Does C-reactive Protein Add Prognostic Value to GRACE Score in Acute Coronary Syndromes?

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Abstract

Background: The incremental prognostic value of plasma levels of C-reactive protein (CRP) in relation to GRACE score has not been established in patients with acute coronary syndrome (ACS) with non-ST segment elevation.

Objective: To test the hypothesis that CRP measurements at admission increases the prognostic value of GRACE score in patients with ACS.

Methods: A total of 290 subjects, consecutively admitted for ACS, with plasma material obtained upon admission CRP measurement using a high-sensitivity method (nephelometry) were studied. Cardiovascular outcomes during hospitalization were defined by the combination of death, nonfatal myocardial infarction or nonfatal refractory angina.

Results: The incidence of cardiovascular events during hospitalization was 15% (18 deaths, 11 myocardial infarctions, 13 angina episodes) with CRP showing C-statistics of 0.60 (95% CI = 0.51-0.70, p = 0.034) in predicting these outcomes. After adjustment for the GRACE score, elevated CRP (defined as the best cutoff point) tended to be associated with hospital events (OR = 1.89, 95% CI = 0.92 to 3.88, p = 0.08). However, the addition of the variable elevated CRP in the GRACE model did not result in significant increase in C-statistics, which ranged from 0.705 to 0.718 (p = 0.46). Similarly, there was no significant reclassification of risk with the addition of CRP in the predictor model (net reclassification = 5.7 %, p = 0.15).

Conclusion: Although CRP is associated with hospital outcomes, this inflammatory marker does not increase the prognostic value of the GRACE score. (Arq Bras Cardiol. 2014; 102(5):449-455)

Keywords: C-Reactive Protein; Acute Coronary Syndrome; Prognosis; Probability.

Introduction

In patients with acute coronary syndrome (ACS) with non-ST-segment elevation, the inflammatory phenomenon hinders the atherosclerotic plaque stabilization, making it vulnerable to recurring coronary events[1]. This is the rationale for the prognostic value of inflammatory markers in ACS. Among these markers, High-Sensitivity C-Reactive Protein (hs-CRP) is the best studied as a risk predictor in clinical practice[2]. Actually, several studies have shown an association between CRP and cardiovascular risk in patients with ACS[3].

The prognostic association, however, is not a sufficient criterion to define the clinical usefulness. A new biomarker usefulness depends on the demonstration of its incremental value in prognostic models traditionally used in clinical practice[4]. Our group previously demonstrated that CRP modestly increases the TIMI risk score[5]. In recent years, the GRACE score has shown to be the multivariate model with the best accuracy[6]. However, the incremental value of CRP in relation to GRACE score is yet to be established.

To test the hypothesis that the measurement of CRP increases the prognostic value of the GRACE score, this marker was measured at admission in patients with ACS with non-ST segment elevation and recurrent events were recorded prospectively. Discriminatory analysis (C-statistics) and net reclassification were used as measures of incremental value.

Methods

Sample Selection

Individuals consecutively admitted to the Coronary Care Unit of two tertiary hospitals between August 2007 and December 2011, with a diagnosis of unstable angina or myocardial infarction with non-ST segment elevation, were candidates for the Acute Coronary Syndrome Registry (RESCA). The inclusion criteria for this registry is defined by typical chest discomfort and at rest in the past 48 hours, associated with at least one of the following: 1) positive myocardial necrosis marker, defined by troponin T ≥ 0.01 ug/L or troponin I > 0.034 g/L, which

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correspond to values above the 99th percentile[7,8]; 2) ischemic electrocardiographic alterations, consisting of T-wave inversion (≥ 0.1 mV) or transient ST-segment depression (≥ 0.05 mV); 3) previously documented coronary artery disease, defined as history of myocardial infarction or previous angiography demonstrating coronary obstruction ≥ 50%. We excluded patients whose admission plasma samples were insufficient for CRP measurement and those that refused to participate in the study. The protocol complies with the Declaration of Helsinki and was approved by the Research Ethics Committee of the institution and all patients signed the free and informed consent form.

High-Sensitivity C-Reactive Protein measurement

The measurement of hs-CRP was carried out in a blood sample collected immediately after hospital admission, aiming at attaining minimum delay between symptom onset and material collection. The plasma was frozen at -70°C for simultaneous measurement of the sample. The nephelometry method (Dade - Behring, Newark, Delaware, USA) was used[9]. The assistant team was blinded to the CRP values during patient hospitalization.

GRACE score

To calculate the GRACE score, patients' clinical data collected at the emergency department, electrocardiograms performed within 6 hours of treatment, troponin T measurements related to the first 12 hours of care and the value of the first plasma creatinine were used. Elevation of myocardial necrosis marker as component of the scores was defined as troponin > 99th percentile[8]. The Killip classification was also applied to patients with unstable angina so that the GRACE score could be calculated. The GRACE score consists of eight variables: five of them are computed semiquantitatively, i.e., different weight for each stratum of age, systolic blood pressure, heart rate, plasma creatinine and Killip class; three of them computed dichotomously (ST-segment depression, myocardial necrosis marker elevation, cardiac arrest on admission). The final score can range from 0 to 372[10].

Cardiovascular outcomes

The primary outcome was defined by the combination of cardiovascular death, nonfatal myocardial infarction or nonfatal refractory angina during hospitalization. Nonfatal myocardial infarction was recorded during hospitalization when there was elevation of troponin > the 99th percentile in patients whose values were negative in the first 24 hours. For patients with infarction on admission, a new CK-MB peak (>50% of the previous value and above the normal value) was required for the definition of reinfarction. Elevation of necrosis markers induced by percutaneous coronary procedure or CABG was not recorded as a recurrent event. Refractory angina during hospitalization was defined by recurrent chest pain at least twice, despite the use of nitrates and controlled double product.

Additionally, patients were contacted by telephone after 30 days, 6 months, and annually thereafter for the detection of combined cardiovascular death, myocardial infarction or readmission for unstable angina. Readmission was identified by telephone contact and the reason was checked through an interview with the patient and medical record data. Cardiovascular death was defined as sudden death or cardiovascular hospitalization followed by death.

Statistical Analysis

Initially, a Receiver Operating Characteristic (ROC) curve of CRP levels was constructed to be used as predictors of cardiovascular outcome. Once the accuracy by the ROC curve was demonstrated, the best cutoff point was identified.

This cutoff was used to define *elevated* CRP, which was entered into a logistic regression model with the GRACE score. If elevated CRP reached statistical significance at the 10% level ($p < 0.10$), a new GRACE-CRP score would be created, by adding points when CRP was elevated. Additional points were determined by the ratio between the regression coefficient of elevated CRP and the regression coefficient of the GRACE score.

In the discriminant analysis, C-statistics of the GRACE and GRACE-CRP models were compared by the Hanley – McNeil test[11]. The calibration of the models was described by the Hosmer-Lemeshow test. Furthermore, we evaluated the capacity of the new model (GRACE- CRP) to correctly reclassify information from the traditional GRACE model (high risk *versus* low risk). The best cutoff from each model in our sample was used for risk definition. The Pencina method (Net Reclassification Improvement-NRI) was used in the net reclassification analysis[12] (Figure 1).

CRP values were described as median and interquartile range (IQR) and compared between groups by the non-parametric Mann-Whitney test. Statistically significant p value was defined as < 0.05. SPSS software, version 21 (IBM North America, New York, NY) was used.

Sample size calculation

The sample was sized to provide statistical power for two predefined statistical analysis. First, the logistic regression analysis, in which we evaluated the predictive value of CRP, regardless of the GRACE score. As this analysis requires two covariates (elevated CRP and GRACE), 20 outcomes are necessary to maintain the recommended ratio of 10 outcomes per covariable[13]. Second, comparison of the GRACE C-statistics *versus* GRACE-CRP: assuming a correlation coefficient between the values of two models of 0.95 for a statistical power of 80% (one-tailed alpha of 0.05) in the detection of 0.05 superiority of C-statistics (e.g., 0.65 *versus* 0.70) of the most complete model (GRACE- CRP) a total of 42 outcomes are required[11]. Thus, we sequentially included the number of patients necessary to total 42 hospital outcomes, which was enough for both analyses described herein.

Results

Selected sample

A total of 290 patients aged 68 ± 13 years, 52 % females, 53% with a diagnosis of myocardial infarction with non-ST segment elevation and the rest with unstable angina were studied.

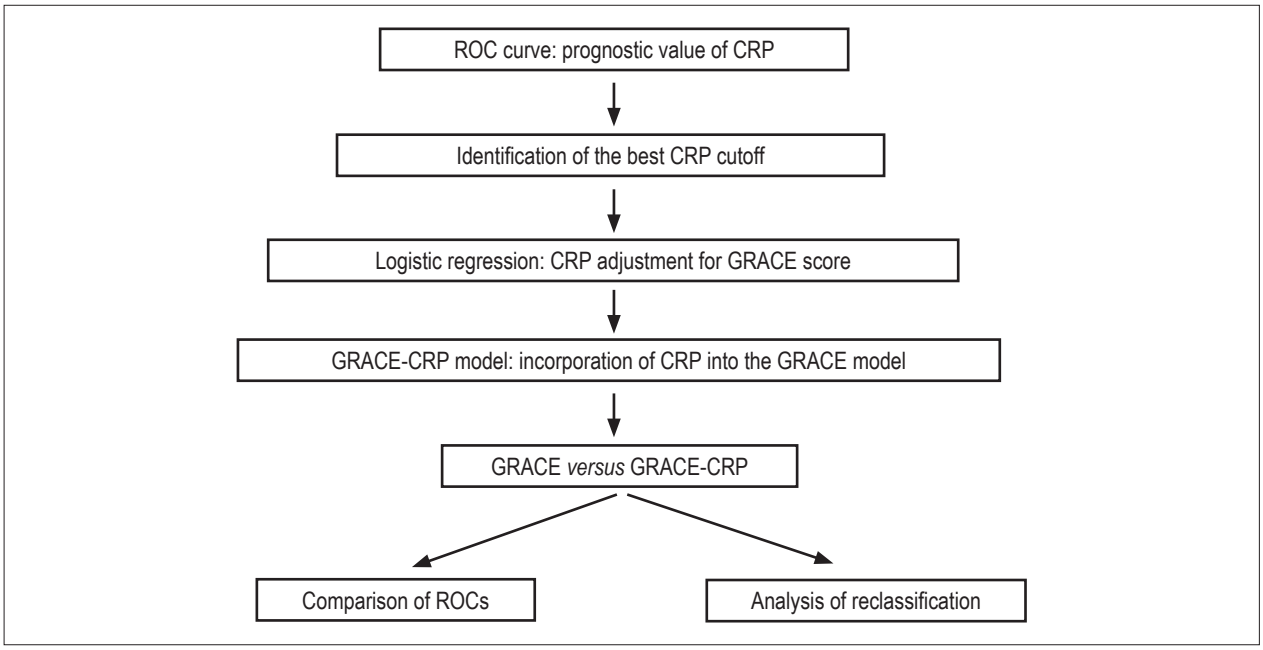

Figure 1 – *Flowchart of data analysis. CRP: C-reactive protein; ROC: Receiver operating characteristic.*

The GRACE score showed a median of 115 (IQR = 94-140), with 43% being low risk, 32% medium risk and 25% high risk. The median time between symptom onset and CRP measurement was 6.7 hours (IQR = 3.3 to 24). CRP showed a median of 4.5 mg/L (IQR = 1.4 to 13 mg/L), showing increased inflammatory activity exacerbated by the acute clinical picture. The incidence of cardiovascular outcomes during hospitalization was 15% (18 cardiovascular deaths, 11 nonfatal AMIs, 13 cases of nonfatal refractory angina). After discharge, 244 patients were followed for 518 ± 446 days, with an incidence of cardiovascular outcomes of 24% (11 cardiovascular deaths, 18 hospitalizations for AMI and 28 hospitalizations for angina).

Prognostic value of C-reactive protein

Patients who developed hospital outcome showed median CRP of 9.1 mg/L (IQR = 2.1 to 22 mg/L), significantly higher than the median of 4.3 mg/L (IQR = 1.3 to 11 mg/ L) observed in patients free of outcomes (p = 0.034). The predictive capacity of CRP in relation to hospital outcomes was characterized by C-statistics of 0.60 (95% CI = 0.51-0.70). In this analysis, the definition of elevated CRP that showed the best accuracy corresponded to a cutoff of 8.83 mg/L.

Analysis of clinical characteristics showed that the group with elevated CRP had modestly older mean age, higher prevalence of positive troponin and Killip > 1, all variables found in the GRACE score, not requiring their entering the multivariate model. Variables not covered by GRACE, as well as treatment variables, were similar between groups (Table 1). When the CRP was adjusted for the GRACE score, statistical significance was reduced to a borderline value (OR = 1.9, 95% CI = 0.92- 3.9, p = 0.08). In this model, the association between the GRACE regression coefficient and the CRP coefficient was 30. Thus, at the construction of the GRACE-CRP score 30 points were added when CRP was elevated.

Different from the in-hospital phase, CRP values showed no predictive accuracy for cardiovascular outcomes in the late follow-up, with C-statistics of 0.51 (95 % CI = 0.42 to 0.59, p = 0.90). The same occurred when only the hard endpoints of death and nonfatal myocardial infarction were considered (C -statistics = 0.59, 95% CI = 0.49-0.69, p = 0.11).

Incremental value of CRP during hospitalization

The addition of the variable elevated CRP to the GRACE model did not result in significant increase in C-statistics, which ranged from 0.705 to 0.718 (p = 0.46) (Figure 2). The GRACE score showed satisfactory calibration with $|^2$ using the Hosmer - Lemeshow test of 7.5 (p = 0.48). After inclusion of elevated CRP in the model, there was no improvement in calibration, which evolved into $|^2$ of 12.1 and p value = 0.15 (Table 2).

Reclassification of the GRACE score by C-reactive protein

Among the 42 patients who had hospital outcomes, two were wrongly reclassified from high to low risk, whereas there was no correct reclassification. This resulted in negative net reclassification index for patients with outcomes (- 4.8%).

Among the 248 patients free of hospital outcomes, 26 were correctly reclassified from high to low risk, with no incorrect reclassifications. This resulted in a positive net reclassification index for patients without outcomes (10.5 %).

In the final analysis, when all patients were considered, the net reclassification index was 5.7 % (p = 0.15), indicating that CRP has no value as reclassifying variable of the GRACE score (Table 3).

Table 1 – Comparison of clinical characteristics between patients with and without elevated C-reactive protein

	CRP ≥ 8.83 mg/L	CRP < 8.83 mg/L	p value
Sample	91	199	
Age (years)	71 ± 13	67 ± 13	0.07
Male gender	48 (53%)	90 (45%)	0.23
Diabetes	38 (42%)	77 (39%)	0.62
Positive troponin	62 (68%)	93 (47%)	0.001
ST segment elevation	22 (24%)	35 (18%)	0.19
Killip > 1	29 (32%)	22 (11%)	< 0.001
Creatinine clearance (mL/min)	49 ± 25	57 ± 22	0.01
GRACE score	136 ± 39	113 ± 35	< 0.001
In-Hospital treatment			
Aspirin	87 (97%)	197 (100%)	0.10
Clopidogrel /Ticagrelor	80 (89%)	184 (93%)	0.25
Subcutaneous enoxaparin	76 (84%)	167 (84%)	1.0
Intravenous unfractionated heparin	3 (88%)	4 (86%)	0.68
GP IIb / IIIa antagonist	6 (6.6%)	7 (3.5%)	0.36
Nitrate	69 (76%)	139 (70%)	0.33
Beta-blocker	67 (74%)	141 (72%)	0.77
Statin	85 (96%)	193 (98%)	0.38
Percutaneous coronary intervention	27 (30%)	60 (30%)	1.0
Coronary artery bypass grafting	10 (11%)	15 (8.0%)	0.30

CRP: C-reactive; GP: Platelet dycoprotein.

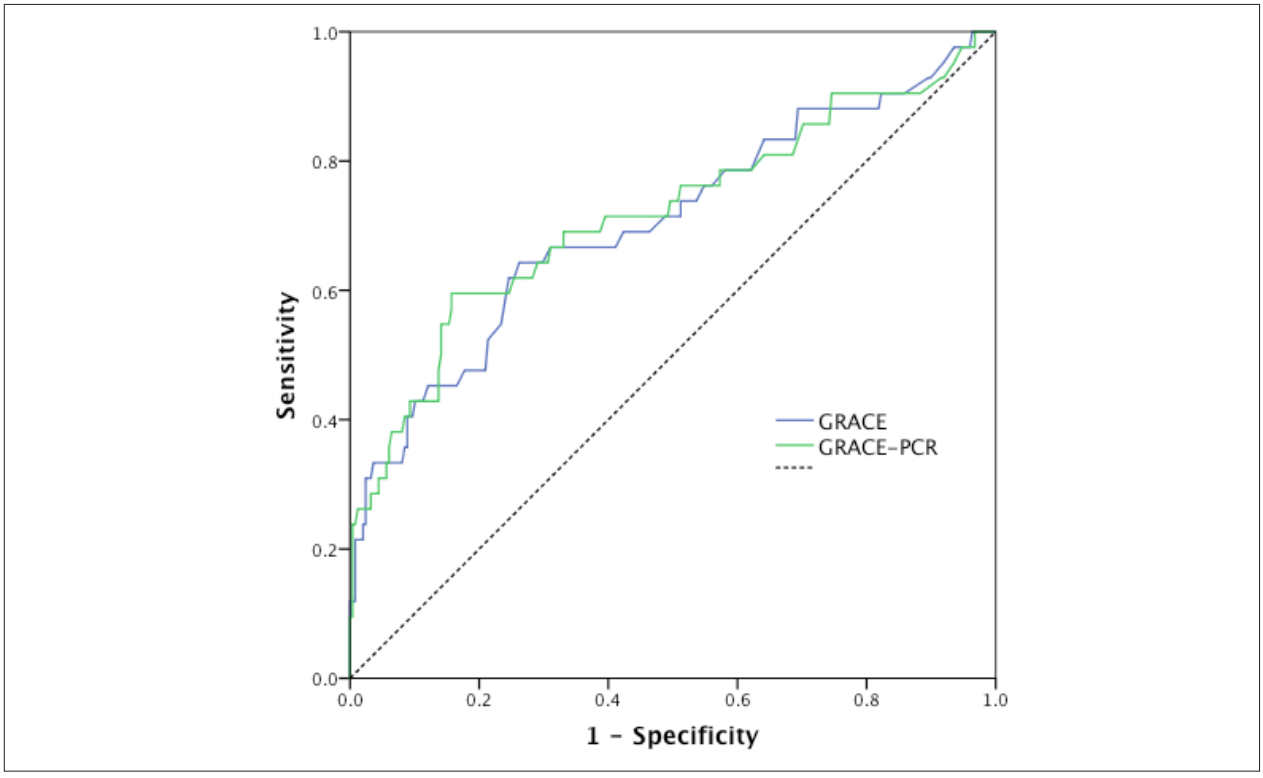

Figure 2 – *Comparison of ROC curves between GRACE and GRACE-CRP shows similar C-statistics between the two scores (p = 0.46).*

Table 2 – Logistic regression model containing GRACE and CRP in predicting hospital outcomes

Variable	Coefficient ®	Odds Ratio (95%CI)	p value
Elevated CRP (dichotomy)	0.638	1.89 (0.92 – 3.9)	0.08
GRACE score (numeri`cal)	0.021	1.02 (1.01 – 1.03)	< 0.001

CI: confidence interval

Table 3 – Analysis of net reclassification by CRP-GRACE score in relation to the GRACE score for the definition of high risk

	N	Reclassification for more	Reclassification for less	NRI	p value
Outcome	42	0	2	- 4.8%	
No outcome	248	0	26	10.5%	
Total	290	0	28	5.7%	0.15

Discussion

This prospective cohort study tested the prognostic value of CRP measured at admission of patients with ACS with non-ST segment elevation. Consistent with previous studies, CRP was associated with cardiovascular outcomes during hospitalization. However, CRP incremental analysis indicated the lack of usefulness for this marker in clinical practice. This apparent contradiction between association with outcome and the lack of incremental value needs to be interpreted.

The strength of the inflammatory hypothesis as a mechanism of genesis and destabilization of atherosclerotic plaques increased in the 1990s, based on experimental studies[1], followed by evidence of the association of CRP with cardiovascular risk in the general population[14]. In the 2000s, several studies were published in journals of high impact, favorable to the prognostic value of CRP in patients with ACS. These studies were analyzed as a systematic review and meta-analysis by our group, which was published in 2010[3]. Unlike the enthusiastic attitude of some authors, our review concluded that there was no conclusive evidence of the incremental prognostic value of CRP. Moreover, only two studies had made incremental evaluation (preliminary studies)[5,15], while the remainder was limited to the assessment of independent association .

It is noteworthy that an independent association is not enough to establish the usefulness of a biomarker. To interrupt the predictor evaluation at this stage, considering it validated for clinical use, has been a common error[16]. The most important question is whether the new risk marker has incremental usefulness in models applied in clinical practice. This response should be obtained by comparing the performance of a predictive model that uses the usual variables with the performance of an alternative model resulting from the incorporation of the new marker into the traditional model. That is, after inserting a new variable to a risk score, how much does the performance of this score improve? The most common way to evaluate this question is to measure the increase in C-statistics after incorporation of the new biomarker, which was not done by most of the studies in that review. Furthermore, we analyzed the net reclassification, which identifies the correct reclassifications (upwards in a patient that will have an outcome and downwards in a patient without outcome) and subtract from the incorrect ones. This method shows the proportion of patients in which the advent of the new biomarker promoted a correct change in relation to the risk.

Over the past three years, two new studies have been published. A Spanish study where Lopes-Cuenca et al. showed no increase in CRP in the C-statistics of GRACE[17] and a French study, in which He et al[18] seem to have demonstrated positive data. However, when analyzing the details, one can see that the data of He et al[18] suggest the same negative conclusion of our study. As for the discriminatory value, those authors describe a modest increase in C-statistics, from 0.795 to 0.823. Although this difference was statistically significant, its magnitude is of little clinical relevance. Second, the authors take into account a correct reclassification of 12%. However, the net reclassification in which the incorrect are subtracted from the correct is not calculated. If this had been done, absence of reclassification would have been the conclusion. In the present study, we performed C-statistical analysis and correctly applied the Pencina method of reclassification, concluding realistically for the absence of clinical usefulness in incorporating CRP into the routine assessment of patients with ACS.

Thus, the apparent contradiction between the enthusiasm of initial studies and recent evidence is explained by the lack of careful analysis that the first studies performed in their own data. In recent years, the evolution of the scientific community regarding the concept of usefulness of a new biomarker has become stricter regarding data analysis, which ultimately should include incremental value. The CRP is not approved according to this analysis and our study is further evidence in this direction.

The main limitation of this study is its sample size, and thus, our data cannot be considered definitive regarding the lack of any prognosis increment with CRP. On the other hand, we must emphasize that this result is in line with previous studies, which showed no significant improvement

in C-statistics[17,18]. In addition, our number of outcomes resulted in enough statistical power to identify any clinically relevant increase in C-statistics. As for the late follow-up, there was a loss of 16% in the sample, which is not desirable. Moreover, we emphasize that this follow-up represents a secondary objective of the study and it is unlikely that there would be such difference regarding the characteristics of 46 patients without follow-up to the point of modifying a prior entirely negative result.

We must acknowledge that these data do not definitively rule out the usefulness of other inflammatory markers such as cytokines. In a previous study, our group demonstrated the potential value of a composite score with several inflammatory markers[19] and this year a Spanish study showed very significant increase and reclassification with interleukin - 6 in relation to GRACE[17].

Conclusion

The limited incremental value of CRP in relation to GRACE score suggests that the incorporation of this new biomarker in clinical practice for patients with ACS with non-ST-segment elevation is not indicated.

Author contributions

Conception and design of the research: Correia LCL, Silva A, Noya-Rabelo MM; Acquisition of data: Vasconcelos I, Garcia G, Kalil F, Silva A, Oliveira R, Carvalhal M, Freitas C, Ferreira F; Analysis and interpretation of the data: Correia LCL, Carvalhal M, Noya-Rabelo MM; Statistical analysis: Correia LCL; Writing of the manuscript: Correia LCL, Noya-Rabelo MM; Critical revision of the manuscript for intellectual content: Correia LCL, Vasconcelos I, Garcia G, Kalil F, Silva A, Carvalhal M, Ferreira F, Noya-Rabelo MM.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

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