Marburg, Germany. Fax: +49-6421-39-3126
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In the past two decades significant advances in the understanding of basic processes underlying hemostasis and thrombosis have been made [1,2].

Especially the development of sensitive and specific laboratory assays for measuring inhibitors and activators of coagulation/fibrinolysis, their complexes as well as activation products has allowed to perform extensive studies in various clinical conditions for better understanding the processes of thrombophilia and hypercoagulability, and the causes of thrombosis [3,4].

Thrombophilia and hypercoagulability

Increased interest has been given in the last years particularly to the markers of thrombophilia and activation of coagulation/fibrinolysis [5,6,7] (tab.1).

Thrombophilia is characterized as a familial or acquired abnormality of the hemostatic system likely to predispose to thrombosis such as deficiency of antithrombin III, protein C or protein S or carrier state for the FV Leiden mutation.

On the other hand, hypercoagulability reflects a shift in the hemostatic balance towards an increased risk to develop thromboembolism. This is connected with an increased thrombin generation and/or decreased thrombin inhibition which in turn may promote inappropriate or excessive fibrin formation and/or platelet aggregation. The measurement of the activation markers thrombin-antithrombin III complex (TAT), prothrombin fragment 1+2 (F1+2), fibrin monomer (FM), D-Dimer and plasmin-α_2-antiplasmin complex (PAP) allows to determine the extent of hypercoagulability and prethrombotic states. Activation markers provide new insights in the physiologic and pathophysiologic activation of the hemostatic system and are useful for a more differentiated assessment of hemostatic alterations in an individual patient [8].

Formation of activation markers

From the scheme of the relevant part of the coagulation and fibrinolysis cascade (fig. 1) it is evident that the key event in the activation of the plasmatic coagulation is the conversion of prothrombin to thrombin, since in vivo only thrombin can convert fibrinogen into fibrin. The enzyme complex prothrombinase splits prothrom-

Table 1 Markers of hemostasis activation

Parameter	It reflects
TAT [thrombin-antithrombin complex]	The amount of the short-term generated thrombin
F1+2 [prothrombin fragment 1 + 2]	The amount of the long-term generated thrombin
Fibrin monomer	The in-vivo active thrombin -Thrombin activity -Fibrinogen consumption
D-Dimer	Secondary fibrinolysis Interaction between coagulation and fibrinolysis
PAP [plasmin-α_2-antiplasmin complex]	The amount of the generated plasmin
FDP [fibrin(ogen) degradation products]	The truly active plasmin

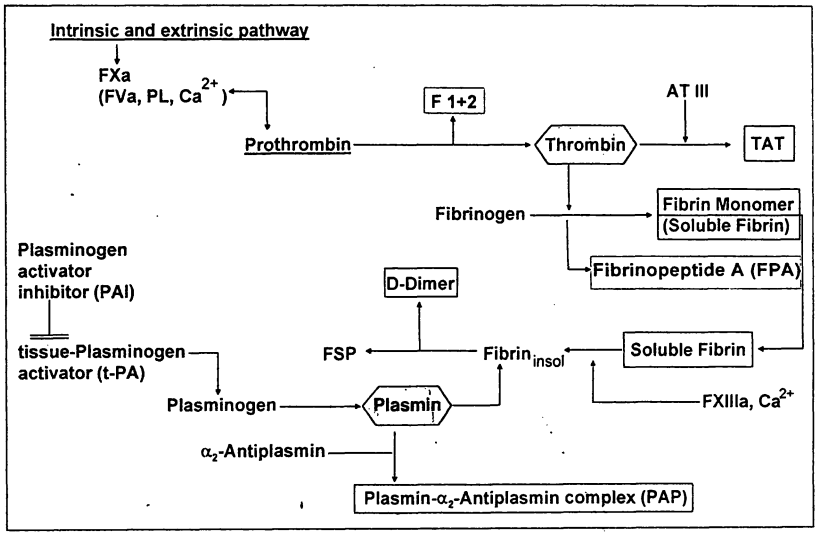

Figure 1 Formation of activation markers

bin into thrombin and prothrombin fragment 1 + 2 (F1+2). This parameter can be used as a marker of in vivo thrombin generation.

When thrombin is generated, it is partially inhibited by formation of an irreversible complex with antithrombin III, i.e. the thrombin-antithrombin III complex TAT). The amount of this complex is proportional to the thrombin formed and inhibited in vivo and therefore it reflects also the current state of coagulation activation.

Once formed, thrombin acts on the fibrinogen converting it into fibrin monomer (FM) (also called soluble fibrin (SF)), which is a direct indicator of the thrombin activity.

The key event in the activation of the fibrinolytic system is the conversion of the proenzyme plasminogen to the active proteolytic enzyme plasmin. The latter is bound immediately to fibrin or is rapidly inactivated by α_2-antiplasmin leading to the formation of an inactive protease-inhibitor complex, the plasmin-α_2-antiplasmin complex (PAP) also called plasmin-α_2-antiplasmin inhibitor complex (PIC). Determination of PAP is a promising tool for monitoring of fibrinolytic activity in circulation.

When plasmin acts on fibrin clots, which derive from the F XIIIa mediated cross-linking of aggregated fibrin molecules, there is a cleavage of the fibrin network with release of various molecules, among other of the D-fragment, which occurs as a dimer, the D-Dimer (DD). D-Dimer is a true fibrin split product and its measurement reflects the extent of secondary fibrinolysis, which has taken place because of a previous increased coagulation activity.

Nonstandard abbreviations: AMI, acute myocardial infarction; APTT, activated partial thromboplastin time; AT III, antithrombin III; DIC, disseminated intravascular coagulation; DD, D-Dimer; DVT, deep venous thrombosis; ELISA, enzyme-linked immunosorbent assay; F1+2, prothrombin fragment 1 + 2; FM, fibrin monomer; FPA, fibrinopeptide A; FSP, fibrin split products; LA, lupus anticoagulants; PAP, plasmin-α_2-antiplasmin complex; PL, phospholipids; PT, prothrombin time; SF, soluble fibrin; SLE, systemic lupus erythematosus; t-PA, tissue plasminogen activator; TAT, thrombin-antithrombin III complex.

Methods for measurement of activation markers

The molecular markers of activation of coagulation and fibrinolysis are mainly measured by means of solid phase enzyme immunoassays (ELISA), either with two different antibodies like in the case of TAT (one directed to thrombin, the other to antithrombin III), or using a monoclonal antibody directed against the neoantigen [3,4,9,10,11].

In the case of F1+2 the use of monoclonal antibodies was not satisfactory. The break-through was provided by Behring coworkers (Pelzer, Stueber) who synthesized a peptide from the C-terminal end of the fragment F1+2 which is the cleavage site of prothrombin by factor Xa [11,12]. Antibodies raised against this peptide and immunoadsorbed were then used to develop an ELISA which is very specific for F1+2 and highly sensitive for detection of low amounts of F1+2, allowing to monitor even a decreased thrombin formation during anticoagulation treatment.

Usefulness of activation markers

The usefulness of laboratory tests for markers of hypercoagulability and thrombophilia can be seen especially in the following conditions (tab. 2)

- *diagnosis, evaluation and prevention of thrombotic diseases* like in the case of venous or arterial thrombosis.
- *diagnosis and monitoring of inherited thrombophilia,* especially in congenital and familial abnormalities of coagulation inhibitors. In these conditions the most important parameters are surely APC Resistance/FV Leiden, Protein C, Protein S, AT III and antiphospholipid antibodies/lupus anticoagulants.
- *diagnosis and monitoring of disseminated intravascular coagulation (DIC)* (further important adjunct is AT III, especially when substitution therapy with AT III concentrate is performed).
- *monitoring of anticoagulant therapy* with heparin/hirudin and vitamin K antagonists.
- *monitoring of thrombolytic therapy* in case of acute myocardial infarction and thrombosis (especially pulmonary embolism)

Alterations connected with thromboembolic risk

There are various alterations in the coagulations system which are characterized by an increased risk for thromboembolism. This predisposition to thrombosis connected with an increased coagulation or decreased fibrinolysis has been termed hypercoagulability, i.e. it is associated with hypercoagulable states [2,14,15].

Alterations in the coagulation system in hypercoagulable states are:

- reduced inhibitor capacity (FV Leiden mutation, defects/deficiency of AT III, protein C, protein S, heparin cofactor II), presence of lupus anticoagulants and increased procoagulant activity (high prothrombin, F VIII, F VII, fibrinogen) [16,17].

Alterations in the fibrinolytic system in hypercoagulable states are: dysfibrinogenemia, deficiency of plasminogen, defects or diminished release of plasminogen activators, increased inhibitors, F XII deficiency.

Other secondary causes of hypercoagulable states are: clinical conditions associated with substantial thromboembolic events like tissue injury, myeloproliferative disorders, pregnancy, estrogen therapy, cancer, diabetes, nephrotic syndrome, postoperative thrombopathy, obesity, etc.

Pathophysiology of DIC

DIC is not a specific disease entity, but a pathophysiologic mechanism that underlies many disorders ran-

Table 2 Usefulness of Laboratory Tests for Markers of Thrombophilia and Hypercoagulability

- Diagnosis, evaluation and prevention of thrombotic diseases (venous thrombosis / thromboembolism) (arterial thrombosis) (risk pregnancy)
- Diagnosis and monitoring of inherited thrombophilia (congenital and familial abnormalities of coagulation inhibitors)
- Diagnosis and monitoring of DIC (e.g. in sepsis, trauma, malignancy)
- Monitoring of anticoagulation (heparin / hirudin) (vitamin K antagonists)
- Monitoring of thrombolytic therapy (acute myocardial infarction) (thrombosis)

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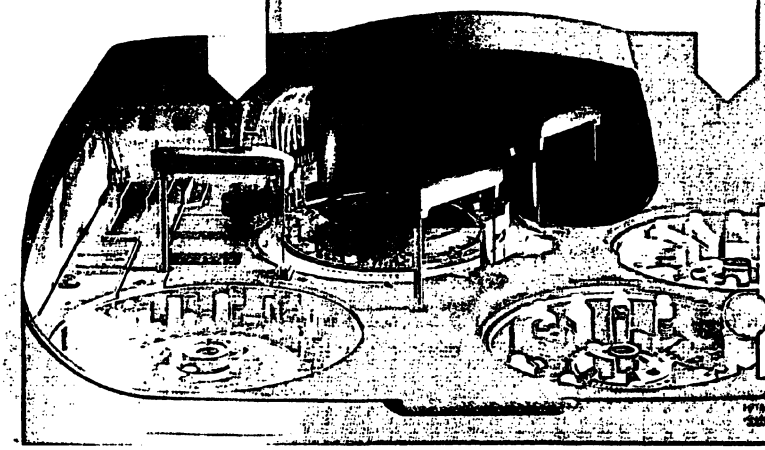

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Durch die Erkenntnis, daß ein Zusammenhang zwischen HPV-Infektion und Krebsentwicklung – besonders im Genitaltrakt der Frau – besteht, hat das Interesse an den Warzenkrankheiten beim Menschen und ihren Erregern, den humanpathogenen Papillomviren (HPV) in den letzten beiden Jahrzehnten enorm zugenommen.

In diesem Buch wird versucht, das derzeitige Wissen über Warzen, humanpathogene Papillomviren und HPV-abhängige Karzinome darzulegen, wobei der Bogen der Darstellung von der Klinik und Therapie der Warzenkrankheiten bis zur Molekularbiologie der Viren und Wechselwirkungen mit den infizierten Wirtszellen gespannt wird. Damit wenden sich die Autorinnen an einen breiten Leserkreis, der Dermatologen, Gynäkologen und Ärzte für Allgemeinmedizin, aber auch Mediziner anderer Fachrichtungen sowie Virologen und Biologen umfaßt.

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Table 3 Trigger mechanisms precipitating intravascular coagulation (DIC) and diseases which are frequently associated with DIC

Mechanism	Syndroms
Endothelial damage: endotoxins, immune complexes	Septicemia with gram-negative bacteria Hepatic insufficiency Malaria
Reduced clearance and impaired degradation of coagulation factors	Shock, giant hemangioma Aortic aneurysm Liver damage Portal hypertension
(Tissue-) thromboplastin and thromboplastin-like substances; colloidal substances	Tumors Acute leukemia Hepatic cell necrosis Multiple trauma Viral infections Septic abortion, retained abortion Amniotic fluid embolism Hemolysis (hemolytic-uremic syndrome, thrombotic-thrombocytopenic purpura)
Proteolytic enzymes	Leukemia Snake bite
Foreign surfaces Antigen/antibody complexes	Extracorporeal circulation Multiple transfusions Graft rejection
Inborn defects	Protein C deficiency (Purpura fulminans) Hereditary fructose intolerance

adapted from *Matthias* [39]

ging from sepsis to malignancy. In DIC there is simultaneous activation of the coagulation, fibrinolytic, and platelet systems with resultant systemic hemorrhage and microvascular thrombosis [18] (fig. 2).

Stimuli that act as triggering events for DIC include endotoxins, immune complexes, thromboplastin, thromboplastin-like and colloidal substances, proteolytic enzymes, foreign surfaces, antigen/antibody complexes (tab. 3).

Laboratory testing in DIC

In disseminated intravascular coagulation (DIC) there are several laboratory parameters which make possible its detection and the therapy monitoring [5,9,19,20] (tab. 4).

Abnormal values of laboratory tests in DIC are both numerous and variable owing to the wide spectrum of underlying diseases. Presentation of common abnormalities include elevation of prothrombin time (PT) and activated partial thromboplastin time (APTT). Persistent thrombin formation leads to continued fibrinogen to fibrin conversion with formation/elevation of TAT, F1+2, FPA, fibrin monomer and with consumption / decrease of AT III, fibrinogen, platelets and various' coagulation factors.

Fibrinolytic activation with degradation of fibrin and plasmin-induced changes is connected with elevation of D-Dimer and PAP and with decrease of fibrinogen, plasminogen and α_2-antiplasmin.

Application of activation markers in various clinical conditions

Lupus anticoagulants (LA) and increased thrombin generation in patients with systemic lupus erythematosus (SLE) [21]

In patients with lupus anticoagulants as defined by the prolongation of at least two different, lipid-depending coagulation tests and positivity of a confirmatory test increased F1+2 levels were found. The presence of LA in SLE patients seems to be strictly related to an ongoing prothrombotic state.

Activation markers and hypercoagulability [22,23]

Patients with perioperative hypercoagulability, as detected by increased levels of F1+2 and TAT, treated by high dose heparin show improving health conditions

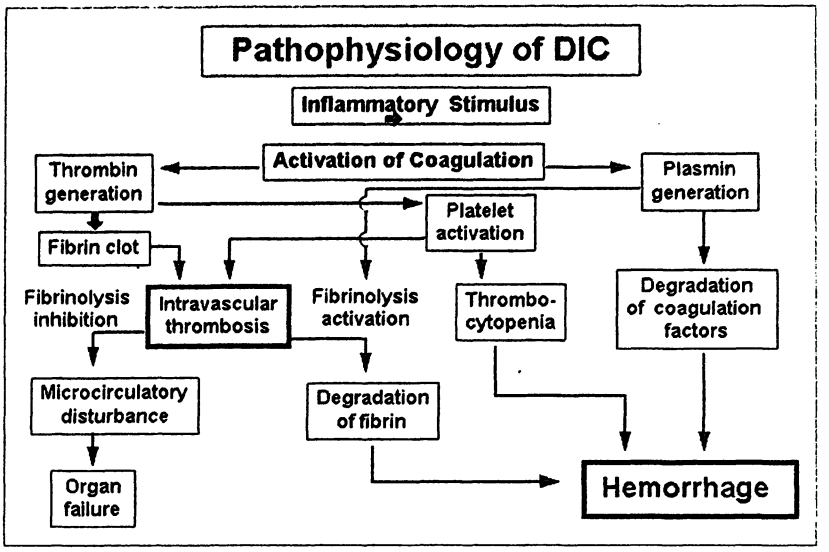

Figure 2 Pathophysiology of DIC

indicated by normalization of F1+2 and especially of TAT concentrations. The measurement of heparin concentrations is often not relevant for the monitoring of therapy success.

Monitoring of DIC [24]
DIC patients show often an excessive activation of coagulation as demonstrated by elevated concentrations of TAT and F1+2.

The TAT / F1+2 ratio is variable in DIC. The TAT / F1+2 ratio seems to be relatively high when TAT is elevated to a greater extent. Generally, a lower ratio of TAT / F1+2 could be used to demonstrate the rate of thrombin inactivation by antithrombin III/heparin.

Hypercoagulability in cancer [25,26]
Markers of coagulation and fibrinolysis activation (TAT, D-Dimer and PAP) are often elevated in lung cancer patients and are even more markedly increased in patients with metastases. These results confirm the presence of a subclinical chronic activation of the coagulation and fibrinolysis in cancer patients, detectable by the activation markers which may be useful as potential markers of the clinical progression and prognosis of lung cancer.

Imbalance between thrombin and plasmin activity in DIC [27]
The measurement of TAT and PAP in DIC allows to obtain information on the degree of thrombin and plasmin activity.

In mild DIC both thrombin and plasmin activity were increased, while thrombin activity was predominant in moderate DIC, and plasmin activity became excessive when DIC was severe. The differences in the elevation of TAT and PAP levels may be partly due to the delay of subsequent plasmin formation after thrombin generation. Not only the underlying disease (in fact TAT/PAP ratio is higher in patients with sepsis or cancer than in those with hematologic malignancies) but also the severity of DIC affects the imbalance between thrombin and plasmin activity. Such results may contribute to the decision on the proper therapy, possibly using a combination of anticoagulants and antifibrinolytic agents.

Conclusions

TAT and F1+2 are markers of activation of coagulation
- TAT is a useful tool for the diagnosis of hypercoagulable states and for monitoring of therapy in DIC, tumors and risk pregnancy [14, 28].

Table 4 Changes of laboratory tests results in disseminated intravascular coagulation (DIC)

Thrombin-induced changes in DIC	
Thrombin-antithrombin III complex (TAT)	↑
Fibrin monomer (FM) (soluble fibrin/SF)	↑
Fibrinopeptide A (FPA)	↑
Antithrombin III (ATIII)	↓
Fibrinogen	↓
Coagulation factors	↓
Plasmin-induced changes in DIC	
D-Dimer	↑
Plasmin-α_2-Antiplasmin Complex (PAP)	↑
Fibrinogen	↓
α_2-Antiplasmin	↓

- TAT is a marker of still-present thrombin generation/inhibition after thrombolysis in AMI [29,30,31] and a prognostic marker for reocclusion [32].
- F1+2 is useful for diagnosis not only of hypercoagulable but also of hypocoagulable states [4,23].
  It can be used for monitoring of thrombin generation during anticoagulant therapy with coumarins and heparins [33,34,35].
  F1+2 is, like TAT, a good parameter for monitoring therapy of DIC [35].
- Preoperative plasma levels of F1+2 may indicate the incidence of deep venous thrombosis after high risk surgery, e.g. total hip replacement [38].

D-Dimer and PAP are markers of activation of fibrinolysis

- D-Dimer is useful for diagnosis of secondary fibrinolysis in response to activation of coagulation [25].
  D-Dimer is the best laboratory parameter for exclusion of deep-vein thrombosis and pulmonary embolism. It can serve as diagnostic parameter for DIC [2].
- PAP can be used in the diagnosis of hypofibrinolytic and hyperfibrinolytic states [27].
  PAP is useful for the monitoring of DIC being a prognostic marker for such condition. It is also a prognostic marker for bad outcome (e.g. AMI) in patients with unstable angina pectoris [37].

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Table 5 Characteristics of activation of coagulation and fibrinolysis

	TAT Thrombin-antithrombin III complex	**F 1+2** Prothrombin fragment 1+2	**D-Dimer** Degradation product of crosslinked fibrin	**PAP** Plasmin-α_2-antiplasmin complex
Reference range	< 4.1 µg/l	0.4 - 1.1 nmol/l	< 78 µg/l	120 - 700 µg/l
Biological half-life	10 - 15 min	90 min	8 hours	12 hours
Indications	Diagnosis of *hypercoagulable states* *Monitoring of therapy in DIC, tumors and risk pregnancies* Prognostic marker for reocclusion after successful fibrinolytic therapy of myocardial infarction	Diagnosis of *hypercoagulable and hypocoagulable states* *Monitoring of anticoagulant therapy* • *Oral anticoagulant therapy* • *Heparin* Monitoring of therapy in DIC, tumors and risk pregnancies	Diagnosis of *secondary fibrinolysis* in response to activation of coagulation *Exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE)* Diagnosis of DIC	Diagnosis of *hypofibrinolytic and hyperfibrinolytic states* Diagnosis of primary hyperfibrinolysis Monitoring of therapy in DIC and prognostic marker Prognostic marker for AMI in unstable angina

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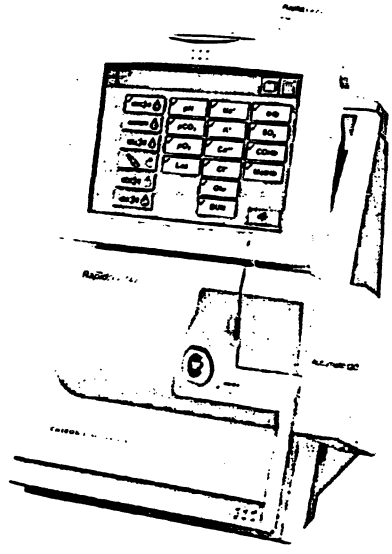

WELCHE HILFE ERWARTEN SIE IN EINER KRITISCHEN SITUATION ?

Wenn Sekunden über Leben und Tod entscheiden, braucht man schnell exakte Antworten. Wir bieten sie in einem Gesamtkonzept mit dem Rapidpoint™ 400, der den medizinischen, technischen und ökonomischen Anforderungen gerecht wird. Dieses System wurde von Chiron Diagnostics speziell für das POC-Segment „Criticalpoint", also für die Intensiv- und Notfallmedizin, entwickelt. Das (voll-) automatische und wartungsfreie Analysesystem ist das Ergebnis jahrelanger Erfahrung, weltweiter Marktführung und stetiger Kundennähe. Wir sind eine der wenigen Diagnostik-Firmen, die mit verschiedenen Blutgas- und Notfallanalyse-Systemen Lösungen für das Labor und den dezentralen Einsatz bieten.
Rapidpoint™ 400 zeichnet sich durch flexible Parameterwahl und schnellste Verfügbarkeit von Ergebnissen aus. Die neue Technologie gewährleistet eine kontinuierliche Parameter-Aktualisierung. Das konsequent durchdachte Konzept von Rapidpoint™ 400 sorgt für Kosteneffektivität und damit bessere Nutzbarkeit der Personalressourcen durch ein weniger zeit- und pflegeintensives Analysesystem. Ein integriertes Kosten-Management-Programm macht die Ausgaben für den Anwender kalkulierbar. Die intuitive Menüführung über einen Farbbildschirm mit Sensortechnik ermöglicht die Gerätebedienung vom ersten Augenblick an.

Haben Sie noch weitere Fragen?

Wir antworten Ihnen gerne unter der Rufnummer: 0641/4003-0.

ANTWORTEN AUF LEBENSWICHTIGE FRAGEN.

TÜV CERT DIN EN ISO 9002

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CRITICAL CARE SYSTEMS

CHIRON DIAGNOSTICS GMBH SIEMENSSTRASSE 3 D-35463 FERNWALD TELEFON (0641) 4003-0 TELEFAX (0641) 4003-111