ABSTRACTS - Hypertension, Vascular Disease, and Prevention

MODERATED POSTER SESSION

1007MP Moderated Poster Session...Tissue Factor, Tissue Factor Pathway Inhibitor, and Fibrinolysis: Role in Atherosclerosis

Sunday, March 17, 2002, 9:00 a.m.-11:00 a.m.
Georgia World Congress Center, Hall G

9:00 a.m.

1007MP-121 Tissue Factor Elicits Thrombin Generation in Human Atherosclerotic Plaques

Pier Angelica Merlini, Maurizio Ferrari, Ezio Bramucci, Luigi Angoli, Alessandra Repetto, Umberto Canosi, Diego Ardissino, Cardiologo, Polisclino San Matteo, Pavia, Italy, Cardiologo, Ospedale Niguarda, Milano, Italy.

Background: Tissue Factor (TF, the initiator of blood coagulation) is more concentrated in coronary atherosclerotic plaques of patients (pts) with acute coronary syndromes (ACS) than in coronary plaques obtained from pts with stable angina pectoris (AP). However, it is not clear whether this difference is associated with an in vivo increased thrombogenic response to plaque rupture. The aim of the study was to evaluate the thrombogenic potential of coronary plaques of pts with either ACS or stable AP, by measuring the local thrombin generation under basal conditions and after plaque rupture obtained by directional coronary angiography (DCA).

Methods: We studied 40 consecutive pts undergoing DCA: 22 pts with stable AP, 18 pts with ACS (12 with unstable AP, 6 with AMI). Blood samples were directly obtained, by a specially designed sampling catheter, proximal and distally to the coronary atherosclerotic plaque, both before and after the procedure. Plasma levels of prothrombin fragment 1+2 (F1+2, a marker of thrombin generation) have been quantified by double antibody radioimmunoassay.

Results:

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<tr>
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<th>Stable AP</th>
<th>ACS</th>
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</thead>
<tbody>
<tr>
<td>Stable</td>
<td>N=22</td>
<td>N=18</td>
</tr>
<tr>
<td>F1+2 proximal</td>
<td>0.95 (0.79-1.37)</td>
<td>1.16 (0.86-1.49)</td>
</tr>
<tr>
<td>F1+2 distal</td>
<td>1.00 (0.72-0.0)</td>
<td>1.50 (1.15-2.07)</td>
</tr>
<tr>
<td>Change</td>
<td>-0.065 (0.2-0.15)</td>
<td>0.37 (0.04-0.63)</td>
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<table>
<thead>
<tr>
<th></th>
<th>Stable AP</th>
<th>ACS</th>
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<tr>
<td>After DCA</td>
<td></td>
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<tr>
<td>F1+2 proximal</td>
<td>0.95 (0.86-1.39)</td>
<td>1.03 (0.99-1.66)</td>
</tr>
<tr>
<td>F1+2 distal</td>
<td>0.81 (0.37-2.14)</td>
<td>1.31 (1.04-2.02)</td>
</tr>
<tr>
<td>Change</td>
<td>0.01 (+0.06-0.14)</td>
<td>0.25 (0.02-0.42)</td>
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Data are expressed as median; interquartile ranges are reported.

Conclusion: TF-rich plaques of pts with ACS are associated with a local increase in thrombin generation detected in pts with stable AP, both under baseline conditions and after disruption by DCA. This data suggest a link between plaque composition and thrombogenicity, in vivo.

9:12 a.m.

1007MP-122 Increased Circulating Tissue Factor and Blood Thrombogenicity In Type-2 Diabetes

Antonia Sanzolo, James Hathcock, Julia Osendo, Yale Nemerson, Valentin Fuster, Jill Crandall, Juan Jose Badimon, Mount Sinai School of Medicine, New York, New York, New York.

Background: Several studies suggest a role for circulating tissue factor activity (TF-AcT) in atherothrombotic diseases. Type-2 Diabetes Mellitus (T2DM) is associated with a high rate of thrombotic complications. We have previously shown an increase in the blood thrombogenicity (BT) in poorly controlled T2DM patients. Improvements in glycaemic control showed a significant reduction in circulating TF-AcT levels. These findings suggest that the hyperthrombotic state associated with T2DM may be mediated by high levels of TF-AcT and these observations may help to develop future therapies in T2DM patients.

Methods: A total of 39 patients with T2DM and stable AP, were randomized into diet modification plus troglitazona or diet modification plus placebo. HbA1c was significantly correlated to the reduction in TF-AcT levels (p=0.014). No changes in BT were detected in pts with stable AP, both under baseline conditions and after plaque rupture obtained by directional coronary angiography (DCA).

Results: Our data demonstrate that the TF score is predictive of TA. We found no correlation between TF expression and RHB rejection score. RHB specimens from patients without TA were more likely to have a low TF score; similarly specimens from patients with TA were more likely to have a high TF score (Table, p=0.009). TF score from biopsy specimens from patients within 2 years after transplant had a positive predictive value of 89% and a negative predictive value of 100%.

Conclusion: Our data demonstrate a correlation between increased TF expression and the development of TA. TF causes increased local thrombin production leading to (i) microvascular thrombosis, (ii) SMC proliferation, and (iii) EC activation. Furthermore, our data suggests that TF could be the target of antioxidant therapy, as well as future therapies directed at TA.

9:36 a.m.

1007MP-125 Inhibitory Effect of C-Reactive Protein on the Release of Tissue Factor Pathway Inhibitor From Human Endothelial Cells: Reversal by Low Molecular Weight Heparin

Shaker A. Moussa, Jeffrey M. Bozarth, DuPont, Wilmington, Delaware.

Elevated C-reactive protein (CRP) is associated with a higher risk of cardiac events in patients with acute coronary syndrome. Elevated CRP levels has been shown to promote the expression of tissue factor in monocytes, which may lead to fibrin deposition and}

1007MP-124 Tissue Factor Expression Is Increased in Cardiac Transplant Recipients Who Develop Cardiac Transplant Arteriopathy

Michael H. Yen, Guy Pilkington, Norman Rastiff, Patrick M. McCarthy, James B. Young, Randall C. Starling, Guy M. Chioldori, Marc S. Penn, The Cleveland Clinic Foundation, Cleveland, Ohio.

Background: We have demonstrated that oxidant stress upregulates tissue factor activity (TF) activity in smooth muscle (SMC) and endothelial cells (EC) by an antioxidant inhibitable mechanism. These data, along with the observations that (i) fibrin deposition and oxidant stress predict transplant arteriopathy (TA) and that (ii) TA progression may be inhibited by antioxidants, lead us to hypothesize that TF could play a role in TA.

Methods: We developed a TF scoring index for TF expression in the arteriopathy in heart biopsies (RHB). We studied 63 consecutive patients who underwent routine RHB and surveillance angiography >2 years (n=30), <2 years (n=20) after transplant.

Results: Our data demonstrate that the TF score is predictive of TA. We found no correlation between TF expression and RHB rejection score. RHB specimens from patients without TA were more likely to have a low TF score; similarly specimens from patients with TA were more likely to have a high TF score (Table, p=0.009). TF score from biopsy specimens from patients within 2 years after transplant had a positive predictive value of 89% and a negative predictive value of 100%.

Conclusion: Our data demonstrate a correlation between increased TF expression and the development of TA. TF causes increased local thrombin production leading to (i) microvascular thrombosis, (ii) SMC proliferation, and (iii) EC activation. Furthermore, our data suggests that TF could be the target of antioxidant therapy, as well as future therapies directed at TA.

9:48 a.m.

1007MP-126 Inhibitory Effect of C-Reactive Protein on the Release of Tissue Factor Pathway Inhibitor From Human Endothelial Cells: Reversal by Low Molecular Weight Heparin

Shaker A. Moussa, Jeffrey M. Bozarth, DuPont, Wilmington, Delaware.

Elevated C-reactive protein (CRP) is associated with a higher risk of cardiac events in patients with acute coronary syndrome. Elevated CRP levels has been shown to promote the expression of tissue factor in monocytes, which may lead to fibrin deposition and
microcirculatory disturbances. However, the possible effects of CRP on vascular cells are not known. In the present investigation, the effects of CRP and heparin derivatives on the release of tissue factor pathway inhibitor (TFPI) from human umbilical vein endothelial (HUVE) cells were examined. Methods: Confluent HUVE cells were resuspended and plated in 48 well plate. Cells were attached to fibronectin for 3 hours, washed and fresh medium with and without CRP, different LMWH or heparin molecular weight (HMW) fractions were added. TFPI released in the medium was measured using specific total TFPI immunoassay. Results: CRP demonstrated a potent inhibitory effect on TFPI release. In contrast, heparin demonstrated a potent stimulatory effect on TFPI release. The degree of TFPI release was shown to be dependent on the HMW distribution, with minimal to no effect at 3,000 dalton and maximal at 8,000-12,000 dalton. Furthermore, LMWH containing relatively higher HMW fractions demonstrated greater potency. LMWH effectively reversed the inhibitory effects of CRP on TFPI release from HUVEC. These findings support the hypothesis that CRP may play direct role in promoting hypercoaguable state that is correctable by LMWH.

The Effect of CRP on TFPI Release from Human Endothelial Cells (T = 4 hours)

CRP ng/ml 0 5 10 15 20
TFPI (ng/ml)

10:00 a.m.

1007MP-128 Attenuation of Migration of Vascular Smooth Muscle Cells by Overexpression of Plasminogen Activator Inhibitor Type 1
Michael G. Hayes, Burton E. Sobel, Douglas J. Taaltes, Mercedes Rincon, David J. Schneider, University of Vermont, Burlington, Vermont.

Background: Acute coronary syndromes are generally precipitated by rupture of vulnerable plaques. A thin, relatively acellular cap overlapping a necrotic lipid core characterizes vulnerable plaques. We have implicated decreased vascular smooth muscle cell (VSMC) migration as one factor predisposing to plaque vulnerability. Elevated arterial content of plasminogen activator inhibitor type-1 (PAI-1) has been associated with increased risk of plaque rupture. VSMC migration depends on cell surface expression of plasminogen activators. PAI-1 is the primary physiologic inhibitor of plasminogen activators. Thus, we sought to determine whether increased expression of PAI-1 decreases VSMC migration.

Methods: Constitutive, VSMC-specific overexpression of PAI-1 was induced in transgenic mice with the use of the Sm2620 promoter. VSMC migration was characterized in a well insert microplate system. Matrigel was used as the extracellular matrix (2 µm thickness) and rat platelet-derived growth factor-BB was used as a chemoattractant. Migration was quantified with laser scanning cytometry.

Results: Immunohistochernical analysis of aortic tissue demonstrated increased PAI-1 in transgene positive mice compared with transgene negative littermates. VSMC (50,000 cells) were seeded and migration through Matrigel was quantified after 20 hours. Migration was consistently attenuated with transgene positive VSMC (4.45 ± 1.313 [SD]) VSMC from transgene positive mice and 7.323 ± 0.822 VSMC from transgene negative mice, p<0.03. Similar significant differences were seen with cells from 3 pairs of littermates.

Conclusion: Thus, selective overexpression of PAI-1 in VSMC attenuates their migration and may potentiate evolution of VSMC-poor atherosclerotic plaques that are particularly prone to rupture.