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Joana Cristina Gouveia Santos

Patência do canal arterial no recém-nascido de pré-termo: experiência de um hospital terciário

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Patência do canal arterial no recém-nascido de pré-termo: experiência de um hospital terciário

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NOME

Joana Cristina Gouveia Santos

NÚMERO DE ESTUDANTE	E-MAIL
200203685	joana.cris.santos@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

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ORIENTADOR

Professora Doutora Hercília Guimarães

COORIENTADOR (se aplicável)

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Assinatura conforme cartão de identificação: Joana Santos

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Abreviaturas

CA	Canal arterial
CHUSJ	Centro Hospitalar Universitário de São João
COX	Enzima ciclooxigenase
CPAP	Ventilação com pressão positiva contínua das vias aéreas
DBP	Displasia broncopulmonar
DMH	Doença das membranas hialinas
EVPV	enfarte venoso periventricular
FO	forâmen ovale
HIV	hemorragia intraventricular
IG	Idade gestacional
NEC	Enterocolite necrosante
PCA	Patência do canal arterial
PCA-HS	Patência do canal arterial hemodinâmicamente significativa
RNPT	Recém-nascidos de pré-termo
ROP	Retinopatia da prematuridade
RVP	Resistência vascular pulmonar
TORCH	Acrónimo de toxoplasmose, outras (sífilis, vírus varicela-zoster, parvovírus B19), rubéola, citomegalovírus, e vírus herpes simples.
VAFO	Ventilação de alta frequência oscilatória
VM	Ventilação mecânica

Patência do canal arterial no recém-nascido de pré-termo: experiência de um hospital terciário

Joana Santos[1], Paulo Soares[1,2], Cristina Ferreras[1,3], Filipa Flor-de-Lima[1,2] Hercília Guimarães[1,4]

[1] Faculdade de Medicina da Universidade do Porto, Portugal
[2] Serviço de Neonatologia, Centro Hospitalar Universitário de São João, Porto, Portugal
[3] Serviço de Pediatria, Centro Hospitalar Universitário de São João, Porto, Portugal
[4] Cardiovascular R&D Center, Faculty of Medicine University of Porto, Portugal

Resumo

Introdução: A patência do canal arterial (PCA) nos recém-nascidos de pré-termo (RNPT) tem vindo a ser associada ao aumento de mortalidade e de co-morbilidades. Este estudo objetivou caracterizar a população de RNPT diagnosticados com PCA e identificar fatores preditivos de resposta ao tratamento médico do mesmo.

Métodos: Foi realizado um estudo observacional retrospetivo de oito anos, que incluiu todos os RNPT com idade gestacional compreendida entre as 23 e as 32 semanas com diagnóstico de PCA, admitidos no Serviço de Neonatologia do Centro Hospitalar Universitário de São João (CHUSJ). Realizou-se análise comparativa univariada, e foram explorados os modelos preditivos da eficácia do tratamento de PCA com ibuprofeno, por análise de regressão logística multivariável.

Resultados: Cumpriram critérios de inclusão no estudo 115 casos e foram excluídos 34, obtendo-se a amostra final de 81 RNPT com PCA. A análise univariável revelou diferenças significativas na eficácia de encerramento pelo tratamento médico com ibuprofeno em diversas variáveis, e obteve-se um modelo de regressão logístico multivariado (capacidade discriminativa 72,2%, sensibilidade 98,1%, especificidade 57,1%), considerando o efeito das variáveis: idade gestacional, tipo de parto, necessidade de tratamento com diuréticos e de transfusão de plaquetas.

Conclusão: Este estudo permitiu caraterizar a população de RNPT com diagnóstico de PCA e a identificação de um modelo preditivo que poderá auxiliar na previsão da eficácia de resposta ao tratamento médico e deste modo contribuir para otimizar a estratégia de abordagem aos não respondedores ao tratamento médico.

Palavras chave: Recém-nascido pré-termo, patência do canal arterial, ibuprofeno

Patent ductus arteriosus in preterm newborns: experience at a tertiary hospital

Joana Santos[1], Paulo Soares[1,2], Cristina Ferreras[1,3], Filipa Flor-de-Lima[1,2] Hercília Guimarães[1,4]

[1] Faculdade de Medicina da Universidade do Porto, Portugal
[2] Serviço de Neonatologia, Centro Hospitalar Universitário de São João, Porto, Portugal
[3] Serviço de Pediatria, Centro Hospitalar Universitário de São João, Porto, Portugal
[4] Cardiovascular R&D Center, Faculty of Medicine University of Porto, Portugal

Abstract

Introduction: Patent ductus arteriosus (PDA) in preterm newborns has been associated with increased mortality and co-morbidities. This study aimed to characterize the population of preterm infants diagnosed with PDA and to identify predictive factors of response to medical treatment of PDA.

Methods: An eight-year retrospective observational study was carried out, which included all PTNBs with gestational age between 23 and 32 weeks diagnosed with PDA, admitted to the HSJ Obstetrics Service. Univariate comparative analysis was performed, and models for predicting the effectiveness of PDA treatment with ibuprofen were explored by multivariate logistic regression analysis.

Results: Were included in the study 115 cases and 34 were excluded, with a final sample of 81 PTNB with PDA. The univariable analysis revealed significant differences in the closure efficacy by medical treatment with ibuprofen in several variables, and a multivariate logistic regression model was obtained (discriminative capacity 72.2%, sensitivity 98.1%, specificity 57.1%), considering the effect of gestational age, type of delivery, need for diuretics treatment and platelet transfusion.

Conclusion: This study allowed to characterize the population of preterm infants diagnosed with PDA and the identification of a predictive model that can aid to predict the effectiveness to the medical treatment and thus contribute to optimize the medical approach to the non-responders.

Keywords: preterm newborns, patent ductus arteriosus, ibuprofen

Introdução

A transição para a vida extrauterina representa uma fase crítica de adaptação fisiológica com impacto significativo em diversos órgãos e sistemas, particularmente no pulmão e coração. A maioria dos neonatos completam esta fase de transição sem complicações, no entanto a desregulação da normal adaptação pós-natal pode conduzir a instabilidade cardiopulmonar, com necessidade de cuidados intensivos avançados, principalmente em recém-nascidos prematuros.[1,2]

No feto existem dois *shunts*, o forâmen ovale (FO) da aurícula direita para a esquerda, e o canal arterial (CA) da artéria pulmonar para a aorta. Quase todo o débito cardíaco direito, não oxigenado, circula através do CA para a aorta descendente onde é transportado pela aorta e artérias umbilicais até à placenta. Dada a baixa tensão de oxigénio fetal é mantida a vasoconstrição pulmonar com alta resistência pulmonar o que promove o *shunt* direito-esquerdo através do FO e CA.[1]

Nas primeiras 48-72 horas após o nascimento ocorre a diminuição progressiva da resistência vascular pulmonar (RVP) em resposta ao recrutamento e aumento da concentração de oxigénio alveolar. Á medida que a RVP decresce, a direção do fluxo através do CA e FO passa para um padrão bidirecional ou direção esquerda-direita exclusiva, o que promove a circulação pulmonar.[1] O aumento da saturação arterial de oxigénio, a produção de bradicinina endotelial e a diminuição dos níveis de prostaglandinas E2 placentária em circulação, induzem a constrição do CA, seguido do seu encerramento fisiológico.[3] Deste modo, em cerca de 96% dos recém-nascidos saudáveis de termo o encerramento funcional do CA ocorre até às 48h de vida, podendo permanecer nos restantes casos um pequeno canal com fluxo esquerdo-direito restritivo.[4] Por outro lado, a patência de canal arterial (PCA) é a alteração cardiovascular mais frequente em recém-nascidos de pré-termo (RNPT), sendo inversamente proporcional à idade gestacional (IG) e ao peso ao nascimento.[5] Deste modo, a PCA ocorre em cerca de 33% dos prematuros de muito baixo peso (igual ou inferior a 1500 gramas), e em cerca de 65% dos prematuros de extremo baixo peso (igual ou inferior a 1000 gramas).[6,7] Estimando-se uma frequência de PCA de cerca de 20% em prematuros de 32 semanas de IG, enquanto que em prematuros de extremo baixo peso com IG igual ou inferior a 26 semanas a frequência ronda os 80-90%.[8] A presença de mediadores inflamatórios sistémicos condiciona um aumento de espécies reativas de oxigénio, assim como de prostaglandinas, que poderão contribuir para a falência do encerramento espontâneo do CA. Adicionalmente, outros aspetos que poderão contribuir para a PCA em RNPT são o aumento da sensibilidade das células musculares lisas aos efeitos das substâncias vasodilatadoras,[9] a insufiência da glândula supra-renal,[10] a trombocitopenia,[11-13] e a disfunção plaquetária.[14] Por outro lado, fatores

relativos à ressuscitação e cuidados pós-natais em RNPT tais como a exposição a ventilação com pressão positiva, a concentração de oxigénio, e o recurso a surfactante exógeno, poderão também contribuir para a PCA.[3]

A importância clínica da PCA relaciona-se com as suas dimensões, a magnitude do *shunt* e da consequente repercussão cardiovascular e respiratória resultantes do hiperfluxo pulmonar, sobrecarga cardíaca e hipoperfusão sistémica.[15] O quadro clínico de PCA hemodinâmicamente significativa (PCA-HS) inclui sinais respiratórios (necessidade crescente de oxigénio, dependência de ventilação e apneias), e sinais hemodinâmicos (sopro sistólico ou contínuo, precórdio hiperdinâmico, pulsos amplos, hipotensão diastólica, cardiomegalia, hepatomegalia ou acidose metabólica).[16] A PCA-HS no RNPT tem vindo a ser associada ao aumento de mortalidade e de co-morbilidades.[5] Os RNPT com PCA apresentam frequentemente várias outras complicações da prematuridade, tais como a hemorragia pulmonar, a hemorragia peri/intraventricular (HIV), a enterocolite necrosante (NEC), a displasia broncopulmonar (DBP) e a leucomalácia periventricular,[5] estando contudo, ainda por esclarecer se estas complicações surgem num quadro geral relacionado com a imaturidade do RNPT ou se existe uma relação com a PCA.

O diagnóstico de PCA com significado hemodinâmico deve ser precoce e assenta num conjunto de vários parâmetros ecográficos. Esta avaliação ecocardiográfica deve ser realizada nas primeiras 72 horas nos recém-nascidos com idade gestacional igual ou inferior a 28 semanas e/ou peso ao nascer igual ou inferior a 1000 gramas; ou recém-nascidos com idade gestacional entre as 28 e 30 semanas com fatores de risco associados (ausência de corticoterapia pré-natal, sepsis, ventilação invasiva, asfixia peri-parto, e mãe sob terapêutica com sulfato de magnésio). Em todos os restantes RNPT a avaliação ecocardiográfica deve ser realizada se existir quadro clínico sugestivo.[16]

O tratamento médico para o encerramento precoce da PCA, tem o intuito de evitar as repercussões clínicas e deve ser iniciado nos primeiros 5 dias de vida com um ciclo de ibuprofeno (3 doses 10 mg/kg/dia por perfusão endovenosa de 15 minutos).[16] A eficácia de encerramento de PCA após o primeiro ciclo de tratamento com ibuprofeno é de 70%.[17] No caso de falência de resposta está indicado um segundo ciclo de tratamento, podendo ser ponderado um terceiro ciclo em casos excecionais.[16] O encerramento cirúrgico da PCA está indicado apenas nos casos de falência do tratamento farmacológico, ou na presença de outras co-morbilidades que contraindicam o tratamento farmacológico: insuficiência renal, trombocitopenia, hemorragia ativa ou alterações da coagulação, enterocolite necrosante, sepsis grave, hipertensão pulmonar, hiperbilirrrubinemia e perfuração intestinal. A abordagem cirúrgica é bastante eficaz e globalmente segura. Contudo existem riscos de perturbação grave hemodinâmica com

alguns casos descritos de falência cardiovascular potencialmente grave no pós-operatório imediato. Todavia as complicações mais frequentemente associadas à laqueação cirúrgica de PCA incluem hemorragia, hipotensão arterial, disfunção cardíaca aguda, lesão dos nervos recorrente ou frénico, derrame pleural, pneumotórax e quilotórax.[17]

Neste estudo pretendeu-se caracterizar a população de RNPT diagnosticados com PCA, e identificar fatores preditivos de resposta ao tratamento médico, contribuindo assim para uma melhor compreensão desta condição e das co-morbilidades mais frequentemente associadas e permitindo uma melhor estratificação da prestação de cuidados a RNPT com PCA-HS.

Métodos

População em estudo

Foi realizado um estudo observacional retrospetivo tendo sido incluídos todos os RNPT com idade gestacional entre as 23 e as 32 semanas (23 semanas e 0 dias e 31 semanas e 6 dias), determinada por ecografia até às 20 semanas, e admitidos no Serviço de Neonatologia procedentes do Serviço de Obstetrícia/bloco de partos do Centro Hospitalar São João (CHUSJ), entre janeiro de 2010 e dezembro de 2018, com diagnóstico de PCA. Os critérios de exclusão foram: (1) RNPT nascido noutra instituição e submetido a transporte neonatal para o Serviço de Neonatologia do CHUSJ; (2) RNPT com diagnóstico adicional de: a) infeção do grupo TORCH; b) anomalia congénita major; c) cromossomopatia: d) asfixia (índice de Apgar aos 5 minutos menor ou igual a 5 ou pH do sangue do cordão umbilical inferior a 7,0); e) síndrome de transfusão feto-fetal; f) discrepância de crescimento fetal (diferença superior a 20% em relação ao peso do maior feto); g) anemia severa na admissão (hemoglobina inferior a 12 g/dl); h) diagnóstico de erro inato do metabolismo efetuado em consulta pré-natal ou durante o período neonatal; i) suspeita ou diagnóstico de doença neuromuscular.

Dados clínicos e demográficos

Os dados relativos à história pré-natal, do nascimento e reanimação na sala de partos, co-morbilidades e tratamentos efetuados foram recolhidos através da consulta da base de dados clínicos. De modo a garantir a confidencialidade dos dados foi atribuído um código a cada processo dos doentes incluídos no estudo, do conhecimento exclusivo do investigador. Este estudo obteve parecer e aprovação favorável da Comissão de Ética e autorização do Conselho de Administração e Responsável pelo Acesso à informação do Centro Hospitalar de São João.

Análise estatística

A avaliação da normalidade foi testada com recurso ao teste de Kolmogorov-smirnov. As variáveis categóricas foram descritas em número total e percentagem, as variáveis contínuas de distribuição normal foram descritas pela média e desvio padrão (σ), e as variáveis contínuas de distribuição não normal descritas pela mediana, valor mínimo e máximo. Foi estudada a análise comparativa univariada utilizando os testes de X^2 para variáveis categóricas, o teste *T de student* para variáveis contínuas de distribuição normal e o teste Wilcoxon-Mann-Whitney para as variáveis contínuas de distribuição não normal. Foi utilizada regressão logística multivariável (método forward) para explorar modelos preditivos da eficácia do tratamento médico de PCA com ibuprofeno, a partir das associações encontradas pela análise univariável ($p<0.25$). Foi considerado

nível de significância de alfa de 0.05. A análise estatística foi realizada com o *software* SPSS 26.0 ® (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

Resultados

Análise descritiva da população em estudo

Entre janeiro de 2010 e dezembro de 2018, registaram-se 115 diagnósticos de PCA em RNPT com IG compreendida entre as 23 e as 32 semanas, admitidos no Serviço de Neonatologia do Centro Hospitalar Universitário de São João. Destes, foram excluídos 34 RNPT: 29 nascidos noutra instituição e submetidos a transporte neonatal para o Serviço de Neonatologia do CHUSJ, dois por diagnóstico de anomalia congénita major, dois por asfixia (índice de Apgar aos 5 minutos inferior a 5) e um por infeção do grupo TORCH. As caraterísticas da população de 81 recém-nascidos pré-termo incluídos no estudo estão representadas na Tabela 1 e os dados de diagnóstico, abordagem e tratamento de patência do canal arterial representados na Figura 1.

Análise univariada

A análise univariável entre a eficácia de encerramento pelo tratamento médico com ibuprofeno e as diversas variáveis estudadas revelou diferenças significativas para o tipo de parto (eutócico ou cesariana); para a idade gestacional, a média do peso, o comprimento, o perímetro cefálico, a média da hemoglobina e o volume globular ao nascimento; para o número de dias de utilização de CPAP nasal e em nutrição parentérica total; para a necessidade e número de transfusão de glóbulos vermelhos e plaquetas; para a necessidade de ventilação mecânica (VM) invasiva durante o internamento; para a necessidade de tratamento com corticoides e broncodilatadores inalados e diuréticos; para a necessidade de oxigénio suplementar na alta; e para o diagnóstico de retinopatia da prematuridade (ROP), HIV e de enfarte venoso periventricular (EVPV) associado a HIV (Tabela 3).

Regressão logística binominal

A regressão logística multivariável (método *forward*) explorou modelos preditivos da eficácia do tratamento médico de PCA com ibuprofeno, a partir das associações encontradas pela análise univariável (p<0,25). O modelo de regressão logístico que considerou o efeito das variáveis: idade gestacional, tipo de parto, necessidade de tratamento com diuréticos e de transfusão de plaquetas foi estatisticamente significativo, $\chi^2(4) = 35{,}947$, $p < 0{,}0001$. O modelo explica 64,3% (Nagelkerke R^2) da variância da eficácia do tratamento médico de PCA com ibuprofeno e classifica corretamente 89,7% dos casos. A sensibilidade do modelo foi de 98,1%, a especificidade de 57,1%, e obteve-se um valor preditivo positivo de 89,8%, e um valor preditivo negativo de 88,8%. A capacidade discriminativa do modelo dada pela área sob a curva ROC foi 0,782

(Intervalo de Confiança a 95%, 0,624 - 0,941) o que é um nível de discriminação aceitável de acordo com o teste de Hosmer e Lemeshow (Figura 2).[18]

Discussão

A sobrevivência dos RNPT tem vindo a aumentar significativamente ao longo das últimas duas décadas.[19] Devendo-se este facto à identificação precoce das patologias específicas dos RNPT e na sua melhoria assistencial. Uma das entidades cujo diagnóstico e tratamento precoce tem vindo a melhorar a sobrevida dos RNPT é a PCA. Permanece, no entanto, por esclarecer se as diversas co-morbilidades identificadas surgem como resultado da prematuridade, da existência de PCA com significado hemodinâmico ou com as intervenções terapêuticas. Adicionalmente, o tempo ideal para a intervenção terapêutica após o diagnóstico de PCA continua incerto, uma vez que aguardar pelo encerramento espontâneo poderá prevenir o sobretratamento e os efeitos adversos associados e o próprio tratamento com ibuprofeno parece ser efetivo mesmo quando aplicado relativamente mais tarde.[7] Todavia, tem vindo a ser recomentado o tratamento agressivo e precoce da PCA de modo a prevenir outras complicações. O conhecimento e caracterização das diferentes variáveis, entre as quais da história pré-natal, do nascimento e reanimação na sala de partos, de outras co-morbilidades e dos tratamentos efetuados, poderá permitir a estratificação dos RNPT com PCA e deste modo melhorar a intervenção e o *outcome* destes prematuros.

Na prática clínica, nem todos os RNPT com diagnóstico de PCA respondem ao tratamento com inibidores da enzima ciclooxigenase (COX). Lago e colaboradores, observaram uma resposta eficaz ao tratamento com ibuprofeno em 86% dos indivíduos incluídos no estudo.[20] Deste modo, torna-se fundamental determinar os fatores preditores do sucesso terapêutico para o encerramento de PCA com ibuprofeno de modo a melhorar a abordagem individual a este grupo de prematuros, evitando assim a exposição desnecessária a fármacos e eventualmente considerar a abordagem cirúrgica mais precocemente no algoritmo de decisão. Observou-se o encerramento eficaz do CA após o tratamento com ibuprofeno em 80,6% dos RNPT incluídos no estudo. Porém ao final do 1º ciclo de tratamento com ibuprofeno a eficácia de encerramento foi de 62,5%. Os valores encontrados, são ligeiramente inferiores à eficácia de encerramento descrita quer global quer ao final do 1º ciclo de tratamento (86% e 73%, respetivamente),[17] o que poderá estar relacionado com o intervalo de idade gestacional mais baixos incluídos neste estudo (até às 31 semanas e 6 dias).

Adicionalmente, neste estudo observou-se superioridade na eficácia de encerramento de PCA pelo tratamento com ibuprofeno para IG, peso, comprimento e perímetro cefálico ao nascimento superiores. Outros estudos relacionaram a eficácia do tratamento com inibidores da COX com a maturação do CA, tendo sido demonstrada que o peso ao nascimento e IG inferiores estão associados ao maior diâmetro ductal, dificultando deste modo o encerramento farmacológico.[21-23]

Os nossos dados sugerem que o parto por cesariana poderá promover uma melhor resposta e eficácia ao tratamento com ibuprofeno. Esta observação é apoiada por alguns estudos que estimaram efeitos protetores do parto por cesariana particularmente em RNPT com muito baixo peso, quando comparados com o parto vaginal espontâneo.[24] No entanto são necessários estudos prospetivos em larga escala de modo a estabelecer essa associação.

Foi proposto por alguns autores que as plaquetas desempenham um papel importante no encerramento do canal arterial fisiológico após a constrição funcional inicial do CA.[25] No presente estudo, nos RNPT que necessitaram de transfusão de plaquetas a eficácia de encerramento com o tratamento com ibuprofeno foi de apenas 50% e o número médio de transfusões de plaquetas foi superior no grupo em que este tratamento não foi eficaz. Estudos anteriores, descreveram contagens iniciais de plaquetas mais altas nos RNPT que responderam eficazmente ao tratamento com indometacina em comparação aos que não responderam.[26] Por outro lado, Akar e colaboradores observaram que a massa plaquetária não afeta a eficácia do tratamento com ibuprofeno para PCA em prematuros.[27] Os dados do presente estudo sugerem que a necessidade de transfusões de plaquetas estará associada a pior resposta ao tratamento com ibuprofeno, contudo serão necessários mais estudos que esclareçam esta relação. Não obstante, no subgrupo de RNPT que necessitaram de transfusões de plaquetas (n=20; IG entre as 23 e 29 semanas e peso compreendido entre 410 e 1110 gramas), seis necessitaram de laqueação cirúrgica e nove vieram a falecer, o que corrobora o pior prognóstico deste subgrupo de prematuros. No entanto, salienta-se a relação da contagem de plaquetas e a necessidade de transfusão com outros fatores, tais como a infeção, que podem contribuir para o pior prognóstico e mortalidade neste subgrupo.

A doença das membranas hialinas (DMH) não só aumenta a incidência de PCA em RNPT como também foi associado à eficácia de resposta ao tratamento de PCA com inibidores da COX.[28] Adicionalmente, a administração de surfactante provoca uma rápida diminuição da resistência vascular pulmonar, contribuindo para o aumento de fluxo esquerdo-direito através do canal arterial.[29] No entanto, no presente estudo observou-se a presença de DMH em 90,1% da amostra, tendo sido utilizado surfactante em 84% dos RNPT incluídos no estudo, o que dificulta a atribuição de uma associação para estas variáveis.

A DBP é definida como a dependência de oxigénio às 36 semanas de IG, e apresenta uma incidência superior quanto menor o peso dos recém-nascidos ao nascimento.[30] A patogénese da DBP é multifatorial e associada a alguns fatores de risco da prematuridade.[30] No período pós-natal, diversas medidas na abordagem do RNPT têm sido utilizadas de modo a prevenir e tratar a DBP. Recorre-se ao uso de diuréticos de

ansa, tais como a furosemida, para melhorar a função pulmonar e diminuir a resistência vascular pulmonar.[31] Contudo, o uso de furosemida tem vindo a ser associado a diversos efeitos colaterais, entre os quais a inibição da resposta ao tratamento com inibidores da COX.[32] Na nossa amostra verificou-se também que o tratamento com diuréticos foi estatisticamente associado à redução da eficácia de encerramento de PCA após o tratamento. Adicionalmente, os broncodilatadores e os corticoides inalados que são também utilizados na melhoria nas trocas gasosas e na mecânica pulmonar na prevenção da DBP,[33] foram associados a uma resposta menos eficaz ao tratamento com ibuprofeno no presente estudo. Por outro lado, vários estudos associam a presença de PCA com o desenvolvimento de DBP[34], destacando a necessidade de ser esclarecida a relação entre estas variáveis.

Adicionalmente a utilização de ventilação mecânica ao nascimento foi associado ao aumento de risco de PCA com significado hemodinâmico.[35] A necessidade de ventilação mecânica mais agressiva poderá assim relacionar a existência de PCA e o aumento de risco de displasia broncopulmonar em RNPT. Por outro lado, o encerramento farmacológico de PCA está associado com a diminuição do edema pulmonar e logo com a diminuição de DBP e necessidade de ventilação.[36] Os resultados obtidos neste estudo associam a menor eficácia de encerramento de PCA com a necessidade de ventilação mecânica invasiva.

Neste estudo, observamos associação de eficácia do tratamento com ibuprofeno com os valores de hemoglobina e de volume globular ao nascimento. Salientando-se que todos os RNPT que não necessitaram de transfusão de glóbulos vermelhos durante o internamento (n=20) responderam ao tratamento com ibuprofeno. Sabe-se que a transfusão de hemácias melhora a condição cardio-respiratória pelo aumento de hemoglobina em circulação e consequente melhoria da oxigenação tecidual. No entanto, alguns estudos, associam a transfusão de hemácias a resultados clínicos adversos em RNPT, tais como a NEC, a DBP, a HIV e a ROP.[38]

Na série em estudo, excecionalmente, foi utilizado paracetamol para o tratamento da PCA em três RNPT. Estudos recentes sobre a utilização deste fármaco no encerramento de PCA têm demonstrado que este é igualmente seguro e eficaz quando comparado com os tratamentos com ibuprofeno ou indometacina, apresentando poucos efeitos adversos.[39] Deste modo, poderá ser uma solução segura em situações que contraindicam o uso de ibuprofeno.[40] Contudo, vários estudos estão atualmente em curso de modo a averiguar a possibilidade da utilização de paracetamol de modo mais alargado, uma vez que alguns estudos sugerem a sua associação com lesões pré-renais e complicações relacionadas com o neurodesenvolvimento.[39]

No caso de falência de resposta ao tratamento médico após o segundo ciclo, poderá ser ponderado em casos excecionais a realização de um terceiro ciclo.[16] Na nossa série

este foi realizado em cinco RNPT tendo sido eficaz em todos. Esta amostra compreendia RNPT de IG entre as 24 e 31 semanas, com peso ao nascimento entre 685 e 1925 gramas. Estes resultados salientam a importância do censo clínico na tomada de decisão do algoritmo de tratamento de PDA.

O encerramento cirúrgico de PCA reduz o tempo em ventilação mecânica, melhora a resposta hemodinâmica e a compliance pulmonar. Contudo, não está isento de efeitos adversos e por isso reservado para os casos em que ocorre falência do tratamento médico.[40] Na nossa amostra, em 13 casos foi necessário realizar a laqueação cirúrgica do canal arterial, tendo ocorrido diversas complicações pós-cirúrgicas, enfatizando deste modo a necessidade de definir o subgrupo de RNPT com PCA-HS nos quais a cirurgia tem maior probabilidade de ser benéfica.

Este estudo apresenta as desvantagens associadas ao facto de ser um estudo retrospetivo e como tal haver um controlo limitado das variáveis da amostra e de existirem processos de dados clínicos incompletos, contudo foi possível obter uma amostra robusta para a análise pretendida. Apresenta ainda a limitação de ter sido realizado apenas num único centro, no entanto com a vantagem de se tratar de um centro de nível III e centro de referência de cardiopatias congénitas o que permite a garantia de assistência diferenciada e integrada dos RNPT, garantindo a acessibilidade, eficácia, segurança e excelência dos cuidados prestados obedecendo aos mais elevados padrões éticos e científicos internacionais.

Conclusão

A patência do canal arterial é uma condição frequentemente observada em RNPT e a sua abordagem terapêutica continua a ser um desafio. O encerramento da PCA, por tratamento médico ou cirúrgico não é isento de complicações e a decisão continua controversa. Os inibidores da cicloxigenase (COX), tais como o ibuprofeno, são frequentemente utilizados para o tratamento de PCA em RNPT. No entanto, observa-se na prática clínica que nem todos os RNPT com PCA respondem ao tratamento com ibuprofeno. Alguns estudos têm demonstrado que algumas variáveis tais como a IG, o peso ao nascimento e o diâmetro do canal poderão auxiliar a prever a resposta terapêutica aos inibidores da COX. Neste estudo, procuramos caraterizar a população de RNPT com diagnóstico de PCA e descrever os fatores que poderão prever o sucesso terapêutico do uso de ibuprofeno no encerramento de PCA. Segundo o modelo de regressão logístico multivariado que considera o efeito das variáveis idade gestacional, tipo de parto, necessidade de tratamento com diuréticos e de transfusão de plaquetas é possível prever com elevada sensibilidade a eficácia de resposta ao tratamento médico. Contudo, mais estudos serão necessários com o intuito de melhorar este modelo, no sentido de otimizar as estratégias terapêuticas a oferecer aos RNPT com diagnóstico de PCA.

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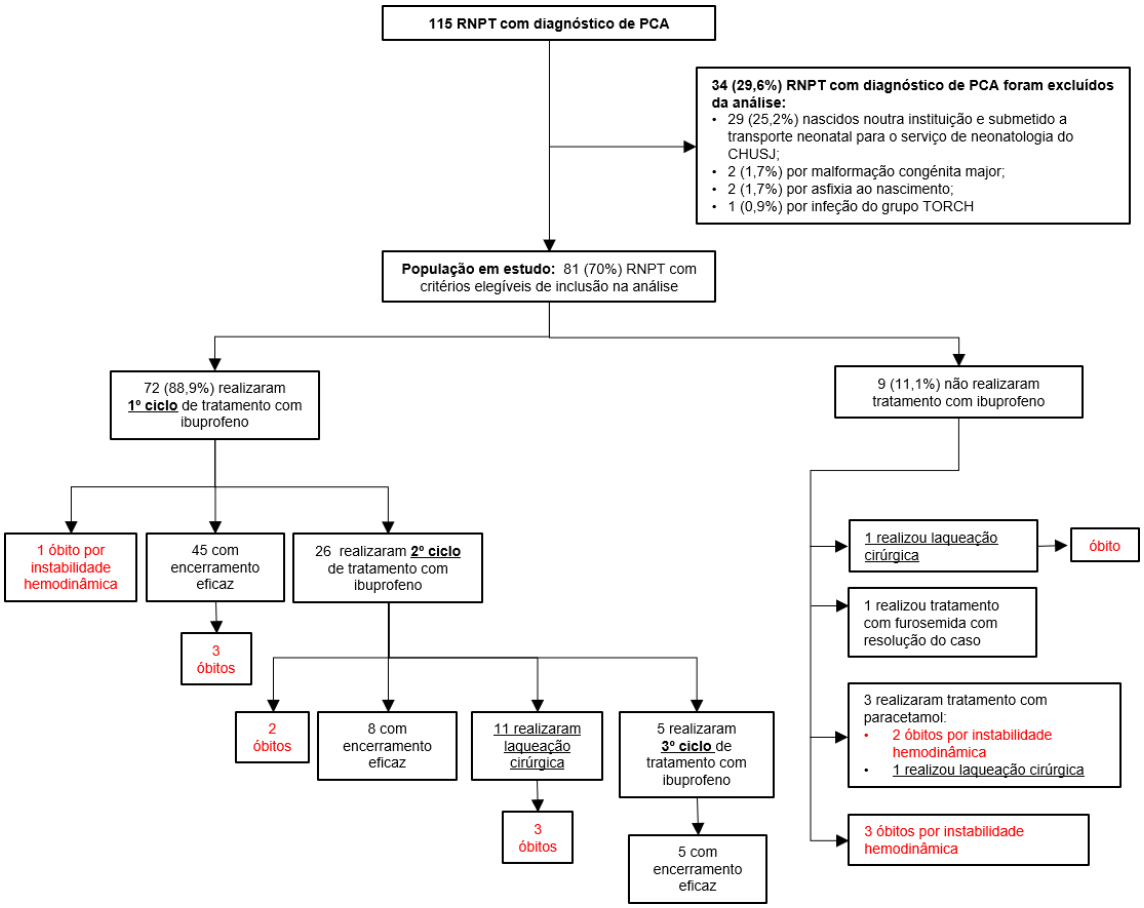

Figura 1 – Abordagem terapêutica e resultados obtidos nos recém-nascidos de pré-termo com patência do canal arterial incluídos no estudo. Legenda: RNPT: recém-nascidos de pré-termo; PCA: patência do canal arterial; CHUSJ: Centro Hospitalar Universitário de São João; TORCH acrónimo de: Toxoplasmose, Outras (sífilis, vírus varicela-zoster (VVZ), parvovírus B19), Rubéola, Citomegalovírus (CMV), e vírus herpes simples (HSV).

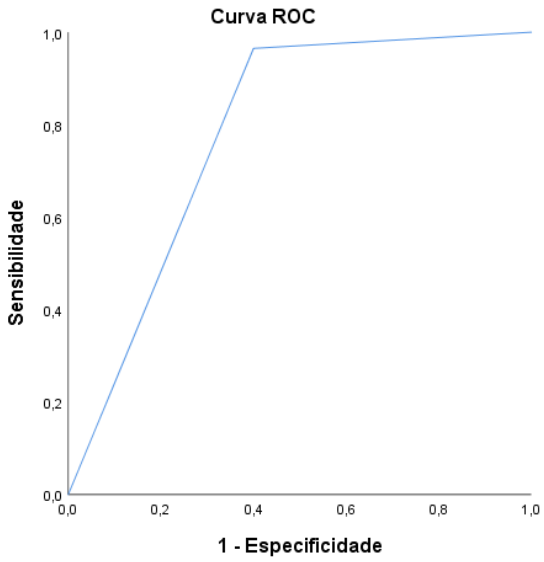

Figura 2 - Capacidade discriminativa do modelo preditivo da ocorrência de eficácia do tratamento com ibuprofeno no encerramento do canal arterial (área sob a curva ROC = 0,782; intervalo de confiança a 95% 0,624 a 0,941) em recém-nascidos de pré-termo com idade gestacional entre as 23 e 32 semanas.

Tabela 1 - Caraterísticas da população de recém-nascidos pré-termo incluídos no estudo.

Dados dos recém-nascidos ao nascimento	
Peso (gramas) [média (desvio padrão)]	995,84 (301,25)
Comprimento (centímetros) [mediana (mínimo-máximo)]	34,5 (25,0-52,0)
Perímetro cefálico (centímetros) [mediana (mínimo-máximo)]	25,5 (15,0-33,0)
Idade Gestacional (semanas) [mediana (mínimo-máximo)]	27 (23-32)
Idade materna (anos) [mediana (mínimo-máximo)]	33 (19-47)
Sexo masculino [nº (%)]	38 (46,9)
Hemoglobina (grama/decilitro) [média (desvio padrão)]	16,2 (2,6)
Volume globular (%) [média (desvio padrão)]	45,9 (7,1)
Leucócitos (x 10^9/litro) [mediana (mínimo-máximo)]	7,3 (2,6-53,2)
Neutrófilos (%) [média (desvio padrão)]	33,5 (17,4)
Linfócitos (%) [média (desvio padrão)]	52,2 (19,0)
Contagem de plaquetas [média (desvio padrão)]	185873 (48635)
Fatores Pré-natais	
Primigesta [nº (%)]	46 (56,8)
Gestação espontânea [nº (%)]	70 (86,4)
Gestação vigiada [nº (%)]	77 (95,0)
Gestação única [nº (%)]	52 (64,2)
Corticoterapia antenatal [nº (%)]	70 (86,4)
Ciclo completo de corticoterapia [nº (%)]	55 (78,6)
Sulfato de magnésio (protocolo neuroprotector) [nº (%)]	11 (13,6)
Ciclo completo [nº (%)]	10 (91,0)
Parto por cesariana [nº (%)]	56 (69,1)
Rutura prematura de membranas (superior a 18 horas) [nº (%)]	9 (11,1)
Corioamnionite clínica [nº (%)]	6 (7,4)
Incompetência cervical [nº (%)]	10 (12,4)
Descolamento prematuro de placenta normalmente inserida [nº (%)]	12 (14,8)
Grávida com hipertensão arterial crónica [nº (%)]	3 (3,7)
Pré-eclâmpsia [nº (%)]	19 (23,5)
Eclâmpsia [nº (%)]	1 (1,2)
Síndrome HELLP [nº (%)]	4 (5,0)
Hipertensão arterial gestacional [nº (%)]	1 (1,2)
Diabetes tipo I [nº (%)]	1 (1,2)
Diabetes gestacional [nº (%)]	5 (6,2)
Necessidade de insulina na gestação [nº (%)]	0 (0,0)
Tabagismo na gestação [nº (%)]	6 (7,4)
Restrição de crescimento fetal [nº (%)]	6 (7,4)
Ação na Sala de Partos	
Ventilação Mecânica [nº (%)]	67 (82,7)
Ventilação mecânica invasiva com tubo endotraqueal [nº (%)]	35 (43,2)
Ventilação com pressão positiva contínua das vias aéreas (CPAP) nasal [nº (%)]	47 (58,0)
Oxigénio suplementar [nº (%)]	76 (93,8)
Fração inspirada de oxigénio (FiO_2) máximo [mediana (mínimo-máximo)]	0,3 (0,0-1,0)
Índice de Apgar ao 1º minuto [mediana (mínimo-máximo)]	6 (2-9)
Índice de Apgar ao 5º minuto [mediana (mínimo-máximo)]	8 (4-10)
Período pós-natal	
Displasia broncopulmonaren [nº (%)]	28 (34,6)
Doença das membranas hialinas [nº (%)]	73 (90,1)
Ligeira [nº (%)]	31 (42,5)
Moderada [nº (%)]	31 (42,5)
Grave [nº (%)]	11 (15,1)
Utilização de surfactante [nº (%)]	68 (84,0)
Uma dose [nº (%)]	28 (41,2)
Duas doses [nº (%)]	25 (36,8)
Três doses [nº (%)]	13 (19,1)
Quatro doses [nº (%)]	2 (2,9)
Pneumotórax [nº (%)]	11 (13,6)

Atelectasia pulmonar [nº (%)]	6 (7,4)
Utilização de Ventilação mecânica [nº (%)]	78 (96,3)
Duração de utilização de ventilação mecânica (dias) [média (desvio padrão)]	38,5 (23,3)
Utilização de pressão positiva contínua das vias aéreas (CPAP) nasal [nº (%)]	69 (85,2)
Duração de utilização de CPAP nasal (dias) [média (desvio padrão)]	25,8 (18,6)
Utilização de ventilação mecânica (VM) invasiva [nº (%)]	65 (80,2)
Duração de utilização de VM invasiva [mediana (mínimo-máximo)]	8 (1-73)
Utilização de ventilação de alta frequência oscilatória (VAFO) [nº (%)]	9 (11,1)
Duração de utilização de VAFO [mediana (mínimo-máximo)]	8 (3-23)
Fração inspirada de oxigénio máximo no internamento [mediana (mínimo-máximo)]	0,4 (0,21-1,0)
Número de dias com oxigénio suplementar [mediana (mínimo-máximo)]	35 (0-157)
Necessidade de oxigénio suplementar na alta [nº (%)]	28 (34,6)
Tratamento com corticóide sistémico [nº (%)]	10 (12,3)
Tratamento com corticóide inalado [nº (%)]	18 (22,2)
Tratamento com broncodilatador inalado [nº (%)]	19 (23,5)
Tratamento com diuréticos [nº (%)]	9 (11,1)
Dias de nutrição parentérica total [mediana (mínimo-máximo)]	3 (0-206)
Necessidade de transfusão de glóbulos vermelhos [nº (%)]	58 (71,6)
Necessidade de transfusão de plaquetas [nº (%)]	20 (24,7)
Enterocolite necrosante [nº (%)]	5 (6,2)
Sépsis precoce (inferior a 72h de vida) [nº (%)]	2 (2,5)
Sépsis hospitalar (superior a 72h de vida) [nº (%)]	33 (40,7)
Pneumonia [nº (%)]	12 (14,8)
Meningite [nº (%)]	2 (2,5)
Hemorragia intraventricular [nº (%)]	39 (48,1)
Enfarte venoso periventricular associado a hemorragia intraventricular [nº (%)]	10 (25,6)
Leucomalácia periventricular [nº (%)]	51 (63,0)
Grau 1 [nº (%)]	44 (86,2)
Grau 2 [nº (%)]	6 (11,8)
Grau 3 [nº (%)]	1 (2,0)
Retinopatia da prematuridade [nº (%)] [a]	43 (53,1)
Grau I [nº (%)]	27 (62,8)
Grau II [nº (%)]	9 (21,0)
Grau III [nº (%)]	7 (16,3)
Cirurgia por retinopatia da prematuridade [nº (%)]	13 (30,2)
Óbito [nº (%)]	15 (18,5)
Óbitos com idade gestacional inferior a 36 semanas [nº (%)]	14 (93,3)
Óbitos com idade gestacional superior a 36 semanas [nº (%)]	1 (6,7)
Idade no óbito [mediana (mínimo-máximo)]	11,5 (6-96)

Dados na alta	
Duração do internamento (dias) [média (desvio padrão)]	58,44 (37,8)
Peso (gramas) [mediana (mínimo-máximo)]	2175 (485-3420)
Comprimento (centímetros) [mediana (mínimo-máximo)]	43 (30-50)
Perímetro cefálico (centímetros) [mediana (mínimo-máximo)]	32 (22,5-38)

[a] a avaliação de ROP é desconhecida em 7 dos casos incluídos no estudo.

Tabela 2 - Diagnóstico, abordagem e tratamento de patência do canal arterial.

Diagnóstico e tratamento de patência do canal arterial	
Recém-nascidos pré-termo com diagnóstico de patência do canal arterial	81
Dia de diagnóstico de patência do canal arterial [mediana (mínimo-máximo)]	3 (1-50)
Tratamento de patência do canal arterial com ibuprofeno [nº (%)]	73 (90,1)
Um ciclo [nº (%)]	46 (63,0)
Dois ciclos [nº (%)]	22 (30,1)
Três ciclos [nº (%)]	5 (6,8)
Dia de início de tratamento com ibuprofeno [mediana (mínimo-máximo)]	3 (1-31)
Encerramento eficaz após o tratamento com ibuprofeno [nº (%)]	58 (80,6)
Tratamento de patência do canal arterial com paracetamol [nº (%)]	3 (3,7)
Encerramento cirúrgico [nº (%)]	13 (16,0)
Dia de vida do encerramento cirúrgico [mediana (mínimo-máximo)]	14 (7-50)
Complicações pós-cirurgia [nº (%)]	2 (15,4)

Tabela 3 – Análise univariável entre a eficácia de encerramento pelo tratamento médico com ibuprofeno e as diversas variáveis estudadas.

	Tratamento eficaz	Tratamento não eficaz	Valor *p*
Idade gestacional [média (desvio padrão)]	28,0 (1,9)	26,1 (2,4)	0,000
Idade gestacional inferior a 28 semanas [nº (%)]	24 (42,1)	13 (86,7)	0,002
Idade gestacional igual ou superior 28 semanas [nº (%)]	33 (57,9)	2 (13,3)	
Tipo de parto - Eutócico [nº (%)]	13 (22,8)	8 (53,3)	0,021
- Cesariana [nº (%)]	44 (77,2)	7 (46,7)	
Peso ao nascimento (gramas) [média (desvio padrão)]	1069,3 (290,5)	752,4 (216,6)	0,000
Comprimento (centímetros) [média (desvio padrão)]	35,8 (4,2)	32,3 (4,5)	0,000
Perímetro cefálico (centímetros) [média (desvio padrão)]	26,1 (2,3)	23,9 (3,6)	0,000
Hemoglobina (grama/decilitro) [média (desvio padrão)]	16,8 (2,7)	14,3 (1,6)	0,000
Volume globular (%) [média (desvio padrão)]	47,3 (7,5)	41,5 (3,9)	0,003
Transfusão de Glóbulos Vermelhos (não) [nº (%)]	20 (35,1)	0 (0,0)	0,007
(sim)	37 (64,9)	15 (100,0)	
Transfusão de plaquetas (não) [nº (%)]	48 (84,2)	6 (40)	0,000
(sim)	9 (15,8)	9 (60)	
Número de transfusões de eritrócitos [média (desvio padrão)]	2,4 (3,6)	8,6 (8,0)	0,000
Número de transfusões de plaquetas [média (desvio padrão)]	0,35 (1,2)	3,4 (7,4)	0,002
Ventilação mecânica (não) [nº (%)]	12 (21,1)	0 (0,0)	0,046
(sim)	45 (78,9)	15 (100)	
Duração de utilização de CPAP nasal [média (desvio padrão)]	29,5 (16,0)	21,6 (23,7)	0,034
Necessidade de oxigénio na alta (sim) [nº (%)]	43 (75,4)	7 (46,7)	0,031
Dias de nutrição parentérica [média (desvio padrão)]	3,1 (3,5)	24,4 (49,9)	0,001
Tratamento com corticóide inalado (não) [nº (%)]	46 (80,7)	8 (53,3)	0,029
(sim)	11 (19,3)	7 (46,7)	
Tratamento com broncodilatador inalado (não) [nº (%)]	45 (78,8)	8 (53,3)	0,045
(sim)	12 (21,1)	7 (46,7)	
Tratamento com diurético (não) [nº (%)]	54 (94,7)	9 (60,0)	0,000
(sim)	3 (5,3)	6 (40,0)	
Hemorragia intraventricular (não) [nº (%)]	35 (61,4)	4 (26,7)	0,016
(sim)	22 (38,6)	11 (73,3)	
EVPV associado a HIV (não) [nº (%)]	55 (96,5)	12 (80,0)	0,025
(sim)	2 (3,5)	3 (20,0)	
Retinopatia da prematuridade (não) [nº (%)]	21 (38,2)	2 (14,3)	0,002
(sim)	33 (60,0)	8 (57,1)	

CPAP - ventilação com pressão positiva contínua das vias aéreas; EVPV - enfarte venoso periventricular; HIV - hemorragia intraventricular

Anexo I - Normas da revista de cardiologia portuguesa

Revista Portuguesa de Cardiologia

AUTHORS INFORMATION PACK

GUIDE FOR AUTHORS

INTRODUCTION

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The Journal accepts the following categories of articles:

Research (Original Investigation and Meta-Analysis), **Review and Education** (Narrative Reviews, Systematic Reviews -without meta-analysis, Guidelines, Case Reports, Images in Cardiology and Snapshots), **Opinion** (Current Perspective), **Correspondence** (Editorial Comment, Letters to the Editor, Research Letter and Observation)

Types of article

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Summary table of *Revista Portuguesa de Cardiologia* types of article characteristics.

Original Investigation

Original Investigation articles cover areas of clinical or basic research: Clinical trial, Meta-analysis, Intervention study, Cohort study, Case-control study, Epidemiologic assessment, Survey with high response rate, Cost-effectiveness analysis, Decision analysis, Study of screening and diagnostic tests, Other observational studies) . They should have a maximum of 5000 words, with a total of up to 15 tables and/or figures, and should be structured as follows: Abstract (maximum 250 words; divided into Introduction and Objectives, Methods, Results and Conclusion(s)); 3-10 keywords; Introduction; Objectives; Methods; Results; Discussion; Conclusion(s); Acknowledgements, if any; References (up to 75); and figure legends, if any. Follow EQUATOR Reporting Guidelines.

Review Articles and Systematic Reviews

Review Articles should have a maximum of 5000 words, with a total of up to 15 tables and/or

figures, and should be structured as follows: Abstract (maximum 250 words; unstructured); 3-10 keywords; Introduction; thematic sections at the discretion of the authors; Conclusion(s); Acknowledgements, if any; References (up to 100); and figure legends, if any.

Systematic Reviews should be structured as Introduction, Methods, Results, Discussion and Conclusion(s). The subject should be clearly defined. The objective of a systematic review should be to produce an evidence-based conclusion. The Methods should give a clear indication of the literature search strategy, data extraction, grading of evidence and analysis.

Systematic Reviews should not normally exceed 4000 words, with a total of up to 6 tables and/or figures and up to 100 references.

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To minimize confusion and to enhance transparency, such statements should begin with the following questions, followed by brief comments addressing each question:

- What other guideline statements are available on this topic?
- Why was this guideline developed?
- How does this statement differ from existing guidelines?
- Why does this statement differ from existing guidelines?

The statement should have an unstructured abstract of up to 350 words, 3 to 10 keywords and can include up to 4000 words, a total of up to 6 tables and/or figures and up to 100 references.

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Authors should use the CARE guidelines as a guiding framework. Case reports should not exceed 1500 words of body text, with up to 15 references and four tables or figures. They must include an abstract (unstructured, maximum 250 words) and bulleted statements (maximum 70 words) in answer to the following questions: What's already known about this topic? and What does this study add?
Please see the Ethics section of the Instructions regarding preservation of patients' privacy. Case Reports must have no more than 5 authors.

Images in Cardiology

Images in Cardiology should have a maximum of 250 words, without Abstract, keywords, tables, or division into sections and up to 5 references may be included.

Snapshots

This section is intended for the publication of rare or educational cases or novel techniques in cardiology. The text should not exceed 500 words and up to 3 figures with brief captions and up to 5 references may be included. Snapshots must have no more than 3 authors.

Current Perspective

This type of manuscript is submitted upon invitation by the Editorial Board. It may cover a broad diversity of themes focusing on cardiology and healthcare: current or emerging problems, management and health policies, history of medicine, society issues and epidemiology, among others. An author who wishes to propose a manuscript in this section is requested to send an abstract to the Editor-in-Chief including the title and Author list for evaluation. The text should not exceed 1200 words, and up to 10 references, two tables or two figures are allowed. An abstract is not required.

Editorial Comment

Editorials are submitted at the invitation of the Editor. They should not exceed 1500 words and can contain up to 20 references and 1 table and 1 figure. They do not have an Abstract or keywords.

Letters to the Editor

Letters to the Editor on articles previously published in the Journal will be considered up to 8 weeks after the publication of the article in question. They should not exceed 800 words and can contain up to 2 figures but without Abstract, keywords or tables. They should have no more than 3 authors.

Research Letter

Research Letters are concise, focused reports of original research. These should not exceed 600 words of text and 6 references and may include up to 2 tables or figures. Online supplementary material is not allowed. Research Letters may have no more than 7 authors.

Observation

Observations consisting of short reports of 1 or 2 complicated, unique cases should not exceed 600 words of text (not including acknowledgment, tables, figures, acknowledgments, and references) and 6 references and may include up to 2 tables or figures. Online supplementary material is not allowed. Observations may have no more than 7 authors.

If the patient(s) described in these manuscripts is identifiable, a Patient Permission form must be completed and signed by the patient(s) and submitted with the manuscript. Omitting data or making data less specific to deidentify patients is acceptable but changing any such data is not acceptable.

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Language

This journal is published in Portuguese and in English language.
The title (and abstract and key words if applicable) must be submitted in both English and Portuguese.

Articles submitted to the Journal should be clearly written in Portuguese (from Portugal) and/or English of a good standard. Text may be edited to maintain linguistic quality and to conform with standard American English.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

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BEFORE YOU BEGIN

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Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Studies in humans and animals

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

The privacy rights of human subjects must always be observed. A statement must be included to the effect that the study was conducted in accordance with the amended Declaration of Helsinki, that the local institutional review board or independent ethics committee approved the

protocol, and that written informed consent was obtained from all patients. The name of the committee, the name of the chairperson of the committee (or the person who approved the protocol), the date of approval and the approval number should follow this statement in the Methods section. For multicenter studies, a list of the relevant approvals may be provided in a separate document to be published as supplementary material.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

Conflicts of Interest and Financial Disclosures

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. A conflict of interest may exist when an author (or the author's institution or employer) has financial or personal relationships or affiliations that could influence (or bias) the author's decisions, work, or manuscript. All authors are required to report potential conflicts of interest including specific financial interests relevant to the subject of their manuscript.

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Authorship

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. According to the guidelines of the International Committee of Medical Journal Editors (ICMJE), authorship credit should be based on the following 4 criteria:

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interpretation of data for the work; and
2. drafting of the work or revising it critically for important intellectual content; and
3. final approval of the version to be published; and
4. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Changes to authorship. Role of the corresponding author

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· Completed trial checklist
· Registry at an appropriate online public clinical trial registry
· A Data Sharing Statement to indicate if data will be shared or not. Specific questions regarding the sharing of data are included in the manuscript submission system.

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Omitting data or making data less specific to deidentify patients is acceptable, but changing any such data is not acceptable. Only those details essential for understanding and interpreting a specific case report or case series should be provided. Although the degree of specificity needed will depend on the context of what is being reported, specific ages, race/ethnicity, and other sociodemographic details should be presented only if clinically or scientifically relevant and important. Cropping of photographs to remove identifiable personal features that are not essential to the clinical message may be permitted as long as the photographs are not otherwise altered. Please do not submit masked photographs of patients. Patients' initials or other personal identifiers must not appear in an image.

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Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article

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PREPARATION

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It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Revista Portuguesa de Cardiologia

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- Why was this guideline developed?
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Please see the Ethics section of the Instructions regarding preservation of patients' privacy. Case Reports must have no more than 5 authors.

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This section is intended for the publication of rare or educational cases or novel techniques in cardiology. The text should not exceed 500 words and up to 3 figures with brief captions and up to 5 references may be included. Snapshots must have no more than 3 authors.

Current Perspective

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2. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *Heliyon*. 2018;**19**:e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.

Reference to a book:
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