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# First inflammatory risk score for aortic endoprostheses

## *Primeiro escore de risco inflamatório das endopróteses de aorta*

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*Abstract*

***Objective:*** **To propose an inflammatory risk score for aortic aneurysm endovascular treatment.**

***Methods:*** **Twenty-five patients were followed-up from the preoperative period to the third postoperative month (1 hour, 6 hours, 24 hours, 48 hours, 7 days, 1 month, 2 months and 3 months). Inflammatory variables were C-reactive protein, the blood sedimentation velocity, interleukins (IL-6, IL-8), tumor necrosis factor-Alpha, L-selectin, intercellular adhesion molecule (ICAM-1), red blood cell transfusion, volume of crystalloid solution, volume of contrast, type of endoprosthesis, number of endoprostheses and total leukocyte and lymphocyte counts. Spearman test defined the variables considered candidates for higher inflammatory risk based on a P ≤ 20%. Logistic regression defined the variables considered in the selection of the final score based on a *P* ≤ 10%. ROC curve analysis revealed the cut-off values for variables selected by logistic regression.**

***Results:*** **Variables defined by the Spearman test were: volume of crystalloid (*P*=0.04), type of endoprosthesis (P=0.04), volume of contrast (*P*=0.02), preoperative IL-8 (*P* = 0.10), 1-month ICAM-1 (*P*=0.03) and 1-month L-selectin (*P*=0.06). Logistic regression revealed that the volume of crystalloid and preoperative IL-8 are relevant in the composition of the inflammatory risk score for aortic aneurysm endovascular treatment. The risk score would be divided into three categories (mild, moderate and severe) based on numeric intervals of these two variables with the categories being correlated to clinical findings.**

***Conclusion:*** **Volume of crystalloid and preoperative IL-8 are variables that might contribute to categorize inflammatory risk and thus they might play a prognostic role in aortic aneurysm endovascular treatment.**

***Descriptors:*** **Prostheses and implants. Inflammation. Aorta/surgery. Risk. Risk assessment.**

*Resumo*

***Objetivo:*** **Propor um escore de risco inflamatório para tratamento endovascular dos aneurismas da aorta.**

***Métodos:*** **Vinte e cinco pacientes foram seguidos do período pré-operatório até 3º mês de pós-operatório (1 hora, 6 horas, 24 horas, 48 horas, 7 dias, 1 mês, 2 meses e 3 meses). Variáveis inflamatórias avaliadas foram proteína C reativa, velocidade de hemossedimentação, interleucinas (IL-6, IL-8), fator de necrose tumoral alfa, L-selectina, molécula de adesão intercelular (ICAM-1), transfusão de hemáceas, volume de cristalóide, volume de contraste, material da prótese, número de próteses, contagem total de leucócitos e linfócitos. O teste de Spearman apontou as variáveis candidatas ao maior risco inflamatório, segundo *P* ≤ 20%. A regressão logística apontou variáveis selecionáveis para escore final segundo *P* ≤ 10%. A análise da curva ROC revelou valores de corte para variáveis selecionadas pela regressão logística.**

***Resultados:*** **Variáveis apresentadas pelo teste de Spearman foram: volume de cristalóide (*P* = 0,04), material da prótese (*P* = 0,04), volume de contraste (*P*=0,02), IL-8 pré-operatória (*P*=**

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**0,10), ICAM-1 1 mês (*P*=0,03) e L-selectina 1 mês (*P* = 0,06). A regressão logística revelou que os valores do volume de cristalóide e IL-8 pré-operatória são primordiais para constituição do escore de risco inflamatório para tratamento endovascular dos aneurismas da aorta. O escore de risco seria dividido em três categorias (leve, moderado e grave), com base em intervalos numéricos das duas variáveis selecionadas e as categorias seriam correlacionadas com achados clínicos.**

***Conclusão:*** **Volume de cristalóide e IL-8 pré-operatória são variáveis que poderiam contribuir para categorizar risco inflamatório e, desse modo, ter um papel prognóstico no tratamento endovascular dos aneurismas da aorta.**

***Descritores:*** **Próteses e implantes. Inflamação. Aorta/ cirurgia. Risco. Medição de risco.**

## INTRODUCTION

The prognosis and life expectancy of individuals with aortic aneurisms depends on several factors, including the time of diagnosis, the adequate choice of therapeutic modality, as well as the postoperative radiological follow up.

For many years, the most indicated surgical treatment for aortic aneurisms was the substitution of the dilated segment using a prosthetic material, with or without the re-implantation of related arterial branches [1].

In 1991, the success obtained by Parodi et al. in the correction of an abdominal aortic aneurism using an endoprosthesis, gave vascular and cardiovascular surgeons another option of a novel and promising therapy, in particular for individuals with numerous or considerably deleterious comorbidities [2]. Despite of the satisfactory results obtained with the endovascular treatment of aortic aneurisms, some complications have been documented, such as the occurrence of strokes, paraplegia, prosthetic migration, embolic phenomenon and leaks [3-6].

Gabriel et al. [7] recently demonstrated that the endovascular procedure for the correction of aortic aneurisms involves factors related to a systemic inflammatory response, both in the acute phase and in a later phase of the postoperative follow up. These authors postulated that inflammatory mediators, such as cytokines and cellular adhesion molecules, can be better evaluated by means of curves that register the variability of their serum levels over time. This knowledge is of notable relevance for the professional that performs the endovascular procedure, largely because it enables the correlation of different postoperative clinical manifestations with the inflammatory role that each marker may play in the organism. Moreover, by knowing and understanding this correlation, it will be possible, if necessary, to institute an effective medicinal treatment.

However, there are no studies that define which inflammatory variables are elementary to the prognosis of individuals submitted to the endovascular treatment of aortic aneurisms [7].

Hence, the aim of this study is to propose an inflammatory risk score for individuals submitted to the endovascular correction of aortic aneurisms.

## METHODS

This research was approved by the Research Ethics Committee of the Federal University of Sao Paulo (UNIFESP) and complies with the Declaration of Helsinki. All the individuals signed written consent forms before participating in the study.

In the period from March to December 2005, 25 patients with thoracic or abdominal aortic aneurisms were prospectively enrolled. The exclusion criteria were acute dissections, traumatic dissections, inflammatory aneurisms, conjunctive tissue diseases and patients presenting with any sign of infection or immunodeficiency at the time of the endovascular procedure. The demographic characteristics and operative aspects are shown in Table 1. Some inflammatory variables considered in this study were evaluated in the preoperative period (24 hours before the endovascular procedure) and at several intervals during the postoperative follow up (1 hour, 6 hours, 24 hours, 48 hours, 7 days, 1 month, 2 months and 3 months). All these variables were considered parametric except for intramural thrombi and material of the endoprosthesis, which were analyzed as non-parametric. The parametric variables were employed to obtain a risk score model, considering only the time at which they were most prevalent (Table 2), based on the study performed by Gabriel et al. [7]. The hypothesis was, that the higher the values of the parametric variables, the greater the risk of inflammation; on the other hand, the simple presence of non-parametric variables would be compatible with a greater probability of risk. The raw data of 25 patients in relation to the variables and intervals of time of greatest prevalence, as demonstrated in Tables 3 and 4, allows us to apply a step-by-step method to configure a risk score.

Initially, the Spearman test determined which inflammatory variables can be classified as candidates for the score model based on a level of significance d” 20%

Table 1. Demographic and operative aspects

| Variable | N | % |
|---|---|---|
| *Gender* | | |
| Men | 21 | 84 |
| Women | 4 | 16 |
| *Comorbidities* | | |
| Hypertension | 25 | 100 |
| Diabetes mellitus - ID | 0 | 0 |
| Diabetes mellitus - NID | 2 | 8 |
| Obesity | 8 | 32 |
| Smoking | 18 | 72 |
| COPD | 6 | 24 |
| Previous strokes | 1 | 4 |
| Previous acute myocardial infarction | 5 | 20 |
| instable angina | 1 | 4 |
| stable angina | 2 | 8 |
| congestive heart failure | 1 | 4 |
| chronic renal failure * | 2 | 8 |
| Dyslipidemia | 8 | 32 |
| liver failure | 0 | 0 |
| atrial fibrillation | 0 | 0 |
| other arrhythmias | 4 | 16 |
| peripheral vascular disease | 0 | 0 |
| Gout | 2 | 8 |
| *Volume of crystalloid solution* | | |
| < 2000 mL | 13 | 52 |
| 2000 - 3000 mL | 7 | 28 |
| > 3000 mL | 5 | 20 |
| *Transfusion of red blood cells* | | |
| Yes | 6 | 24 |
| No | 19 | 76 |
| *Volume of contrast* | | |
| 40 - 160 mL | 20 | 80 |
| 160 - 280 mL | 5 | 20 |
| *Material of the endoprosthesis* | | |
| Stainless steel | 22 | 88 |
| Nitinol | 2 | 8 |
| Stainless steel + nitinol | 1 | 4 |
| *Number of endoprostheses* | | |
| 1 - 3 | 23 | 92 |
| 4 - 5 | 2 | 8 |
| *Thrombi* | | |
| Yes | 17 | 68 |
| No | 8 | 32 |

*ID: Insulin-dependent; NID: non-insulin-dependent; DPOC: Chronic occlusive pulmonary disease; * (serum creatinine > 2mg/dL)*

Table 2. Inflammatory variables and period of greatest prevalence

| Variable | Time |
|---|---|
| total neutrophil count | 24 hours |
| total lymphocyte count | 1 month |
| Volume de crystalloid solution – mL | * |
| Volume de contrast - mL | * |
| Transfusion of red blood cells | * |
| Presence of intraluminal thrombi | ** |
| Material of endoprosthesis | ** |
| Number of endoprostheses | * |
| Velocity of blood sedimentation - mm/h | 7 days |
| C-reactive protein (CRP) - mm/dL | 48 hours |
| Interleukin 6 (IL-6) - pg/mL | 24 hours |
| Interleukin 8 (IL-8) - pg/mL | pre-operative |
| tumoral necrosis factor alpha (TNF-α)-pg/mL | pre-operative |
| intercellular adhesion Molecule (ICAM-1)-pg/mL | 1 month |
| L-selectin - pg/mL | 1 month |

** parametric variables related to the intra-operative period;*
*** non-parametric variables*

(Table 5). Subsequently, logistic regression was applied to select variables that effectively would be used in the establishment of an inflammatory risk score. In this final selection phase, a level of significance ≤ 10% was adopted. Analysis of the ROC curve was utilized to determine cut-off values for the variables identified by the logistic regression test.

## RESULTS

The logistic regression test identified the volume of crystalloid solution and the preoperative level of IL-8 as possible variables for the formation of an inflammatory risk score. The analysis of the ROC curve (Figure 1) indicated that the highest values of sensitivity and specificity found for the volume of crystalloid solution and the preoperative IL-8 level were 1850 mL and 33.53 pg/mL, respectively and, thus, these should be the cut-off values for the variables.

Hence, it was possible to allocate the values of both variables, found for the 25 patients, to different categories of inflammatory risk, as well as to estimate the maximum probability of risk (Table 6). Table 7 demonstrates the model of inflammatory risk score of aortic endoprostheses based on the correlation of the cut-off values and different numeric intervals with the most common clinical manifestations.

Table 3. Raw dada of the 25 patients (part I)

| Pacient | Thrombus | Tr | VC | ME | NE | VCON | VHS 7d | PCR 48h | IL6 24h | pre IL8 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Yes | No | 3000 | 1 | 3 | 50 | 45 | 9.42 | 105.85 | 28.36 |
| 2 | Yes | No | 3500 | 1 | 3 | 58 | 51 | 13.00 | 74.02 | 106.07 |
| 3 | Yes | Yes | 1200 | 1 | 3 | 80 | 9 | 40.50 | 211.75 | 646.98 |
| 4 | No | Yes | 1750 | 1 | 1 | 170 | 51 | 32.80 | 121.04 | 59.34 |
| 5 | No | No | 2000 | 1 | 3 | 140 | 23 | 4.13 | 75.47 | 11.05 |
| 6 | No | Yes | 2000 | 1 | 3 | 160 | 39 | 9.20 | 44.19 | 15.11 |
| 7 | Yes | No | 2000 | 1 | 3 | 120 | 62 | 15.80 | 0.00 | 2.15 |
| 8 | Yes | Yes | 3500 | 1 | 4 | 140 | 0 | 21.70 | 981.70 | 51.85 |
| 9 | Yes | No | 1500 | 1 | 3 | 120 | 51 | 8.66 | 49.02 | 6.47 |
| 10 | Yes | Yes | 3500 | 1 | 3 | 200 | 120 | 19.25 | 155.54 | 45.37 |
| 11 | Yes | No | 1500 | 1 | 2 | 40 | 78 | 6.11 | 2.54 | 15.11 |
| 12 | Yes | No | 1250 | 1 | 3 | 90 | 57 | 14.30 | 18.68 | 0.00 |
| 13 | No | No | 2500 | 1 | 3 | 105 | 36 | 26.00 | 125.43 | 15.11 |
| 14 | Yes | Yes | 4000 | 1 | 5 | 188 | 7 | 19.50 | 768.70 | 1802.09 |
| 15 | No | No | 2500 | 1 | 2 | 100 | 18 | 23.00 | 59.51 | 2.15 |
| 16 | No | No | 1500 | 1 | 3 | 120 | 25 | 21.20 | 768.70 | 230.03 |
| 17 | Yes | No | 2500 | 1 | 3 | 60 | 35 | 22.30 | 218.84 | 13.63 |
| 18 | Yes | No | 2500 | 2 | 3 | 180 | 51 | 11.40 | 89.40 | 221.82 |
| 19 | Yes | No | 3000 | 1 | 2 | 280 | 9 | 15.00 | 24.15 | 59.80 |
| 20 | Yes | No | 1500 | 1 e 2 | 3 | 130 | 5 | 15.00 | 2000.00 | 23.40 |
| 21 | Yes | No | 3000 | 1 | 3 | 150 | 67 | 15.00 | 39.54 | 54.89 |
| 22 | Yes | No | 3500 | 2 | 2 | 120 | 96 | 15.00 | 1500.00 | 38.70 |
| 23 | Yes | No | 1500 | 1 | 3 | 110 | 25 | 9.73 | 17.37 | 0.00 |
| 24 | Yes | No | 1500 | 1 | 3 | 110 | 0 | 30.40 | 259.70 | 21.59 |
| 25 | No | No | 1000 | 1 | 2 | 110 | 112 | 14.21 | 325.42 | 25.63 |

*Tr –Red blood cell transfusion; VC - volume de crystalloid solution; ME - material of the endoprosthesis ; NE - number of endoprostheses; VCON - volume of contrast*

Table 4. Raw dada of the 25 patients (part II)

| Pacient | ICAM1m | Lsel 1m | pre TNF | Leuk 24h | Ly 1m |
|---|---|---|---|---|---|
| 1 | 895.01 | 2130.02 | 98.21 | 7500 | 1600 |
| 2 | 879.95 | 3030.18 | 18.21 | 13000 | 1100 |
| 3 | 810.91 | 1512.48 | 168.20 | 14600 | 2800 |
| 4 | 719.56 | 2479.06 | 26.43 | 13600 | 1600 |
| 5 | 2120.00 | 3466.66 | 6.37 | 12600 | 2700 |
| 6 | 2100.00 | 2655.86 | 12.86 | 8700 | 2400 |
| 7 | 4.75 | 0.00 | 6.09 | 20500 | 2600 |
| 8 | 855.98 | 27.60 | 16.81 | 21400 | 938 |
| 9 | 785.44 | 15.23 | 8.12 | 9200 | 1900 |
| 10 | 664.18 | 9.35 | 18.12 | 14600 | 1700 |
| 11 | 806.05 | 9.65 | 11.51 | 11900 | 1400 |
| 12 | 59.70 | 3.00 | 12.18 | 9000 | 1200 |
| 13 | 1274.81 | 1619.29 | 14.19 | 16900 | 2000 |
| 14 | 519.93 | 16.44 | 31.74 | 16800 | 800 |
| 15 | 1613.10 | 3948.30 | 24.02 | 8900 | 1500 |
| 16 | 1200.00 | 3948.30 | 20.09 | 9000 | 1700 |
| 17 | 739.40 | 2508.91 | 33.74 | 14500 | 2000 |
| 18 | 1836.74 | 5000.00 | 0.00 | 10600 | 2400 |
| 19 | 2.20 | 1575.40 | 4589.00 | 10900 | 2200 |
| 20 | 1836.74 | 3265.13 | 2588.70 | 9800 | 1800 |
| 21 | 1850.00 | 3566.59 | 1568.40 | 6500 | 1700 |
| 22 | 1872.55 | 3566.59 | 3217.40 | 12900 | 3400 |
| 23 | 11.70 | 987.70 | 19.43 | 5000 | 1200 |
| 24 | 416.89 | 12.82 | 6.77 | 17000 | 2600 |
| 25 | 405.40 | 1306.70 | 40.09 | 12000 | 1800 |

*ICAM - intercellular adhesion molecule; Lsel - L-selectin; TNF - tumoral necrosis factor; Leuk - total leukocyte count; Ly - total lymphocyte count*

Table 5. Candidate variables for the risk score model

| Variable | Level of significance (*P*)* |
|---|---|
| Volume de crystalloid solution | 0.04 |
| Material of endoprosthesis | 0.04 |
| Volume of contrast | 0.02 |
| pre-operative IL-8 | 0.10 |
| ICAM-1 1 month | 0.03 |
| L-selectin 1 month | 0.06 |

** Spearman Test - P≤ 20%.*
*ICAM - intercellular adhesion molecule*

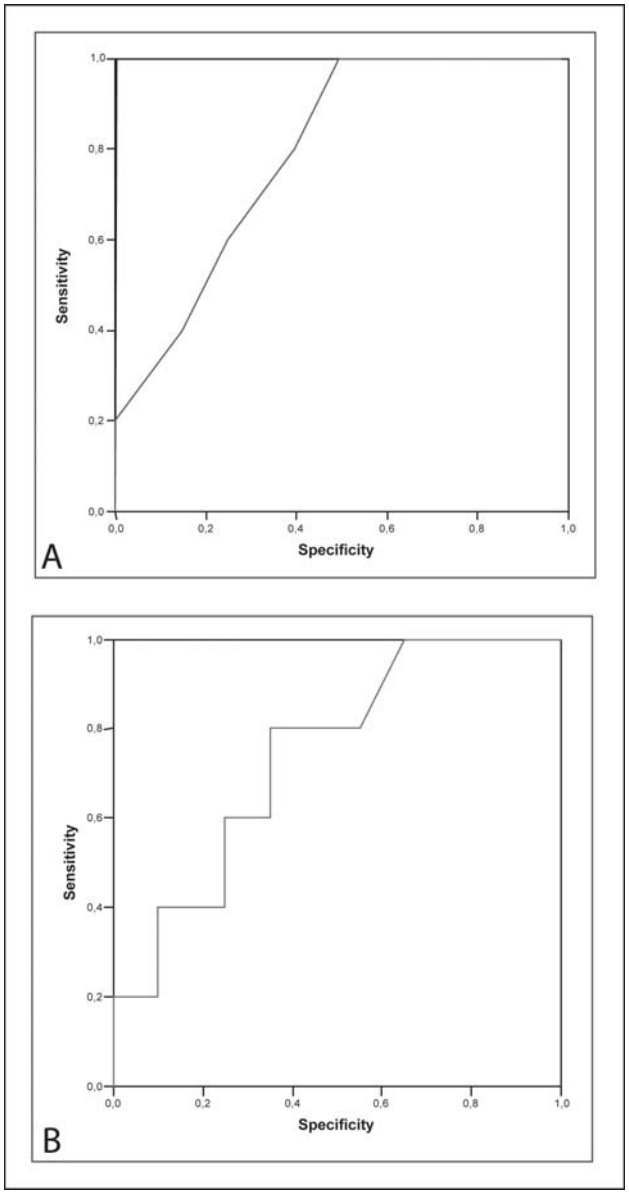


*Fig. 1 - A: Analysis of the ROC curve for the volume of crystalloid solution; B: Analysis of the ROC curve for the pre-operative values of IL-8*

Table 6. Numeric intervals and risk categories

| Volume de crystalloid solution (mL) | IL-8 pre (pg/mL) | Risk | Probability |
|---|---|---|---|
| Up to 1850 | Up to 33.53 | Mild | Up to 70% |
| 1850 - 3250 | 33.54 – 53.37 | Moderate | 71% - 82% |
| > 3250 | > 53.37 | Severe | > 82% |
| 3500 | 38.7 | Severe | 86.59% * |

** maximum probability of risk*

Table 7. Inflammatory risk score

| Volume of crystalloid solution (mL) | IL-8 pre (pg/mL) | Risk | Clinical manifestations |
|---|---|---|---|
| Up to 1850 | Up to 33.53 | Mild | Fever/ Leukocytosis |
| 1850 - 3250 | 33.54 – 53.37 | Moderate | Fever/ Leukocytosis/ Hypotension |
| > 3250 | > 53.37 | Severe | SIRS*/Sepsis |

** SIRS - Systemic Inflammatory Response Syndrome*

## DISCUSSION

The treatment of aortic aneurisms by open surgery with the associated complications results, in some circumstances, in a high risk of morbidity and mortality. Added to this is the fact that repair of this disease by the conventional approach requires, in most cases, the use of cardiopulmonary bypasses, which confers a greater risk of postoperative complications.

The viability and efficacy of endovascular therapy in the correction of aortic aneurisms have been consolidated due to the possibility of performing less invasive procedures, in particular when there are associated risk factors, such as age, chronic obstructive pulmonary disease, hypertension, smoking, chronic renal failure and cardiovascular diseases [8-10].

The complex reactions resulting from the interaction between the aortic endothelium and the endoprosthesis can be conceptualized as post-implantation syndrome, which is characterized by the expression of multiple and, often, lethal organic effects. Some subjacent events are being studied in order to clarify the main mechanisms that cause this syndrome. Extensive endothelial activation after the implantation of an endoprosthesis, activation due to the contact of blood components with the surface of the endoprosthesis, as well as ischemia-reperfusion lesions owing to prolonged periods of clamping of the femoral arteries, have been considered possible etiologies of this process. Additionally, from the physiopathological point of view, some clinical manifestations may be correlated to these events including leukocytosis, fever and coagulation disorders.

An estimation of inflammatory risk in the endovascular treatment of aortic aneurisms is still not possible due to the inexistence of a specific score that encompasses the inflammatory variables inherent to this type of therapy. In this study, the follow up of 25 patients submitted to the endovascular treatment demonstrates that there are several

inflammatory variables involved in the systemic inflammatory response induced by contact of the endothelium with the endoprostheses; however, the volume of crystalloid solution and the preoperative value of IL-8, in particular, were identified as probable variables to be included in the creation of an original model of an inflammatory risk score.

Several mechanisms are involved in the inflammatory response induced by the infusion of crystalloid solution. A number of authors have postulated that, the more crystalloid solution utilized, the greater the transcription of pro-inflammatory genes, the greater the expression of cellular adhesion molecules, such as E-selectin and P-selectin, the greater the neutrophil activation and the greater the release of cytokines and hydrogenated metabolites will be [11-15]. Pascual et al. [16,17] demonstrated that the infusion of hypertonic solutions might reduce the adhesion and transmigration of inflammatory cells.

The majority of aortic aneurisms are primarily associated with the atherosclerotic process and, secondly, correlated with transmural degenerative processes, neovascularization, reduction in the quantity of smooth muscle cells and chronic inflammatory infiltration, The dominant cells of this infiltration are T helper 2 lymphocytes, that participate in the synthesis of inflammatory mediators such as IL-8 and TNF-α. Lindeman et al. [18] removed fragments of the aneurismal walls from the human aorta and demonstrated that, in this type of tissue, there is increased expression and activation of interleukins, in particular IL-6 and IL-8. These findings are compatible with the relevance of preoperative values of IL-8 identified in the current study, which is fundamental to an adequate estimation of inflammatory risk of aortic endoprostheses [18-21].

Although the inflammatory risk score for aortic endoprostheses is useful in obtaining better postoperative results, its applicability should not discard the impact on the cost of the procedure and, thus, attention should be paid to this question.

## CONCLUSION

The authors of the current study propose a model of an inflammatory risk score for the endovascular treatment of aortic aneurisms, in an attempt to determine which inflammatory factors effectively might have a reasonable impact in prognostic terms. In the first analysis, the volume of crystalloid solution utilized in the endovascular procedure and the pre-operative value of IL-8 have been indicated for this evaluation. Nevertheless, this investigation must be amplified with further studies to optimize the results.

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