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Intermedin and calcitonin gene-related peptide fail to shine in acute coronary syndrome

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Abstract

Aims: To measure levels of intermedin and calcitonin gene-related peptide (CGRP) in acute coronary syndrome (ACS) and to determine if they are elevated.

Methods and results: 81 patients admitted with suspected ACS were enrolled into the study. 50 were confirmed ACS by ACC (2000) guidelines and 31 were in a control group as non-cardiac chest pain. Intermedin was non-significantly elevated 6.14 pg/ml vs 4.84 pg/ml < 8 h in the ACS group; sensitivity 68%, specificity 63% on presenting sample. Intermedin was significantly elevated in those patients who had an initially negative troponin T (0.03 ng/ml) on presentation, 6.67 pg/ml vs 4.84 pg/ml, p = 0.03.

CGRP was significantly elevated in ACS patients, 8–<16 h after pain onset, 8.67 pg/ml vs 7.08 pg/ml, p = 0.036. However, it didn’t aid diagnosis in initially negative troponin patients; sensitivity 61%, specificity 60% on presenting sample. Both intermedin and CGRP were elevated in STEMI patients on a first sample, but only intermedin was significantly elevated; 7.03 pg/ml vs 4.84 pg/ml, p = 0.02 and 8.87 pg/ml vs 7.03 pg/ml, p = 0.093, respectively.

High sensitivity troponin T was significantly elevated in the ACS group at < 8 h (414.9 vs 17.22, p = 0.006) and at 8–<16 h (3225.27 vs 21.54, p = 0.002).

Conclusions: Both intermedin and CGRP are detectable in human patients. Levels show a trend to elevation in ACS, with CGRP being significantly raised >8 h after pain onset. The degree of elevation will have limited clinical applicability.

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1. Introduction

Chest pain remains a common presenting complaint to the Emergency Department, but only 15% of chest pain attendees actually have an ischaemic origin to their pain [1]. Separating acute coronary syndrome (ACS) from non-ischaemic chest pain or unstable angina can be performed by measurement of biomarkers of cardiac injury. Thygesen’s redefinition of acute myocardial infarction [2] defined the diagnosis of myocardial infarction as a rise and fall of troponin greater than the 99th percentile in a normal population. This was applicable as long as the assay used, had acceptable precision at this level, clinically defined as a coefficient of variation less than 10% [3]. The recently introduced highly sensitive troponin assays meet these criteria [4–6].

The enhanced clinical sensitivity of the highly sensitive troponins is accompanied by a reduced specificity for diagnosing myocardial infarction compared to the standard troponin assays. The highly sensitive troponin can be raised in conditions other than ACS [7]. A delta change in the high sensitivity troponin T level necessitating a second sample after a few hours is therefore required. This means further blood sampling and prolonging the patient’s period of uncertainty diagnosis. Another means of determining an ischaemic basis to the rise in troponin is to use another marker with the troponin. This study assesses two new markers, intermedin and calcitonin gene-related peptide, in the diagnosis of acute coronary syndrome.

The calcitonin gene-related peptide family is a group of peptides that includes calcitonin gene-related peptide (CGRP), adrenomedullin, amylin and intermedin [8].

Intermedin or adrenomedullin 2 was discovered simultaneously by two different research groups [8,9]. It is a 47 amino acid peptide which has some similarities to CGRP. Whilst initially found in the pituitary (from the intermediate lobe of the anterior pituitary, hence its name) it is also found in animal models in the kidney, brain, GI tract skin, pancreas, lung, spleen, thymus and ovary [10]. At human autopsy intermedin has been localised to cardiomyocytes and in lesser

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blood was collected in EDTA tubes with the addition of aprotinin taken. Twenty millilitres of blood was taken at each time point. The infarction patients presenting after 12 h still had the later samples.

CGRP is a 37 amino acid peptide that is found throughout the central and peripheral nervous system, most commonly in nerves that are associated with blood vessels. It’s release into the blood stream causes mainly local vasodilatation [14]. In the heart where there is a high concentration of CGRP nerve fibres [15] there is immunoreactive evidence of an increase in CGRP levels following infarction and at nerve endings [16]. When the LAD was occluded in dogs, with subsequent reperfusion, CGRP improved the contractile function [17]. Kallner found raised levels of CGRP in pig hearts 10–20 min after onset of myocardial ischaemia in coronary sinus sampling. However when exogenous CGRP was administered following an infarct, it precipitated hypotension, and failed to reduce the size of the infarct [18].

No data exists for these markers in human myocardial ischaemia/infarction.

2. Aims and objectives

The study aimed to document levels of intermedin and CGRP in patients with chest pain and determine if plasma levels are increased in acute coronary syndrome.

3. Methods

Subjects were enrolled into the study over a 15-month period from February 2008. The study conformed to the declaration of Helsinki and all patients gave informed written consent to enter the study, with the study protocol having been approved by the NHS research ethics committee for Northern Ireland. Patients were recruited on weekdays from those admitted to the Belfast City Hospital with chest pain of a suspected ischaemic nature.

All subjects were eligible for inclusion, the only exclusion being an age less than 18 years or an inability to consent. Subjects received a standard evaluation, including history, physical examination and 12-lead ECG. These details were recorded along with cardiovascular and cardiac non-vascular cells from oxidative stress and ischaemic reperfusion injury [12]. Infusion of intermedin at time of myocardial infarction in rat hearts did appear to attenuate the ischaemia reperfusion injury [13].

CGRP is a 37 amino acid peptide that is found throughout the central and peripheral nervous system, most commonly in nerves that are associated with blood vessels. It’s release into the blood stream causes mainly local vasodilatation [14]. In the heart where there is a high concentration of CGRP nerve fibres [15] there is immunoreactive evidence of an increase in CGRP levels following infarction and at nerve endings [16]. When the LAD was occluded in dogs, with subsequent reperfusion, CGRP improved the contractile function [17]. Kallner found raised levels of CGRP in pig hearts 10–20 min after onset of myocardial ischaemia in coronary sinus sampling. However when exogenous CGRP was administered following an infarct, it precipitated hypotension, and failed to reduce the size of the infarct [18].

No data exists for these markers in human myocardial ischaemia/infarction.

3.2. Assays

The peptides were solidified from the plasma using a solid phase extraction technique with the serum loaded onto washed Sep-Pak C18 cartridges (Waters SepPak©). The columns were washed with a buffer of trifluoroacetic acid, and then collected in a buffer of acetonitrile. This eluant was evaporated to 40% dryness by spinning in a centrifugal concentrator (Hetero Vac VR-1) and finally, freeze dried using a lyophilizer (Modulyo Freeze Dryer).

Peptide values were obtained using a radioimmunoassay kit (Phoenix Pharmaceuticals). The samples were incubated with a primary antibody and then radioactive iodine. The primary antibody was rabbit anti-peptide serum and was specific for the three active forms of intermedin or two active forms of CGRP, as shown in Appendix A. The bound sample was then precipitated out with the use of a secondary antibody and the radioactive count measured using a gamma counter. Using known standards, a binding curve could then be generated which allowed the amount of peptide to be derived. They were analysed in batches of 49 in duplicate samples [19].

The coefficient of variation in our laboratory for CGRP was 9.72% and for intermedin 2.8%.

This method was used to measure intermedin and calcitonin gene-related peptide, all other biochemical results were carried out by the CPA (Clinical Pathology Accreditation UK) hospital laboratory.

Statistical analysis was performed using SPSS version 19, with values given as mean ± SD. Differences were assessed using the student’s t-test, chi-squared test or Fisher’s exact test as appropriate. Significance was at the 5% level and was a two-sided analysis.

4. Results

The patients were divided into two groups depending on their diagnosis (ACS or non-cardiac chest pain), which was decided by an

![Fig. 1. Patient flow in the study.](image-url)
independent clinical team. The ACS group was further subdivided into ST elevation, non-ST elevation and unstable angina groups (Fig. 1).

4.1. Baseline characteristics

The baseline characteristics are summarized in Table 1. The mean age of the ACS group was older (66.72 vs 60.26 years, p = 0.048) than the non-cardiac chest pain (NCCP) group. Both groups had a preponderance of males with similar incidences of risk factors except for hypertension. This was found more often in non-cardiac chest pain group 65% vs 40%, p = 0.032.

Electrocardiogram (ECG) analysis showed that 77% of the NCCP group had a normal ECG or non-specific changes, compared to only 20% of the ACS group. Of these 20%, 75% received thrombolysis, 2 received primary PCI, 2 had transient elevation, which resolved with medical therapy and 1 had a previous sub-arachnoid haemorrhage and was treated conservatively.

4.1.1. Intermedin (IMD) levels

Within the ACS group, 6 time periods were established indicating the time from symptom onset to first sampling and to subsequent samples. The NCCP group only had samples taken up to 16 h after pain onset. The mean intermedin levels are shown in Table 2 and pictorially for ACS in Fig. 2.

The levels of intermedin were non-significantly elevated in the ACS group (6.14 pg/ml ± 2.17) versus the non-cardiac chest pain group (4.84 pg/ml ± 2.01) level <8 h after chest pain (p = 0.057). At the 8–16 hour time period the ACS mean of 5.87 ± 2.34 was not significantly different from the non-cardiac chest pain group 4.88 pg/ml ± 1.70, p = 0.098.

For those samples at exactly 12 h after pain, mean intermedin levels 5.90 pg/ml were statistically no different from the mean level 4.81 pg/ml in the non-cardiac chest pain group, p = 0.21. Looking at the presenting sample, the sensitivity for intermedin detecting ACS was 68%, specificity 63% with an area under the ROC curve of 0.341.

Within the ACS group 10 patients had no elevation of troponin on their presenting sample but it was subsequently raised at 12 h. In this subgroup the presenting intermedin level of 6.67 pg/ml ± 2.32 was significantly different from the non-cardiac chest pain mean 4.84 pg/ml ± 2.01, p = 0.03 (mean time of sample was 308 min for ACS and 341 for non-cardiac chest pain).

Similarly STEMI patients had a high presenting (<11 h) intermedin mean level of 7.03 pg/ml ± 1.60 which was significantly different
from a mean non-cardiac chest pain value of 4.84 pg/ml ± 2.01, p = 0.02.

4.1.2. Calcitonin gene-related peptide (CGRP)

Samples were measured in 80 patients, 49 in the ACS group and 31 in the non-cardiac chest pain group (there was not enough serum collected from one patient to allow CGRP analysis). The results are shown in Table 3 and pictorially in Fig. 3.

The CGRP level at 8–16 h in the ACS group was significantly different from the non-cardiac chest pain group, 8.67 pg/ml ± 2.71 vs 7.08 pg/ml ± 2.36, p = 0.0036. However there was no significant difference between the ACS and non-cardiac chest pain groups before 8 h. The sensitivity of CGRP on a presenting sample of predicting ACS was 61%, specificity 60% and area under ROC curve 0.32.

In the 10 patients who had an initially negative troponin, but subsequent elevation at 12 h, the ACS group had a mean value of 8.87 pg/ml ± 2.66 which compared non-significantly to the non-cardiac chest pain group prior to 12 h of 7.03 pg/ml ± 2.92, p = 0.093. At 12 h the mean CGRP level in the ACS group was 9.76 ± 2.58 which was significantly different from the 12-hour non-cardiac chest pain value of 6.64 pg/ml ± 2.05, p = 0.001.

Surprisingly in STEMI patients, where 8 patients had samples prior to 12 h, their mean CGRP level was 9.43 pg/ml ± 2.71, which wasn’t significantly different from the non-cardiac chest pain group.

4.1.3. High sensitivity troponin T (HsTnT)

The same group of patients subsequently had high sensitivity troponin T measured. This was done after completion of the study and had no bearing on the clinical management of the patient. Results were available in 77 patients, 49 in the ACS cohort and 28 in the non-cardiac chest pain group, Table 4.

Comparison of the ACS HsTnT mean 414.9 ng/ml ± 561 with the control mean 17.22 ng/ml ± 10.4 shows they are significantly different with a p value of 0.006. Comparison at the time point 8 h to 16 h is also significant, p = 0.02.

Of the 30 patients in the non-cardiac chest pain group, 8 patients had a HsTnT > 14 ng/l on admission (the 99th percentile value). Of these 7 stayed within the biological variation [9] or fell in value. The intermedin and CGRP values for this group were not significantly elevated.

In 1 patient who presented at 500 min, the HsTnT was 14.6 ng/l which increased to 45.4 ng/l at 12 h. The standard troponin remained <0.03 ng/ml at both time points.

5. Discussion

ACS patients are initially differentiated by the ECG, which will mark out those patients with a STEMI (ST elevation myocardial infarction) group. This is a declining proportion of ACS patients. The remainder are subdivided into those that have had myocardial damage from those that have not. The current gold standard biomarker diagnosing this myocardial damage is the cardiac troponin, namely the high sensitivity troponins [20]. The highly sensitive troponin has a >95% negative predictive value on a first presentation sample [7,21]. However the improved analytical ability of the assay has revealed a chronic elevation in a cohort of patients who don’t have acute coronary syndrome. Therefore similar to the contemporary troponin, again, a repeat sample is required 3–6 h after presentation to rule out a significant change [22,23]. Another marker with the troponin could fill this void.

This study provides the first human data on the biologically plausible biomarker intermedin (IMD). It shows intermedin is detectable, at low levels, in both normal control patients and patients with acute coronary syndrome; it appears to be at its highest elevation on presentation and again at 24 h, with a trend towards elevation in ACS patients.

In those ACS patients who are initially troponin T negative, the mean intermedin level was 6.65 pg/ml and was significantly different from the control value (4.84 pg/ml) at this early time period, <8 h. However, the sensitivity and specificity for a presenting sample are disappointing, 68% and 63% respectively, which is not better than the high sensitivity troponins.

In this cohort the increase from a normal control value to a diseased value is only an increase of 25–30%. This is a small increase when you consider a troponin can increase several hundred times. Estimating a normal distribution using the summary statistics in our study leads to an ACS curve, which overlaps with the upper values of ‘normal’ in the

**Table 3**

<table>
<thead>
<tr>
<th>CGRP</th>
<th>&lt;8 h</th>
<th>8 h–16 h</th>
<th>16 h–24 h</th>
<th>24 h–36 h</th>
<th>36 h–48 h</th>
<th>&gt;48 h</th>
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<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
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</tr>
</tbody>
</table>

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**Fig. 2.** Mean intermedin levels (pg/ml) with 95% confidence intervals at selected time points in the ACS patients.

**Fig. 3.** Mean CGRP levels (pg/ml) with 95% confidence intervals at selected time points in the ACS patients.

**Table 4**

CGRP levels in both groups.

Mean CGRP levels (pg/ml) and standard deviations of the ACS and NCCP groups at time points after chest pain onset.
shown a lot of variation from 1.86 pg/ml to 18.2 pg/ml in treated hypertensive patients. One analysis in ACS patients. In the previous studies of CGRP, a found for intermedin. The mean level of CGRP at the earliest time ACS patients and controls. The CGRP levels were higher than those young normal people found mean values of 42.8 ± 7.12 pg/ml. This is re non-cardiac chest pain group. This is reflected in the low sensitivity, specificity and ROC values obtained. It is therefore likely that intermedin may not be particularly helpful in discriminating ACS patients from the chest pain population.

With the limited exploration of intermedin, confounders are unknown, but some studies suggest that hypertension or renal dysfunction may influence levels.

5.1. CGRP

In our study CGRP was measureable peripherally in all patients, both ACS patients and controls. The CGRP levels were higher than those found for intermedin. The mean level of CGRP at the earliest time point, was 7.09 pg/ml in the control patients and 7.81 pg/ml in the ACS patients. In the previous studies of CGRP, a ‘normal’ value has shown a lot of variation from 1.86 pg/ml to 18.2 pg/ml in treated hypertensive patients. One analysis in young normal people found mean values of 42.8 ± 7.12 pg/ml. This may be the affect of different assays and antibody characteristics.

The ACS patients again showed a trend to a higher elevation at the earliest time point, and this was statistically significant at 12 h after chest pain onset, p = 0.005. The time course of CGRP appears to peak at 8 to 16 h after pain, before falling back to a plateau level, which is still higher than control values.

However as with intermedin the sensitivity and specificity at just over 60% are not rigorous enough to be useful as a discriminating test for ACS.

A possible confounder is the use of nitroglycerin or long acting nitrate. CGRP and nitric oxide (NO) appear to be interlinked, where treatment with nitroglycerin causes a decrease in blood pressure and an increase in CGRP levels. High levels of CGRP cause an increase in endogenous NO levels. When the nerve stores are depleted, such as with capsaicin, or CGRP antagonist, then the effect of nitroglycerin is significantly impaired. This could impact our results, where patients have received GTN spray prior to blood sampling, which could raise CGRP levels, when not actually in the setting of ACS. This may be an explanation for the high levels seen on presentation in a few of the control samples. However, even with these high levels in the controls, there was still a significant difference in means at the 12 hour time point. The ACS group would have been as likely to receive nitroglycerin as a treatment therapy on presentation.

In those patients who present with a negative troponin, CGRP was not significantly raised in comparison to controls until we reached the 12-hour time period. Therefore unlike intermedin, CGRP appears to be elevated later. This is surprising, given that CGRP is stored and released from the nerves on nerve initiation. Intermedin needs to be cleaved and manufactured, which you would expect to take longer than the process of simple release from vesicle stores. One possible explanation for this is the use of peripheral sampling. Kallner in his assessment of CGRP post CABG ischaemia, found levels significantly elevated in coronary sinus blood, but not raised from peripheral venous sampling. The animal studies have mainly used central sampling, hence it may take prolonged ischaemia/infarction for CGRP levels to become exceedingly elevated that they can be detected peripherally.

5.2. Troponin

Out of 50 ACS patients, the contemporary troponin was elevated in 37, on a presenting sample. In comparison the high sensitivity was elevated in 48 out of 49 patients on their presenting sample. Only 1 patient had a value less than the 99th percentile cut-off, which was a sample taken before 4 h after chest pain onset.

It would have re-classified one of the non-cardiac chest pain and 1 of the unstable anginas to a NSTEMI.

The spread of results show why HsTnT is a better marker. It has extremely low values in control patients, <14 ng/l and increases to exceedingly high levels in positive cases. The percentage increase from a ‘normal' value to a ‘diseased' value is many hundredfold, making differentiating diseased from a normal much easier to do.

6. Limitations

There are several limitations within the study, the first is the small numbers of patients within the study. The groups are small and numbers at some of the time points are limited, which means we have to be guarded in our overall conclusions.

We know some of the interactions of CGRP in hypertension, congestive cardiac failure and possibly how intermedin’s levels are affected in these conditions. But overall a full understanding of what happens to these molecules in humans in various conditions is not established. CGRP’s full interaction with nitrates and how one affects the other, needs to be elucidated further as nitrates are a mainstay of angina therapy and a first line therapy in myocardial infarction.

These peptides may have more local effects than systemic effects and they may not be released in great enough quantities to be detected systemically/peripherally.

Currently the method of detecting CGRP and intermedin is by use of a 3 day radio-immunoassay, which is acceptable for a research basis, but not if you wish to decide urgent patient management. An ELISA assay has been made by Phoenix Pharmaceuticals for intermedin, but it’s sensitivity is much less than the radioimmunoassay kit, with a lower reading of 100 pg/ml. This level is far in excess of the values we were obtaining. Similarly with CGRP, the lower level of detection in the ELISA kit is 280 pg/ml.

Finally, this was a proof of concept study and didn’t look at long-term morbidity and mortality, hence the prognostic implications of raised levels are uncertain.

7. Conclusions

This is the first in man study of the cardioprotective peptide intermedin, it does appear to have a small rise in acute coronary syndrome, but the magnitude (25–30%) of this may make its clinical applicability limited. Its clinical confounders remain uncertain.

CGRP also rises in ACS, later than intermedin, but the release appears to be more sustained. CGRP has a lot of local in-vitro effects that may not translate to a measurable systemic/peripheral level.

The HsTnT is a better marker of ACS than both experimental markers at all time points.
Appendix A

Intermedin primary antibody reactivity

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<tr>
<th>Cross reactivity</th>
<th>Peptide</th>
<th>% cross-reactivity</th>
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<td>Intermedin/AM-2 (mouse)</td>
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<td>CGRP</td>
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<td>CGRP (8–37) (human)</td>
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Calcitonin gene-related peptide reactivity.

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<th>Cross reactivity</th>
<th>Peptide</th>
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References


