AVALIAÇÃO DO ÂNGULO DE FASE E DA DINAMOMETRIA MANUAL EM PACIENTES SUBMETIDOS À CIRURGIA CARDÍACA: ESTUDO DE COORTE PROSPECTIVO

Tese de doutorado

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CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

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“O sucesso é a soma de
pequenos esforços,
repetidos o tempo todo”.

Robert Collier.

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1. Introdução;
2. Revisão da literatura;
3. Justificativa;
4. Objetivos;
5. Referências da introdução e da revisão da literatura;
6. Artigos;

   Artigo 1: Artigo original a ser submetido para publicação no periódico *"European Journal of Clinical Nutrition".*

   Artigo 2: Artigo original submetido para publicação no periódico *"European Journal of Cardio - Thoracic Surgery".*
7. Conclusões;
8. Considerações finais.

SUMÁRIO

LISTA DE ABREVIATURAS

Abreviaturas da revisão da literatura

AF: ângulo de fase

AHA: *American Heart Association*

AUC: área sob a curva (*area under the curve*)

BIA: bioimpedância elétrica (*bioimpedance analysis*)

CEC: circulação extracorpórea

CRM: cirurgia de revascularização do miocárdio

DAC: doença arterial coronariana

DAV: dispositivo de assistência ventricular

DCVs: doenças cardiovasculares

EuroSCORE II: *European system for cardiac operative risk evaluation II*

GNRI: *geriatriac nutritional risk index*

IC: insuficiência cardíaca

PO: pós-operatório

TV: troca valvar

UTI: unidade de terapia intensiva

VE: ventrículo esquerdo

VM: ventilação mecânica

Xc: reactância

Z: impedância

Abreviaturas dos artigos:

ANOVA: analysis of variance

AUC: area under the curve

B: slope

BIA: bioelectrical impedance analysis

BICS: Bioimpedance in Cardiac Surgery

BMI: body mass index

CABG: coronary artery bypass grafting

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CI: confidence interval

CNPq: Conselho Nacional de Desenvolvimento Científico e Tecnológico

CPB: cardiopulmonary bypass

EuroSCORE II: European system for cardiac operative risk evaluation II

FIPE: Fundo de Incentivo à Pesquisa e Eventos

GEE: generalized estimating equation

HCPA: Hospital de Clínicas de Porto Alegre

HGS: handgrip strength

HGS-AUC: area under the curve of handgrip strength

HR: hazard ratio

ICU: intensive care unit

LOS: length of stay

MV: mechanical ventilation

PA: phase angle

PA-AUC: area under the curve of phase angle

PO: postoperative

R: resistance

ROC: receiver operating characteristic

RR: relative risk

SD: standard deviation

SE: standard error

STS: Society of Thoracic Surgeons

Xc: reactance

Z: impedance

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RESUMO

O ângulo de fase (AF) da bioimpedância elétrica é interpretado como indicador de integridade da membrana celular e a dinamometria manual como indicador de capacidade funcional. O objetivo foi avaliar suas variações e associações com desfechos clínicos em pacientes submetidos à cirurgia cardíaca ao longo de 1 ano. **Métodos:** Estudo de coorte prospectivo com 272 pacientes. As medidas de AF e dinamometria manual ocorreram em seis momentos. **Resultados:** Tanto o AF quanto a dinamometria manual apresentaram redução dos valores pré-operatórios para o pós-operatório na unidade de terapia intensiva (UTI). O AF se recuperou totalmente em 12 meses enquanto a dinamometria manual em 3 meses. O AF pré-operatório foi associado com mortalidade em 1 ano, infecções, reinternação na UTI e permanência hospitalar ≥ 8 dias. **Conclusão:** O AF e a dinamometria manual podem ser usados para monitorar pacientes submetidos à cirurgia cardíaca e reitera o AF como marcador prognóstico nesses pacientes.

Palavras-chave: ângulo de fase; bioimpedância elétrica; cirurgia cardíaca; dinamometria manual; prognóstico.

ABSTRACT

The bioelectrical impedance phase angle (PA) is interpreted as a cell membrane integrity indicator, and the handgrip strength (HGS) as a functional capacity indicator. The objective was to evaluate their variations and associations with clinical outcomes in patients undergoing cardiac surgery over 1 year. **Methods:** Prospective cohort study with 272 patients. The measurements of PA and HGS occurred in six moments. **Results:** Both PA and HGS showed a reduction in preoperative to postoperative values in the intensive care unit (ICU). PA was fully recovered in 12 months while HGS in 3 months. Preoperative PA was associated with 1-year mortality, infections, ICU readmission and hospital length of stay ≥ 8 days. **Conclusion:** The PA and HGS can be used to monitor patients undergoing cardiac surgery and reinforce PA as a prognostic marker in those patients.

Keywords: cardiac surgery; electrical impedance; handgrip strength; phase angle; prognosis.

1 INTRODUÇÃO

As doenças cardiovasculares (DCVs) são a principal causa de mortalidade no mundo (1). Visando a melhoria do prognóstico e da qualidade de vida, em alguns casos, apesar de orientação médica e tratamento medicamentoso, a cirurgia cardíaca é recomendada. Pacientes com doença arterial coronariana (DAC) ou doença valvar que têm persistência dos sintomas, são exemplos dessa indicação (2, 3). A cirurgia de revascularização do miocárdio (CRM) e a troca valvar (TV) são os tipos de cirurgia mais prevalentes (4).

Essas intervenções cardiovasculares podem causar estresse ao organismo. Considerando as limitações de escores de risco existentes no que se refere a medidas que envolvam o status biológico e função muscular ao longo do tempo, há espaço para melhorias na modelagem de avaliação de riscos e de monitoramento desses pacientes. Parâmetros de avaliação capazes de quantificar alterações funcionais e orgânicas no pré e pós-operatório (PO) tornam-se importantes tanto para entender a dinâmica do processo terapêutico quanto para planejar intervenções necessárias, potencialmente impedindo o desenvolvimento de limitações funcionais (5-8).

No entanto, apesar das cirurgias cardíacas serem procedimentos comuns e bem difundidos mundialmente (2, 3) há uma escassez de estudos que acompanhem as alterações orgânicas ao longo do tempo após esses procedimentos.

Nesse contexto, o ângulo de fase (AF), que é derivado da análise de bioimpedância elétrica (*bioimpedance analysis* - BIA), é um método prático e não invasivo que pode ser medido à beira do leito e é interpretado como um indicador de integridade da membrana e preditor de massa celular corporal (9). Valores mais altos de AF estão associados à boa função celular e valores mais baixos podem indicar apoptose e componentes reduzidos da matriz extracelular (10, 11). O AF também tem

sido usado como um indicador prognóstico em determinadas situações clínicas como pacientes críticos, cirúrgicos, cardíacos, oncológicos, com doença pulmonar, renal ou hepática (12-18). Além do uso como indicador prognóstico, alguns estudos vêm utilizando medidas longitudinais do AF para o acompanhamento de pacientes cirúrgicos (19, 20).

A dinamometria manual, por sua vez, é considerada um teste útil de capacidade funcional para avaliar a força muscular na população em geral, além de pessoas hospitalizadas e não hospitalizadas com doenças (7, 21-24). Trata-se de um método com aplicabilidade em diversos cenários da prática clínica e, por ser simples e de fácil mensuração, investiga-se cada vez mais sua capacidade de predizer mortalidade e prognóstico clínico (7, 25-28). Em um estudo com pacientes cardíacos cirúrgicos a dinamometria manual foi avaliada diariamente no pré-operatório e nos primeiros 7 dias de PO para avaliação da recuperação da força muscular pré-operatória (29), no entanto sem acompanhamento posterior.

Nesse sentido, o AF e a dinamometria manual por serem métodos práticos, não invasivos e com associação com diversas doenças, parecem ser importantes instrumentos na predição de desfechos clínicos e no acompanhamento desses pacientes.

Dessa forma, a presente tese teve o objetivo de avaliar as variações do AF e da dinamometria manual, associando os mesmos com desfechos clínicos ao longo de 1 ano em pacientes submetidos à cirurgia cardíaca eletiva.

2 REVISÃO DA LITERATURA

2.1 Cirurgias cardíacas

As DCVs representam um problema significativo e crescente no mundo, representando a principal causa global de mortalidade (1). Elas denominam um grupo de doenças do coração e vasos sanguíneos que incluem: DAC, doença cerebrovascular, doença arterial periférica, doenças cardíacas reumáticas e congênitas, trombose venosa profunda e embolia pulmonar (30). Seu tratamento é baseado em mudanças nos hábitos alimentares, atividade física, medicação e cirurgia (30, 31).

As cirurgias cardíacas são procedimentos de grande porte difundidas mundialmente. Elas são indicadas quando a probabilidade de sobrevida é maior com o tratamento cirúrgico do que com o tratamento clínico (2, 3). Dentre os tratamentos, o cirúrgico é o mais complexo e vem aumentando exponencialmente ao longo dos anos, embora apresente morbidade e tenha uma taxa de mortalidade significativa. Muitas de suas complicações estão relacionadas com a situação pré-operatória do paciente (31).

As principais complicações no PO são as relacionadas às funções respiratória, renal, neurológica e cardiovascular, além do tempo de permanência hospitalar prolongado, reinternação e mortalidade. As complicações cardiovasculares são mais prevalentes nos casos de infarto agudo do miocárdio e insuficiência cardíaca congestiva. Nas primeiras 24 horas após a cirurgia uma das complicações neurológicas que podem ocorrer é o acidente vascular encefálico. Dentre as complicações de origem pulmonar estão: atelectasia, pneumonia, insuficiência respiratória aguda e derrame pleural (31-35).

Os tipos de cirurgia cardíaca mais prevalentes são a CRM e a TV (4). A CRM consiste em um enxerto arterial coronário utilizando mais comumente a veia safena ou a artéria mamária autógena com o objetivo de isolar o vaso obstruído e, assim, restabelecer a perfusão da artéria coronária. Esse tipo de cirurgia tem a finalidade de preservar o miocárdio e possui como vantagem a durabilidade (2).

O tratamento através da CRM tem mostrado melhorar a sobrevida (36, 37). A intervenção de revascularização do miocárdio se faz necessária para os pacientes nos quais o tratamento clínico não consegue controlar a angina pectoris, quando há diminuição da força de contração do coração e para os que possuem um elevado grau de obstrução de artérias coronárias principais levando ao risco de óbito (2).

As cirurgias de válvula cardíaca podem ser divididas em plastia ou troca da válvula nativa. A plastia preserva a válvula, fazendo uma reconstituição da mesma e promovendo o retorno do seu funcionamento normal. Quando as condições da válvula não permitem esse remodelamento, ela é trocada por uma prótese (3, 38).

A TV é recomendada para pacientes com estenose aórtica grave. Em pacientes sintomáticos o grau de recomendação é classe I, já em pacientes assintomáticos, mas com comprometimento do ventrículo esquerdo (VE), progressão rápida da estenose aórtica ou um teste ergométrico com alterações a recomendação é II. Há indicação também em pacientes com insuficiência aórtica sintomática com grau de recomendação I e pacientes assintomáticos com fração de ejeção do VE < 50%. Nos casos de estenose mitral a TV é recomendada quando a área da válvula é menor que 1,5 cm^2 e na insuficiência mitral quando essa for considerada grave, na presença de alterações valvares degenerativas, anormalidades do movimento do VE, dilatação do VE e cardiomiopatia dilatada. Outras indicações, mais raras, são em casos de endocardite infecciosa e febre reumática (3, 39).

As próteses valvares podem ser biológicas ou mecânicas. As próteses biológicas são desenvolvidas a partir de tecidos biológicos de pericárdio bovino ou porcino. Essas possuem baixa trombogenicidade, boa hemodinâmica, não apresentam ruídos no PO e, em decorrência do fluxo central, apresentam baixa turbulência. No entanto, a limitação ao uso dessas próteses está diretamente relacionada com a sua durabilidade, calcificação e necessidade de reoperações, com aumento do risco cirúrgico. A sua indicação está bem estabelecida, principalmente em idosos e naqueles impossibilitados de se submeterem a esquemas de anticoagulação (3, 38).

As próteses mecânicas, também conhecidas como metálicas, são consideradas mais duráveis, sendo uma boa opção para adultos jovens e crianças, que possuem o inconveniente da rápida degeneração estrutural com as biopróteses. No entanto, essas próteses possuem a desvantagem da necessidade do uso contínuo de anticoagulantes. Portanto, deve ser considerado o perfil social do paciente, a presença de comorbidades, história prévia de sangramento e possibilidade de gestação. Os eventos tromboembólicos, trombose de prótese e hemorragias pelo uso obrigatório e contínuo dos anticoagulantes, compreendem os maiores riscos com as próteses mecânicas (3, 38).

Em vista de tantos aspectos que envolvem as cirurgias cardíacas, vários modelos de estratificação de risco têm sido propostos para predizer mortalidade em cirurgia cardíaca, sendo o *European System for Cardiac Operative Risk Evaluation II* (*EuroSCORE II*) e o *Society of Thoracic Surgeons* escore os mais utilizados (40-43). Na avaliação clínica antes da cirurgia cardíaca, os escores de risco são utilizados para avaliar a mortalidade em 30 dias, mas não avaliam a médio e longo prazo (44).

Em função das modelagens de risco avaliarem desfechos a curto prazo em pacientes submetidos à cirurgia cardíaca, essas modelagens de risco ainda podem ser aprimoradas. Além disso, considerando as complicações pós-operatórias, se faz necessário um acompanhamento no pré e no PO para compreender a dinâmica do processo terapêutico e planejar a assistência necessária para esses pacientes na prática clínica, auxiliando na prevenção de limitações funcionais (5, 6, 8).

Mesmo as cirurgias cardíacas sendo procedimentos rotineiros na prática hospitalar (2, 3) a compreensão a respeito do comportamento das alterações orgânicas ao longo do tempo após esses procedimentos é uma lacuna a ser preenchida no meio científico.

2.2 Bioimpedância elétrica e ângulo de fase em pacientes cardíacos cirúrgicos

A BIA é um método indireto de avaliação da composição corporal considerado um procedimento simples, seguro, não invasivo, de custo relativamente baixo e que reproduz resultados rapidamente. Diferente de outros instrumentos pode ser aplicada tanto na avaliação de indivíduos saudáveis quanto enfermos e pode ser aferida à beira do leito (9, 45, 46).

A BIA fundamenta-se no princípio da oposição dos tecidos corporais à passagem de um fluxo elétrico alternado. Essa oposição, denominada impedância (Z), tem dois vetores, denominados resistência (R) e reactância (Xc) (10, 47). Dessa forma, a BIA é realizada através da medida da resistência total do corpo à passagem de uma corrente elétrica de baixa amplitude (800 μA) e alta frequência (50 kHz), fornecendo através dessas medidas propriedades como Z, R, Xc e AF (10). A R se caracteriza pela oposição à corrente dos tecidos para a condução de corrente elétrica:

o tecido adiposo e o tecido ósseo são maus condutores, e a corrente flui melhor no meio extracelular, com soluções eletrolíticas. A Xc ocorre devido ao efeito de isolamento das membranas celulares, que atuam retendo a energia elétrica (10).

O AF é o valor em graus obtido através da relação entre diversas medidas de R e Xc e é calculado pela equação (AF = Arco Tangente Xc/R), como pode ser visto na Figura 1. Esse valor é interpretado como indicador de integridade da membrana celular e de distribuição de água nos espaços intra e extracelular. Dessa forma, possibilita predizer a quantidade de massa celular corpórea intacta, estando essa associada ao estado clínico do paciente.

Conforme a literatura, as medidas cruas da BIA (R e Xc) são peso independentes, por esse motivo são ideais para pacientes acamados, como pacientes críticos e cirúrgicos. Valores menores de AF parecem ser consistentes com Xc baixa e morte celular ou interrupção da permeabilidade seletiva da membrana celular. Já valores maiores de AF parecem ser mais compatíveis com Xc alta e maior integridade das membranas celulares (48).

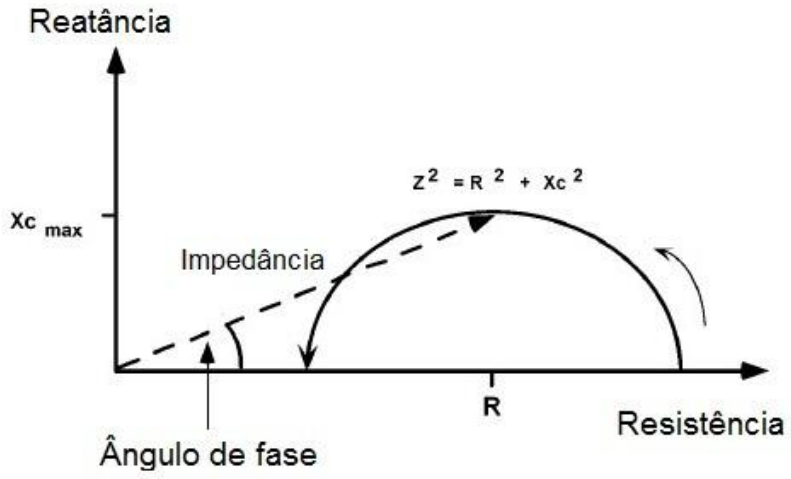

Figura 1. Derivação gráfica do ângulo de fase.
Fonte: adaptado de BAUMGARTNER; CHUMLEA; ROCHE, 1988. (49)

Nesse sentindo o AF tem sido bastante estudado e descrito como um marcador prognóstico e preditor de sobrevida em diversas condições clínicas (50), como pacientes críticos (12), cirúrgicos (13), cardíacos (14), oncológicos (15), com doença pulmonar (16), renal (17) ou hepática (18).

Em alguns países como Canadá, Holanda e Lituânia, o AF tem sido estudado como um indicador de desnutrição, de fragilidade e determinante de resultados adversos após cirurgia cardíaca (20-23). No entanto, há poucos estudos que avaliaram seu uso como marcador específico de mortalidade, dentre esses um estudo que associou o AF apenas com mortalidade hospitalar (51) e outro com mortalidade em 30 dias e 1 ano (52). Desfechos clínicos adversos como maior tempo de internação na unidade de terapia intesiva (UTI) e internação hospitalar foram observados em pacientes cardíacos cirúrgicos, que apresentaram AF < 5,38º (51). No entanto, não há estudos realizados no Brasil associando o AF com desfechos clínicos em médio prazo.

Outro aspecto do AF a ser estudado em pacientes de cirurgia cardíaca é a sua avaliação ao longo do tempo, o que permite observar quais as variações do AF em médio prazo e se esse comportamento geral pode estar associado a desfechos clínicos, ao contrário de uma única medida. Há um estudo que acompanhou esses pacientes em 3 momentos: pré-operatório, alta hospitalar e 3 meses após a cirurgia, no qual foi visto um declínio dos valores pré-operatórios de AF quando comparado às duas avaliações no PO, não havendo sinal de recuperação do AF em 3 meses (20). Nesse contexto, são necessários estudos com maior tempo de acompanhamento e com maior número de avaliações do AF para saber qual o seu comportamento em médio prazo, permitindo inferir se a integridade de membrana se recupera ao longo do tempo ou se continua declinando em pacientes submetidos à cirurgia cardíaca.

2.3 Dinamometria manual em pacientes cardíacos cirúrgicos

Na cirurgia cardíaca, especialmente em pacientes com comorbidades, a capacidade funcional no pré-operatório e no PO desempenha um papel crucial no que se refere à autonomia nas atividades de vida diária e, consequentemente na qualidade de vida logo após o procedimento cirúrgico (53). Nesta perspectiva, uma declaração científica da *American Heart Association* (AHA) (54) aponta a necessidade de priorizar a capacidade funcional global como um objetivo vital do cuidado para terapias orientadas em pacientes com DCVs, especialmente nos idosos, que atualmente perfazem cerca de 75% dos cardíacos cirúrgicos (55).

Nesse sentido, a dinamometria manual constitui uma das métricas mais utilizadas para avaliação da capacidade funcional através da força muscular (56). Essa é considerada um teste funcional útil para avaliar não só a força muscular global de indivíduos saudáveis (57, 58), mas também de indivíduos com doenças crônicas ou situações agudas (29, 59-62), incluindo pacientes cirúrgicos (28, 29, 51). Assim, esse parâmetro tem sido utilizado em estudos clínicos e epidemiológicos (63).

Em indivíduos saudáveis a idade e o sexo são os fatores que mais influenciam nos valores de força muscular (64). Porém, na doença aguda ou crônica, fatores adicionais, como severidade da doença, comorbidades, tratamento medicamentoso, falta de utilização muscular, desequilíbrio hidroeletrolítico, inflamação, infecção e estresse oxidativo podem ocasionar debilidade muscular (65).

Nesse contexto, a força muscular reduzida está associada à perda de funcionalidade física e ao impacto negativo sobre a recuperação do paciente após uma doença ou cirurgia, o que em parte explica o alto poder preditivo dos testes de função muscular (7, 22).

Uma revisão sistemática da literatura avaliando a fraqueza muscular em pacientes cirúrgicos, por meio da dinamometria manual, identificou que valores reduzidos de dinamometria manual pré-operatória podem estar associados ao aumento do tempo de permanência hospitalar, à morbidade e à mortalidade no PO (28). No entanto, tanto o comprometimento da força muscular aferida pela dinamometria manual, quanto a morbidade no PO foram medidas de forma diferenciada e inconsistente entre os estudos, sendo sugerido pelos próprios autores que novos estudos são necessários para avaliar de forma clara o conceito de comprometimento funcional, além de avaliar prospectivamente e de forma objetiva a morbidade no PO.

Pacientes submetidos à cirurgias cardíacas apresentam elevada morbidade, sendo muitas de suas complicações relacionadas com sua situação pré-operatória (28, 56, 66). Dentro desse panorama, as Diretrizes da AHA e do *American College of Cardiology* consideram a avaliação de aspectos relacionados à fragilidade dos pacientes, determinada, entre outros aspectos pela diminuição da força muscular, como um fator importante na determinação de risco em cirurgias de TV (67). Sua avaliação por meio de aferições de seus componentes, como a força muscular, constitui fator preditor independente de desfechos após substituição da válvula aórtica transcateter (56).

São poucos os estudos que avaliam a capacidade funcional em pacientes submetidos a procedimentos cardíacos ou cirurgia cardíaca (20, 59, 68-70). O quadro 1 sintetiza alguns desses estudos.

Quadro 1. Dinamometria manual como um instrumento de avaliação da capacidade funcional em pacientes de cirurgia cardíaca

Estudo	População avaliada	Dinamômetro utilizado	Principais resultados	Medida utilizada
Da Silva et al., 2018 (20)	50 pacientes submetidos à cirurgia cardíaca	*Jamar*	Foi observada uma diminuição da dinamometria manual entre as avaliações pré-operatória e pré-alta hospitalar (p <0,001) e uma recuperação em 3 meses de PO (p <0,001). O EuroSCORE teve uma correlação inversa nas três avaliações com a dinamometria manual.	Maior valor de 3 forças
Ogawa et al., 2017 (68)	131 idosos submetidos à cirurgia cardíaca	*Takei Scientific Instruments Niigata, Japão*	Após o ajuste para possíveis fatores de confusão, a dinamometria manual pré-operatória foi significativamente melhor no grupo com alto GNRI quando comparado com aqueles com baixo GNRI (p = 0,034).	Maior valor de 2 forças
Yost et al., 2017 (59)	90 pacientes com IC submetidos à implantação de dispositivo de DAV	*Jamar*	Pacientes com dinamometria manual <28,5% da dinamometria manual ajustada dividida pelo peso corporal (kg) apresentaram maior risco de maior tempo de permanência hospitalar (p <0,001).	Média do valor de 3 forças
Chung et al., 2014 (70)	72 pacientes com IC submetidos à implantação de dispositivo de DAV	*Jamar*	Pacientes com dinamometria manual <25% do seu peso corporal apresentaram maior risco de mortalidade, aumento das complicações pós-operatórias e menor sobrevida após a implantação de DAV.	Média do valor de 3 forças
Visser et al., 2013	325 pacientes submetidos à cirurgia cardíaca	*Jamar*	83,3% dos pacientes com obesidade sarcopênica apresentaram baixos valores de dinamometria manual. Pacientes com valores menores de dinamometria manual apresentaram maior tempo de VM.	Média do valor de 3 forças

DAV; Dispositivo de assistência ventricular; IC: insuficiência cardíaca; GNRI: Geriatric Nutritional Risk Index; VM: ventilação mecânica.

Como pode ser visto, no quadro acima, apenas um dos estudos realizou medidas de dinamometria manual antes e após a cirurgia (20). Assim, se reforça a importância de novos estudos nessa população que monitorem as variações longitudinais da dinamometria manual nesses pacientes, com o objetivo de planejar as intervenções necessárias e evitar limitações funcionais.

3 JUSTIFICATIVA

Estudos realizados com diversos tipos de pacientes demonstram que o AF, derivado da bioimpedância elétrica, e a dinamometria manual estão associados a prognóstico clínico, sendo o AF interpretado como indicador de integridade da membrana celular e a dinamometria manual como indicador de capacidade funcional. Por estes serem métodos práticos e não invasivos com associação positiva com diversas doenças, os mesmos parecem ser importantes instrumentos para estimar resultados clínicos e monitorar pacientes submetidos à cirurgia cardíaca.

Buscando compreender o comportamento das medidas de AF e de dinamometria manual e sua associação com desfechos clínicos, foi proposto um estudo de coorte prospectivo. Em vista da escassez de estudos abordando estes aspectos em pacientes cardíacos cirúrgicos, emergiu como problema de pesquisa: Quais as variações nos valores de AF e de dinamometria manual e associações com desfechos clínicos que ocorrem no pré-operatório e no PO ao longo de 1 ano em pacientes submetidos à cirurgia cardíaca?

4 OBJETIVOS

Objetivo geral

Avaliar as variações do AF, derivado da bioimpedância elétrica, e da dinamometria manual, associando os mesmos com desfechos clínicos em pacientes submetidos à cirurgia cardíaca eletiva ao longo de 1 ano.

Objetivos específicos

- Avaliar a associação das variações do AF e da dinamometria manual com aspectos demográficos (sexo e idade);
- Avaliar a associação das variações do AF e da dinamometria manual com indicadores clínicos, como o EuroSCORE II e os tempos de: cirurgia, circulação extracorpórea (CEC), isquemia, ventilação mecânica (VM), internação na unidade de terapia intensiva (UTI) no pós-operatório (PO) e internação hospitalar no PO;
- Avaliar a associação das variações do AF e da dinamometria manual com os tipos de cirurgia, insuficiência cardíaca e desfechos clínicos: infecções, reintubação, reinternação na UTI, reinternação hospitalar e reoperação;
- Avaliar o AF pré-operatório como marcador prognóstico de desfechos clínicos adversos: VM prolongada (≥ 12h), reintubação, infecções, internação prolongada na UTI (≥ 4 dias); reinternação na UTI, internação hospitalar prolongada (≥ 8 dias), reinternação hospitalar e reoperação;
- Avaliar o AF pré-operatório como marcador prognóstico de mortalidade precoce (em 30 dias) e de mortalidade de médio prazo (em 1 ano).

5 REFERÊNCIAS DA INTRODUÇÃO E DA REVISÃO DA LITERATURA

1. WHO. World Health Organization; 2018. Top 10 causes of death https://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/
2. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2019;55(1):4-90.
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
4. Stephens RS, Whitman GJ. Postoperative Critical Care of the Adult Cardiac Surgical Patient. Part I: Routine Postoperative Care. Crit Care Med. 2015;43(7):1477-97.
5. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. Clin Nutr. 2010;29(2):151-3.
6. Waitzberg DL, Ravacci GR, Raslan M. [Hospital hyponutrition]. Nutr Hosp. 2011;26(2):254-64.
7. Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr. 2011;30(2):135-42.
8. Di Dedda U, Pelissero G, Agnelli B, De Vincentiis C, Castelvecchio S, Ranucci M. Accuracy, calibration and clinical performance of the new EuroSCORE II risk stratification system. Eur J Cardiothorac Surg. 2013;43(1):27-32.
9. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr. 2004;23(6):1430-53.
10. Silva LMDL, Caruso L, Martini LA. Aplicação do ângulo de fase em situações clínicas. Revista Brasileira de Nutrição Clínica [Internet]. 2007; 22(4):[317-21 pp.].
11. Zarowitz BJ, Pilla AM. Bioelectrical impedance in clinical practice. DICP. 1989;23(7-8):548-55.
12. da Silva TK, Berbigier MC, Rubin BeA, Moraes RB, Corrêa Souza G, Schweigert Perry ID. Phase angle as a prognostic marker in patients with critical illness. Nutr Clin Pract. 2015;30(2):261-5.
13. Pena NF, Mauricio SF, Rodrigues AMS, Carmo AS, Coury NC, Correia MITD, et al. Association Between Standardized Phase Angle, Nutrition Status, and Clinical Outcomes in Surgical Cancer Patients. Nutr Clin Pract. 2019;34(3):381-6.
14. Alves FD, Souza GC, Clausell N, Biolo A. Prognostic role of phase angle in hospitalized patients with acute decompensated heart failure. Clin Nutr. 2016;35(6):1530-4.
15. Pereira MME, Queiroz MDSC, de Albuquerque NMC, Rodrigues J, Wiegert EVM, Calixto-Lima L, et al. The Prognostic Role of Phase Angle in Advanced Cancer Patients: A Systematic Review. Nutr Clin Pract. 2018;33(6):813-24.
16. Maddocks M, Kon SS, Jones SE, Canavan JL, Nolan CM, Higginson IJ, et al. Bioelectrical impedance phase angle relates to function, disease severity and prognosis in stable chronic obstructive pulmonary disease. Clin Nutr. 2015;34(6):1245-50.
17. Shin JH, Kim CR, Park KH, Hwang JH, Kim SH. Predicting clinical outcomes using phase angle as assessed by bioelectrical impedance analysis in maintenance hemodialysis patients. Nutrition. 2017;41:7-13.

18. Belarmino G, Gonzalez MC, Torrinhas RS, Sala P, Andraus W, D'Albuquerque LA, et al. Phase angle obtained by bioelectrical impedance analysis independently predicts mortality in patients with cirrhosis. World J Hepatol. 2017;9(7):401-8.
19. Koehler KB, Moraes RAG, Rodrigues JB, Portela BSM, Miguel GPS, Pedrosa RG, et al. Bioimpedance phase angle is associated with serum transthyretin but not with prognostic inflammatory and nutritional index during follow-up of women submitted to bariatric surgery. Clin Nutr ESPEN. 2019;33:183-7.
20. da Silva TK, Perry IDS, Brauner JS, Wender OCB, Souza GC, Vieira SRR. Performance evaluation of phase angle and handgrip strength in patients undergoing cardiac surgery: Prospective cohort study. Aust Crit Care. 2018;31(5):284-90.
21. Bohannon RW. Dynamometer measurements of hand-grip strength predict multiple outcomes. Percept Mot Skills. 2001;93(2):323-8.
22. Humphreys J, de la Maza P, Hirsch S, Barrera G, Gattas V, Bunout D. Muscle strength as a predictor of loss of functional status in hospitalized patients. Nutrition. 2002;18(7-8):616-20.
23. Cereda E, Vanotti A. The new Geriatric Nutritional Risk Index is a good predictor of muscle dysfunction in institutionalized older patients. Clin Nutr. 2007;26(1):78-83.
24. Guerra RS, Fonseca I, Pichel F, Restivo MT, Amaral TF. Handgrip strength and associated factors in hospitalized patients. JPEN J Parenter Enteral Nutr. 2015;39(3):322-30.
25. Ibrahim K, May C, Patel HP, Baxter M, Sayer AA, Roberts H. A feasibility study of implementing grip strength measurement into routine hospital practice (GRImP): study protocol. Pilot Feasibility Stud. 2016;2:27.
26. Arvandi M, Strasser B, Meisinger C, Volaklis K, Gothe RM, Siebert U, et al. Gender differences in the association between grip strength and mortality in older adults: results from the KORA-age study. BMC Geriatr. 2016;16(1):201.
27. Lee WJ, Peng LN, Chiou ST, Chen LK. Physical Health Indicators Improve Prediction of Cardiovascular and All-cause Mortality among Middle-Aged and Older People: a National Population-based Study. Sci Rep. 2017;7:40427.
28. Sultan P, Hamilton MA, Ackland GL. Preoperative muscle weakness as defined by handgrip strength and postoperative outcomes: a systematic review. BMC Anesthesiol. 2012;12:1.
29. Fu L, Zhang Y, Shao B, Liu X, Yuan B, Wang Z, et al. Perioperative poor grip strength recovery is associated with 30-day complication rate after cardiac surgery discharge in middle-aged and older adults - a prospective observational study. BMC Cardiovasc Disord. 2019;19(1):266.
30. WHO. World Health Organization; 2015. Cardiovascular diseases Fact Sheet Nº317. http://who.int/mediacentre/factsheets/fs317/en/
31. Matos AA, Silvo DB, Jesus MLd, Guimarães AR, Cordeiro ALL. Incidence of complications after cardiac surgery. Int Physi Med Rehab J. 2020;5(1):25-8.
32. Ball L, Costantino F, Pelosi P. Postoperative complications of patients undergoing cardiac surgery. Curr Opin Crit Care. 2016;22(4):386-92.
33. Nearman H, Klick JC, Eisenberg P, Pesa N. Perioperative complications of cardiac surgery and postoperative care. Crit Care Clin. 2014;30(3):527-55.
34. Crawford TC, Magruder JT, Grimm JC, Suarez-Pierre A, Sciortino CM, Mandal K, et al. Complications After Cardiac Operations: All Are Not Created Equal. Ann Thorac Surg. 2017;103(1):32-40.
35. Gonzalez AA, Dimick JB, Birkmeyer JD, Ghaferi AA. Understanding the volume-outcome effect in cardiovascular surgery: the role of failure to rescue. JAMA Surg. 2014;149(2):119-23.

36. Shah S, Benedetto U, Caputo M, Angelini GD, Vohra HA. Comparison of the survival between coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with poor left ventricular function (ejection fraction <30%): a propensity-matched analysis. Eur J Cardiothorac Surg. 2019;55(2):238-46.
37. Karim MN, Reid CM, Huq M, Brilleman SL, Cochrane A, Tran L, et al. Predicting long-term survival after coronary artery bypass graft surgery. Interact Cardiovasc Thorac Surg. 2018;26(2):257-63.
38. Braunwald E, Zipes DP, al e. ***Braunwald's Heart Disease:*** e: A Textbook of Cardiovascular Medicine. 10 ed2014.
39. Geissler HJ, Schlensak C, Südkamp M, Beyersdorf F. Heart valve surgery today: indications, operative technique, and selected aspects of postoperative care in acquired valvular heart disease. Dtsch Arztebl Int. 2009;106(13):224-33; quiz 34.
40. Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. Ann Thorac Surg. 2000;69(3):823-8.
41. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):734-44; discussion 44-5.
42. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. Ann Thorac Surg. 2018;105(5):1411-8.
43. O'Brien SM, Feng L, He X, Xian Y, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2-Statistical Methods and Results. Ann Thorac Surg. 2018;105(5):1419-28.
44. Bäck C, Hornum M, Olsen PS, Møller CH. 30-day mortality in frail patients undergoing cardiac surgery: the results of the. Scand Cardiovasc J. 2019;53(6):348-54.
45. Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. Curr Opin Clin Nutr Metab Care. 2005;8(3):311-7.
46. Frankenfield DC, Cooney RN, Smith JS, Rowe WA. Bioelectrical impedance plethysmographic analysis of body composition in critically injured and healthy subjects. Am J Clin Nutr. 1999;69(3):426-31.
47. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. 2004;23(5):1226-43.
48. Schiper L, Sadigursky D, Rosario DA, Schiper SP, Passos LC, Faintuch J. Hip fracture prognosis: could bioimpedance be an alternative to conventional nutritional assessment? Nutr Hosp. 2011;26(4):904-6.
49. Baumgartner RN, Chumlea WC, Roche AF. Bioelectric impedance phase angle and body composition. Am J Clin Nutr. 1988;48(1):16-23.
50. Garlini LM, Alves FD, Ceretta LB, Perry IS, Souza GC, Clausell NO. Phase angle and mortality: a systematic review. Eur J Clin Nutr. 2019;73(4):495-508.
51. Visser M, van Venrooij LM, Wanders DC, de Vos R, Wisselink W, van Leeuwen PA, et al. The bioelectrical impedance phase angle as an indicator of undernutrition and adverse clinical outcome in cardiac surgical patients. Clin Nutr. 2012;31(6):981-6.
52. Mullie L, Obrand A, Bendayan M, Trnkus A, Ouimet MC, Moss E, et al. Phase Angle as a Biomarker for Frailty and Postoperative Mortality: The BICS Study. J Am Heart Assoc. 2018;7(17):e008721.
53. Pratesi A, Orso F, Ghiara C, Lo Forte A, Baroncini AC, Di Meo ML, et al. Cardiac surgery in the elderly: What goals of care? Monaldi Arch Chest Dis. 2017;87(2):852.

54. Forman DE, Arena R, Boxer R, Dolansky MA, Eng JJ, Fleg JL, et al. Prioritizing Functional Capacity as a Principal End Point for Therapies Oriented to Older Adults With Cardiovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2017;135(16):e894-e918.
55. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18-e209.
56. Chauhan D, Haik N, Merlo A, Haik BJ, Chen C, Cohen M, et al. Quantitative increase in frailty is associated with diminished survival after transcatheter aortic valve replacement. Am Heart J. 2016;182:146-54.
57. Schlüssel MM, dos Anjos LA, de Vasconcellos MT, Kac G. Reference values of handgrip dynamometry of healthy adults: a population-based study. Clin Nutr. 2008;27(4):601-7.
58. Alahmari KA, Silvian SP, Reddy RS, Kakaraparthi VN, Ahmad I, Alam MM. Hand grip strength determination for healthy males in Saudi Arabia: A study of the relationship with age, body mass index, hand length and forearm circumference using a hand-held dynamometer. J Int Med Res. 2017;45(2):540-8.
59. Yost G, Bhat G. Relationship Between Handgrip Strength and Length of Stay for Left Ventricular Assist Device Implantation. Nutr Clin Pract. 2017;32(1):98-102.
60. Bragança RD, Ravetti CG, Barreto L, Ataíde TBLS, Carneiro RM, Teixeira AL, et al. Use of handgrip dynamometry for diagnosis and prognosis assessment of intensive care unit acquired weakness: A prospective study. Heart Lung. 2019;48(6):532-7.
61. Delanaye P, Quinonez K, Buckinx F, Krzesinski JM, Bruyère O. Hand grip strength measurement in haemodialysis patients: before or after the session? Clin Kidney J. 2018;11(4):555-8.
62. Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. BMJ. 2018;361:k1651.
63. Leal VO, Mafra D, Fouque D, Anjos LA. Use of handgrip strength in the assessment of the muscle function of chronic kidney disease patients on dialysis: a systematic review. Nephrol Dial Transplant. 2011;26(4):1354-60.
64. Budziareck MB, Pureza Duarte RR, Barbosa-Silva MC. Reference values and determinants for handgrip strength in healthy subjects. Clin Nutr. 2008;27(3):357-62.
65. Wagenmakers AJ. Muscle function in critically ill patients. Clin Nutr. 2001;20(5):451-4.
66. Laizo A, Delgado FE, Rocha GM. Complications that increase the time of Hospitalization at ICU of patients submitted to cardiac surgery. Rev Bras Cir Cardiovasc. 2010;25(2):166-71.
67. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70(2):252-89.
68. Ogawa M, Izawa KP, Satomi-Kobayashi S, Kitamura A, Ono R, Sakai Y, et al. Poor preoperative nutritional status is an important predictor of the retardation of rehabilitation after cardiac surgery in elderly cardiac patients. Aging Clin Exp Res. 2017;29(2):283-90.

69. Visser M, van Venrooij LM, Vulperhorst L, de Vos R, Wisselink W, van Leeuwen PA, et al. Sarcopenic obesity is associated with adverse clinical outcome after cardiac surgery. Nutr Metab Cardiovasc Dis. 2013;23(6):511-8.
70. Chung CJ, Wu C, Jones M, Kato TS, Dam TT, Givens RC, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. J Card Fail. 2014;20(5):310-5.

6 ARTIGOS ORIGINAIS

ARTIGO 1 - ARTIGO ORIGINAL

VARIATIONS IN PHASE ANGLE AND HANDGRIP STRENGTH IN PATIENTS UNDERGOING CARDIAC SURGERY: PROSPECTIVE COHORT STUDY

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VARIATIONS IN PHASE ANGLE AND HANDGRIP STRENGTH IN PATIENTS UNDERGOING CARDIAC SURGERY: PROSPECTIVE COHORT SUTDY

RUNNING TITLE: PHASE ANGLE AND HANDGRIP STRENGTH IN CARDIAC SURGERY

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ABSTRACT

Background/objectives: Bioimpedance phase angle (PA) can assess cell membrane integrity, and handgrip strength (HGS) evaluates functional capacity. This study aimed to follow PA and HGS variations in patients undergoing cardiac surgery over 1 year and associating those with clinical outcomes.

Subjects/methods: Prospective cohort study with 272 consecutively patients (aged ≥18 years) undergoing cardiac surgery. PA and HGS measures were performed at six set times: preoperative and five postoperative (PO). Generalized estimating equations (GEE) were constructed by surgery type and by gender to analyze variations along time. Associations of area under the curve (AUC) of PA (PA-AUC) and HGS (HGS-AUC) by multivariate regression analysis were studied.

Results: Analyzing GEE results PA values showed reduction from preoperative to intensive care unit (ICU). Gradual recovery of these values started between ICU and hospital discharge, reaching values similar to those of preoperative in 12 months PO. HGS showed decreases in values between preoperative and hospital discharge and then a progressive and accelerated recovery, reaching in 3 months preoperative values and higher values in 12 months. In multivariable model of PA–AUC, age, combined surgery and gender were significant ($p < 0.001$, $p = 0.005$, $p < 0.001$, respectively). At the same analysis with HGS-AUC by gender, age ($p < 0.001$) and hospital length of stay ($p = 0.003$) remained significant in women, but only age in men ($p = 0.010$).

Conclusion: These findings suggest PA and HGS can be used to monitor patients undergoing cardiac surgery and shows the importance in following their variations over 1 year.

Keywords: Cardiac surgery. Electrical impedance. Handgrip strength. Phase angle.

INTRODUCTION

The cardiovascular disease is the main global cause of mortality (1). In several cases the cardiac surgery is indicated to correct anatomic dysfunctions (valve replacement) or myocardial revascularization to improve prognosis (2).

In surgical procedures there occur alterations of membrane integrity and muscle function. Comparing preoperative and postoperative (PO) modifications help to understand the importance of dynamic body changes, plan for necessary interventions, and prevent functional limitations. These alterations could be evaluated by measuring phase angle (PA) and handgrip strength (HGS) (3-5). Both are influenced by clinical disorders (6, 7) and also by gender and age (8, 9).

PA is a bioelectrical impedance analysis (BIA) derived parameter. It is calculated directly from reactance (Xc) and resistance (R) of the human body in response to the application of an external current, and provides a noninvasive opportunity to assess body composition (10). It reflects changes in cellular membrane integrity and alterations in fluid balance (11). PA has been used as a prognostic indicator in several clinical situations such as critical patients, cardiac, and cancer (12-15).

HGS is a useful test of functional capacity to assess muscle strength in clinical and epidemiological studies (16-18). HGS measuring was seen as a simple and effective method to assess functional status and the risk of increased length of stay (LOS) after left ventricular assist device implantation (19).

The aim of this study was to monitor longitudinal variations of PA and HGS in preoperative and PO over 1 year in patients undergoing elective cardiac surgery, and associate those with clinical outcomes.

METHODS

Prospective cohort study with 272 consecutively patients (aged ≥18 years) undergoing cardiac surgery from January 2015 to September 2017, at Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Patients were recruited from the Cardiovascular Surgery Service‘s schedule. The inclusion criteria were: elective cardiac surgery (coronary artery bypass grafting – CABG, valve replacement or combined surgery – CABG plus valve replacement) and patients aged ≥ 18 years. The exclusion criteria were: patients with cognitive impairment, pregnancy, ascites, anasarca, cancer, transplant, cardiac reoperation within three months, impediments to BIA (people with cardiac devices, orthopedic prosthesis, metal implants, amputees, skin integrity issues, body mass index (BMI) ≥ 34.0 kg/ m^2) and inability to perform the HGS test (limitation of movement of the dominant arm and reduction of the usual strength of the dominant hand due to some previous disease). The informed consent was obtained from patient or legal guardian.

The sociodemographic data (age and gender) and clinical data such as previous heart failure, type of operative procedure (CABG and/or valve replacement surgery), surgery time (in minutes), cardiopulmonary bypass (CPB) time (in minutes), aortic cross-clamp time (in minutes), bleeding (in mL), mechanical ventilation (MV) (in hours), LOS at PO intensive care unit (ICU) (days) and hospital LOS (days), infections on hospital and clinical outcomes over 1 year such as hospital readmission, reoperation and mortality were extracted from medical files. The operative risk was calculated previous to cardiac surgery using European system for cardiac operative risk evaluation II (EuroSCORE II) (20).

Measures of PA and HGS were carried out at six set times: preoperative (up to 24 hours before surgery), in PO ICU (first PO day), at hospital discharge (within 24

hours before hospital discharge), 3, 6 and 12 months after surgery. Data obtained from a previous study which evaluated patients just three set times (preoperative, hospital discharge, 3 months PO) were also included in the analysis (21, 22). The three last evaluations were performed at the Clinical Research Center of the hospital, prescheduled by telephone. There are some patients that did not participate in all evaluations.

It was used a portable tetrapolar BIA device (Biodynamics 450: Biodynamics Corp. Seattle, Washington, USA) to measure PA and a portable hydraulic dynamometer (Jamar, Sammons Preston Rolyan, Bolingbrook, IL, USA) for HGS measurements.

All BIA measurements were accomplished with the patient fasting of 4 hours, in duplicate and with the patient lying down, with legs apart and electrodes glued on his right hand and foot. The PA is calculated by the relation between R and Xc measures by electric current (800 microA and frequency of 50 kHz) flow in the tissues (PA = Tangent Arc Xc / R) (10).

The HGS was evaluated in the dominant hand, adjusted for the size of the patients' hand, measured in triplicate where the highest value was used. The tests were conducted with the patient sitting with their elbow flexed at 90° and pressing the dynamometer with the dominant hand at full strength for three seconds (94% were right-handed) (23, 24).

All stages of the study were performed by a trained researcher and patients were handled according to the protocols for infection control.

The study adhered to the ethical principles of research involving human subjects outlined in the Declaration of Helsinki and was approved by the HCPA Research Ethics Committee (protocol 140698).

Statistical analysis

Analysis of variance (ANOVA) or Kruskal-Wallis test and Chi-Square test for comparison by gender and by surgical groups.

The analysis of the outcomes associated with area under the curve (AUC) of PA (PA–AUC) and of HGS (HGS–AUC) was realized through linear regression or Poisson regression with robust variances. Univariate regression was analyzed to identify possible predictors and confounders. In the multivariable regression analysis, the variables with p-value ≤ 0.2 were considered as possible predictors. Only the predictors with p-value < 0.05 were maintained in multivariable model.

Generalized estimating equations (GEE) were used to evaluate PA and HGS changes over time. The Bonferroni post-hoc test was used for multiple comparisons when the effect was significant.

Categorical variables were expressed as absolute or relative frequencies, and continuous variables by mean and standard deviation (SD) or median and interquartile range, respectively. Regression model estimates were described by slope ± standard error (B ± SE) or relative risk (RR) and 95% confidence interval (CI), according to the adjustment model.

All statistical analyses were performed with IBM SPSS Statistics version 18 (Chicago: SPSS Inc.). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

There were 272 patients enrolled and they all were evaluated in preoperative, 134 at PO in ICU and 127 patients underwent 1-year follow-up. The 30-day mortality was 10 patients (3.79%) and the total mortality was 19 patients (7.20%). All patients had at least three evaluations (the preoperative and at least two in PO).

Patients characteristics

There was a predominance of male (60.29%) and CABG (51.47%) patients, with a mean age of 62.19 ± 11.27 years. The profile of the patients and the three groups of surgery compared to each other are summarized in Table 1.

Combined surgery group had patients with greater severity (medium risk), showing a significantly higher EuroSCORE II ($p < 0.001$) compared to the other types of surgery. The same results were observed in relation to ICU LOS in PO ($p = 0.007$) and hospital LOS in PO ($p < 0.001$) (Table 1).

Preoperative PA showed higher values in the CABG group compared to other types of surgery ($p < 0.001$). The same result by type of surgery was observed in women ($p < 0.001$), but it did not show this difference in men ($p = 0.103$). The initial HGS values had no significant difference among the groups, regardless of whether the analysis was separated or not by gender (Table 1).

Factors that influence PA and HGS

The mean ± SE of the GEE for PA was statistically significant at the various times measured by types of surgery. There was a reduction in the mean in all groups at PO period in ICU evaluation with progressive recovery from 3 months PO until the end of the study. In the 12-month evaluation the values were similar to the preoperative. The same course was observed in relation to genders (Table 2; Figure 1: letters “a” and “b”).

There was a significant reduction in muscle strength in all surgical groups from preoperative to PO in ICU values, with a progressive recovery over time. It was observed greater values of HGS at ending of follow-up time in CABG and valve replacement surgeries in relation to preoperative. There was no difference in the

values of muscle strength among all types of surgery at all set times when analyzing the mean ± SE of the GEE for HGS (Table2; Figure: 2a).

Regarding genders, both showed recovery of muscle strength over time with a tendency to higher values without statistical significance in relation to the preoperative period (Table 2; Figure 2b).

In regression analysis of PA–AUC, after univariate analysis, in multivariable model, only age, combined surgery and gender remained significant in the final model ($p < 0.001$, $p = 0.005$, $p < 0.001$, respectively) (Table 3).

In the multivariate analysis of all patients of HGS–AUC, only time of MV and gender remained significant ($p = 0.026$ and $p < 0.001$, respectively) (Table 3).

When the multivariable analysis of HGS–AUC by gender was performed, age and hospital LOS remained significant in the female model ($p < 0.001$ and $p = 0.003$ respectively), whereas in the male model only age remained significant ($p = 0.003$) (Table 4).

DISCUSSION

The main findings in this study were that variations in PA and HGS over time showed total recovery of PA related to membrane integrity in 6 to 12 months. The return to the initial value of muscle strength by HGS was seen after 3 months. After the surgical aggression there was a reduction in these parameters with progressive recovery, reaching similar to the preoperative values, but with different behavior between variables.

Regarding gender, as in other studies, PA and HGS values were higher in men compared to women. This can be explained by differences in body composition, where muscle and cell mass are higher in men than in women (6, 9, 25).

The PA values were significantly higher in patients undergoing CABG compared to other surgeries in the preoperative period, without maintaining this difference at the end of 12 months. Considering the whole sample, there was no difference in behavior between genders, but the onset of recovery of cell membrane integrity was earlier in men, with a significant difference from discharge in women after 3 months PO. This can be explained by the quicker clinical improvement of these patients than other types of surgery that also evaluated PA over time, such as in female patients who underwent bariatric surgery without recovery within 3 months of PO despite an initial PA of 7.1° (26).

The evaluation of muscle strength through HGS shows a significant reduction in its preoperative values compared with those from the PO period until hospital discharge. This decrease could be justified by the immobility in the bed after surgical procedures, the use of CPB and MV, the pain caused by sternotomy and saphenectomy, the presence of drains and venous access, peripheral edema, among other factors that are conditions which limits bed mobility and therefore functionality (27). Between the period of hospital discharge and 3 months after surgery there is a reestablishment of muscle strength reaching values similar to the preoperative period. From 3 months PO a progressive recovery of muscle strength was observed with values higher than the initial ones at the end of 12 months. This could be explained by the clinical improvement of the patient after the surgical procedure leading to the return of their daily activities, often limited before surgery, and the inclusion of new activities.

Our findings diverged from a study that evaluated the perioperative recovery of HGS and associated it with complications 30 days after discharge from cardiac surgery in middle-aged patients and older adults and observed that on the fifth day after surgery patients were able to return to their preoperative walking skills and

preoperative HGS. In addition, were observed that recovery of HGS became smoother on the fifth, sixth and seventh days. However, the authors did not evaluate recovery of HGS in the long term for further comparisons (28).

In the multivariate regression analysis of PA for the studied population, age, combined surgery and gender were significant. In the HGS model the time of MV and gender remained significant. This was better evaluated for having a bimodal distribution and its analysis showed that for male gender only age was significant, but in female gender, in addition to age also hospital LOS stay was significant. There are no studies in literature comparing the behavior of these markers in cardiac surgical patients over 1 year.

There are many studies evaluating HGS as a predictor of outcomes in surgery (19, 29-31), but there are almost no studies that assess which factors interfere in the behavior of HGS in the PO period. According to our findings, that some factors of surgery influence HGS and studies already carried out on prognosis and HGS, it could be assumed that there is a bidirectional relationship between HGS and surgical outcomes.

It was observed that although PA seems to start to recover quicker after surgery until hospital discharge, HGS showed a faster recovery after hospital discharge. Thus, the measurement of these two markers allows us to monitor and clinically evaluate patients undergoing cardiac surgery. Partial recovery in PA was observed earlier at patient's discharge, which allows us to monitor the alterations in hospital. It can also be used clinically in patients with motor disabilities and sensory changes in the immediate PO period of cardiac surgery after extubation. However, the improvement of cell membrane integrity has a slower response up to 12 months. HGS, on the other

hand, showed a better performance after the third month PO, and it can be performed on an outpatient basis and useful for detecting early motor changes.

Despite our study having limitations such as data collection in only one hospital and just in elective patients, this is the first study of our knowledge to assess simultaneously the variations in PA and HGS over 1 year, associating both parameters with clinical outcomes. These findings may contribute to a better understanding of the response to surgical injury and recovery of these patients and to a better application and interpretation of these markers in clinical practice.

CONCLUSIONS

These findings suggest the importance in following variations of PA and HGS over 1 year. Even in the adjusted model, the reduction in PA–AUC was associated with age, combined surgery and gender. The reduction in HGS–AUC by gender was shown to be associated with age in both genders and also with the hospital LOS in women. Thus, these two parameters appear to be promising recovery markers of membrane integrity and functional capacity that can be used to monitor patients undergoing cardiac surgery, independently of other known risk factors. There is a need for further studies to reinforce our findings.

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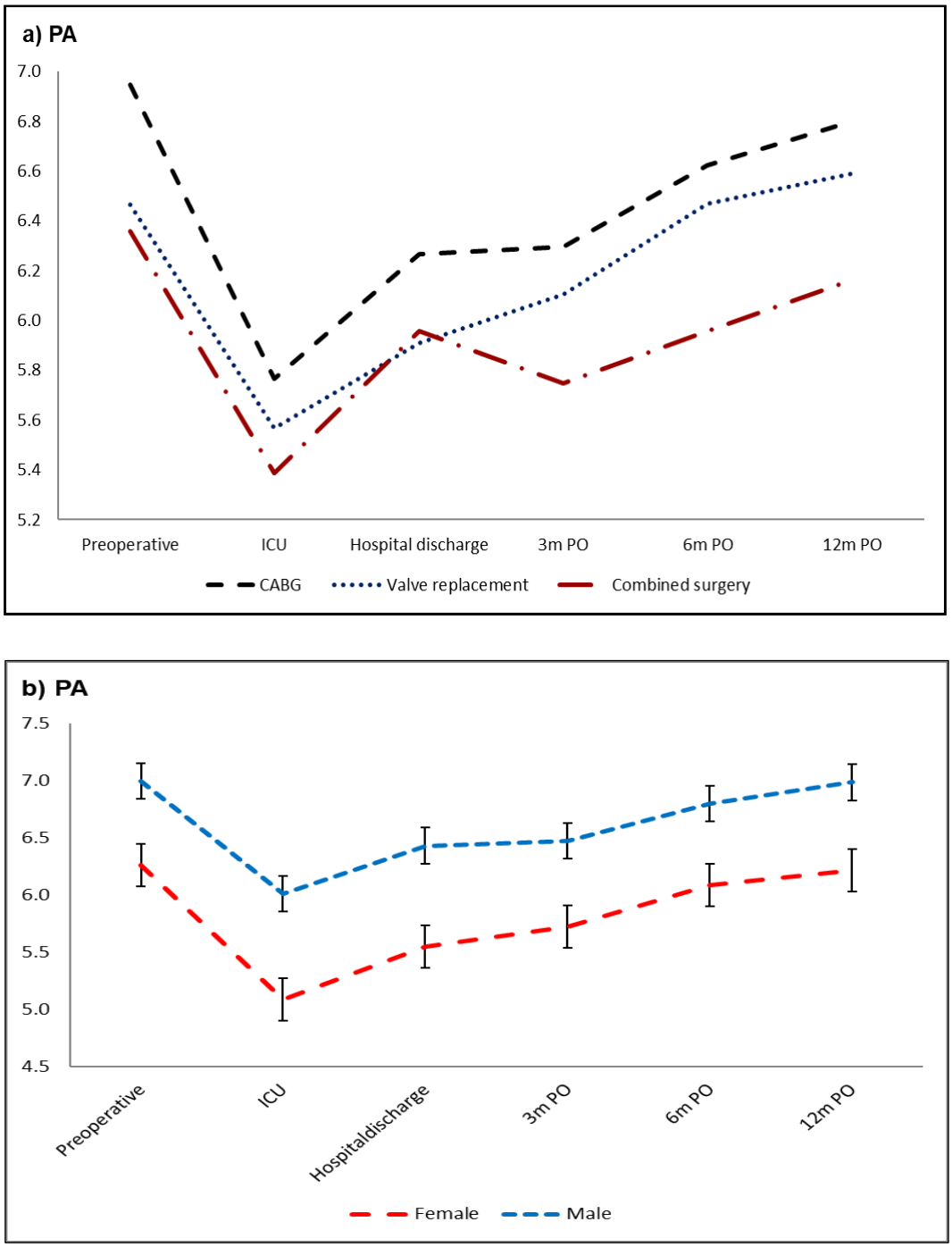
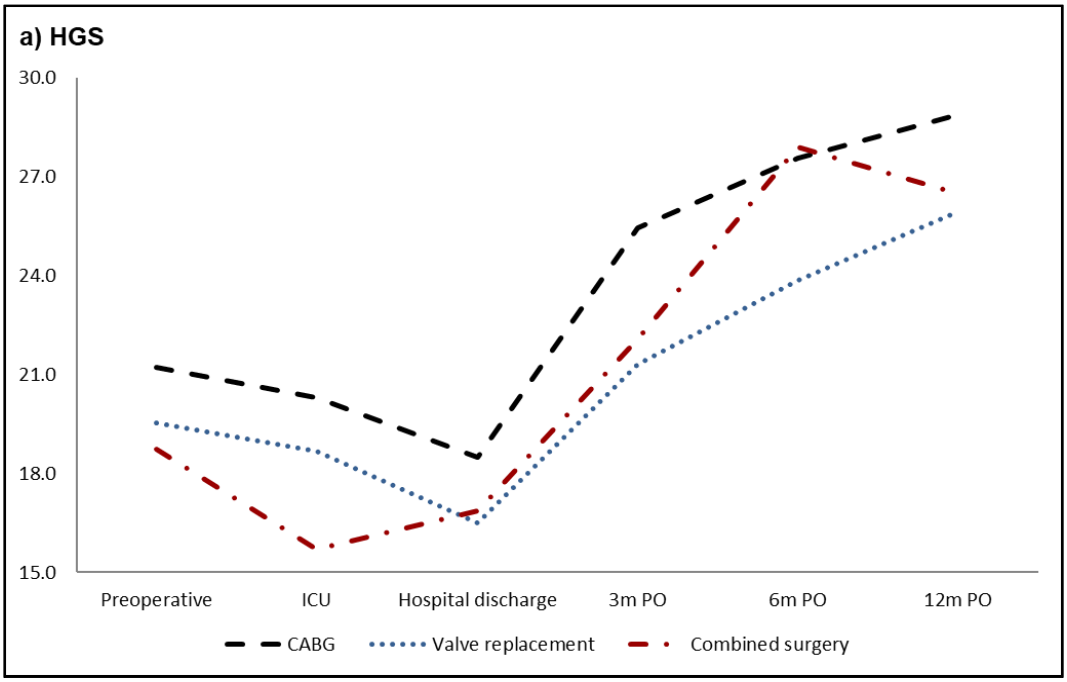


Figure 1. Line graph of means of PA by surgery type and by gender at set times.

a) GEE for PA (°) by surgery type at set times (mean).

b) GEE for PA (°) by gender at set times (mean ± SE).

CABG: coronary artery bypass grafting; Combined surgery: CABG plus valve replacement; GEE: generalized estimating equation; ICU: intensive care unit; PA: phase angle; PO: postoperative; SE: standard error; 3m: three months; 6m: six months; 12m: twelve months.



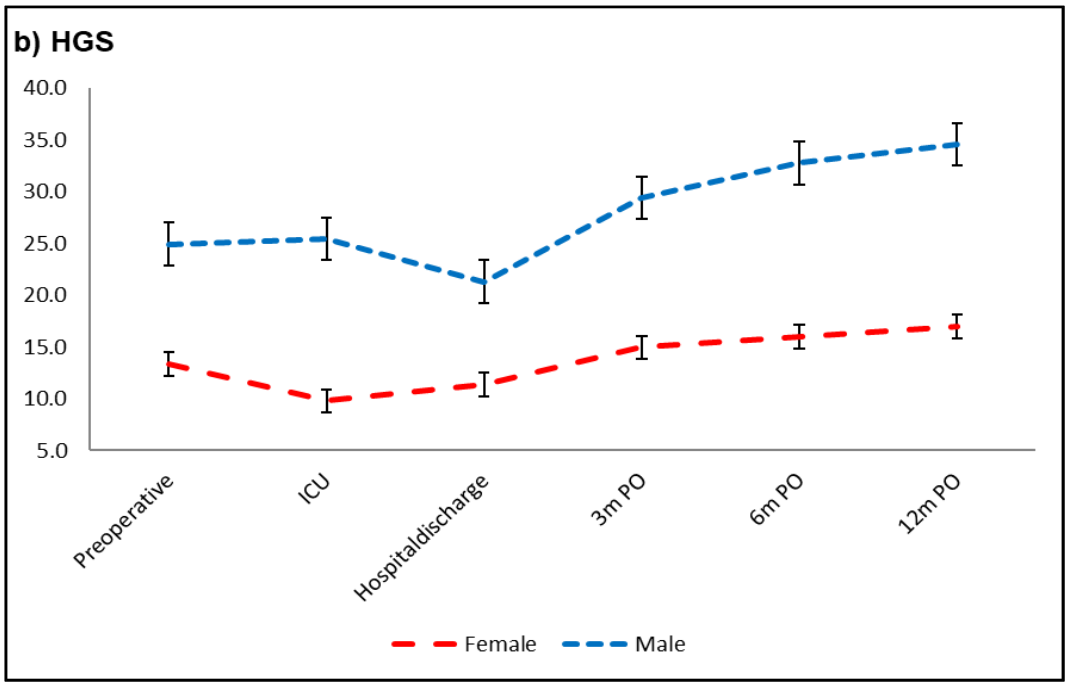


Figure 2. Line graph of means of HGS by surgery type and by gender at set times.

a) GEE for HGS (kgf) by surgery type at set times (mean).

b) GEE for HGS by (kgf) gender at set times (mean ± SE).

CABG: coronary artery bypass grafting; Combined surgery: CABG plus valve replacement; GEE: generalized estimating equation; HGS: handgrip strength; ICU: intensive care unit; PO: postoperative; SE: standard error; 3m: three months; 6m: six months; 12m: twelve months.

Table 1. Clinical and demographic data of patients undergoing cardiac surgery (n = 272)

	Overall n = 272	CABG n = 140	Valve replacement n = 105	Combined surgery n = 27	p-value
Gender (male)	164 (60.3)	88 (62.9)	56 (53.3)	20 (74.1)	0.098
Age (years)	62.19 ± 11.27	61.74 ± 8.69	61.62 ± 14.35	66.78 ± 8.47	0.083
BMI (kg/m²)	27.19 ± 3.79	27.77 ± 3.45[a]	26.60 ± 3.99[b]	26.48 ± 4.28[ab]	0.034
EuroSCORE II	1.53 (0.90 – 2.70)	1.30 (0.85 – 2.24)[a]	1.64 (0.90 – 2.50)[a]	3.17 (2.06 – 8.02)[b]	<0.001
Bleeding (mL)	250 (200 – 350)	250 (200 – 300)	250 (200 – 400)	300 (200 – 500)	0.076
Surgery time (min)	179 (150 – 210)	188 (162 – 212)[a]	153 (131 – 181)[b]	219 (181 – 262)[c]	<0.001
CPB time (min)	74 (62 – 93)	70 (60 – 85) [a]	74 (64 – 93)[a]	105 (90 – 137)[b]	<0.001
Aortic cross clamp (min)	54 (45 – 70)	45 (38 – 54)[a]	60 (52 – 70)[b]	90 (75 – 110)[c]	<0.001
MV time (hours)	6.92 (5.10 – 12.42)	6.88 (5.00 – 12.33)	6.83 (5.04 – 11.83)	10.00 (6.00 – 13.08)	0.338
ICU LOS (days)	3 (3 – 4)	3 (3 – 4) [a]	3 (3 – 4)[a,b]	4 (3 – 7)[b]	0.007
Hospital LOS (days)	7 (7 – 9)	7 (6 – 8)[a]	7 (7 – 10)[b]	8 (7 – 13)[b]	<0.001
PA (°)	6.70 ± 1.06	6.94 ± 0.98[a]	6.46 ± 1.05[b]	5.87 ± 1.22[b]	<0.001
PA (°) in men	6.99 ± 0.96	7.12 ± 0.93	6.91 ± 0.88	6.65 ± 1.19	0.103
PA (°) in women	6.25 ± 1.06	6.64 ± 0.99[a]	5.95 ± 1.01[b]	5.52 ± 0.97[b]	0.001
HGS (kgf)	18 (10 – 29)	18 (11 – 30)	17 (10 – 28)	18 (10 – 28)	0.302
HGS (kgf) in men	24 (16 – 33)	24 (16 – 34)	26 (14 – 33)	20 (10 – 31)	0.408
HGS (kgf) in women	12 (9 – 18)	12 (10 – 17)	10 (7 – 18)	10 (7 – 15)	0.398

Data expressed as frequency (percentage), mean ± standard deviation or median (range). ANOVA or Kruskal-Wallis test and Chi-Square test for comparison of the three surgical groups. Different letters for significantly different estimates. BMI: body mass index; CAGB: coronary artery bypass grafting; Combined surgery: CABG plus valve replacement; CPB: cardiopulmonary bypass; EuroSCORE II: European system for cardiac operative risk evaluation; HGS: handgrip strength; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; PA: phase angle.

Table 2. GEE for PA and HGS by surgery type and gender at set times (mean ± SE).

		Set times					
	Surgery and gender	**Preoperative (n = 272)**	**ICU (n = 134)**	**Hospital discharge (n = 254)**	**3m PO (n = 167)**	**6m PO (n = 121)**	**12m PO (n = 128)**
PA	CABG	6.9 ± 0.08^{Aa}	5.8 ± 0.10^{Ab}	6.3 ± 0.09^{Acd}	6.3 ± 0.09^{Ad}	6.6 ± 0.11^{Ace}	6.8 ± 0.11^{Ae}
	Valve replacement	6.5 ± 0.10^{Ba}	5.6 ± 0.14^{Ab}	5.9 ± 0.12^{Ac}	6.1 ± 0.15^{ABc}	6.5 ± 0.14^{ABa}	6.6 ± 0.13^{Aa}
	Combined Surgery	6.4 ± 0.24^{Ba}	5.4 ± 0.30^{Ab}	6.0 ± 0.24^{Bbc}	5.7 ± 0.18^{Babc}	6.0 ± 0.23^{Bac}	6.2 ± 0.40^{Aac}
	Female	6.3 ± 0.10^{Aa}	5.1 ± 0.11^{Ab}	5.5 ± 0.11^{Ab}	5.7 ± 0.12^{Ac}	6.1 ± 0.11^{Aa}	6.2 ± 0.10^{Aac}
	Male	7.0 ± 0.07^{Ba}	6.0 ± 0.10^{Bb}	6.4 ± 0.08^{Bcd}	6.5 ± 0.09^{Bc}	6.8 ± 0.10^{Bad}	7.0 ± 0.11^{Ba}
HGS	CABG	21.2 ± 0.98^{Aa}	20.3 ± 1.39^{Ab}	18.5 ± 0.91^{Ac}	25.5 ± 1.12^{Aad}	27.5 ± 1.36^{Aa}	28.9 ± 1.41^{Ad}
	Valve replacement	19.5 ± 1.20^{Aa}	18.7 ± 1.63^{Ab}	16.5 ± 1.06^{Ac}	21.3 ± 1.48^{Aad}	23.9 ± 1.58^{Ad}	25.9 ± 1.54^{Ae}
	Combined surgery	18.7 ± 2.09^{Aab}	15.7 ± 2.41^{Ac}	16.9 ± 1.51^{Abc}	22.1 ± 2.31^{Aab}	27.9 ± 3.24^{Aa}	26.5 ± 4.32^{Aab}
	Female	13.4 ± 0.62^{Aa}	9.80 ± 0.74^{Ab}	11.4 ± 0.58^{Ac}	14.9 ± 0.70^{Aad}	16.0 ± 0.90^{Ad}	17.0 ± 0.98^{Aad}
	Male	24.9 ± 0.96^{Ba}	25.4 ± 1.07^{Bb}	21.3 ± 0.84^{Bb}	29.4 ± 1.00^{Ba}	32.8 ± 0.91^{Ba}	34.5 ± 0.89^{Ba}

Data expressed mean ± SE. GEE analysis multiple purchases by Bonferroni. Different letters for significantly different estimates. Lower case letters for comparison by times. Capital letters for comparison by groups. CABG: coronary artery bypass grafting; Combined surgery: CABG plus valve replacement; GEE: generalized estimating equation; HGS: handgrip strength; ICU: intensive care unit; PA: phase angle; PO: postoperative; SE: standard error; 3m: three months; 6m: six months; 12m: twelve months.

Table 3. Regression analyses of PA-AUC and HGS-AUC

	PA				*HGS*			
	Univariate		***Multivariable***		***Univariate***		***Multivariable***	
Variables	**B ± SE**	**P**	**B ± SE**	**P**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
Gender (female)	-225.140 ± 55.864	< 0.001	-216.557 ± 48.137	< 0.001	5.921 (3.124 - 11.224)	< 0.001	0.171 (0.092 - 0.319)	< 0.001
Age (years)	-12.041 ± 2.514	<0.001	-9.659 ± 2.278	<0.001	1.020 (0.996 - 1.045)	0.101	-	-
BMI (kg/m²)	5.130 ± 9.061	0.571	-	-	1.049 (0.983 - 1.120)	0.149	-	-
EuroSCORE II	-43.801 ± 18.416	0.017	-	-	1.053 (0.957 - 1.159)	0.286	-	-
Bleeding	-0.089 ± 0.119	0.454	-	-	1.000 (0.999 - 1.001)	0.983	-	-
Surgery time	0.274 ± 0.690	0.691	-	-	0.998 (0.993 - 1.003)	0.447	-	-
CPB time	-0.388 ± 1.250	0.756	-	-	0.994 (0.984 - 1.005)	0.279	-	-
Aortic cross clamp	-0.852 ± 1.423	0.549	-	-	0.996 (0.985 - 1.007)	0.498	-	-
MV time (hours)	-4.316 ± 4.544	0.342	-	-	1.027 (1.005 - 1.050)	0.018	1.027 (1.003 - 1.052)	0.026
Infections	-194.075 ± 142.609	0.174	-	-	1.537 (0.838 - 2.819)	0.165	-	-
ICU LOS (days)	-22.572 ± 17.727	0.203	-	-	1.059 (0.992 - 1.130)	0.085	-	-
Infections	-194.075 ± 142.609	0.174	-	-	1.537 (0.838 - 2.819)	0.165	-	-
Hospital LOS	-11.924 ± 8.504	0.161	-	-	1.010 (1.004 - 1.015)	0.001	-	-
Hospital readmission	-71.845 ± 79.534	0.366	-	-	1.081 (0.638 - 1.833)	0.771	-	-
Reoperation	-95.43 ± 129.286	0.462	-	-	1.367 (0.744 - 2.510)	0.314	-	-
Heart failure	40.907 ± 67.390	0.544	-	-	0.840 (0.509 - 1.386)	0.495	-	-
CABG	36.980 ± 60.337	0.540	-	-	0.872 (0.575 - 1.324)	0.521	-	-
Valve replacement	53.52 ± 61.591	0.383	-	-	1.100 (0.722 - 1.675)	0.658	-	-
Combined surgery	-297.510 ± 106.285	0.005	-252.849 ± 89.346	0.005	1.157 (0.587 - 2.280)	0.673	-	-

PA: Linear regression. Multivariable analyses adjusted for age, gender and surgery. B: slope; SE: standard error.

HGS: Poisson Regression with robust variances. Multivariable analyses adjusted for gender and MV time. CI: confidence interval; RR: relative risk;

AUC: area under the curve; BMI: body mass index; CABG: coronary artery bypass grafting; Combined surgery: CABG plus valve replacement; CPB: cardiopulmonary bypass; EuroSCORE II: European system for cardiac operative risk evaluation II; HGS: handgrip strength; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; PA: phase angle.

Table 4. Regression analyses of HGS-AUC by gender

Variables	*Female Univariate*		*Female Multivariable*		*Male Univariate*		*Male Multivariable*	
	B ± SE	**p**	**B ± SE**	**p**	**B ± SE**	**P**	**B ± SE**	**p**
Age	-77.41 ± 25.29	0.002	-93.54 ± 17.11	<0.001	-77.02 ± 29.96	0.010	-77.02 ± 29.96	0.010
BMI (kg/m²)	-55.574 ± 99.20	0.575	-	-	-13.228 ± 87.91	0.880	-	-
EuroSCORE II	-83.11 ± 270.24	0.758	-	-	-328.94 ± 57.57	0.037	-	-
Bleeding	-1.71 ± 2.75	0.534	-	-	-1.04 ± 0.95	0.274	-	-
Surgery time	6.16 ± 9.72	0.526	-	-	-1.87 ± 6.19	0.762	-	-
CPB time	11.20 ± 17.01	0.510	-	-	5.29 ± 11.11	0.634	-	-
Aortic cross clamp time	5.78 ± 20.05	0.773	-	-	3.30 ± 12.44	0.791	-	-
MV time (hour)	-84.77 ± 58.41	0.147	-	-	-32.46 ± 39.84	0.415	-	-
ICU LOS	-304.20 ± 174.01	0.080	-	-	-133.58 ± 194.32	0.492	-	-
Infections	-1235.08 ± 1261.57	0.328	-	-	11832.36 ± 295.41	0.719	-	-
Hospital LOS	-49.52 ± 25.00	0.048	-46.91 ± 15.75	0.003	-114.34 ± 74.62	0.125	-	-
Hospital readmission	-19.15 ± 888.55	0.983	-	-	- 466.86 ± 796.00	0.558	-	-
Reoperation	-1655.25 ± 1248.84	0.185	-	-	-747.00 ± 1228.47	0.543	-	-
Heart failure	-1451.88 ± 811.42	0.074	-	-	-327.71 ± 616.41	0.595	-	-
Surgery (CABG)	-293.47 ± 691.12	0.671	-	-	471.17 ± 593.99	0.428	-	-
Surgery (valve replacement)	-102.13 ± 688.71	0.882	-	-	-1144.88 ± 618.36	0.064	-	-
Surgery (combined surgery)	-1967.19 ± 1509.21	0.192	-	-	1414.94 ± 955.34	0.139	-	-

Linear regression (B: slope). Multivariable analyses adjusted for gender and MV time. AUC: area under the curve; BMI: body mass index; CABG: coronary artery bypass grafting; Combined surgery: CABG plus valve replacement; CPB: cardiopulmonary bypass; EuroSCORE II: European system for cardiac operative risk evaluation II; HGS: handgrip strength; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; SE: standard error.

REFERENCES

1. WHO. World Health Organization. Top 10 causes of death https://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/2018
2. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2019;55(1):4-90.
3. Di Dedda U, Pelissero G, Agnelli B, De Vincentiis C, Castelvecchio S, Ranucci M. Accuracy, calibration and clinical performance of the new EuroSCORE II risk stratification system. Eur J Cardiothorac Surg. 2013;43(1):27-32.
4. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. Clin Nutr. 2010;29(2):151-3.
5. Waitzberg DL, Ravacci GR, Raslan M. [Hospital hyponutrition]. Nutr Hosp. 2011;26(2):254-64.
6. Stobäus N, Pirlich M, Valentini L, Schulzke JD, Norman K. Determinants of bioelectrical phase angle in disease. Br J Nutr. 2012;107(8):1217-20.
7. Norman K, Stobäus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr. 2011;30(2):135-42.
8. Bosy-Westphal A, Danielzik S, Dörhöfer RP, Later W, Wiese S, Müller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. JPEN J Parenter Enteral Nutr. 2006;30(4):309-16.
9. Schlüssel MM, dos Anjos LA, de Vasconcellos MT, Kac G. Reference values of handgrip dynamometry of healthy adults: a population-based study. Clin Nutr. 2008;27(4):601-7.
10. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. 2004;23(5):1226-43.
11. Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. Am J Clin Nutr. 2005;82(1):49-52.
12. Pereira MME, Queiroz MDSC, de Albuquerque NMC, Rodrigues J, Wiegert EVM, Calixto-Lima L, et al. The Prognostic Role of Phase Angle in Advanced Cancer Patients: A Systematic Review. Nutr Clin Pract. 2018;33(6):813-24.
13. da Silva TK, Berbigier MC, Rubin BeA, Moraes RB, Corrêa Souza G, Schweigert Perry ID. Phase angle as a prognostic marker in patients with critical illness. Nutr Clin Pract. 2015;30(2):261-5.
14. Alves FD, Souza GC, Clausell N, Biolo A. Prognostic role of phase angle in hospitalized patients with acute decompensated heart failure. Clin Nutr. 2016;35(6):1530-4.
15. Garlini LM, Alves FD, Ceretta LB, Perry IS, Souza GC, Clausell NO. Phase angle and mortality: a systematic review. Eur J Clin Nutr. 2019;73(4):495-508.
16. Bohannon RW. Dynamometer measurements of hand-grip strength predict multiple outcomes. Percept Mot Skills. 2001;93(2):323-8.
17. Humphreys TL, Schnizlein-Bick CT, Katz BP, Baldridge LA, Hood AF, Hromas RA, et al. Evolution of the cutaneous immune response to experimental Haemophilus ducreyi infection and its relevance to HIV-1 acquisition. J Immunol. 2002;169(11):6316-23.

18. Cereda E, Vanotti A. The new Geriatric Nutritional Risk Index is a good predictor of muscle dysfunction in institutionalized older patients. Clin Nutr. 2007;26(1):78-83.
19. Yost G, Bhat G. Relationship Between Handgrip Strength and Length of Stay for Left Ventricular Assist Device Implantation. Nutr Clin Pract. 2017;32(1):98-102.
20. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):734-44; discussion 44-5.
21. da Silva TK, Perry IDS, Brauner JS, Wender OCB, Souza GC, Vieira SRR. Performance evaluation of phase angle and handgrip strength in patients undergoing cardiac surgery: Prospective cohort study. Aust Crit Care. 2018;31(5):284-90.
22. Perry IS, Pinto LC, da Silva TK, Vieira SRR, Souza GC. Handgrip Strength in Preoperative Elective Cardiac Surgery Patients and Association With Body Composition and Surgical Risk. Nutr Clin Pract. 2019;34(5):760-6.
23. Hillman TE, Nunes QM, Hornby ST, Stanga Z, Neal KR, Rowlands BJ, et al. A practical posture for hand grip dynamometry in the clinical setting. Clin Nutr. 2005;24(2):224-8.
24. Joy M, Gary S, Kristin V, Therapists ASoH. Grip. In: Mount Laurel NJASoHT, editor. Clinical Assessment Recommendations. 3rd ed ed. Chicago, IL: Mount Laurel, N.J.: American Society of Hand Therapists; 2015. p. 1-20.
25. Luna-Heredia E, Martín-Peña G, Ruiz-Galiana J. Handgrip dynamometry in healthy adults. Clin Nutr. 2005;24(2):250-8.
26. Koehler KB, Moraes RAG, Rodrigues JB, Portela BSM, Miguel GPS, Pedrosa RG, et al. Bioimpedance phase angle is associated with serum transthyretin but not with prognostic inflammatory and nutritional index during follow-up of women submitted to bariatric surgery. Clin Nutr ESPEN. 2019;33:183-7.
27. Diretriz de Reabilitação Cardíaca. **Arq Bras Cardiol**. 2005;84(5):431-40.
28. Fu L, Zhang Y, Shao B, Liu X, Yuan B, Wang Z, et al. Perioperative poor grip strength recovery is associated with 30-day complication rate after cardiac surgery discharge in middle-aged and older adults - a prospective observational study. BMC Cardiovasc Disord. 2019;19(1):266.
29. Prasitsiriphon O, Pothisiri W. Associations of Grip Strength and Change in Grip Strength With All-Cause and Cardiovascular Mortality in a European Older Population. Clin Med Insights Cardiol. 2018;12:1179546818771894.
30. Bragança RD, Ravetti CG, Barreto L, Ataíde TBLS, Carneiro RM, Teixeira AL, et al. Use of handgrip dynamometry for diagnosis and prognosis assessment of intensive care unit acquired weakness: A prospective study. Heart Lung. 2019;48(6):532-7.
31. Celis-Morales CA, Welsh P, Lyall DM, Steell L, Petermann F, Anderson J, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. BMJ. 2018;361:k1651.

ARTIGO 2 - ARTIGO ORIGINAL

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PHASE ANGLE AS A PROGNOSTIC MARKER IN PATIENTS UNDERGOING CARDIAC SURGERY: PROSPECTIVE COHORT STUDY

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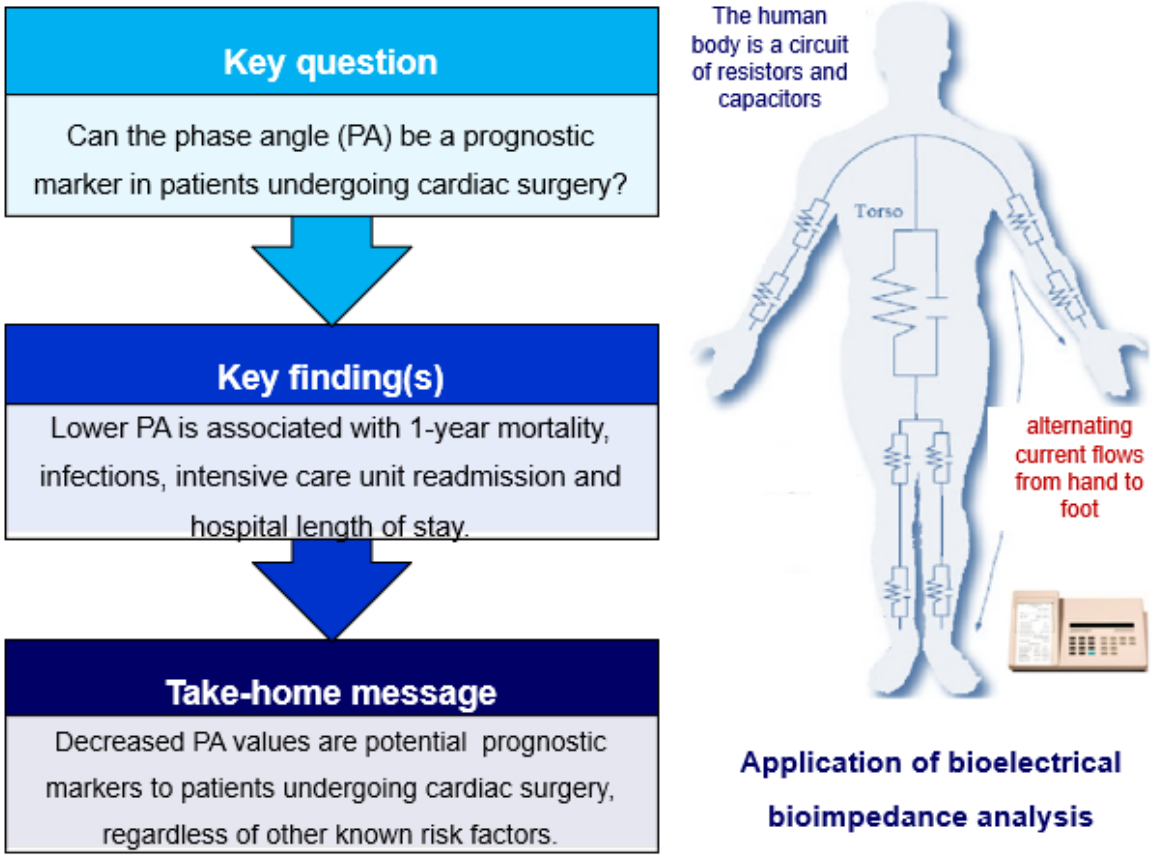

ABSTRACT

Objectives: Studies carried out with several types of patients demonstrate that bioimpedance phase angle (PA) is associated with clinical prognosis, but in cardiac surgical patients is more studied as marker of frailty and undernutrition. This study aims to evaluate PA as a prognostic marker in patients undergoing cardiac surgery, associating this with adverse clinical outcomes.

Methods: Prospective cohort study conducted from January 2015 to November 2018 with 272 patients undergoing cardiac surgery. Bioimpedance measurement was performed as close as possible to the preoperative admission time (up to 24 hours before surgery). PA was analyzed with following early and midterm clinical outcomes: infections, intensive care unit (ICU) readmission, hospital length of stay (LOS) ≥ 8 days and 30-day and 1-year mortality after surgery.

Results: Mean age was 62.19 ± 11.27 years with predominance of male patients 60.29% (n=164). Median EuroSCORE II was 1.54% (0.90 – 2.70%) and mean PA was 6.70 ± 1.06°. Surgical procedures were: 51.47% (n=140) coronary artery bypass grafting, 38.60% (n=105) valve replacement and 9.93% (n=27) combined surgery. The 30-day mortality was 3.79% (n=10) and the 1-year mortality was 7.20% (n = 19). Lower levels of PA were associated with 1-year mortality (HR 1.69, 95%CI 1.11 – 2.56, p=0.013), infections (RR 1.59, 95%CI 1.06 – 2.39, p=0.025), ICU readmission (RR 2.21, 95%CI 1.30 – 3.77, p=0.003) and hospital LOS ≥ 8 days (RR 1.28, 95%CI 1.11 – 1.48, p=0.001).

Conclusions: These findings reinforce a prognostic potential of PA to patients undergoing elective cardiac surgery.

Keywords: Cardiac surgery. Electrical impedance. Phase Angle. Prognosis.

INTRODUCTION

Several risk stratification models have been proposed for predicting mortality in cardiac surgery (1-4). In clinical evaluation before cardiac surgery, risk scores are used to assess 30-day mortality (5).

The European system for cardiac operative risk evaluation II (EuroSCORE II) and the Society of Thoracic Surgeons (STS) score (3, 4) are the most used. However, EuroSCORE seems to overestimate the perioperative risk in the elderly population, while scoring the STS presents an underestimation of the risk (6). One of the reasons that might justify this fact is that none of the risk scores incorporate the biological status of the patients (7).

Risk models targeted to different heart diseases and statistical methods of established risk systems should be improved (8, 9). There is space for improvements in the risk modeling through evaluation parameters that are capable of quantifying functional and organic alterations, which has an influence on health care quality (10, 11).

The phase angle (PA), determined by bioelectrical impedance analysis (BIA), is a non-invasive method for measuring altered electrical properties of biological tissues and membrane integrity. This is a practical, non-invasive method that can be measured at the bedside, and conventionally used to assess body composition (12). Besides, it has been recognized as an objective prognostic marker of disease severity like some cancers, critical illness, heart failure, frailty and others (13-19).

In several countries (Canada, Netherlands, Lithuania) PA has been studied as an indicator of malnutrition and determines adverse outcomes after cardiac surgery (20-23). There are no studies in Brazil about this concern and late outcomes.

The aim of this study was to evaluate PA as a prognostic marker in patients undergoing cardiac surgery, associating this with adverse clinical events and 30-day and 1-year mortality after surgery.

METHODS

This was a prospective cohort study conducted at Hospital de Clínicas de Porto Alegre (HCPA), Brazil, from January 2015 to November 2018. Patients were recruited consecutively from the Cardiovascular Surgery Service‘s schedule. The inclusion criteria were: elective cardiac surgery (coronary artery bypass grafting – CABG, valve replacement or combined surgery – CABG plus valve replacement) and patients aged ≥ 18 years. The exclusion criteria were: patients with cognitive impairment, pregnancy, ascites, anasarca, cardiac reoperation within three months, cancer, transplant or impediments to BIA (people with cardiac devices, amputees, skin integrity issues and body index mass (BMI) ≥ 34.0 kg/m²). The informed consent was obtained from patient or legal guardian.

Patients characteristics including age, gender, operative risk (EuroSCORE II)(2) calculated previous to cardiac surgery, data about type of operative procedure (CABG and/or heart valve surgery), surgery time (in minutes), cardiopulmonary bypass (CPB) time (in minutes), ischemia/ aortic cross-clamp time (in minutes), bleeding and clinical outcomes were extracted from medical files.

Early adverse clinical outcomes studied: infections, mechanical ventilation (MV) ≥ 12h, reintubation, intensive care unit (ICU) length of stay (LOS) ≥ 4 days, ICU readmission, hospital LOS ≥ 8 days and 30-day mortality. Midterm outcomes evaluated: hospital readmission, reoperation and 1-year mortality.

The BIA was performed twice as close as possible to the preoperative admission time (up to 24 hours before surgery), with the patient fasting four hours. The BIA is a measure of total body resistance to low amplitude (800 μA), single and low frequency (50 Khz) electrical current; it includes properties such as impedance (Z), resistance (R), and reactance (Xc). The PA is obtained through a ratio of R and Xc (PA = arctangent Xc / R) and reflects cell stability and water distribution in intra and extracellular spaces (13, 14). For these measures, a Biodynamics 450® analyzer, version 5.1 (Biodynamics Corp., Seattle, WA, USA), and resting ECG electrodes (tab style) (Conmed Corporation, Utica, NY, USA) were used. The Biodynamics device requires the age, sex, weight and height of the patient to be entered. A digital scale was used (Lider, Araçatuba, SP, Brazil) to measure the patients' body weight, and a wall-mounted vertical anthropometer (Sanny, São Bernardo do Campo, SP, Brazil) was used to measure their height.

The BIA was performed with the patient lying supine on a bed with legs apart and arms not touching the torso. Four electrodes were placed in specific locations according to BIA Protocol (the dorsal surface of the right wrist, the third metacarpal, the surface of the right anterior ankle between the prominent bones, and the dorsal surfaced of the third metatarsal) (14). The electrodes were used exclusively for each patient, which had their skin surface cleaned with alcohol gel before application.

The study adhered to the ethical principles of research involving human subjects outlined in the Declaration of Helsinki and was approved by the HCPA Research Ethics Committee (protocol 140698).

Sample Calculation

To calculate the sample size, it was used the *power.roc.test* function of pROC package's (R-Project program, version 3.5.1). Considering power of 80%, significance level of 5% and AUC of 0.60 (20), the calculated sample size was 248, with a 10% error margin for possible losses, resulting in 275.

Statistical analysis

A description and definition of the outcomes associated with PA was realized through Cox Univariate Regression for 1-year mortality or Poisson regression with robust variances for the other outcomes. Possible predictors and confounders were defined through Spearman correlation (ρ) for continuous variables and t-test for independent samples for gender and heart failure. In the multivariable regression analysis with PA, the variables with $\rho \geq 0.2$ or p-value ≤ 0.1 were considered as predictors. Only the predictors with p-value < 0.05 were maintained in model. In every model the inverted PA (the numbers were multiplied by -1) was used, aiming the risk interpretation instead of protection. In the last stage, the receiver operating characteristic (ROC) curves of the results in which the PA remained significant in the adjusted model were analyzed.

Categorical variables were expressed as absolute or relative frequencies, and continuous variables by mean and standard deviation or median and interquartile range, respectively. Regression model estimates were described by hazard ratio (HR) or relative risk (RR) and 95% confidence interval (CI), according to the adjustment model.

All statistical analyses were performed with IBM SPSS Statistics version 18 (Chicago: SPSS Inc.) and R-Project version 3.5.1. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 414 patients were referred for cardiac surgery during the study. Two hundred and seventy-two patients were enrolled. It was not possible to obtain data about hospital readmission, reoperation, 30-day mortality and 1-year mortality of 8 patients (Figure 1).

Patient characteristics

There was a predominance of male (60.29%) and CABG (51.47%) surgery patients. The profile of patients and adverse clinical outcomes are summarized in Table 1 and Table 2, respectively.

The patients had previous history of hypertension (84.56%), ischemic heart disease (62.87%), valve disease (47.79%), diabetes mellitus (35.66%), heart failure (33.09%), myocardial infarction (32.72%), dyslipidemia (30.51%), stroke (10.29%), chronic renal failure (6.99%) and chronic obstructive pulmonary disease (5.51%). Additionally, abstinence rates (41.91%) and smoking (15.07%) were found.

The median EuroSCORE II for all cardiac surgeries was 1.53% (0.90 – 2.70%). Analyzing the EuroSCORE II by type of surgery, most patients who underwent CABG (72.14%) and valve replacement (60.95%) had a low risk in the EuroSCORE II with a median 1.30% (0.86 – 2.24%), and 1.64% (0.90 – 2.50%), respectively. Patients who underwent CABG plus valve replacement had a median EuroSCORE II 3.17 (2.06 – 8.02%) characterizing a medium risk (24).

The 30-day mortality was 3.79% (n = 10). However, in regression analysis of PA (inverted) with 30-day mortality there was no statistical significance (p = 0.346). The 1-year mortality was 7.20% and when analyzing by type of surgery it was 5.93% in CABG, 7.69% in valve replacement and 20.00% in combined surgery.

PA in relation to adverse clinical outcomes

All adverse outcomes studied with the PA in univariate regression analysis and controlled by type of surgery were statistically significant, except hospital readmission (p = 0.323). In the multivariable analyses adjusted for gender, age, surgery, heart failure and EuroSCORE II were statistically significant: 1-year mortality, infections, ICU readmission and hospital LOS ≥ 8 days (Table 3).

The inverted PA evaluate the risk of adverses outcomes showed that every one degree decrease in PA was associated with a higher risk of morbidity (infections, ICU readmission and hospital LOS ≥ 8 days) and total mortality in 1-year follow-up (Table 3).

ROC curve analysis

Analyzing the ROC curves of the outcomes which the PA was significant (p < 0.05), a poor association with 1-year mortality (AUC: 0.690; 95%CI 0.557 – 0.824), a fair association with infections (AUC: 0.711; 95%CI 0.592 – 0.831), a good association with ICU readmission (AUC: 0.857; 95%CI 0.772 – 0.942) and a poor association with hospital LOS ≥ 8 days (AUC: 0.654; 95%CI 0.585 – 0.723) were observed (Figure 2).

DISCUSSION

This is one of the few existing studies that use PA to evaluate 30-day mortality and 1-year mortality and complications in major cardiac surgeries (23). Among the main results are that reduced PA values were associated with an increase in risk of 1-year mortality, infections, ICU readmission and hospital LOS ≥ 8 days.

These findings reaffirm the prognostic potential of this noninvasive and low-cost marker to patients undergoing cardiac surgery, independently of other known risk factors for the prognosis.

The PA is known to be dependent on several factors, like age, gender and ethnicity (25), as well as by disease severity (26). So, to improve precision of PA in predicting survival, the regression analyses were corrected for the factors gender, surgery type, presence of previous heart failure and EuroSCORE II.

The kind of the sample studied was similar to data found in the literature (20, 21, 23), such as regarding the prevalence of male patients and the mean of age was 62 years old (20, 21, 23). There was a predominance of CABG in surgical procedures, but with a high percentage of valve replacement. This can be explained by the prevalence of rheumatic fever in developing countries (27). The mortality rate in the types of surgery was similar to the literature (28).

Regarding PA, it is known that women have lower values than men because they have less muscle and cell mass (29, 30). Elder subjects have also lower PA (25). The values found in our sample were similar to the healthy population variation considering sex and age (25).

The reduction in PA values can lead to a higher risk of mortality (20, 23). PA is related to the nutritional status of patients and the health of the cell membrane, with higher PA values indicating better membrane integrity and cell function (20). In our

study every one degree decrease in PA conferred an 1.69 higher hazard ratio of 1-year mortality, an 1.59 higher risk of infections, a 2.21 higher risk of ICU readmission, an 1.28 higher risk of prolonged hospital stay (hospital LOS ≥ 8 days). The prediction of 1-year mortality was similar to the Bioimpedance in Cardiac Surgery (BICS) study concerning midterm mortality (23). Other studies analyzed only the early mortality (30-day mortality and hospital mortality) and found the same results that our study (20, 21).

Consistent with previous studies, the PA was predictive of postoperative (PO) morbidity: infections, ICU readmission and prolonged LOS (20-23). The association of PA with prolonged LOS in the present study occurred despite the fact that we considered 8 or more days as prolonged LOS, unlike studies performed on Netherlands and Lithuania, which considered as more than 10 and 14 days, respectively (20, 21).

By analyzing the performance of ROC curves for PA and outcomes, 1-year mortality and hospital LOS ≥ 8 days showed poor values. Unlike our study, the AUC for 1-year mortality in the literature was 0.84 with the addition of PA to the STS risk (23), while the hospital LOS was similar to a Dutch research that showed AUC of 0.58 (95%CI 0.51 – 0.65) (20). The infections ROC curve showed a fair value and ICU readmission showed a good value of 0.856 in our sample. We did not find these results analyzed individually in the literature of cardiac surgery. It is important to say that the group that had the highest mortality rate was combined surgery.

Despite a significant AUC, the confidence intervals in between were wide and therefore it was decided not to establish a cutoff point for PA, which remains for future studies.

Despite some limitation of this study, like data collection only in one hospital and the specificity of the studied population, its originality is based on the use of PA in

cardiac surgery patients in a population of southern Brazil, and its association with early outcomes as ICU readmission, infections, LOS ≥ 8 days and midterm outcome 1-year mortality. The expansion of prognostic assessment possibilities for these patients using biological parameters in addition to those already traditional, may contribute to improving early interventions.

Given this association between PA and mortality found in this study and others studies (20, 23), the question that arises is if there is a cutoff of the specific PA associated with a higher risk of mortality. Thus, it might be more useful to rely on the evolution of PA to assess the prognosis than on a single measurement.

CONCLUSIONS

Even on the adjusted model, the preoperative PA was associated with PO 1-year mortality, infections, ICU readmission and hospital LOS ≥ 8 days. These findings reinforce PA potential utility as a prognostic marker in patients undergoing elective cardiac surgery, regardless of other known risk factors for the prognosis.

FUNDING

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Conflict of interest: None declared.

AUTHOR CONTRIBUTION STATEMENT

Aline Castello Branco Mancuso: The statistical analysis and interpretation of data for the work. Gabriela Corrêa Souza, Ingrid Schweigert Perry, Janete Salles Brauner, Sílvia Regina Rios Vieira: The conception and design of the work; analysis and interpretation of data for the work; final approval of the version to be submitted. Taís Kereski da Silva: The conception and design of the work; the acquisition, analysis and interpretation of data for the work; final approval of the version to be submitted; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work were appropriately investigated and resolved.

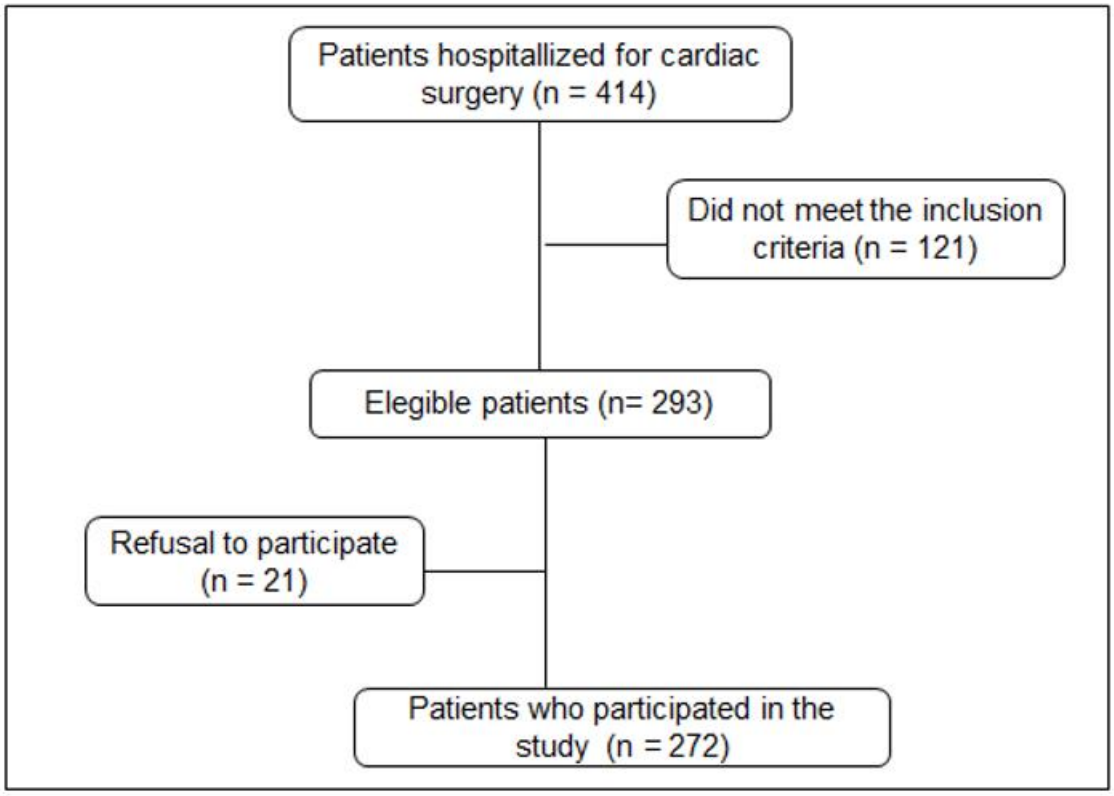

Figure 1: Sample selection flowchart. Exclusions for not meeting the criteria include BMI ≥ 34 kg/m² (n = 33), cardiac devices/ intensive care unit (n = 43), amputee limb (n = 4), anasarca/ascites (n = 3), cognitive impairment (n = 5), no skin integrity (n = 7), cancer (n = 6), cardiac reoperation within three months (n = 3), emergency surgery (n = 4) and others (n = 13). BMI: body mass index.

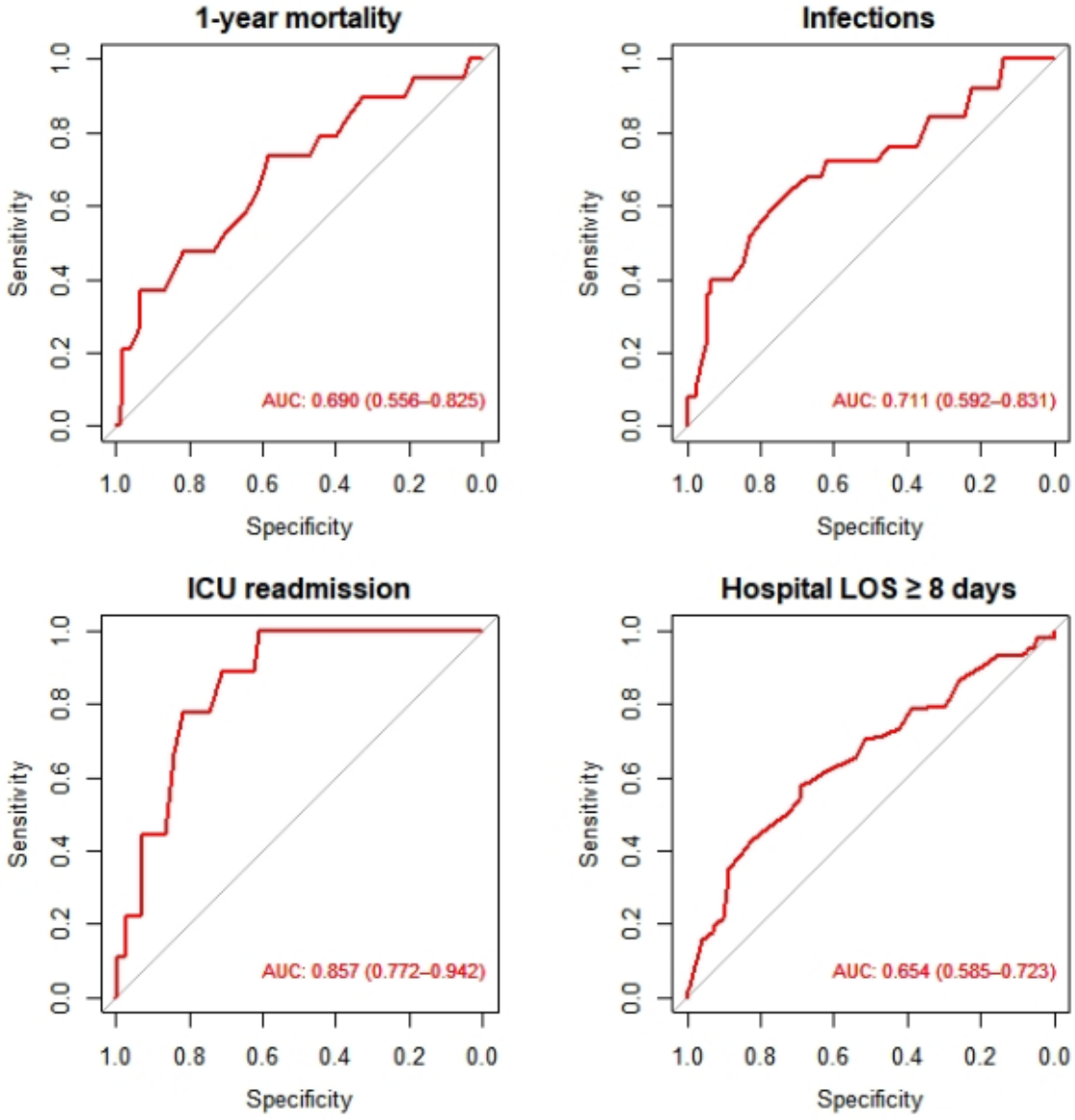

Figure 2: ROC curves of associated outcomes with PA.

AUC (95%CI): area under the curve; (95% confidence interval); ICU: intensive care unit; LOS: length of stay.

Table 1. Clinical and demographic data of patients undergoing cardiac surgery

Variables	Overall (n= 272)
Male	164 (60.29)
Age (years)	62.19 ± 11.27
BMI (kg/m²)	27.19 ± 3.79
Surgical procedure	
CABG	140 (51.47)
Valve replacement	105 (38.60)
Combined surgery	27 (9.93)
EuroSCORE II	1.53 (0.90 – 2.70)
CABG	1.30 (0.86 – 2.24)
Valve replacement	1.64 (0.90 – 2.50)
Combined surgery	3.17 (2.06 – 8.02)
Bleeding (mL)	250 (200 – 350)
CPB time (minutes)	74 (62 – 93)
Aortic cross-clamp time (minutes)	54 (45 – 70)
MV time (minutes)	415 (306 – 745)
ICU LOS (days)	3 (3 – 4)
Hospital LOS (days)	7 (7 – 9)
PA (°)	6.70 ± 1.06
PA (°) in men	6.99 ± 0.96
PA (°) in women	6.25 ± 1.06

Data expressed as frequency (percentage), mean ± standard deviation or median (interquartile range). BMI: body mass index; CAGB: coronary artery bypass grafting; Combined surgery: CABG + valve replacement; CPB: cardiopulmonary bypass; EuroSCORE: European system for cardiac operative risk evaluation; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation.

Table 2. Prevalence of adverse clinical outcome parameters in patients undergoing cardiac surgery

Variables	n (%)	n total
30-day mortality	10 (3.79)	264
1-year mortality	19 (7.20)	264
Infections	25 (9.19)	272
MV ≥ 12h	79 (29.04)	272
Reintubation	11 (4.04)	272
ICU LOS ≥ 4 days	109 (40.07)	272
ICU readmission	9 (3.30)	272
Hospital LOS ≥ 8 days	102 (37.50)	272
Hospital readmission	62 (23.48)	264
Reoperation	22 (8.33)	264

ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation.

Table 3. Regression analyses of PA (inverted) and adverse clinical outcomes.

Clinical outcome	*Univariate*		*Univariate controlled by surgery*		*Multivariable*[c]	
	HR (95% CI)[a]	**P**	**HR (95% CI)**[a]	**p**	**HR (95% CI)**[a]	**P**
30-day mortality	1.95 (1.10 - 3.44)	0.021	1.99 (1.07 - 3.69)	0.030	1.35 (0.72 - 2.53)	0.346
1-year mortality	1.94 (1.28 - 2.93)	0.002	1.77 (1.16 - 2.72)	0.009	1.69 (1.11 - 2.56)	0.013
	RR (95% CI)[b]	**P**	**RR (95% CI)**[b]	**p**	**RR (95% CI)**[b]	**P**
Infections	2.01 (1.46 - 2.78)	< 0.001	2.01 (1.41 - 2.87)	<0.001	1.59 (1.06 - 2.39)	0.025
MV ≥ 12h	1.29 (1.09 - 1.53)	0.003	1.30 (1.09 - 1.56)	0.003	0.93 (0.76 - 1.14)	0.477
Reintubation	2.37 (1.49 - 3.77)	< 0.001	2.18 (1.37 - 3.48)	0.001	1.60 (0.92 - 2.76)	0.093
ICU LOS ≥ 4 days	1.19 (1.04 - 1.36)	0.010	1.14 (0.99 - 1.30)	0.058	1.05 (0.91 - 1.20)	0.504
ICU readmission	3.18 (2.13 - 4.74)	< 0.001	2.89 (1.91 - 4.36)	<0.001	2.21 (1.30 - 3.77)	0.003
Hospital LOS ≥ 8 days	1.35 (1.17– 1.55)	< 0.001	1.28 (1.11 – 1.48)	0.001	1.28 (1.11– 1.48)	0.001
Hospital readmission	1.11 (0.90 - 1.37)	0.323	1.12 (0.90 - 1.39)	0.327	-	-
Reoperatiom	1.54 (1.12 - 2.10)	<0.007	1.35 (0.97 - 1.88)	0.072	1.35 (0.97 - 1.88)	0.072

[a] Cox Regression (HR: Hazard Ratio); [b] Poisson Regression with robust variances (RR: Relative Risk); [c] Multivariable analyses adjusted for gender, age, surgery, heart failure and EuroSCORE II. CI: confidence interval; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation.

REFERENCES

1. Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. Ann Thorac Surg. 2000;69(3):823-8.
2. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):734-44; discussion 44-5.
3. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. Ann Thorac Surg. 2018;105(5):1411-8.
4. O'Brien SM, Feng L, He X, Xian Y, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2-Statistical Methods and Results. Ann Thorac Surg. 2018;105(5):1419-28.
5. Bäck C, Hornum M, Olsen PS, Møller CH. 30-day mortality in frail patients undergoing cardiac surgery: the results of the. Scand Cardiovasc J. 2019;53(6):348-54.
6. Shih T, Paone G, Theurer PF, McDonald D, Shahian DM, Prager RL. The Society of Thoracic Surgeons Adult Cardiac Surgery Database Version 2.73: More Is Better. Ann Thorac Surg. 2015;100(2):516-21.
7. Di Dedda U, Pelissero G, Agnelli B, De Vincentiis C, Castelvecchio S, Ranucci M. Accuracy, calibration and clinical performance of the new EuroSCORE II risk stratification system. Eur J Cardiothorac Surg. 2013;43(1):27-32.
8. Bai Y, Wang L, Guo Z, Chen Q, Jiang N, Dai J, et al. Performance of EuroSCORE II and SinoSCORE in Chinese patients undergoing coronary artery bypass grafting. Interact Cardiovasc Thorac Surg. 2016;23(5):733-9.
9. Chalmers J, Pullan M, Fabri B, McShane J, Shaw M, Mediratta N, et al. Validation of EuroSCORE II in a modern cohort of patients undergoing cardiac surgery. Eur J Cardiothorac Surg. 2013;43(4):688-94.
10. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. Clin Nutr. 2010;29(2):151-3.
11. Waitzberg DL, Ravacci GR, Raslan M. [Hospital hyponutrition]. Nutr Hosp. 2011;26(2):254-64.
12. Frankenfield DC, Cooney RN, Smith JS, Rowe WA. Bioelectrical impedance plethysmographic analysis of body composition in critically injured and healthy subjects. Am J Clin Nutr. 1999;69(3):426-31.
13. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. 2004;23(5):1226-43.
14. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr. 2004;23(6):1430-53.
15. Pereira MME, Queiroz MDSC, de Albuquerque NMC, Rodrigues J, Wiegert EVM, Calixto-Lima L, et al. The Prognostic Role of Phase Angle in Advanced Cancer Patients: A Systematic Review. Nutr Clin Pract. 2018;33(6):813-24.
16. Belarmino G, Gonzalez MC, Torrinhas RS, Sala P, Andraus W, D'Albuquerque LA, et al. Phase angle obtained by bioelectrical impedance analysis independently predicts mortality in patients with cirrhosis. World J Hepatol. 2017;9(7):401-8.

17. Shin JH, Kim CR, Park KH, Hwang JH, Kim SH. Predicting clinical outcomes using phase angle as assessed by bioelectrical impedance analysis in maintenance hemodialysis patients. Nutrition. 2017;41:7-13.
18. Alves FD, Souza GC, Clausell N, Biolo A. Prognostic role of phase angle in hospitalized patients with acute decompensated heart failure. Clin Nutr. 2016;35(6):1530-4.
19. da Silva TK, Berbigier MC, Rubin BeA, Moraes RB, Corrêa Souza G, Schweigert Perry ID. Phase angle as a prognostic marker in patients with critical illness. Nutr Clin Pract. 2015;30(2):261-5.
20. Visser M, van Venrooij LM, Wanders DC, de Vos R, Wisselink W, van Leeuwen PA, et al. The bioelectrical impedance phase angle as an indicator of undernutrition and adverse clinical outcome in cardiac surgical patients. Clin Nutr. 2012;31(6):981-6.
21. Ringaitiene D, Gineityte D, Vicka V, Zvirblis T, Norkiene I, Sipylaite J, et al. Malnutrition assessed by phase angle determines outcomes in low-risk cardiac surgery patients. Clin Nutr. 2016;35(6):1328-32.
22. Ringaitiene D, Gineityte D, Vicka V, Sabestinaite A, Klimasauskas A, Gaveliene E, et al. Concordance of the new ESPEN criteria with low phase angle in defining early stages of malnutrition in cardiac surgery. Clin Nutr. 2018;37(5):1596-601.
23. Mullie L, Obrand A, Bendayan M, Trnkus A, Ouimet MC, Moss E, et al. Phase Angle as a Biomarker for Frailty and Postoperative Mortality: The BICS Study. J Am Heart Assoc. 2018;7(17):e008721.
24. Borde D, Gandhe U, Hargave N, Pandey K, Khullar V. The application of European system for cardiac operative risk evaluation II (EuroSCORE II) and Society of Thoracic Surgeons (STS) risk-score for risk stratification in Indian patients undergoing cardiac surgery. Ann Card Anaesth. 2013;16(3):163-6.
25. Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. Am J Clin Nutr. 2005;82(1):49-52.
26. da Silva TK, Perry IDS, Brauner JS, Wender OCB, Souza GC, Vieira SRR. Performance evaluation of phase angle and handgrip strength in patients undergoing cardiac surgery: Prospective cohort study. Aust Crit Care. 2018;31(5):284-90.
27. Hansen LS, Hjortdal VE, Andreasen JJ, Mortensen PE, Jakobsen CJ. 30-day mortality after coronary artery bypass grafting and valve surgery has greatly improved over the last decade, but the 1-year mortality remains constant. Ann Card Anaesth. 2015;18(2):138-42.
28. Gardner SC, Grunwald GK, Rumsfeld JS, Cleveland JC, Schooley LM, Gao D, et al. Comparison of short-term mortality risk factors for valve replacement versus coronary artery bypass graft surgery. Ann Thorac Surg. 2004;77(2):549-56.
29. Stobäus N, Pirlich M, Valentini L, Schulzke JD, Norman K. Determinants of bioelectrical phase angle in disease. Br J Nutr. 2012;107(8):1217-20.
30. Kumar S, Dutt A, Hemraj S, Bhat S, Manipadybhima B. Phase Angle Measurement in Healthy Human Subjects through Bio-Impedance Analysis. Iran J Basic Med Sci. 2012;15(6):1180-4.

7 CONCLUSÕES

Nos pacientes submetidos à cirurgia cardíaca eletiva, as variações nos valores de AF e da dinamometria manual ao longo de 1 ano de seguimento sugerem os mesmos como promissores marcadores de recuperação da integridade da membrana e capacidade funcional.

Essa assertiva encontra amparo nos achados de que houve redução dos valores de AF e da dinamometria manual após a cirurgia, com recuperação progressiva, atingindo valores semelhantes aos pré-operatórios, mas com comportamento diferente entre as variáveis. As variações no AF e na dinamometria ao longo do tempo mostraram, portanto, recuperação total do AF em 6 a 12 meses e retorno aos valores pré-operatórios da força muscular, medidas através da dinamometria manual, após 3 meses.

Também foi observado comportamento diferenciado entre os dois parâmetros em relação às associações dessas variações com seus preditores:

- A idade, o sexo e a cirurgia combinada foram associados a maior risco de redução da área sobre a curva (AUC) do AF.
- A idade foi associada a maior risco de redução da AUC da dinamometria manual em ambos os sexos e o tempo de permanência hospitalar aumenta o risco apenas nas mulheres.
- A CRM, a cirurgia de troca valvar, insuficiência cardíaca e os desfechos clínicos infecções, reinternação hospitalar e reoperação não foram associados com a AUC do AF e da dinamometria manual.
- Os indicadores clínicos EuroSCORE II, sangramento e os tempos de cirurgia, CEC, isquemia e de internação na UTI não foram associados com a AUC do AF e da dinamometria manual.

Avaliando o papel do AF como marcador prognóstico nesses pacientes, esse estudo reforça seu potencial, considerando sua associação com desfechos clínicos e mortalidade em médio prazo:

- Valores reduzidos de AF pré-operatório foram associados a maior risco de infecções, reinternação na UTI e internação hospitalar prolongada (≥ 8 dias).
- O AF pré-operatório não está associado com: VM prolongada (≥ 12h), reintubação, internação prolongada na UTI (≥ 4 dias), reinternação hospitalar e reoperação.
- Valores reduzidos de AF pré-operatório foram associados a maior risco de mortalidade em 1 ano, contudo não estão associados com mortalidade em 30 dias.

Em síntese, esses achados sugerem a importância de acompanhar as variações do AF e da dinamometria manual ao longo de 1 ano, tendo em vista que mesmo no modelo ajustado, a redução da AUC do AF foi associada à idade, cirurgia combinada e sexo, além da redução da AUC da dinamometria manual mostrar-se associada à idade em ambos os sexos e também ao tempo de permanência hospitalar em mulheres.

Adicionalmente, os achados desse estudo, evidenciam que valores reduzidos de AF pré-operatórios estão associados à mortalidade pós-operatória em 1 ano, infecções, readmissão na UTI e tempo de internação hospitalar ≥ 8 dias, confirmam a utilidade potencial do AF como marcador prognóstico em pacientes submetidos à cirurgia cardíaca eletiva, independentemente de outros fatores de risco conhecidos.

8 CONSIDERAÇÕES FINAIS

Embora as cirurgias cardíacas sejam procedimentos comuns e bem difundidos mundialmente, há uma escassez de estudos longitudinais que acompanhem alterações em relação à integridade da membrana celular e à função muscular. O acompanhamento e a compreensão dessas mudanças orgânicas dinâmicas podem nos ajudar a planejar intervenções necessárias e evitar limitações funcionais.

Apesar disso, no nosso conhecimento o presente estudo foi o primeiro a avaliar simultaneamente as variações no AF, derivado da bioimpedância elétrica, e na dinamometria manual ao longo de 1 ano, associando ambos os parâmetros com desfechos clínicos.

O AF e a dinamometria manual são medidas de fácil obtenção, não invasivas ambas podem ser incorporadas na prática clínica, tanto na UTI, nas enfermarias como nos ambulatórios. Assim, a mensuração desses dois marcadores nos permite monitorar e avaliar clinicamente pacientes submetidos à cirurgia cardíaca.

Embora o AF pareça começar a se recuperar mais rapidamente após a cirurgia até a alta hospitalar, a dinamometria manual mostrou uma recuperação mais rápida após a alta hospitalar. Assim, o AF nos permite monitorar as alterações no hospital e a dinamometria manual pode ser realizada em nível ambulatorial e sendo útil para detectar alterações motoras precoces. Dessa forma, esses parâmetros podem nos ajudar a implementar intervenções nutricionais tanto no período pré-operatório quanto no PO. No entanto, há necessidade de mais estudos para reforçar nossas descobertas.

Além disso, nossos achados reforçam o potencial do AF como marcador prognóstico não apenas de mortalidade em 1 ano, mas também de desfechos como infecções, reinternação na UTI e tempo e permanência hospitalar em pacientes

submetidos à cirurgia cardíaca. A expansão das possibilidades de avaliação prognóstica para esses pacientes, utilizando parâmetros biológicos além daqueles já tradicionais, pode contribuir para melhorar as intervenções precoces.

APÊNDICES

APÊNDICE I – Termo de consentimento livre e esclarecido

<u>Projeto de Pesquisa</u>: "Ângulo de fase como marcador prognóstico em pacientes que serão submetidos à cirurgia cardíaca: estudo de coorte prospectivo"

Você está sendo convidado(a) a participar de uma pesquisa científica que tem por objetivo verificar o ângulo de fase (AF) através da avaliação da Bioimpedância Elétrica (BIA). A BIA tem o objetivo de avaliar a composição corporal medindo a quantidade de gordura, líquido e músculo do corpo. Esse aparelho é composto por 4 (quatro) eletrodos que serão fixados no seu braço e pé, que através de uma corrente elétrica de baixa intensidade e inofensiva são capazes de informar a composição corporal e assim transformar essas informações em um índice chamado ângulo de fase (AF). Desejamos caracterizar o ângulo de fase dos pacientes com indicação de realização de cirurgia cardíaca e comparar com parâmetros clínicos antes e após a cirurgia. Esse método é rápido (em média 5 minutos), prático e não invasivo, e, com ele podemos melhorar a qualidade do cuidado dos pacientes que estiverem nessa situação. Durante sua internação, você será pesado(a) e medido(a) e serão realizadas 6 BIAs. A 1ª BIA será realizada antes da cirurgia, no dia internação hospitalar, a 2ª BIA na UTI após a cirurgia, a 3ª BIA próxima da alta hospitalar. Já a 4ª, 5ª e 6ª BIA serão realizadas 3 (três), 6 (seis) e 12 (doze) meses, após a cirurgia, no Centro de Pesquisa Clínica (CPC) do HCPA. Não são conhecidos riscos advindos destes procedimentos.

Além do procedimento descrito acima, solicitamos sua autorização para consultarmos o seu prontuário, com o objetivo de verificar alguns aspectos de sua condição de saúde, tais como idade, doença que levou à necessidade de cirurgia cardíaca, e qual o tipo de cirurgia cardíaca. Você poderá também ser contatado para completar as informações obtidas no prontuário. Você poderá também ser contatado para completar as informações obtidas no prontuário.

Todas as informações de identificação pessoal dos participantes serão confidenciais, e os resultados do estudo serão publicados de forma agrupada, sem que a divulgação do nome dos participantes. As informações serão utilizadas somente para fins de pesquisa.

Sua participação é totalmente voluntária e a decisão de não participar, ou a desistência após a inclusão no estudo, não influenciará o seu atendimento no Hospital de Clínicas de Porto Alegre. Além disso, a participação na pesquisa não envolve custos e nenhum tipo de remuneração. Porém, você deverá vir ao HCPA para a realização da 3ª BIA, conforme explicado anteriormente.

Em caso de dúvidas você poderá contatar a pesquisadora responsável por esse projeto, Profª. Drª. Silvia Regina Rios Vieira, do Serviço de Medicina Intensiva, pelo telefone 33598632 ou a Nutricionista Taís Kereski da Silva, pelo telefone 33596321. Você poderá

também contatar o Comitê de Ética em Pesquisa, no 2º andar do HCPA, ou pelo telefone 33597640, de segunda à sexta, das 8h às 17h.

Declaro que autorizo voluntariamente minha participação nesse projeto de pesquisa, assinando o TCLE em duas vias, sendo que uma ficará comigo e a outra com o pesquisador. Fui informado(a), de forma clara e detalhada, livre de qualquer forma de constrangimento e correção, sobre os objetivos desse estudo.

A minha assinatura, neste termo de consentimento informado, dará autorização ao pesquisador envolvido para utilizar os dados obtidos quando se fizer necessário, incluindo a divulgação dos mesmos e também a realização de estudos futuros, sempre preservando a minha identificação.

_____

Nome do Paciente Assinatura

_____

Nome do Responsável Assinatura

_____

Nome da Pesquisadora Assinatura

Porto Alegre, _____ de _____ de _____.

APÊNDICE II – Instrumento para coleta de dados

Hospital de Clínicas de Porto Alegre (HCPA)

Universidade Federal do Rio Grande do Sul (UFRGS)

PESQUISA: Ângulo de fase como marcador prognóstico em pacientes que serão submetidos à cirurgia cardíaca: estudo de coorte prospectivo

Nome do Paciente:_____

Prontuário: _____ Leito do andar: _____ Leito UTI: _____

Sexo: 1. F ( ) 2. M ( )

Data de Nascimento: _____ Idade: _____

Motivo de Internação no Hospital: _____

_____

História Clínica: _____

_____

Cirurgia Realizada: 1. CRM ( ) 2. Troca valvar ( ) 3. CRM + Troca valvar ( )

Detalhes da cirurgia: _____

Intercorrências cirúrgicas:

_____

_____

_____

Tempo de cirurgia:_____ Tempo Circulação Extracorpórea:_____ Tempo de isquemia:_____

Critérios de exclusão ou de perdas presentes: 1. SIM ( ) 2. NÃO ( )

Qual:

_____

___

- EuroScore II:_____
- Uso de vasopressor: 1.SIM ( ) 2. NÃO ( ) Vasopressor utilizado: _____

<u>Efeitos clínicos adversos:</u>

- Infecções: 1.SIM ( ) 2. NÃO ( )
- Sangramento: 1.SIM ( ) 2. NÃO ( )
- Necessidade de transfusão: 1.SIM ( ) 2. NÃO ( ) Se sim, quantos CHADs?
- Necessidade de reintervenção cirúrgica: 1.SIM ( ) 2. NÃO ( )

Qual?_____

Dados antropométricos:

	1ª Avaliação Data:	2ª Avaliação Data:	3ª Avaliação Data:	4ª Avaliação Data:	5 ª Avaliação Data:	6ª Avaliação Data:
Peso (kg)						
Altura (cm)						
IMC (kg/m²)						
Força do Aperto de Mão						

Bioimpedância elétrica:

	1ª Avaliação Data:	2ª Avaliação Data:	3ª Avaliação Data:	4ª Avaliação Data:	5ª Avaliação Data:	6ª Avaliação Data:
Resistência (R)						
Reactância (Xc)						
Ângulo de Fase (AFº)						
Massa Magra (%)						
Massa Gorda (%)						
Água Intracelular (%)						
Água Extracelular (%)						
Água corporal total (%)						

Parâmetros de Ventilação Mecânica:

	No momento de admissão na UTI cardíaca	Após 12h
Modo ventilatório		
FIO_2		
SPO_2		

Extubação em _____ horas.

Sinais Vitais

	Data:		Data:
PA		FR	
PAM		Temp	
FC		HGT	

DESFECHOS:

1. Tempo de ventilação mecânica: _____
2. Tempo total de internação na UTI cardíaca: _____
3. Tempo total de internação hospitalar: _____
4. Óbito: 1.SIM ( ) 2. NÃO ( )

Outros:_____

FLUXO DA INTERNAÇÃO:

Data da internação: _____/_____/____ Data de alta hospitalar: ___/____/____

Data de internação na UTI cardíaca: ___/____/____ Alta da UTI cardíaca: ___/____/____

Data da cirurgia: ___/____/____ Tempo de internação no CTI : ___/____/____

Tempo total de internação hospitalar (dias): ___/____/____

ANEXOS

ANEXO A – Cálculo do EuroSCORE II

Obs.: Para cálculo do EuroSCORE II foi utilizado o site oficial do EuroSCORE (http://www.euroscore.org/calc.html), em sua versão otiginal em inglês, conforme segue:

Important: The previous additive [1] and logistic [2] EuroSCORE models are out of date. A new model has been prepared from fresh data and is launched at the 2011 EACTS meeting in Lisbon. The n is called EuroSCORE II [3] - this online calculator has been updated to use this new model. If you need to calculate the older "additive" or "logistic" EuroSCORE please visit the old calculator by click here.

Patient related factors			Cardiac related factors		
Age [1] (years)	0	0	NYHA	select	0
Gender	select	0	CCS class 4 angina [8]	no	0
Renal impairment [2] *See calculator below for creatinine clearance*	normal (CC >85ml/min)	0	LV function	select	0
Extracardiac arteriopathy [3]	no	0	Recent MI [9]	no	0
Poor mobility [4]	no	0	Pulmonary hypertension [10]	no	0
Previous cardiac surgery	no	0	**Operation related factors**		
Chronic lung disease [5]	no	0	Urgency [11]	elective	0
Active endocarditis [6]	no	0	Weight of the intervention [12]	isolated CABG	0
Critical preoperative state [7]	no	0	Surgery on thoracic aorta	no	0
Diabetes on insulin	no	0			
EuroSCORE II — *EuroSCORE II*	0				
Note: This is the 2011 EuroSCORE II	Calculate	Clear			

Notes about euroSCORE II:

[1] Age - in completed years. Some of the weighting for age is now incorporated into the renal impairment risk factor, so it is important that all risk factors are entered to give reliable risk estimations - see note [2]. Of over 20,000 patients in the EuroSCORE database, only 21 patients were aged over 90 - therefore the risk model may not be accurate in these patients. Please exercise clinical discretion in interpreting the score. The oldest patient in the EuroSCORE database was 95 - EuroSCORE II is not validated in patients over this age.

[2] Renal impairment - there are now 3 categories based on creatinine clearance calculated using Cockcroft-Gault formula. Unlike serum creatinine in the old EuroSCORE model, some of the weighting for *age* is directly incorporated into this factor, as *age* is a component of *creatinine clearance.* The 3 categories are:

- on dialysis (regardless of serum creatinine level)
- moderately impaired renal function (50-85 ml/min)
- severely impaired renal function (<50 ml/min) off dialysis

Creatinine clearance (ml/min)= (140-age (years)) x weight (kg) x (0.85 if female)/[72 x serum creatinine (mg/dl)]

Cockroft-Gault creatinine clearance calculator - for euroSCORE II renal impairment

Plasma creatinine *(µmol/L only) *note: 1 mg/dL = 88.4 µmol/L*		**Weight** * (kg)	
Age (years) *note: 18 - 95 for EuroSCORE II*		**Sex** *m or f - lowercase only*	
	Clear		
Creatinine clearance *(ml/min)*	***Click in box for result***		

Weight** (and **creatinine**) have not been directly included in the main EuroSCORE II calculator because they are not ***direct risk factors in the EuroSCORE II model, other than they contribute to creatinine clearance.

[3] Extracardiac arteriopathy - one or more of the following

- claudication
- carotid occlusion or >50% stenosis
- amputation for arterial disease
- previous or planned intervention on the abdominal aorta, limb arteries or carotids

[4] Poor mobility - severe impairment of mobility secondary to musculoskeletal or neurological dysfunction

[5] Chronic lung disease - long term use of bronchodilators or steroids for lung disease

[6] *Active endocarditis* - patient still on antibiotic treatment for endocarditis at time of surgery

[7] *Critical preoperative state* ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or IABP, preoperative acute renal failure (anuria or oliguria <10ml/hr)

[8] *CCS class 4 angina* angina at rest

[9] *Recent MI* myocardial infarction within 90 days

[10] *Pulmonary hypertension* systolic pulmonary artery pressure, now in 2 classes

- **moderate**: PA systolic pressure (31-55 mm Hg)
- **severe**: PA systolic pressure (>55mm Hg)

[11] ***Urgency*** now four classes:

- **elective**: routine admission for operation.
- **urgent**: patients who have not been electively admitted for operation but who require intervention or surgery on the current admission for medical reasons. These patients cannot be sent home without a definitive procedure.
- **emergency**: operation before the beginning of the next working day after decision to operate.
- **salvage**: patients requiring cardiopulmonary resuscitation (external cardiac massage) en route to the operating theatre or prior to induction of anaesthesia. This does not include cardiopulmonary resuscitation following induction of anaesthesia.

[12] ***Weight of the intervention*** - include major interventions on the heart such as

- CABG
- valve repair or replacement
- replacement of part of the aorta
- repair of a structural defect
- maze procedure
- resection of a cardiac tumour

References

1. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg*. 1999 Jun;**15**(6):816-22; discussion 822-3.
2. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J*. 2003 May;**24**(9):882-3.
3. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):734-44; discussion 44-5.

Terms of Use

ANEXO B - NORMAS PARA PUBLICAÇÃO DO PERIÓDICO

"EUROPEAN JOURNAL OF CLINICAL NUTRITION"

Guide to Authors - Article Type Specifications

Article: An Article is a substantial, in-depth, novel research study or report of current or basic clicnical research which is of interest to the readership of the journal. The *European Journal of Clinical Nutrition* strongly encourages authors adhere to the reporting guidelines relevant to their specific research design. Any clinical trials submitted to the *European Journal of Clinical Nutrition* must adhere to the registration requirements listed in the Editorial Policies. The structure an Article should follow is detailed below.

Specifications: *Structured abstract (Background/Objectives; Subjects/Methods; Results; Conclusion) max. 250 words; Main body of text (excluding abstract, tables/figures, and references) not to exceed 3,000 words; Max 6 tables or figures; Max 50 references (please use as recent as possible)*

Preparation of Articles

House Style: Authors should adhere to the following formatting guidelines

- Text should be double spaced with a wide margin.
- All pages and lines are to be numbered.
- Do not make rules thinner than 1pt (0.36mm).
- Use a coarse hatching pattern rather than shading for tints in graphs.
- Colour should be distinct when being used as an identifying tool.
- Commas, not spaces should be used to separate thousands.
- At first mention of a manufacturer, the town (and state if USA) and country should be provided.

- Statistical methods: For normally distributed data, mean (SD) is the preferred summary statistic. Relative risks should be expressed as odds ratios with 95% confidence interval. To compare two methods for measuring a variable the method of Bland & Altman (1986, Lancet 1, 307–310) should be used; for this, calculation of P only is not appropriate.
- Units**:** Use metric units (SI units) as fully as possible. Preferably give measurements of energy in kiloJoules or MegaJoules with kilocalories in parentheses (1 kcal = 4.186kJ). Use % throughout.
- Abbreviations: On first using an abbreviation place it in parentheses after the full item. Very common abbreviations such as FFA, RNA, need not be defined. Note these abbreviations: gram **g**; litre **l**; milligram **mg**; kilogram **kg**; kilojoule **kJ**; megajoule **MJ**; weight **wt**; seconds **s**; minutes **min**; hours **h**. Do not add ‘s’ for plural units. Terms used less than four times should not be abbreviated.

- **Cover Letter:** Authors should provide a cover letter that includes the affiliation and contact information for the corresponding author. Authors should briefly discuss the importance of the work and explain why it is considered appropriate for the diverse readership of the journal. The cover letter should confirm the material is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration. If the manuscript has been previously considered for publication in another journal, please include the previous reviewer comments, to help expedite the decision by the Editorial team. Please also include a Conflict of Interest statement see Editorial Policies for more details.

Title Page: The title page should contain:

- Title of the paper - brief, informative, of 150 characters or less and should not make a statement or conclusion
- Running title – should convey the essential message of the paper in no more than 50 characters. Should not contain any abbreviations
- Full names of all the authors and their affiliations, as well as the e-mail address of the corresponding author. If authors regard it as essential to indicate that two or more co-authors are equal in status, they may be identified by an asterisk symbol with the caption 'These authors contributed equally to this work' immediately under the address list.
- Consortia: Please see autor Guide for full details on this.

Abstract: Articles must be prepared with a structured abstract designed to summarise the essential features of the paper in a logical and concise sequence under the following mandatory headings:

- **Background/Objectives:** What was the main question or hypothesis tested?
- **Subjects/Methods:** How many subjects were recruited, how many dropped out? Was the study randomised, case-controlled etc? Interventions/methods used and duration of administration
- **Results:** Indicate 95% confidence intervals and exact *P* values
- **Conclusions:** Answer (significant or not) to main question

Introduction: The Introduction should assume that the reader is knowledgeable in the field and should therefore be as brief as possible but can include a short historical review where desirable.

Materials/Subjects and Methods: This section should contain sufficient detail, so that all experimental procedures can be reproduced, and include references. Methods, however, that have been published in detail elsewhere should not be described in detail. Authors should provide the name of the manufacturer and their location for any specifically named medical equipment and instruments, and all drugs should be identified by their pharmaceutical names, and by their trade name if relevant.

Results: The Results section should briefly present the experimental data in text, tables or figures. Tables and figures should not be described extensively in the text.

Discussion: The Discussion should focus on the interpretation and the significance of the findings with concise objective comments that describe their relation to other work in the area. It should not repeat information in the results. The final paragraph should highlight the main conclusion(s) and provide some indication of the direction future research should take.

Acknowledgements: These should be brief, and should include sources of technical assistance, critical advice or other assistance, which contributed to the final manuscript.

Conflict of Interest: Authors must declare whether or not there are any competing financial interests in relation to the work described. This information must be included at this stage and will be published as part of the paper, but should also be noted in the cover letter. Please see the Conflict of Interest definition in the Editorial Policies section for detailed information.

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Category 1: Studies financed by industry (in part or total) but with a clear declaration that the industry was not involved in the study hypothesis/design, execution, analysis, or interpretation.

Category 2: Studies sponsored by industry (in part or total), with a clear declaration that industry was involved in the study hypothesis/design, execution, analysis, or interpretation, and the industry involvement in each aspect is clearly outlined. Category 3: Studies funded and conducted by industry, with no external partners. All submitted papers in categories 1 and 2 will need to address the following four points (1–3 from Mozafarrian[1]) in the cover letter or *EJCN* will return the submission for completion.

1. Statement that industry funding was transparent, acknowledged, and appropriately recognized throughout all stages of design, implementation, and reporting.
2. Evidence presented that project design, implementation, analysis, and interpretation had been performed with efforts to maximize academic independence in each of these areas.
3. Confirmation of full academic independence to report and publish all the findings.
4. Statement that all raw data will be uploaded to a publically accessible repository, or be made available to interested scientists if requested; understanding that there could be reasonable caveats for such requests. Any restrictions on material availability or other relevant information to be divulged in the paper's methods section, and should include details of how materials and information may be obtained.

When submitting the manuscript authors whose papers fall under category 2 or 3 must select the Subject Category ‘Industry Research’ from the dropdown list.

[1] Mozaffarian D. Conflict of interest and the role of the food industryin nutrition research. JAMA. 2017;317:1755–6.

Author Contributions: Authors must include a statement about the contribution of each author to the manuscript (see section on Authorship. The initials of each author may be used. Please see example in the Guide to Authors document. Authors must also complete the Confirmation of Authorship form and include this with their Cover Letter upon submission.

Funding: The funding section is mandatory. Authors must declare sources of study funding including sponsorship (e.g. university, charity, commercial organization) and sources of material (e.g. novel drugs) not available commercially. If no financial assistance was received in support of the study, please include a statement to this fact here.

References: Only papers directly related to the article should be cited. Exhaustive lists should be avoided. References should follow the Vancouver format. In the text they should appear as numbers starting at one and at the end of the paper they should be listed (double-spaced) in numerical order corresponding to the order of citation in the text. Where a reference is to appear next to a number in the text, for example following an equation, chemical formula or biological acronym, citations should be written as

(ref. X). Example “detectable levels of endogenous Bcl-2 (ref. 3), as confirmed by western blot”.

All authors should be listed for papers with up to six authors; for papers with more than six authors, the first six only should be listed, followed by *et al.* Abbreviations for titles of medical periodicals should conform to those used in the latest edition of Index Medicus. The first and last page numbers for each reference should be provided. Abstracts and letters must be identified as such. Papers in press may be included in the list of references.

Personal communications can be allocated a number and included in the list of references in the usual way or simply referred to in the text; the authors may choose which method to use. In either case authors must obtain permission from the individual concerned to quote his/her unpublished work.

Examples:

Journal article:

Belkaid Y, Rouse BT. Natural regulatory T cells in infectious disease. Nat Immunol. 2005; 6: 353–360.

Journal article, e-pub ahead of print:

Bonin M, Pursche S, Bergeman T, Leopold T, Illmer T, Ehninger G *et al*. F-ara-A pharmacokinetics during reduced-intensity conditioning therapy with fludarabine and busulfan. Bone Marrow Transplant. 2007; e-pub ahead of print 8 January 2007; doi:10.1038/sj.bmt.1705565

Journal article, in press:

Gallardo RL, Juneja HS, Gardner FH. Normal human marrow stromal cells induce clonal growth of human malignant T-lymphoblasts. Int J Cell Cloning (in press).

Complete book:

Atkinson K, Champlin R, Ritz J, Fibbe W, Ljungman P, Brenner MK (eds). Clinical Bone Marrow and Blood Stem Cell Transplantation. 3rd edn. (Cambridge University Press, Cambridge, 2004).

Chapter in book:

Coccia PF. Hematopoietic cell transplantation for osteopetrosis. In: Blume KG, Forman SJ, Appelbaum FR (eds). Thomas' Hematopoietic Cell Transplantation. 3rd edn. (Blackwell Publishing Ltd, Malden, 2004), pp 1443–1454.

Abstract:

Syrjala KL, Abrams JR, Storer B, Heiman JR. Prospective risk factors for five-year sexuality late effects in men and women after haematopoietic cell transplantation. Bone Marrow Transplant. 2006; 37(Suppl 1): S4 (abstract 107).

Correspondence:

Caocci G, Pisu S. Overcoming scientific barriers and human prudence [letter]. Bone Marrow Transplant. 2006; 38: 829–830.

Figure Legends: These should be brief, specific and appear on a separate manuscript page after the References section.

Tables: Tables should only be used to present essential data; they should not duplicate what is written in the text. All tables must be editable, ideally presented in Excel. Each must be uploaded as a separate workbook with a title or caption and be clearly labelled, sequentially. Please make sure each table is cited within the text and in the correct order, e.g. (Table 3). Please save the files with extensions .xls / .xlsx / .ods / or .doc or .docx. Please ensure that you provide a 'flat' file, with single values in each cell with no macros or links to other workbooks or worksheets and no calculations or functions.

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Plotting individual data points is preferred to just showing means, especially where N<10 If error bars are shown, they must be described in the figure legend Axes on graphs should extend to zero, except for log axes Statistical analyses (including error bars and p values) should only be shown for independently repeated experiments, and must not be shown for replicates of a single experiment. The number of times an experiment was repeated (N) must be stated in the legend

Supplementary Information: Supplementary information is peer-reviewed material directly relevant to the conclusion of an article that cannot be included in the printed version owing to space or format constraints. The article must be complete and self-explanatory without the Supplementary Information, which is posted on the journal's website and linked to the article. Supplementary Information may consist of data files, graphics, movies or extensive tables. Please see our Artwork Guidelines for information on accepted file types.

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Upon submission authors will be asked to select a series of subject terms relevant to the topic of their manuscript from our subject ontology. Providing these terms will

ensure your article is more discoverable and will appear on appropriate subject specific pages on nature.com, in addition to the journal's own pages. Your article should be indexed with at least one, and up to four unique subject terms that describe the key subjects and concepts in your manuscript.

ANEXO C - NORMAS PARA PUBLICAÇÃO NO PERIÓDICO

"*EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY*"

Author Guidelines

The *European Journal of Cardio-Thoracic Surgery* (EJCTS) welcomes scientific contributions in the field of cardio-thoracic surgery. All manuscripts are subject to review by the Editor-in-Chief, Associate Editors, Invited Reviewers and a Statistician when appropriate. Acceptance is based on the originality, significance, and validity of the material presented.

The EJCTS considers a wide range of subject categories: Arrhythmia, Assisted circulation, Cardiac general, Cardiopulmonary bypass, Congenital, Coronary, Esophagus, Experimental, Pulmonary, Thoracic oncologic, Thoracic non-oncologic, Transplantation, Translational research, Valves and Vascular thoracic. The most appropriate subject category should be selected when submitting your paper online.

Submission

All material to be considered for publication in the *European Journal of Cardio-Thoracic Surgery* should be submitted electronically via the journal's online submission system.

Article Types

The journal publishes the following types of papers: Original Articles

Manuscript Format and Style

Manuscripts should be prepared using a word-processing package.

- Font type: Arial or Calibri
- Font size: 11 or 12 points
- Double-spacing for the main text
- Pages and lines should be numbered consecutively

Order of the manuscript contents

Manuscripts should be organized as follows: (a) Title page; (b) Visual abstract; (c) Abstract and Keywords; (d) Text with the following sections: Introduction, Materials and Methods (or Patients and Methods), Results, Discussion, Conclusion, Acknowledgement (optional), Funding statement, Conflict of interest statement; Author contribution statement; (e) Figure (and Video) legends; (f) Tables; (g) References.

Specifications for each article type

Each article type must include a title page and 3-6 keywords. *Important:* the total number of words specified below comprises words on the title page, abstract, keywords, main text, figure and video legends, tables and references. All manuscripts must adhere to the following specifications.

Original Article

- Authors: At the discretion of the Editor-in-Chief
- Abstract (structured): 250 words (sections should be: Objectives, Methods, Results and Conclusions)
- Figures/tables combined: 8 (preferably no more than 6 parts/graphs – at the discretion of the Editor-in-Chief)
- Videos: 2 (total playback time: 5 min)

- References: 30
- Total number of words: 5000

Graphical abstract

A graphical abstract is required for Original Articles, Meta-Analyses and Reviews.

The graphical abstract consists of 2 main elements: a visual abstract comprising 3 text items and a central image summarizing the main findings.

The visual abstract should comprise:

- Key question (120 characters including spaces)
- Key findings (120 characters including spaces)
- Take-home message (140 characters including spaces

This information must be included in the mandatory text field of the manuscript metadata upon submission and also on page 2 (after the title page) of the manuscript.

The central image must be a single, high-quality image that summarizes the main findings of the article in a brief and concise manner (i.e. text should be kept to a bare minimum). It should preferably be created for this purpose only and not reappear in the article.

Specifications for the central image:

- Resolution: minimum 600 dots per inch
- Dimension: 8.4 cm (width) x 8.4 cm (height)
- Font type/size: Arial/10 points
- File format: .tif, .eps or .PDF

The image should be uploaded as a ‘Central image’ in the online submission system.

The manuscript should be organized as follows:

Title page

Title: Should be brief and descriptive (100 characters) - no abbreviations are allowed, even if well known.

Authors: List all authors by full first name, initial of or full middle name and family name. Qualifications are not required. Ensure the author names correspond (in spelling and order of appearance) with the metadata of the system. Remember that all authors must have substantially contributed to the article - see criteria in the authorship section above.

For equal contributions include the statement that 'X and Y contributed equally to this work' below the author list of the manuscript.

Institution(s): Include the name of all institutions with the location (department, institution, city, country) to which the work should be attributed (in English). Use superscript numbers to connect authors and their department or institution.

Corresponding author: The full name, full postal address, telephone number and the e-mail address should be typed at the bottom of the title page.

Word count: The total number of words of the whole article (including title page, abstract, main text, legends, tables and references) must be specified on the title page.

Visual abstract

Include the key question (max. 120 characters), key findings (max. 120 characters) and take-home message (max. 140 characters). The maximum number of characters include spaces.

Abstract

An abstract should be a concise summary of the manuscript. Reference citations are not allowed. The abstract should be factual and free of abbreviations, except for SI units of measurement. A structured abstract must have four sections:

1. *Objectives:* should describe the problem addressed in the study and its purpose.
2. *Methods:* should explain how the study was performed (basic procedures with study materials and observational and analytical methods).
3. *Results:* should describe the main findings with specific data and their statistical significance, if possible.
4. *Conclusions:* should contain the main conclusion of the study.

Keywords

Following the abstract, 3-6 keywords should be given for subject indexing.

Main text

Abbreviations and acronyms: For Original Articles, Meta-Analyses and Reviews, abbreviations and acronyms used in the text should be gathered in a list and included at the beginning of the article before the introduction.

Use of abbreviations renders the text difficult to read so they should be limited to SI units of measurement and to those widely used in the text of the article. Full definitions should be given at first mention in the text, and in the tables and figures. Abbreviations should not be included in headings.

Introduction

Should state the purpose of the investigation and give a short review of pertinent literature.

Materials and methods (or patients and methods): Should be described in detail with appropriate information about patients or experimental animals.

For all articles reporting on human subjects and animals, the first paragraph should comprise a short statement confirming approval of the study by the Institutional Review Board (IRB) or Ethics Committee (EC) of the institution(s) where the work was carried out. The name of the institution, the date and ID number of the IRB approval must be included. Whether written patients informed consent was obtained or waived by the IRB or EC should also be disclosed.

Generic names of drugs and equipment should be used throughout the manuscript, with brand names (proprietary name) and the name and location (city, state, country) of the manufacturer in brackets when first mentioned in the text.

Results: Results should be reported concisely and regarded as an important part of the manuscript. They should be presented either in tables and figures, and briefly commented on in the text, or in the text alone. Repetition of results should be avoided! For statistical analysis, follow the Statistical and data reporting guidelines. The full set of raw data must be available at any time should reviewers or editors request these for more in-depth review during the review process and/or after publication.

Discussion: The discussion is an interpretation of the results and their significance with

reference to pertinent work by other authors. It should be clear and concise. The importance of the study and its limitations should be discussed.

Acknowledgement: This section can be used to acknowledge contributions from other individuals who do not meet the ICMJE criteria for authorship (e.g. those who provided administrative support, writing assistance, language editing).

Author contributions statement: Contributor Roles Taxonomy (CRediT from CASRAI) roles of authors will be published for all accepted articles, hence it is paramount that these are selected carefully and accurately upon submission of the revised manuscript.

Funding statement: See Funding and conflict of interest section.

Conflict of interest statement: See Funding and conflict of interest section.

Figure (and video) legends: A list with legends for each figure (and each video) must be included.

Tables: All tables must be included in the manuscript file, as part of the text, not as images. All tables should start on separate pages and be accompanied by a title, and footnotes (use superscript a,b,c.…) where necessary. The tables should be numbered consecutively using Arabic numerals. Abbreviations and their full definitions should be listed in alphabetical order at the bottom of the table. Avoid overcrowding the tables and the excessive use of words. The format of tables should be in keeping with that

normally used by the journal. Please ascertain that the data given in tables are correct. All tables must be cited in the text.

References: Authors are responsible for checking the accuracy of all references. If you use EndNote or Reference Manager to facilitate referencing citations (not required for submission), this journal's style is available for use.

References should be numbered in order of appearance in the text (in Arabic numerals in parentheses) and must be listed numerically in the reference list. Journal titles and author initials should be abbreviated and punctuated according to PubMed. If an automatic referencing system has been used in the preparation of the paper, the references must not be left embedded in the final text file submitted. The citation of journals, books, multi-author books and articles published online should conform to the following examples:

Journals

[1] Sousa-Uva M, Head SJ, Milojevic M, Collet JP, Landoni G, Castella M *et al.* 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg 2018;53:5-33.

Books

[2] Cooley DA. Techniques in cardiac surgery. Philadelphia: Saunders, 1984:167-76.

Multi-author books

[3] Rastan AJ, Borger MA, Haensig M, Kempfert J, Mohr FW. Recent developments in transcatheter aortic valve implantation in Moorjani N, Ohri SK, Wechsler A (eds). Cardiac Surgery: Recent Advances and Techniques. CRC press 2013.

Online-only publications (please give the doi wherever possible)

[4] Durko A, Mahtab E, Romeo J, Bogers A. Skeletonized internal mammary artery harvest with diathermy and cold dissection. *Multimed Man Cardiothorac Surg* 2017 Dec 12; doi: 10.1510/mmcts.2017.023

or

[5] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cancer-associated Venous Thromboembolic Disease; Version 2.2018. 2018 https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf (10 July 2019, date last accessed).

For references with more than six authors, the first 6 authors should be listed, followed by et al. Personal communications (Jones, personal communication) must be authorized in writing by those involved, and unpublished data should be cited in the text as (unpublished data). References to manuscripts submitted, but not yet accepted, should be cited in the text as (Jones and Smith, manuscript in preparation) and should not be included in the list of references. Authors are encouraged to cite web URLs in parentheses at the appropriate mention in the text.

Figures and Videos: All figures and videos require a legend and must be cited in the text.

Figures: Each figure should contain no more than 4 parts for Original Articles, Meta-Analyses and Reviews. For Case report, Surgical Technique and Images-in-Cardiothoracic Surgery, 6 parts in total are allowed.

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Details of all funding sources for the work in question should be given in a separate section entitled 'Funding'. This should appear before the 'Acknowledgements' section.

The following rules should be followed:

The sentence should begin: ‘This work was supported by …’

The full official funding agency name should be given, i.e. ‘the National Cancer Institute at the National Institutes of Health’ or simply 'National Institutes of Health' not ‘NCI' (one of the 27 subinstitutions) or 'NCI at NIH’ (full RIN-approved list of UK funding agencies)

Grant numbers should be complete and accurate and provided in brackets as follows: ‘[grant number ABX CDXXXXXX]’

Multiple grant numbers should be separated by a comma as follows: ‘[grant numbers ABX CDXXXXXX, EFX GHXXXXXX]’

Agencies should be separated by a semi-colon (plus ‘and’ before the last funding agency)

Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to [author full name]'

An example is given here: 'This work was supported by the National Institutes of Health [P50 CA098252 and CA118790 to John Smith] and the Alcohol & Education Research Council [HFY GR667789].

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