# Influence of Gender on the Prognostic Value of Troponin I After Elective Percutaneous Coronary Interventions

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## Objective

To evaluate the association between troponin I concentrations (TnI) in patients submitted to elective percutaneous coronary interventions (PCI) and adverse coronary events (ACE) during a six month follow-up period

## Methods

One hundred and eleven patients who had been submitted to an elective PCI were consecutively selected during a one year timeframe. The patients had stable angina (SA), unstable angina (UA) or silent ischemia (SI) and were asymptomatic for at least 72 hours before the procedure. TnI concentrations were measured between 8 and 24 hours after the PCI. Each patient was contacted by telephone six months later and interviewed regarding ACE which were defined as death, myocardial infarction, new revascularization and recurrent ischemia.

## Results

Twenty-four patients showed elevated concentrations of TnI (21.6%) after the PCI regardless of clinical characteristics or procedure complications. Those who presented elevated TnI concentrations had higher event rates: 66.7 vs. 42.5% (RR=1.57; CI 95%=1.08-2.28). This risk seems to be higher in the subgroups of females and patients with a previous diagnosis of unstable angina. Multivariate analysis confirmed that gender was the only effect modifying co-variable associated with ACE risk, which is higher for females with elevated TnI concentrations (OR=7.22; CI 95%=1.4 -36.9) and unaltered for males (OR=1.26; CI 95%=0.35-4.55).

## Conclusion

Elevated TnI concentrations were a common occurrence after PCI and is a factor related to the development of ACE in the mid term. However, when adjusted for other variables, this effect is only maintained in female patients.

## Key words

Troponin, percutaneous coronary intervention, prognosis.

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Percutaneous coronary intervention procedures are frequently associated with the development of minimal myocardial necrosis or silent myocardial infarctions which generally speaking are only detected by the elevated serum levels of cardiac necrosis biochemical markers[1-5]. These small heart attacks are usually caused by micro-embolization during the procedure[6,7].

Results documented in recent publications are controversial regarding the prognostic value of these minimal myocardial lesions in relation to the occurrence of events after a PCI [8-10] . Conversely, the prognostic value of elevations, even though minimal, of the cardiac necrosis biochemical markers for acute coronary syndromes (ACS) has been well demonstrated[11]. Previous studies have shown that elevated levels of the creatine kinase-MB (CK-MB) cardiac isoform after a PCI are relevant for prognosis purposes, but only when the levels are at least three times higher than the normal value[12,13]. The specificity and sensitivity of cardiac troponins (TnI and TnT) are considered to be higher than CK-MB[13-15] and are elevated in approximately 13 to 48% of the patients submitted to PCI[7,16,17]. The elevation or re-elevation of TnI after PCI in ACS is associated with a higher risk to develop cardiovascular events in the mid to long terms[5,10,18]. Nevertheless, in the case of elective PCI this association is still questionable[19-21].

The objective of this study is to evaluate whether or not TnI concentrations after elective PCI are associated with adverse cardiac events (ACE) which are defined as death, acute myocardial infarction, new revascularization procedures or recurrent ischemia during a six month follow-up timeframe after hospital discharge.

## Methods

Patients admitted to a coronary care unit after elective PCI surgery were consecutively selected between July 2000 and August 2001. All patients had been previously diagnosed with stable angina (SA), silent myocardial ischemia (SI) or unstable angina (UA) and had been asymptomatic for at least 72 hours before the procedure. Patients who had suffered an AMI within 15 days of the procedure or presented elevated TnI concentrations within 48 hours of the procedure were excluded from the study. The PCI procedures were performed by a team of professionals with extensive experience in this area, who were also responsible for the stent implant indications.

TnI concentrations were taken on all individuals between 8 and 24 hours after the PCI procedure. The measurements were taken using chemiluminescence (DPC - Diagnostics Products Corporation, Los Angeles, California, USA). When more than one measurement was taken the highest value was used as the reference. TnI elevations above 1.0 ng/dl were considered abnormal, based on the manufacturer's recommendation for AMI diagnostic criteria.

A standard questionnaire, detailing clinical characteristics, was filled out for each patient in the study. The angiographical data were analyzed by a single observer who was unaware of the patients' clinical and laboratorial characteristics. Lesions angiographically evaluated before the intervention that presented an image indicative of thrombi, dissection or branch artery involvement, were considered complex PCI lesions. After the procedure, the following complications were observed: acute occlusion, dissection and branch occlusions. Patient follow-up was conducted by a trained interviewer via telephone. All patients consented to participate in the study by telephone. ACE information for one, three and six months after the PCI was supplied by the patient or a representative familiar with the situation. Documented myocardial ischemia was considered when recorded by an ischemic test or Holter monitoring. All other adverse cardiac events, including death, AMI and new myocardial revascularization, whether a new PCI or myocardial revascularization surgery, were based on the information supplied by the person interviewed.

*Statistical analysis* - Elevation of TnI was evaluated as the main independent variable and adverse coronary events evaluated as the main dependent variable.

Based on theoretical data, gender, age and immediate procedure complications were evaluated as possible effect modifiers. In addition to these factors, stent implantation, lesion complexity and a diagnosis of unstable angina before the PCI were evaluated as possible confounding factors.

The age variable did not present a normal distribution and was transformed into a categorical variable, described in ratios. The association between TnI and co-variables was evaluated using the chi-square test.

The association between TnI elevation and cardiovascular events within six months was calculated for all patients by estimating the gross (not adjusted) risk ratio (RR) and using stratification in subgroups of interest. In this stage, interaction evaluations were calculated using the Mantel-Haenszel homogeneity test; if p was less than 0.20 the co-variable would be included in the logistic regression model.

Multivariate analysis with nonconditional logistic regression was used to estimate the odds ratio (OR) between TnI elevation and events within six months. Interaction analysis was conducted using the verisimilitude rate test (log likelihood ratio test) to compare models with and without interaction terms. Confounding analysis was conducted using the OR alteration of the variable in focus (percent change in effect), eliminating variables with the backward stepwise strategy.

The significance level adopted for two tailed hypotheses was 5%. The data collected were processed using the computer program STATA 7.

## Results

The study population was comprised of 111 patients and 24 presented elevated TnI concentrations (21.6%). Stents were used in 86.4% of the interventions and did not present an association with TnI elevations. Table 1 shows the distribution of the co-variables gender, age, diagnosis before the PCI, use of stents, immediate procedure complications and the main six month event outcome variable according to troponin values (normal or elevated).

Males did not represent the highest percentage of patients with elevated TnI concentrations (50 versus 49.4% of the patients with normal troponin, p=0.96), age ≥ 65 years (50 versus 44.8%, p=0.65), a previous diagnosis of unstable angina (41.7 versus 46.0%, p=0.71), stent implants (87.5 versus 87.7%, p=1.0) or immediate procedure complications (37.5 versus 34.5%, p=0.78). The development of ACE within six months was more frequent in those with elevated TnI concentrations (66.7 versus 42.5%, p=0.036). Comparison of the ACE within the six month timeframe between the patients who had elevated TnI concentrations and those who did not revealed: death (4.3 versus 0%, p=0.22); heart attack (17.4 versus 2.5%, p=0.02); new revascularization procedure (8.7 versus 20.0%, p=0.35); ischemia recorded during an ischemic test (50% versus 31.3%, p=0.07).

Table 2 shows the risk levels associated with elevated TnI concentrations. The gross estimate shows a higher relative risk to develop events in those with elevated TnI concentrations (RR=1.57; CI 95%=1.08-2.28). Initially this risk appeared to be higher in the female subgroups when compared to males (RR=2.04 versus 1.13; MH=0.12) and in those with a previous diagnosis of unstable angina (RR=2.15 versus 1.26; MH=0.17). After analysis using logistic regression models only gender was confirmed as a effect modifying co-variable.

As shown in Table 3, the odds ratio obtained by logistic regression for events in those that presented elevated TnI concentrations was 2.70 (CI 95%=1.05-6.98). By applying the logistic regression model, gender was identified as an effect modifier and no other confounding variables were associated with troponin and events.

**Table 1 - Population characteristics according to troponin value.**

| | Elevated Troponin | | Normal Troponinl | | p value |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | |
| Gender | | | | | |
| Male | 12 | 50 | 43 | 49.4 | 0.96 |
| Female | 12 | 50 | 44 | 50.6 | |
| Elderly | | | | | |
| > 65 years | 12 | 50.0 | 39 | 44.8 | 0.65 |
| ≤ 65 years | 12 | 50.0 | 48 | 55.2 | |
| Previous diagnosis of unstable angina | | | | | |
| Yes | 10 | 41.7 | 40 | 46.0 | 0.71 |
| No | 14 | 58.3 | 47 | 54.0 | |
| Immediate PCI complications | | | | | |
| Yes | 9 | 37.5 | 30 | 34.5 | 0.78 |
| No | 15 | 62.5 | 57 | 65.5 | |
| Use of *stent* | | | | | |
| Yes | 21 | 87.5 | 74 | 87.1 | 1.0 |
| No | 3 | 12.5 | 11 | 12.9 | |
| Event within six months | | | | | |
| Yes | 16 | 66.7 | 37 | 42.5 | 0.036 |
| No | 8 | 33.3 | 50 | 57.5 | |

**Table 2 - Stratified analysis using the homogeneity test for the association between troponin and cardiovascular events within six months.**

| | n | RR | CI 95% | p value* |
|---|---|---|---|---|
| **Gross association** | 111 | 1.57 | 1.08- | |
| Gender | | | | |
| Male | 55 | 1.13 | 0.59- | |
| Female | 56 | 2.04 | 1.32- | |
| Adjusted | | 1.57 | 1.08- | |
| M-H # | | | | 0.12 |
| **Age** | | | | |
| ≥ 65 years | 48 | 1.63 | 0.85- | |
| < 65 years | 63 | 1.52 | 0.98- | |
| Adjusted | | 1.59 | 1.10- | |
| M-H # | | | | 0.92 |
| **Diagnóstico de anginia** | | | | |
| Yes | 50 | 2.15 | 1.18- | |
| No | 61 | 1.16 | 0.78- | |
| Adjusted | | 1.55 | 1.06- | |
| M-H # | | | | 0.17 |
| **Lesão complexa** | | | | |
| Yes | 82 | 1.38 | 0.84- | |
| No | 29 | 1.94 | 1.03- | |
| M-H # | | 1.56 | 1.06- | 0.41 |
| **Complicação** | | | | |
| Yes | 39 | 1.19 | 0.59- | |
| No | 72 | 1.82 | 1.18- | |
| Adjusted | | 1.56 | 1.08- | |
| M-H # | | | | 0.31 |

*RR- risco relativo; IC 95%=intervalo de confiança de 95%; # método de Mantel-Haenszel pelo STATA com intervalo de confiança e teste de homogeneidade; *valor de p para teste de homogeneidade: através do método de Mantel-Haenszel pelo STATA.*

**Tabela 3 - Associação entre troponina elevada e eventos com seis meses.**

| | n | OR | IC 95% | Valor de p |
|---|---|---|---|---|
| Risco relativo | 111 | 1,57 | 1,08-2,28* | 0,036 |
| *Odds ratio** | 111 | 2,70 | 1,05-6,98 | 0,04 |
| Sexo feminino | 56 | 7,22 | 1,41-36,96 | 0,017 |
| Sexo masculino | 55 | 1,26 | 0,35-4,55 | 0,72 |

**obtido através de regressão logística.*

## Discussion

This study, conducted in a single center, confirms that the elevation of cardiac troponins is a common condition after PCI and is an important prognostic factor for ACE in the mid-term[5]. This elevation was not related to the angiographic characteristics or immediate procedure complications; findings that to date are controversial issues[1-4,6,7,12]. The mechanisms that confirm a greater necessity of subsequent revascularization due to elevated TnI concentrations after the procedure have not yet been discovered[16].

During patient follow-up after the PCI, the combination of events including cardiovascular death, AMI, new revascularization procedures and recurrent myocardial ischemia has been used often. Different criteria are used to define recurrent ischemia which include recurrent angina, hospital admission for angina or ischemia recorded during an ischemic test[22]. Ischemic tests are more dependable than the presence of angina and were used to increase the reliability of the results in this study.

The results of recent studies are still controversial regarding the importance of elevated CK-MB and troponin concentrations to predict mortality in the

mid and long term. Even though troponins are more sensitive markers in the detection of myocardial necrosis[23] than CK-MB, some authors have not found an association between elevated troponin concentrations and increased mortality rates in the mid and long term. However, these authors relate that the elevation of CK-MB is an independent predicting mortality factor for these patients[24,25]. There are still controversies regarding definite cut-off points for cardiac enzyme levels to determine clinically important cardiac necrosis and whether or not a minimal elevation of these markers has prognostic relevance[26-28].

In this study, TnI elevation after elective PCI was associated with the development of cardiovascular events in the following six months, which could justify a differentiated approach for these patients in terms of both more aggressive treatments and more attentive follow-up that could include routine ischemic tests. This investigation could be beneficial in preventing more serious events such as death and recurrent AMI in the long term. In the short term, there is no indication that the risk of death is associated with these minimal myocardial necrosis marker elevations[29].

The findings of this study should be considered with limitations that have also been encountered by other studies covering this topic[15]. Even though all the patients with a history of unstable angina and AMI underwent basal troponin concentration assessments the stable patients did not, and therefore it is possible that patients with stable symptoms and elevated basal troponin concentrations were included in the study. Nevertheless, it does not seem justifiable to routinely assess these concentrations before the procedure. Furthermore, the use of a categorized value, in our case 1.0 ng/dl, could be questioned since there is no definite data for an exact cut-off value. There was also no differentiation among the groups for the degree of troponin elevation, gender or race and troponin concentrations could be different in these subgroups[30]. Even though an association between troponin concentrations after PCI and adverse events within six months of the procedure has been reported, a causal relation cannot be determined from these data alone. Further studies are necessary to confirm this relationship and to determine a possible relationship in the long term.

The increased risk associated with TnI elevations in female patients could be related to the fact that this subgroup has lower TnI values than men[30]. Since we used the same cut-off point for both genders, we could be including men with proportionately lower values in the elevated troponin subgroup. Considering an arbitrary value for TnI elevation, in our case above 1.0 ng/dl, the treatment for women should be more attentive than for men; a fact to be confirmed in studies directed towards this specific objective.

We concluded that TnI elevations, a common occurrence after PCI, indicating silent myocardial infarctions caused by micro-embolization, are an important predicting factor for ACE in the mid term. Consequently, this type of lesion after iatrogenic coronary manipulation should be systematically predicted, assessed and if detected the doctors should be advised of the risk profile of these patients[27]. Further studies are required to evaluate the efficacy of secondary prevention strategies for mid and long term prognosis in these cases.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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