Cardiac Sympathetic Nerve Stimulation Triggers Coronary t-PA Release

Jan-Arne Björkman, Sverker Jern, Christina Jern

Objective—This study was undertaken to determine whether stimulation of sympathetic cardiac nerves induces release of the thrombolytic enzyme tissue-type plasminogen activator (t-PA) in the coronary vascular bed.

Methods and Results—Anesthetized pigs were studied in an open chest model. Bilateral vagotomy was performed, and sympathetic cardiac nerves were activated by electrical stimulation (1 and 8 Hz). To evaluate possible mediating effects of increased heart rate and enhanced local blood flow, tachycardia was induced by pacing and hyperemia by local infusion of sodium nitroprusside and clevedipine. Furthermore, to study the effects of α- and β-adrenergic receptor stimulation, phenylephrine and isoprenaline were infused locally. In response to low- and high-frequency sympathetic stimulation, mean coronary net release of total t-PA increased approximately 6- and 25-fold, respectively. Active t-PA stimulation,β-adrenergic stimulation by isoprenaline induced an approximately 6-fold increase in coronary t-PA release, whereas no significant change in release rates occurred in response to α-adrenergic stimulation by phenylephrine.

Conclusions—Stimulation of cardiac sympathetic nerves induces a marked coronary release of t-PA, and part of this response may be mediated through stimulation of β-adrenergic receptors. (Arterioscler Thromb Vasc Biol. 2003;23:1091-1097.)

Key Words: tissue-type plasminogen activator ▪ sympathetic nerves ▪ adrenergic ▪ coronary ▪ pigs

Tissue-type plasminogen activator (t-PA) is the main fibrinolytic activator in the vascular compartment.1,2 The endothelium continuously secretes t-PA by a constitutive pathway. In addition, t-PA can be rapidly released from endothelial stores in response to various stimuli by a regulated pathway. Such an acute release of t-PA is a key event in initiating an endogenous fibrinolytic response,2 which in turn may result in endogenous removal of thrombi. Unfortunately, however, regulated release of t-PA in vivo cannot be determined by measurements of systemic plasma levels of t-PA, because plasma t-PA is sensitive to alterations in hepatic blood flow.3–5 To overcome this problem, we adapted the human perfused-forearm model to study local t-PA release6,7 and demonstrated that both mental stress and local infusion of norepinephrine induce an acute release of t-PA in the forearm vascular bed.6,8

It is well-known that sympathetic stimulation induces activation of procoagulant mechanisms on the systemic level.9,10 It is therefore of interest to investigate if an acute t-PA release can be induced also in the coronary circulation by sympathetic activation, because such a response might oppose stress-induced procoagulant activation and thereby protect against clot formation. In the present study, we investigated the effect of sympathetic stimulation on coronary t-PA release in a pig model by determining coronary release of t-PA during electrical stimulation of cardiac sympathetic nerves. If such a stimulatory effect could be demonstrated, a second aim was to investigate if the accompanying hemodynamic alterations that occur during sympathetic stimulation (ie, tachycardia and coronary hyperemia) as such could mediate the response. We also examined the effects of local infusion of the unselective β-adrenergic agonist isoprenaline and the α-adrenergic agonist phenylephrine on coronary t-PA release.

Methods

Animals

The study was performed on 29 healthy, young Swedish farm pigs of either sex. Their body weight ranged from 25 to 35 kg. They were maintained on a standard diet but were fasted with free access to water 12 hours before the study. Animal care and handling conformed with the Guide for the Care and Use of Laboratory Animals, published by the United States National Institutes of Health (NIH Publication No. 85-23, revised 1996). The Committee for Ethical Review of Animal Experiments at the University of Göteborg approved the protocols.

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Preparations and Experimental Protocols

Experiment I: Stimulation of Cardiac Sympathetic Nerves

The hypothesis that activation of sympathetic nerves induces regulated release of t-PA was tested in 7 pigs. Anesthesia was induced by intramuscular injection of 20 mL Saffan (alphaxalone 9% wt/vol and alphadolone acetate 0.3% wt/vol) and maintained by a continuous intravenous infusion of Saffan (3 mL/h) and α-chloralose (90%, Aldrich-Chemie) given as a bolus of 40 mg/kg followed by 20 mg/kg per h. An orotracheal tube was introduced, and volume-controlled mechanical ventilation was instituted (Servo Ventilator 900C, Siemens Elema).

After bilateral vagotomy, the right and left stellate ganglia were carefully isolated from connective tissue. Each of the 2 ansae subclaviae were attached to a silver ring electrode, which was isolated and connected to a computerized stimulator. After median sternotomy, a shunt from a coronary vein to the right auricle of the heart was established. To that end, the coronary vein running parallel to the left anterior descending artery (LAD), draining the ventral part of the heart corresponding to the area supplied by LAD, was gently exposed. A 5- to 10-mm segment of the vein approxi-
mately 80 mm from the apex was separated carefully and cannulated retrogradely with a PE 260 polyethylene catheter (Portex). The catheter was fixed to the vein by a ligature, and the other end was inserted into the right auricle. The shunt permitted rapid blood sampling from the coronary vein and facilitated exact timing of the sampling procedure relative to the start of stimulation. Immediately after establishment of the shunt, the animals were heparinized (bolus 5000 IU followed by 50 IU/kg per h). Blood flow in the vein-auricle line was monitored with an ultrasonic probe (Transonic Ultrasonic Transit-Time, Transonic System Inc). Because of technical difficulties, 1 animal only received unilateral stimulation (right side).

An equilibration period of at least 60 minutes was allowed after the surgical preparation before the actual experiment started with baseline recordings for 10 minutes. Stimulation of sympathetic nerves was induced by supramaximal current, ie, 5 to 15 mA with a pulse duration of 2 ms (Stimulus Isolator A 385, World Precision Instruments, driven by a custom-designed computer system, Astra-Zeneca) to recruit all nerve fibers. Continuous stimulation was performed during 3 minutes with single impulses at 1 and 8 Hz to study the effect of mild and submaximal sympathetic stimulation, respectively. Each animal was left to recover for at least 30 minutes between stimulations.

Experiments II and III: Effects of Tachycardia and Hyperemia

The possibility that increased heart rate or enhanced coronary blood flow contributed to the observed regulated release of t-PA in response to sympathetic stimulation was tested in an additional series of experiments. Seven pigs were exposed to right atrial pacing and local coronary infusion of the NO-donor nitroprusside (sodium nitroprusside, Merck). Animals were premedicated by an intramuscular injection of 2 mg/kg of midazolam (Dormicum 5 mg/mL, Roche) and 10 mg/kg of ketamine hydrochloride (Ketaminol 100 mg/mL, Vetpharma AB). Twenty minutes later, an intravenous infusion of 2 to 5 mg/kg of propofol (Diprivan 10 mg/mL, Zeneca Limited) was started. This was followed by 100 mg/kg of α-chloralose as an intravenous bolus injection and then 25 to 50 mg/kg per hour as a continuous infusion. The reason that a different anesthesia was used compared with the first series was that Saffan was no longer available on the market at this time.

After sternotomy, a 5- to 8-mm segment of the LAD was carefully isolated 50 to 80 mm from apex. A Transonic flow probe (Transonic Ultrasonic Transit-Time) was placed around the LAD to measure coronary blood flow. By the time of this second experimental series, we had developed an alternative simplified procedure to obtain samples from the coronary vein at precisely defined time intervals. To this end, a custom-designed needle (20-gauge) attached to a thin polyethylene catheter (PE 90 Intramedic, Clay Adams) was used. This needle was placed in the local coronary vein accompanying the LAD. For intracoronary infusions, a 16-gauge needle with side holes near the tip was connected to a polyethylene catheter (PE 50 Intramedic, Clay Adams) and inserted into the LAD distal to the flow probe. For pacing of the heart, a bipolar clip electrode was attached to the right atrial appendage.

After surgical preparation, an equilibration period of at least 30 minutes was allowed before the experiment started with baseline recordings for 10 minutes. The heart was then paced during 3 minutes at 150 and 200 bpm, respectively. After an additional 30-minute recovering period and a 10-minute baseline recording period, sodium nitroprusside (SNP) was infused into the coronary artery in 2 dose steps, 0.1 and 0.5 mg/min during 3 minutes each.

Because we could not achieve an enhanced coronary blood flow by local administration of SNP without inducing systemic effects, an additional series of experiments was performed with the ultra-short-acting, vascular selective dihydropyridine calcium antagonist clevedipine (AstraZeneca). Because the half-life of clevedipine is only approximately 12 seconds,12,13 we have earlier been able to enhance coronary blood flow with this substance without inducing systemic effects. Seven animals were included, and surgical preparation, equilibration period, and baseline recordings were as in experiment II. Clevedipine was infused in the coronary artery at incremental doses of 0.001, 0.003, 0.01, and 0.03 μmol/min, and each dose was infused for 3 minutes. Based on results from our pilot experiments, the 4 different doses of clevedipine were chosen to cause an incremental enhancement of coronary blood flow without inducing any systemic effects.

Experiment IV: Effects of Local Myocardial α- and β-Adrenergic Stimulation

The effect of local infusions of the α- and β-sympathomimetic agents phenylephrine (PE) (phenylephrine hydrochloride, Sigma) and isoprenaline (IPR) (isoproterenol, Sigma) were studied in 8 animals. Anesthesia, surgical preparation, equilibration periods, and baseline recordings were as in experiment II. PE and IPR were infused in the coronary artery at increasing doses of 1, 4, 16, and 64 μg/min and 0.1, 0.4, 1.6, and 6.4 μg/min, respectively. Each dose was infused for 5 minutes in sequence. A recovery period of 1 hour was allowed between the 2 drugs. Because IPR were expected to induce systemic effects, the 2 agonists were not infused in randomized order.

In all experiments, arterial pO2, pCO2, and pH were determined (ABL 505 or 725 Radiometer) every hour and kept within the physiological range by adjustments of respiratory tidal volume. Core body temperature was kept close to 38°C by heating of the operating table. Ringer solution (10 mL/kg per h) was infused into a peripheral ear vein to compensate for fluid losses. At the end of each experiment, cardiac arrest was induced by intravenous infusion of an overdose of pentobarbital.

Hemodynamic Measurements

In all experiments, a catheter was placed in the abdominal aorta via the saphenous artery for continuous intraarterial monitoring of systemic blood pressure. Heart rate (HR) was calculated from the ECG. Mean arterial pressure (MAP), ECG, and coronary venous or arterial blood flow were continuously monitored on a Grass polygraph (Grass Instruments Co), and mean values for a 10-second period were stored once every minute by a computer system (PCLAB V5.0, AstraZeneca).14

Blood Sampling

Blood samples were obtained simultaneously from the catheters in the abdominal aorta and the coronary vein. In experiment I, blood samples were obtained at baseline and after 2 minutes of sympathetic stimulation as well as at 1 and 5 minutes after cessation of the stimulation and 10 minutes after cessation of the last high-frequency stimulation. In experiments II through IV, samples were obtained at prestimulation baseline and after 2-minute pacing or infusion at each dose level. The first 3 to 4 mL of blood was always discarded. Blood samples were collected in syringes containing 1/10 0.45 mol/L sodium citrate buffer, pH 4.3. Plasma was isolated within 15 minutes.
by centrifugation at 5000 g for 15 minutes at 4°C. Plasma samples were immediately frozen and stored at -70°C.

**Measurements of Plasma t-PA**

Plasma levels of total t-PA antigen were determined by an enzyme-linked immunosassay (TintElize t-PA, catalogue No. 1105, Biopool AB) that detects free and complexed t-PA with equal efficiency. Calibration was performed with porcine t-PA diluted in t-PA-depleted porcine plasma as earlier described. Active t-PA was determined with a spectrophotometric parabolic rate assay (SpectrolyseTM/fibrin t-PA, catalogue No. 101101, Biopool AB). By quenching with polyclonal goat anti-porcine t-PA IgG (catalogue No. 105301, Biopool AB), we have earlier shown that this assay is specific for t-PA. Human single-chain t-PA calibrated against the International Standard for t-PA (World Health Organization’s First International Standard for t-PA coded 86/670 from the National Institute for Biological Standards and Control, Hertfordshire, England) was used as standard in this assay. Thus, in the following, t-PA activity is expressed in units, 1 unit of porcine t-PA being equivalent in the employed assay to 1 international unit of human t-PA. Samples from each experimental animal were analyzed on 1 single microtiter plate. All samples were analyzed in duplicate, and mean intra-assay coefficients of variation were 2.5% and 3.5% for total and active t-PA, respectively.

**Calculation of Coronary Net Release of t-PA**

Individual venoarterial concentration gradients were obtained by subtraction of the values measured in simultaneously collected venous and arterial plasma. Blood flow was interconverted to plasma flow using individual arterial hematocrits, and net release rate was defined as the venoarterial concentration gradient times plasma flow per unit of time across the coronary vasculature, as described.

**Statistical Analysis**

Standard statistical methods were used. All results are presented as mean and SEM. Wilcoxon’s signed rank sum test was used to evaluate responses of t-PA variables to sympathetic stimulation. Responses to cardiac pacing and coronary infusions were evaluated by two-way ANOVA and nonparametric Friedman’s test for hemodynamic and t-PA variables, respectively. Post hoc analysis was performed by paired Student’s t test and Wilcoxon’s signed rank sum test. Statistical tests were considered significant at \( P < 0.05 \).

**Results**

**Stimulation of Cardiac Sympathetic Nerves (Experiment I)**

Cardiac sympathetic nerve stimulation caused an instant hemodynamic response that remained throughout the stimulation period (Figure 1). HR increased by approximately 40% and 70% and MAP by 15% and 30% in response to low- and high-frequency sympathetic stimulation, respectively. Coronary blood flow increased approximately 2- and 2.5-fold.

At prestimulation baseline, there was a significant step up from the arterial to venous side across the coronary vascular bed for both total and active t-PA (Table 1). The average prestimulation coronary net release rate of total and active t-PA was 7 ng/min (range, 1 to 30 ng/min) and 13 U/min (range, 4 to 22 U/min), respectively (Figure 2). A marked increase in net release rate of both total and active t-PA was observed in response to both stimulation frequencies, but this increase was only statistically significant in response to high-frequency stimulation (Figure 2). Average total t-PA release rates amounted to 40 ng/min (range, 14 to 86 ng/min) and 179 ng/min (range, 11 to 351 ng/min) during low- and high-frequency stimulation, respectively. The corresponding figures for active t-PA were 53 U/min (range, 6 to 111 U/min) and 132 U/min (range, 11 to 303 U/min). No t-PA response was observed in the animal that received unilateral stimulation, and if this animal was excluded, total mean t-PA release rates amounted to 45 and 207 ng/min during low- and high-frequency stimulation, respectively. After cessation of stimulation, net release rates of t-PA rapidly returned to prestimulation levels (Figure 2). Regarding systemic plasma levels, a significant increase in the arterial plasma level of total t-PA was observed during high-frequency stimulation (Table 1).

**Effects of Tachycardia and Hyperemia (Experiments II and III)**

To evaluate whether increased HR could contribute to the observed t-PA response, the heart was paced to similar rates as obtained during low- and high-frequency stimulation, ie, approximately 150 and 200 bpm, respectively. There was a slight reduction in the venous plasma level of t-PA, but no significant alterations in coronary blood flow, arterial plasma levels, or net release of total t-PA were observed in response to either stimulation frequency (Table 2).

To examine if t-PA release was flow dependent, we first infused SNP, and no significant effect on net release of total t-PA was observed (Table 2). Both doses of SNP induced a 1.5-fold increase in coronary blood flow, compared with the 2-fold increase observed in response to high-frequency sympathetic stimulation. However, a significant drop in MAP occurred already at the low dose, and MAP was reduced even
further in response to the high dose (Table 2). Thus, it was not possible to enhance coronary blood flow further by local infusion of SNP without inducing substantial systemic effects. We therefore performed an additional series of experiments in which coronary blood flow was enhanced by local infusion of the ultra-short-acting calcium-antagonist clevedipine. In contrast to SNP, clevedipine induced a dose-dependent increase in coronary blood flow without any significant systemic effects (Table 3). The mean increase in coronary blood flow was 2.5-fold at the highest dose, ie, a similar relative change as observed in response to high-frequency stimulation. However, there was no significant alteration in coronary t-PA release (Table 3).

Effects of Local Myocardial α- and β-Adrenergic Stimulation (Experiment IV)

IPR induced a dose-dependent increase in both HR and coronary blood flow (Table 4). IPR also induced a significant increase in the venous plasma concentrations of t-PA as well as an increase in coronary net release of t-PA that approached statistical significance (*P<0.06; Table 4). In addition, the arterial plasma concentration of t-PA increased, which indi-

### Table 1. Effects of Stimulation of Cardiac Sympathetic Nerves (1 and 8 Hz) on Plasma Concentrations of t-PA

<table>
<thead>
<tr>
<th></th>
<th>Before Stimulation</th>
<th>During Stimulation</th>
<th>After Stimulation</th>
<th>After Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=6</td>
<td>n=7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial total t-PA, ng/mL</td>
<td>6.60 (1.22)</td>
<td>8.37 (1.38)</td>
<td>9.19 (2.02)*</td>
<td>9.39 (2.10)</td>
</tr>
<tr>
<td>Venous total t-PA, ng/mL</td>
<td>7.57 (0.72)</td>
<td>9.48 (2.33)</td>
<td>16.0 (3.06)†</td>
<td>10.7 (2.66)</td>
</tr>
<tr>
<td>AV-gradient total t-PA, ng/mL</td>
<td>0.97 (0.60)</td>
<td>1.11 (0.43)</td>
<td>6.78 (1.39)*</td>
<td>1.34 (0.59)</td>
</tr>
<tr>
<td>Arterial active t-PA, U/mL</td>
<td>2.29 (0.62)</td>
<td>3.47 (1.31)</td>
<td>3.77 (1.46)</td>
<td>4.32 (1.68)</td>
</tr>
<tr>
<td>Venous active t-PA, U/mL</td>
<td>3.88 (0.82)</td>
<td>4.68 (1.77)</td>
<td>8.93 (2.21)*</td>
<td>5.17 (1.86)</td>
</tr>
<tr>
<td>AV-gradient active t-PA, U/mL</td>
<td>1.20 (0.24)</td>
<td>0.58 (0.43)</td>
<td>4.26 (1.41)*</td>
<td>0.65 (0.37)</td>
</tr>
</tbody>
</table>

Values shown are mean (SEM). *P values indicate Wilcoxon’s signed rank sum test for prestimulation baseline vs stimulation. †P<0.01.
The present study demonstrates for the first time that stimulation of sympathetic cardiac nerves induces an acute release of t-PA. Most of the released of t-PA is in its free, active form, indicating that local administration of different pharmacological agonists in the human forearm. Responses of similar magnitude were also recently reported when the human coronary vascular bed was stimulated by infusion of substance P and bradykinin. Several mechanisms may be involved in the observed release of t-PA in response to stimulation of sympathetic nerves. Because neither pacing nor local infusion of vasodilatory agents enhanced coronary t-PA release rates, it is unlikely that the response was attributable to mechanical factors acting on the vessel.
wall by changes in flow or pulsatility. However, in these mechanistic studies, it was not possible to produce a similar relative increase in flow by local infusion of SNP as that induced by high-frequency stimulation without concomitant systemic effects. We therefore also evaluated the effect of increased flow as induced by the ultra-short-acting Ca\(^{2+}\) antagonist clevedipine, although one limitation of this approach is that regulated release of t-PA is dependent on Ca\(^{2+}\) influx.\(^{26,27}\) However, the present data, taken together with several earlier studies showing that SNP is not a stimulus for regulated release of t-PA either in the human forearm or in the human coronary vascular bed,\(^7,18\) indicate that the enhanced blood flow could not explain the observed profound response to phenylephrine in this kind of porcine model. The dose of phenylephrine was based on our experience of doses that give peripheral vasoconstriction in this kind of porcine model. A plausible mechanism is that activation of cardiac sympathetic nerves increases local norepinephrine spillover, which in turn induces a regulated release of t-PA from endothelial stores. However, in the present study, it was not possible to enhance t-PA release rates by infusion of isoprenaline to similar levels as obtained during sympathetic stimulation, presumably because of lesser local concentrations of isoprenaline by the infusion than the local norepinephrine concentration obtained during stimulation sympathetic cardiac nerves.

Another possibility is that t-PA released from the sympathetic nervous system itself contributed to the observed response. O’Rourke and colleagues\(^32\) have shown that sympathetic neurons can synthesize and release t-PA. Interestingly, the same group recently reported that sympathectomy in rats greatly reduced steady-state plasma t-PA activity in intact animals as well as t-PA release from isolated whole-vessel explants,\(^33\) which may suggest that the sympathetic nervous system contributes to plasma t-PA.

One limitation of the present study is that electrical activation of sympathetic cardiac nerves is an experimental stimulus. However, data from our laboratory show that even more pronounced sympathoadrenal stimulation, as judged from hemodynamic responses, can be elicited in intact pigs.

### Table 4. Effects of Local Infusion of Isoprenaline (IPR) and Phenylephrine (PE) on Hemodynamics and Coronary t-PA Release (n=8)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>IPR I</th>
<th>IPR II</th>
<th>IPR III</th>
<th>IPR IV</th>
<th>ANOVA/Friedman</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>116 (16)</td>
<td>147 (15)</td>
<td>176 (16)</td>
<td>204 (17)</td>
<td>219 (17)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>86 (6)</td>
<td>62 (4)</td>
<td>80 (7)</td>
<td>82 (6)</td>
<td>77 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary arterial flow, mL/min</td>
<td>25 (4)</td>
<td>36 (8)</td>
<td>40 (9)</td>
<td>52 (11)</td>
<td>61 (12)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Arterial total t-PA, ng/mL</td>
<td>5.8 (0.9)</td>
<td>6.3 (1.1)</td>
<td>7.0 (1.2)</td>
<td>7.3 (1.2)</td>
<td>8.2 (1.0)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Venous total t-PA, ng/mL</td>
<td>6.9 (1.0)</td>
<td>7.7 (1.3)</td>
<td>7.9 (1.3)</td>
<td>8.4 (1.2)</td>
<td>9.2 (1.1)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>AV-gradient t-PA, ng/mL</td>
<td>1.1 (0.7)</td>
<td>1.0 (0.6)</td>
<td>0.8 (0.4)</td>
<td>1.1 (0.2)</td>
<td>1.0 (0.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary net release total t-PA, ng/min</td>
<td>8.9 (3.4)</td>
<td>45.3 (27.8)</td>
<td>29.6 (13.0)</td>
<td>44.8 (11.7)</td>
<td>40.2 (14.2)</td>
<td>P=0.06</td>
</tr>
</tbody>
</table>

Values shown are mean (SEM).

Statistical analysis as in Table 3. *P<0.05; †P<0.01; ‡P<0.001
by natural stress stimuli. It is therefore reasonable to assume that a coronary t-PA release of similar magnitude is induced also during naturally occurring stress conditions. On the systemic level, prothrombotic mechanisms are activated during stress. The observed local t-PA response may thus constitute a counterregulatory mechanism to prevent formation of occlusive intraluminal thrombi provided that t-PA release occurs proximal or close to the site of thrombus formation. However, at present, no experimental model is available by which the relative contribution of different segments of the coronary vasculature for the observed t-PA release could be determined.

In conclusion, the present data demonstrate for the first time that stimulation of cardiac sympathetic nerves induces a regulated release of t-PA in the porcine coronary vascular bed. The capacity for this response is high, as demonstrated by the 20-fold increase in t-PA release rates in response to high-frequency stimulation. This release could not be obtained by the concomitant hemodynamic alterations, because pacing-induced tachycardia and local hyperemia induced by 2 different vasodilators did not cause an augmented t-PA release. However, by stimulation of the β-adrenoceptors by intracoronary isoproterenol infusion, an acute t-PA release was induced.

Acknowledgments

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