Increased N-terminal CgA in circulation associated with cardiac reperfusion in pigs

Aim: Acute myocardial infarction causes neurohumoral activation characterized by increased sympathetic activity. CgA is a protein released during sympathoadrenal stress from neuroendocrine tissue. Recently, increased CgA concentrations in circulation has been reported and suggested to be an independent predictor of mortality after acute myocardial infarction. Materials & methods: Eighteen pigs underwent 1 h of regional myocardial ischemia followed by 3 h of reperfusion. Blood samples were collected every hour and plasma CgA was measured with two radioimmunoassays. Results: We found a 30% increase in plasma N-terminal CgA 1 h after re-establishment of coronary blood supply. On the other hand, plasma pancreastatin did not change in response to ischemia or reperfusion but decreased during the entire experiment. Conclusion: Our results suggest a differentiated CgA response in myocardial reperfusion after local cardiac anoxia that may reflect tissue-specific post-translational processing and release.

KEYWORDS: CgA, chromogranin A, ischemia/reperfusion, myocardial infarction, natriuretic peptides, neuroendocrine response, pig

Acute myocardial infarction constitutes a global health problem [1], and is associated with excessive activation of the neurohormonal system and increased sympathetic activity [2,3]. CgA is a polypeptide ubiquitously present in neuroendocrine tissue [4]. It is stored in secretory cells and exocytotically coreleased with a variety of substances, such as catecholamines and insulin [5,6], and is correlated with sympathomimetic stress [7]. Well-conserved epitopes and several pairs of basic amino acids along the protein suggest that CgA is a prohormone for shorter peptide fragments. It is post-translationally and tissue-specifically modified, giving rise to several peptides, such as pancreastatin (CgA[250–301]), vasostatin-1 (CgA[1–76]) and catestatin (CgA[352–372]), that are highly preserved derivates [8]. Their functions are not fully disclosed. It is believed that CgA is metabolized in the liver [9] and in the kidneys [9,10].

Plasma CgA measurement is used as a diagnostic and prognostic marker of neuroendocrine disease [11]. Also, plasma CgA is elevated in several systemic diseases, as well as in inflammatory conditions [12–16].

CgA concentrations within the first 24 h and in the subacute phase after myocardial infarction have been suggested as a potential prognostic biomarker of long-term mortality [17–19]. However, the very early phase of cardiac ischemia and reperfusion has not been examined in terms of CgA response. Interestingly, CgA is colocalized in the cardiomyocyte with BNP, which is also a prognostic marker of long-term mortality in cardiac disease [20]. The plasma concentration of the two peptides correlates in patients suffering from chronic heart disease [21], but whether they affect each other is unclear.

In this study, we first examined CgA release during the first 3 h of reperfusion in a porcine model of regional cardiac ischemia. Second, we investigated CgA contents in cardiac tissue and third we tested whether natriuretic peptide (NP) infusion (BNP or chimeric CD-NP) affects the CgA release.

Materials & methods

Animals & surgical procedure

All animal experiments were conducted after approval from the Danish Inspectorate of Animal Experimentation. The study was conducted as an acute study and all animals were euthanized under continued anesthesia on the same day as the experiment. A total of 25 female pigs with a bodyweight of 25 kg comprised the study material as an intervention group and five as a control group. To assess any influence NP infusion may have had on CgA plasma concentration, the pigs were divided into three groups and received intravenous (iv) infusion of either BNP (0.005 µg kg–1 min–1; n = 6), CD-NP (a synthetic peptide consisting of a primary sequence resembling C-type NP extended with the C-terminus of DNP [22]; 0.005 µg kg–1 min–1; n = 5) or saline (equal volume infused as NP groups; n = 7), as described elsewhere [23]. NP/saline infusions were initiated...
after 55 min of cardiac ischemia – 5 min prior to reperfusion – and continued until the pigs were euthanized (Figure 1A). The pigs were sedated before transportation to the operating facilities with intramuscular S-ketamine (5 mg kg\(^{-1}\); Pfizer APS, Denmark) and midazolam (0.5 mg kg\(^{-1}\); Hameln Pharmaceuticals GmbH, Germany). Upon arrival we preanesthetized the pigs with intramuscular S-ketamine (5 mg kg\(^{-1}\)) and midazolam (0.5 mg kg\(^{-1}\)). Anesthesia was induced with iv. pentobarbital (3–5 mg kg\(^{-1}\); Mebumal\(^{®}\), Syge- hus Apotekerne i Danmark [SAD], Denmark). The pigs were intubated and ventilated on 50% oxygen (Datex-Ohmeda s/5 Avance\(^{®}\) Ventilator, GE Healthcare, UK) and anesthesia was maintained with continuous iv. infusion of pentobarbital (10 mg kg\(^{-1}\) h\(^{-1}\)) and fentanyl (100 µg kg\(^{-1}\) h\(^{-1}\); Haldid\(^{®}\), Janssen-Cilag A/S, Denmark). Anticoagulation was ensured by iv. injection of 4000 IU unfractionated heparin followed by 2500 IU h\(^{-1}\) iv. (Heparin\(^{®}\), LEO Pharma Nordic, Sweden). Prophylaxis against arrhythmias was administered by iv. injection of amiodarone (1 mg kg\(^{-1}\); Cordarone\(^{®}\), Sanofi-Aventis, Denmark). The plasma level of potassium was maintained between 4–5 mM by potassium infusion. Isotonic saline was infused at a rate of 10 ml kg\(^{-1}\) h\(^{-1}\). Intravascular access was obtained by insertion of vascular sheaths into the surgically exposed right and left jugular veins (8 Fr) and common carotid arteries (7 Fr).

### Experimental procedure
Myocardial ischemia was induced by use of a balloon-tipped percutaneous intervention catheter with its position verified by contrast-enhanced fluoroscopy [24]. The left anterior descending coronary artery was occluded distal to the second diagonal branch by balloon inflation and maintained for 1 h at seven bars. A total of 3 h of reperfusion followed the ischemic event (Figure 1A).

### Blood sampling
Blood samples were collected just prior to ischemia and every following hour in ethylenediaminetetraacetic acid-coated tubes and stored on ice for 30 min. The samples were centrifuged for 10 min at 4°C and 2500 rpm and stored at -80°C until analysis.

### Radioimmunoassays
CgA in plasma was determined by radioimmunoassays targeting the N-terminus (human CgA[1–9]) and the porcine-specific amino acid sequence for pancreastatin (CgA[250–301]; Figure 1B). Plasma was not extracted owing to the risk of precipitating CgA in the process.

#### N-terminal CgA (CgA[1–9])
The assay targeting N-terminal CgA was previously developed in our laboratory [11,25]. It is ‘end viewing’, as N-terminally truncated peptides (CgA[2–9]-Tyr and CgA[3–9]-Tyr) are not recognized by the antiserum employed. N-terminal fragments of increasing length are recognized equimolarly compared with CgA[1–9]. CgA[1–9]Tyr was used as calibrator, CgA[1–9]125I-Tyr as tracer and Ab.94188 as antiserum, as previously described [25]. Interassay coefficient of variations were 24% at 7.5 pmol l\(^{-1}\), 17% at 30 pmol l\(^{-1}\) and 13% at 60 pmol l\(^{-1}\) (n = 15).

#### Pancreastatin (CgA[250–301])
Pancreastatin was determined by a commercial radioimmuno assay (RK-053-08 Pancreastatin [Porcine] – RIA Kit, Phoenix Pharmaceuticals Inc., Germany). Interassay coefficient (<17% at 6.862 pmol l\(^{-1}\); n = 8) was supplied by the manufacturer.

#### Tissue extracts measurements
Porcine adrenal tissue was used as positive control [26] and porcine heart tissue from the right ventricle was extracted in boiling water (1 g tissue per 10 ml), centrifuged at 10,000 \(×\) g for 30 min, and the supernatant was stored for later analyses with CgA immunoassays. Extraction methods and validation are described in details elsewhere [25].

#### TnT
TnT was measured in plasma samples collected every hour throughout the experiment, using an automated commercial assay (Modular E, Cobas Model, Roche Diagnostics, Germany) targeting conserved epitopes between pig and human TnT.

#### proANP
Plasma concentrations of proANP were measured as described elsewhere [23].

#### Hemodynamic parameters
Left ventricular pressure (LVP) and changes herein – maximum increase ([dP/dt]\(_{\text{max}}\) and maximum decrease (lusitropy = –[dP/dt]\(_{\text{max}}\)) – were measured using a Millar catheter. Mean arterial pressure, mean pulmonary arterial pressure and diuresis were measured throughout the
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Frydland, Kousholt, Larsen et al.

Frydland, Kousholt, Larsen et al.

experiment. All procedures were conducted as described by Kousholt et al. [23].

Statistical analysis
Data were analyzed with Graphpad Prism 5.0 (Graphpad Software, CA, USA). Data are expressed as mean ± standard error of mean. Wilcoxon matched pairs test was used to detect differences in plasma concentrations within each group and Mann–Whitney test was used between the groups. To test for differences between the three intervention subgroups, as well as between the overall intervention group and control group, data were analyzed by two-way analysis of variance. Comparison of all plasma concentrations of N-terminal CgA with all plasma concentrations of pancreastatin as well as TnT was made by Deming regression. Spearman’s analysis was used to test for correlation between CgA concentrations and proANP, hemodynamic parameters and TnT. p-values <0.05 were considered significant.

Results
The study material comprised 30 animals (25 in the intervention group and five in the control group). Seven pigs were excluded in total; three pigs went into cardiac arrest upon induction of ischemia before infusion therapy was instituted; one pig suffered from chronic pericarditis; and three pigs were excluded owing to unsuccessful infusion therapy. Thus, the study comprised 23 pigs (18 in the intervention group and five in the control group). Briefly, the infusion therapy consisted of BNP, CNP or saline infusion, and any differences between the intervention groups will also be stated here. Baseline values are presented in Table 1.

N-terminal CgA in plasma
The CgA level during ischemia was not different from baseline (intervention: 1488 ± 74 vs 1529 ± 77 pmol l⁻¹, respectively, p > 0.05; control: 2980 ± 198 vs 3255 ± 300 pmol l⁻¹, respectively, p > 0.05). However, a 1.3-fold increase in plasma concentrations was observed in the intervention group 1 h after initiation of reperfusion (1488 ± 74 vs 1899 ± 142 pmol l⁻¹, p<0.05). This increase was not noted in the control group (1 h after initiation of reperfusion, 2980 ± 198 vs 2795 ± 154 pmol l⁻¹, p > 0.05; Figure 2A).
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Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Intervention (n = 18)</th>
<th>Control (n = 5)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>91 ± 3.5</td>
<td>86 ± 5.0</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>2.7 ± 0.18</td>
<td>3.0 ± 0.14</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>89 ± 4.6</td>
<td>101 ± 4.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Venous O₂ saturation (%)</td>
<td>0.76 ± 0.02</td>
<td>0.77 ± 0.03</td>
<td>0.70</td>
</tr>
<tr>
<td>Partial pressure of CO₂ in venous blood (kPa)</td>
<td>5.4 ± 0.1</td>
<td>5.4 ± 0.2</td>
<td>0.70</td>
</tr>
<tr>
<td>pH</td>
<td>7.47 ± 0.01</td>
<td>7.49 ± 0.02</td>
<td>0.41</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.2 ± 0.1</td>
<td>38.5 ± 0.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.2 ± 0.1</td>
<td>4.4 ± 0.2</td>
<td>0.36</td>
</tr>
</tbody>
</table>

There were no differences between the groups. Data are expressed as mean ± standard error of mean.

N-terminal CgA in saline, BNP & CD-NP groups
To examine whether infusion of NPs affect the N-terminal CgA plasma concentrations, we tested for differences in between the three groups. No differences were noted (p = 0.79; Figure 2B).

Pancreastatin in plasma
Cardiac ischemia and early reperfusion did not affect plasma pancreastatin concentrations. At the end of reperfusion, a significant decrease was observed (503 ± 30 vs 384 ± 35 pmol l⁻¹, respectively, p<0.001; Figure 2C).

Pancreastatin in saline-, BNP-, & CD-NP groups
To examine whether infusion of NPs affect the N-terminal CgA plasma concentrations, we tested for differences in between the three groups. No differences were found (p = 0.19; Figure 2D).

N-terminal CgA, pancreastatin & TnT
Neither plasma N-terminal CgA (r = 0.07, p = 0.51; Figure 3A) nor plasma pancreastatin (r = -0.13, p = 0.24; Figure 3B) correlated with TnT (data fully presented by Kousholt B et al. [23]).

Deming regression of N-terminal CgA versus pancreastatin
We compared the changes in plasma concentrations of N-terminal CgA and pancreastatin, but found no correlation (p = 0.57; Figure 4).

Hemodynamic parameters
Infusion of NPs influenced animal hemodynamic parameters. The BNP- and CD-NP-treated animals had a decrease in MAP during the last hour of reperfusion (15 mmHg, p<0.0001 and 12 mmHg, p = 0.0052, respectively). A reduction in mean pulmonal arterial pressure was equally found in the two groups (3.3 mmHg, p<0.0005 and 2 mmHg, p<0.005, respectively). LVP max decreased during reperfusion in the BNP-treated animals compared with the controls (p = 0.02). The same trend was found in the CD-NP-treated animals. However, this was not significant. During reperfusion a decrease in dP/dT max and dP/dT min was observed in the BNP-treated animals compared with the control animals (p = 0.025 and 0.022, respectively). Diuresis increased in both groups throughout the experiment (data are presented in detail by Kousholt et al. [23]). We found no correlation between N-terminal CgA/pancreastatin and LVP (r = 0.11/0.12, p = 0.36/0.31, (dP/dt) min (r = -0.12/-0.18, p = 0.30/0.14) and (dP/dt) max (r = 0.12/0.22, p = 0.32/0.06).

proANP
We found no correlation between plasma proANP versus N-terminal CgA (r = -0.1, p = 0.35) and proANP vs pancreastatin (0.14, p = 0.18; data not shown).

Tissue extracts measurements
To assess whether myocardial tissue contained CgA, cardiac tissue extracts from healthy pigs were analyzed with both N-terminal and pancreastatin assays. Porcine adrenal tissue served as a positive control. Neither the N-terminal or pancreastatin immunoassays revealed CgA in myocardial tissue (<1 pmol l⁻¹/g tissue and 24 pmol l⁻¹/0.22 pmol g⁻¹ tissue, respectively), but both assays measured high N-terminal CgA and pancreastatin concentrations in the porcine adrenal tissue (17.600 pmol l⁻¹/189.2 pmol g⁻¹ tissue and 4.180 pmol l⁻¹/44.95 pmol g⁻¹ tissue, respectively; Table 2).

Discussion
In this study, we examined whether plasma CgA concentrations increase in response to acute
myocardial ischemia and subsequent reperfusion in a porcine model.

Assays
We chose to target the N-terminus and pancreastatin as these epitopes are highly preserved [4]. We chose N-terminal CgA as it gives rise to the peptide vasostatin-1, which is a peptide under massive investigation as it is believed to be a cardiac counter-regulatory modulator in ‘zero steady-state error’ homeostasis [27]. Increasing amount of evidence also point toward vasostatin-I as a natural defense against cardiac hyperactivity occurring during the ‘neuroendocrine storm’ [28] that arises during a myocardial infarction.

We chose to target pancreastatin as it is considered a modulator of insulin sensitivity and has been proposed to contribute to insulin resistance and hyperglycemia during sympathomimetic

![Figure 2. Relative changes in plasma CgA.](image)

Relative change in (A) N-terminal CgA and (C) pancreastatin in the intervention groups and the control group over time. Relative changes in N-terminal (B) CgA and (D) pancreastatin in the three intervention groups. (A) There was a significant 1.3-fold (p = 0.01) increase in plasma N-terminal CgA in response to reperfusion in the intervention group whereas there was no difference in the control group (p = 0.44). (B) There was no differences in between the intervention groups throughout the study (p = 0.79). (C) There was a significant 1.3-fold (p = 0.003) decrease in plasma pancreastatin from 0 to 240 min in the intervention groups. (D) No difference in between the three intervention groups throughout the study was observed (p = 0.19).
stress with excessive catecholamine release [29] – a scenario that occurs during a myocardial infarction [30].

- **Plasma concentration of CgA during cardiac ischemia/reperfusion**
  Our data show that acute ischemia per se is not associated with changes in plasma CgA in a porcine model. However, N-terminal CgA in plasma increased 1.3-fold during the reperfusion phase. As pancreastatin decreased throughout the entire experiment, a post-translational modification of CgA may occur.

- **Tissue origin**
  We were not able to detect neither N-terminal CgA nor pancreastatin in the myocardium from healthy pigs. In 1989 Steiner et al. for the first time demonstrated that CgA was present in secretory vesicles along with ANP in the right atrium in rats [31]. In 2000 Weiergräber et al. detected the same colocalization of ANP and CgA in the Purkinje fibers of the conducting system and in cardiomyocytes in both the atrium and ventricle of the rat [32]. In 2006 Glattard et al. found the CgA-derived peptide vasostatin in the rat heart – however they were not able to detect whether CgA was processed intra- or extracellular [33]. In 2007 Pieroni et al. found increased plasma concentration CgA as well as intracellular concentration in the cardiomyocytes of patients suffering from dilated and hypertrophic cardiomyopathies. However, they were only able to detect CgA mRNA and not the protein itself in the myocardium of healthy individuals [21]. Then in 2010 Biswas et al. detected the CgA-derived peptide cestatin in the murine heart [34].

A possible explanation may be that the animals in this study are young, as CgA has been found to increase with age [34]. Another explanation may be that fragments of CgA are secreted in a different manner, as seen in other peptide systems [35], and that N-terminal CgA is continuously secreted from the myocardium of healthy larger mammals and not stored, as observed in patients suffering from chronic heart diseases [21].

By contrast, we were able to detect both N-terminal CgA and pancreastatin in the adrenal gland; N-terminal CgA was present in a fourfold higher concentration than pancreastatin. This is in accordance with a number of previous findings first noticed by Helle et al. in 1965 [36]. The differentiated adrenal content indicates an inhibited post-translational modification, most likely due to the colocalization and release with
catecholamines, as described by Wolkersdorfer et al. [37].

As we and others did not detect CgA in the healthy myocardium, the plasma concentration of CgA-derived peptides originates therefore most likely originate from the adrenal gland. Moreover, no association between plasma CgA and TNF – a highly specific marker of cardiac tissue necrosis – was found. Supporting this theory is that deterioration in cardiac performance did not correlate to CgA.

An intriguing – although hypothetical – thought is that a substance is released from the myocardium during reperfusion that stimulates the adrenal gland to release CgA.

**CgA modification**

The differentiated plasma response of the two CgA-derived peptides is probably under the influence of catecholamine release [37]. An intriguing thought is that post-translational modification occurs in favor of vasostatin – a peptide derived from the N-terminus of CgA – which is protecting the myocardium under a state of reperfusion after acute ischemia in a preconditioning manner as suggested by Capello et al. [38]. Vasostatin-1 may also directly influence the acute inflammatory response that occurs during reperfusion [39–42] and may thereby protect the myocardium from an aggravating innate immune response – although this is hypothetical.

**CgA & NPs**

The link between CgA, NPs and catecholamines has recently been proposed to work as a ‘whip-brake’ system of the endocrine heart [43,44]. Kousholt et al. have recently found a decrease in infarct size after regional cardiac ischemia in response to infusion of NPs – possibly via non-cardiac mechanisms [23]. CgA are shown to have cardioprotective effects against ischemia, not only via an inhibition of catecholamine release [45] and β-receptor inhibition, but also through a direct influence on cardiomyocytes by a still unknown mechanism [46]. It has been suggested to be in both a pre- and post-conditioning manner [38,46]. As CgA is colocalized and coreleased with NPs in the myocardium [21], interference of the two cardioactive components was to be examined. We did not find any correlation between plasma CgA and atrial NP in this study of acute cardiac ischemia. No response in N-terminal CgA and pancreastatin plasma concentrations were detected in response to NP infusion and the mechanism behind the infarct reduction of NPs is therefore not due to enhancement of the cardioinhibitory or cardioprotective effects of CgA.

Taken together, the results suggest that CgA may be released as a response to reperfusion and that the organ source is not the heart but more likely the adrenal gland. Therefore, the increase in N-terminal CgA may reflect overall neuroendocrine activity. In addition, infusion of NPs did not affect plasma concentrations of N-terminal CgA in response to myocardial ischemia or reperfusion.

**Future perspective**

The posts ischemic increase in N-terminal CgA in response to cardiac reperfusion found in this study may reflect overall neuroendocrine activity. In the future, plasma CgA measurements may be a prognostic marker in the assessment of patients suffering from myocardial infarction and other diseases where high neuroendocrine activity is associated with poor prognostic outcomes. A patient-specific stratification profile consisting of several peptides providing prognostic information may help physicians to detect patients in need of high clinical attention and intensive treatment. N-terminal CgA measurements could provide such vital information.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

**Ethical conduct of research**

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.
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Executive summary

Background
- CgA is present in neuroendocrine tissue and is released in response to sympathomimetic stress.
- CgA undergoes tissue-specific post-translational modification into smaller peptides – some of which have cardioprotective abilities.
- CgA is a prognostic biomarker of long-term mortality in patients suffering from myocardial infarction.
- In the cardiomyocyte it is colocalized and released with natriuretic peptides (NPs).

Materials & methods
- A total of 18 pigs underwent 1 h of cardiac ischemia followed by 3 h of reperfusion.
- Plasma concentrations and myocardial contents of CgA were measured by two radioimmunoassays targeting CgA(1–9)Tyr and pancreastatin (CgA[250–301]).
- Influence of infused NPs on plasma CgA during reperfusion was evaluated.

Results
- Plasma CgA did not increase in response to cardiac ischemia but a 1.3-fold increase in N-terminal CgA was observed in response to reperfusion. Plasma concentration of pancreastatin decreased throughout the entire experiment.
- Neither N-terminal CgA nor pancreastatin was detected in the myocardium; however, both were present in the adrenal gland.
- Infusion of BNP and CD-NP did not affect the plasma concentration of N-terminal CgA and pancreastatin.

Discussion
- No CgA were detected in cardiomyocytes. The increase in CgA is hypothesized to be due to increased release from the adrenal gland. It is highly unlikely to originate from the heart as no CgA was found there.
- The differentiated response is probably due to tissue-specific post-translational modification. The increased N-terminal CgA may be an autonomic cardiac protection mechanism under the ‘neuroendocrine storm’ observed during a myocardial infarction.
- The infarct-reducing capabilities of NPs previously found by our group is not due to enhancement of the cardioinhibitory and cardioprotective effects of CgA.

Perspective
- In the future, N-terminal CgA may be a part of a patient-specific stratification profile consisting of several biomarkers in the initial assessment of patients suffering from myocardial infarction.

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Papers of special note have been highlighted as:
* of interest
** of considerable interest
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Research Article

Frydland, Kousholt, Larsen

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The CgA-derived peptide, catestatin, has a cardioprotective effect, reducing post-ischemic myocardial damage and dysfunction in isolated rat hearts.