Hipoxemia Intermitente en Infantes pretérmino: Etiología y Relevancia Clínica

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Brechas en conocimiento

La relevancia de la hipoxemia intermitente (HI) es una observación relativamente nueva con la llegada de los oxímetros de pulso. Hay creciente evidencia asociando HI con pobres resultados en infantes pretérminos.

Objetivos Después de completar este artículo, los lectores deberían estar capacitados para

1. Describir la progresión natural de la hipoxemia intermitente (HI) en infantes pretérmino.
2. Describir los principales factores que ubican a los infantes pretérmino en mayor riesgo para HI.
3. Discutir los desafíos en documentar en forma precisa los eventos de HI para el manejo del cuidado del paciente día –a- día en UCIN.
4. Discutir la evidencia creciente relacionando HI con injuria y pobres resultados.

Abstract

La hipoxemia intermitente (HI), caídas episódicas en la saturación de oxígeno de la hemoglobina, es un problema común en infantes pretérmino. La extensión de la HI no es aparente clínicamente porque documentar en forma precisa los eventos cardiovasculares para el manejo diario del paciente es un desafío. Múltiples factores ponen al PT en alto riesgo para HI aumentada. Estos factores incluyen inmadurez respiratoria, enfermedad pulmonar, y anemia. Breves episodios de desaturación de oxígeno pueden parecer clínicamente insignificantes; sin embargo, estos eventos pueden tener un efecto acumulativo sobre los resultados neonatales. Hay creciente evidencia de modelos animales y estudios clínicos que sugieren que la HI está asociada con injuria y pobres resultados tales como inflamación aumentada, crecimiento deficitario, ROP, y déficit del neurodesarrollo. En este artículo, el autor revisa la etiología y consecuencias de la HI en infantes pretérmino.

INTRODUCCIÓN

Hipoxemia Intermitente (HI), generalmente definid como caídas breves, episódicas en la saturación de oxígeno de la hemoglobina (Spo2), es una alteración común en los infantes pretérmino (PT). Todos los pt están en riesgo de HI, con los extremadamente PT (EPT) sufriendo el mayor riesgo como resultado de su control respiratorio, estructura pulmonar y función extremadamente inmaduros. La HI en PT puede persistir más allá de la edad postmenstrual del término (PMA), aún después de que se haya percibido resolución de síntomas

clínicos y haber sido dado de altas de UCIN. La relevancia clínica de la HI es una observación relativamente nueva con la llegada de los oxímetros de pulso de alta resolución. Breves episodios de de desaturación de oxígeno pueden arecer clínicamente insignificantes, pero estos episodios HI, ocurriendo cientos de veces por día, tienen un efecto acumulativo en la morbilidad y mortalidad neonatal.

La definición específica y el umbral debajo el cual HI se vuelve clínicamente significante son debatibles; sin embargo, la mayoría consideran una caída en la SpO2 a menos de 80% como sustancial. La mayoría de los expertos miden HI a diferentes umbrales para mejor determinar el espectro del problema. (1, 2, 3, 4). Además del número de eventos, el porcentaje de tiempo pasado con SpO2 por debajo del umbral (ej. SpO2 <80%) es un método valioso de evaluar HI. El porcentaje de tiempo con hipoxemia representa los eventos HI acumulados de corta y larga duración. HI debería ser diferenciada de la hipoxemia sostenida debido a sus variadas etiologías y consecuencias. La mayoría de los estudios relacionados a HI han establecido un límite superior para un evento HI entre 180 y 300 segundos. Este artículo revisará factores que influencian HI y discuten la relevancia clínica de HI en PT

PROGRESIÓN NATURAL

La EG está relacionada inversamente con la ocurrencia de apnea y la resultante HI. La incidencia de apnea y de HI va desde 50% en niños moderadamente PT a casi todos (>97%) los EPT. Además, hay una correlación inversa entre a EG al nacer y la PMA en la cual la apnea, bradicardia y desaturaciones de oxígeno, se resuelven. (5, 6) Las características de HI cambian a medida que aumenta la PMA. Eventos prolongados de HI y eventos requiriendo estimulación se resuelven antes que los eventos más cortos y autolimitados. Los niños nacidos pequeños para la EG (PEG) son particularmente proclives a presentar HI aumentada comparados con infantes apropiados para la EG.

La progresión natural de la frecuencia de eventos de HI en el período postnatal temprano es dinámica (1, 2). Hay una baja frecuencia de HI durante la primera semana después del nacimiento, seguida de un progresivo aumento en las semanas 2 a 3, con un pico alrededor de las 4 ó 5 semanas. Los eventos luego se amesetan/ decrecen durante semanas, 6 a 10 (Fig.1).

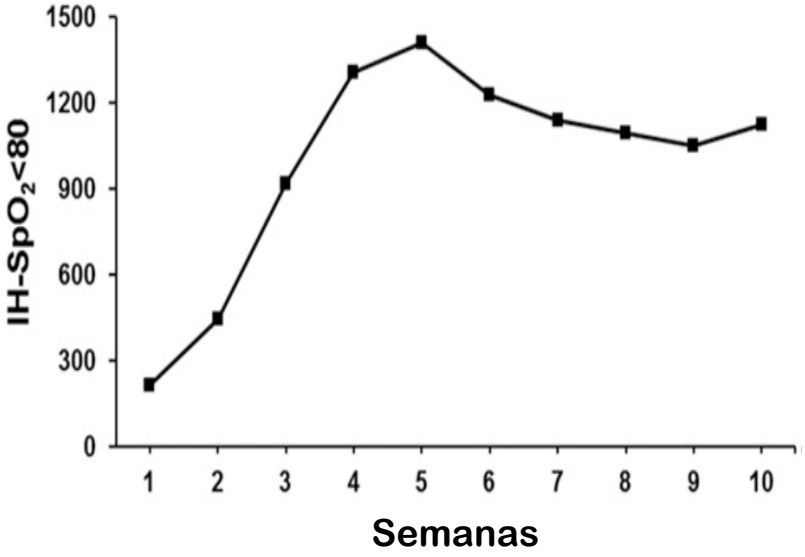

Figura 1. Progresión natural de la hipoxemia intermitente (IH) en los bebés prematuros nacidos con menos de 30 semanas de gestación. La frecuencia de eventos de HI severa (IH-saturación de oxígeno [SpO2] <80%) es baja durante la primera semana después del nacimiento, aumenta durante la edad de 2 a 3 semanas, alcanza su punto máximo al mes de edad, y luego alcanza una meseta hasta 8 a 10 semanas después del nacimiento. Este gráfico es de una cohorte (N = 88) de recién nacidos prematuros reclutados prospectivamente en nuestro centro y monitoreados continuamente con oxímetros de pulso.de alta resolución (2 segundos tiempo promedio, frecuencia de muestreo de 1 Hz)

Las razones que llevan a esta desregulación en HI postnatal están poco definidas, pero HI ocurre muy posiblemente por el pulmón en desarrollo y la desregulación de los quimiorreceptores, posiblemente resultantes de la inflamación e hipoxia (7). Un estudio mostró que, pese a que eventos más prolongados disminuyen a medida que aumenta la PMA, el número de eventos severos (límite inferior) inicialmente aumentan antes de que se comiencen a resolver (8).

FACTORES QUE INFLUENCIAN HI

La apnea es la primera causa de HI en PT. La apnea puede ser central, obstructiva, o mixta. Apnea central es la cesación total de esfuerzo inspiratorio con una vía aérea permeable. En la apnea obstructiva, los infantes exhiben el esfuerzo inspiratorio y movimiento de la pared torácica, a pesar de que el flujo nasal está ausente debido a una vía aérea obstruida. La apnea mixta consiste de esfuerzo respiratorio contra una vía aérea superior obstruida, usualmente precedida o a veces seguida de una pausa respiratoria central. Pese a que tradicionalmente, se clasificaron separadamente, los eventos de apnea central y obstructiva forman un continuo porque la apnea puramente central tiene un componente obstructivo y viceversa (9, 10).

La definición convencional de apnea de la prematurez (ADP) es el cese de la respiración durante más de 15 ó 20 segundos o más de 10 segundos cuando está asociado a desaturación de oxígeno (SpO2 <80%-85%) y/o bradicardia (FC <80 latidos /min ó ≤2/3 del ritmo de base) (II) Esta definición de apnea puede no ser aplicable para la causal de HI en la actual población de la UCIN, especialmente en EPT con enfermedad pulmonar, porque eventos de desaturación de oxígeno pueden ocurrir con frecuencia después de muy breves pausas respiratorias, respiración periódica, o ventilación inefectiva (Fig.2) Debido a que no es la apnea lo relevante para el bienestar de un niño, el foco debería estar en eventos de bradicardia y de HI-resultado final de la ADP. Un hecho llamativo es la estrecha (pocos segundos) relación temporal entre apnea o pausas respiratorias y eventos HI. La secuencia de eventos es usualmente apnea, luego HI, con frecuencia seguida de bradicardia.

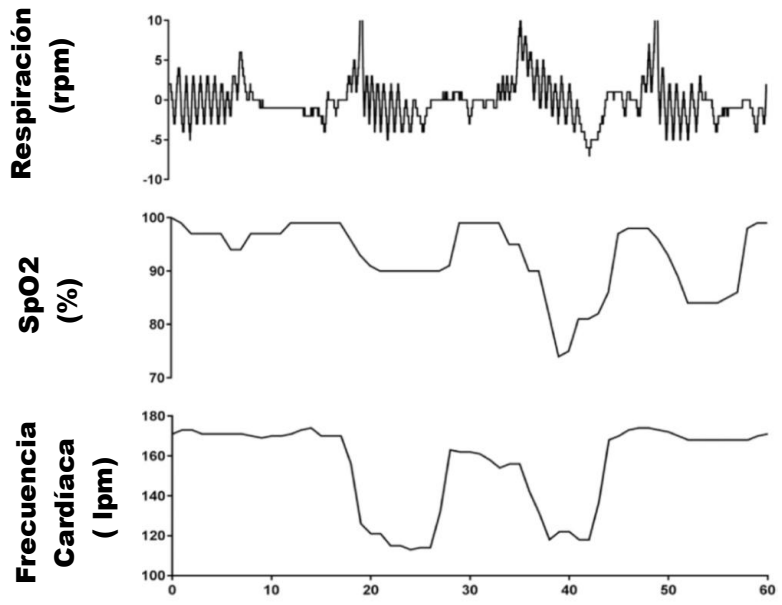

Figura 2. Ejemplo de hipoxemia intermitente (HI) a partir de un estudio de polisomnografía realizado en un recién nacido prematuro nacido a las 26 semanas de edad gestacional en nuestro centro Las fluctuaciones en la saturación de oxígeno ocurren después de pausas respiratorias cortas. Las desaceleraciones de la frecuencia cardíaca se notan simultáneamente con los eventos IH.
Debido a las reservas pulmonares limitadas, incluso pausas breves de respiración pueden conducir a desaturaciones de oxígeno severas.

La etiología de los eventos de bradicardia en el marco de ADP no está completamente comprendida. La apnea puede causar bradicardia como resultado del cese de la insuflación pulmonar ya que el reflejo de inflación pulmonar aumenta la FC. La hipoxemia causaría bradicardia vía la estimulación de quimiorreceptores periféricos. La presencia de bradicardia es más prominente cuando es concurrentemente precedida de apnea y HI. Justamente por la presencia de ambos mecanismos simultáneamente (10).Pese a que los eventos de bradicardia son comunes en PT, no parecen tener importancia pronóstica a menos que se asocien a episodios de hipoxia (3).

LA "TORMENTA PERFECTA"

La combinación de inestabilidad respiratoria y enfermedad/inmadurez pulmonar en PT crea la "tormenta perfecta", llevando a frecuencia aumentada de HI (12). Múltiples factores contribuyen a pausas respiratorias aumentadas y la resultante HI en PT. Los PT tienen neurotransmisores inhibitorios de regulación elevada y quimiosensibilidad central disminuida comparados con los infantes de término. Cambios en la presión parcial de dióxido de carbono (Pco2) juegan un rol mayor en la conducción respiratoria. La respuesta ventilatoria hipercápnica es escasa en PT con apnea, esto es, que respuestas a cambios en la Pco2 es plana comparada con los controles. Además, el umbral apneico de Pco2 es tan pequeño como 1 ó 2 mm Hg (0.13-0.27 kPa) debajo del umbral eupneico. Cuanto más próximo está el umbral eupneico al umbral de Pco2 apneico, la inestabilidad respiratoria es mayor. Por lo tanto, oscilaciones menores en la ventilación inducen apnea y subsiguiente HI (7, 10, 13).

La hipoxemia también controla el área respiratoria en PT. En contraste con adultos y niños, infantes PT tienen una depresión paradójica ventilatoria en respuesta a la hipoxia (es decir, baja oxigenación tisular) que lleva a un manejo respiratorio disminuido. En lugar de un aumento en la ventilación minuto durante hipoxemia, los infantes PT (especialmente aquellos < 30 sem EG) tienen una reducción en la ventilación minuto especialmente por medio de disminución de frecuencia respiratoria. La depresión ventilatoria hipóxica se resuelve alrededor de las 35 semanas PMA (10, 13). El cuerpo de la carótida tiene un rol importante en mantener la respiración basal y en estimular la respiración y el despertar durante la apnea. Los cuerpos carotídeos hiperexcitables presentes en los PT sobreestimulan la respiración, llevando a hiperventilación y a disminución de los niveles de Pco2 circulante que se aproximan al umbral apneico, resultando por tanto en apnea. Interesantemente, las fluctuaciones en la oxigenación por HI alteran la función del quimiorreceptor, llevando a mayor inestabilidad respiratoria y subsiguiente HI (14). Más aún, los infantes PT tienen un quimioreflejo laríngeo inmaduro, resultante en hipoxemia. El quimioreflejo laríngeo evoluciona con la PMA desde apnea prolongada y bradicardia a pausa respiratoria y tos (15).

Los infantes PT nacen con estructura y función pulmonar inmadura. Agregado a la inmadurez pulmonar de base, ellos desarrollan injuria pulmonar por la ventilación a presión positiva y la toxicidad del oxígeno. Ambos inmadurez pulmonar e injuria causan pobres reservas pulmonares, llevando a HI aumentados en presencia de apnea. Hay una relación inversa entre capacidad residual funcional (CRF) y HI. Cuanto más baja es la línea de base de la CRF, más rápida es la desaturación de oxígeno (16). La apnea periódica en infantes PT lleva a una mayor frecuencia de HI comparados con eventos aislados o dispersos de apnea. La saturación de O2 cae dos veces más rápido durante las apneas periódicas que durante los episodios aislados. La

rápida caída en Spo2 es posible resultado de una progresiva caída en el volumen pulmonar y la CRF durante eventos repetidos de apnea. Por ello, infantes PT con CRF basal baja y frecuentes eventos de apnea tienen el perfecto escenario para aumento de la frecuencia y severidad de HI (7, 10, 16). (Fig.3).

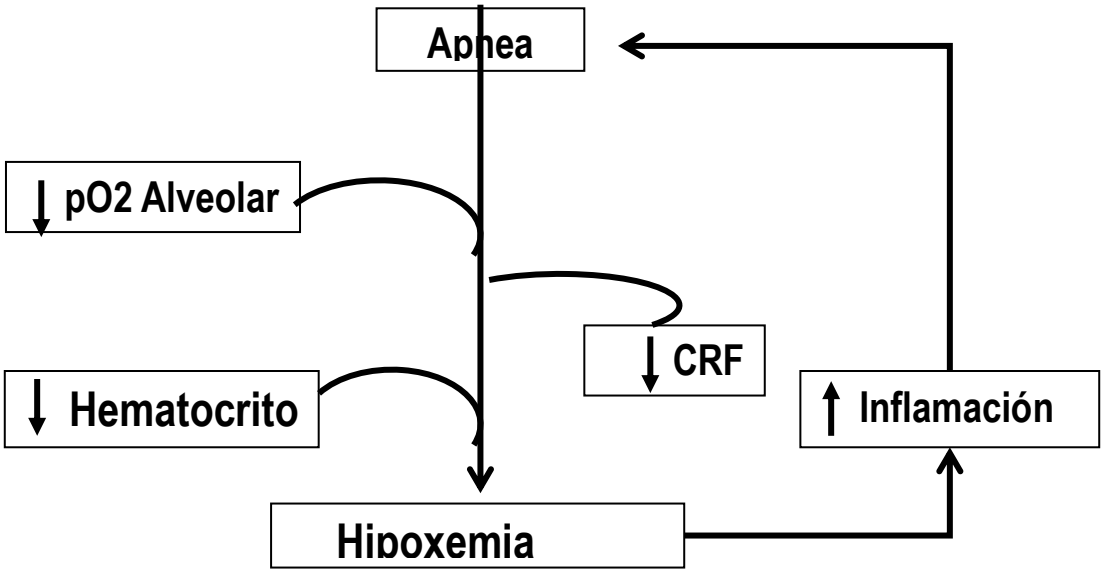

Figura 3. Factores que influyen en la hipoxemia intermitente (IH) en los prematuros. La inmadurez respiratoria / apnea es el principal impulsor de IH. Las desaturaciones de oxígeno se incrementan aún más por: 1) disminución capacidad residual funcional (CRF), inmadurez pulmonar y lesión; 2) disminución de la presión alveolar parcial de oxígeno (PO2) a partir de bajo objetivo de saturación; y 3) disminución del hematocrito debido a la prematuridad y extracciones fercuentes. Además, la relación entre IH e inflamación son bidireccionales, con empeoramiento de la inflamación, apnea y subsecuentemente IH; A su vez, IH aumenta la inflamación, llevando a promover la depresión respiratoria.

ROL DE LA INFLAMACIÓN

La inflamación aumenta los eventos de apnea y subsiguiente HI.Hofstetter et al mostraron que la inflamación sistémica aumentaba la interleukina (IL)-I ß, que se une a sus receptores ubicados en las células endoteliales de la barrera hematoencefálica (17, 18). La activación de receptores IL- I ß lleva al aumento de prostaglandinas en la red de control respiratorio del cerebro, llevando a depresión respiratoria/ apnea y subsiguiente HI. Además, la inflamación sistémica empeora la enfermedad pulmonar y disminuye las reservas pulmonares, llevando a más episodios de HI en presencia de apnea. Notablemente, la inflamación en el sistema pulmonar puede ser transmitida, posiblemente a través del nervio vagal, hacia la red respiratoria central en el tronco cerebral, llevando a mayor inestabilidad respiratoria/ apnea (19).

Sin embargo, la relación entre inflamación y HI puede ser bidireccional. Hay creciente evidencia que sugiere que HI es proinflamatoria. HI como resultado de apnea obstructiva del sueño en niños y adultos está asociada con niveles aumentados de biomarcadores inflamatorios. No hay estudios en infantes PT que apoyen la naturaleza proinflamatoria de HI; sin embargo,

hay evidencia creciente a partir de modelos animales. Crías de ratas recién nacidas expuestas a HI presentan aumento de marcadores séricos inflamatorios, tales como interferón ϒ y la IL-Iß (20). HI crónica en modelos de animales roedores, también aumentaron la inflamación (ej, IL-Iß, factor de necrosis tumoral α, y un aumento de cinco veces en IL-6) en los quimiorreceptores del cuerpo de la carótida, alterando su función y subsiguientemente afectando el control respiratorio y apnea (14, 21, 22, 23). Dado que HI es proinflamatoria en sí misma, esto puede llevar a un circuito de retroalimentación positivo. Los eventos de apnea causan HI e inflamación subsiguiente en la red de control respiratorio y quimiorreceptores periféricos. La inflamación aumentada conduce a mayor ciclo de eventos aumentados de apnea y consecuentemente mayor frecuencia de HI (7) (Fig.3).

ANEMIA

Los infantes PT con anemia están en mayor riesgo de HI. A medida que disminuye el nivel del HTO, la probabilidad de apnea, bradicardia, y eventos HI aumenta (24). A su vez, las transfusiones de glóbulos rojos mejoran HI en infantes PT (1). Los cambios en la hemoglobina afectan HI a través de dos mecanismos propuestos. El primero sugiere que los infantes con anemia han disminuido los depósitos de oxígeno, resultando en mayor inestabilidad de la oxigenación en presencia de apnea. Esto es consistente con un análisis que muestra que la tasa de desaturación arterial de oxígeno durante la apnea aumentó con niveles de hemoglobina más bajos (16).

El segundo mecanismo se relaciona con la depresión ventilatoria hipóxica por la entrega de oxígeno disminuida a la red de control respiratorio. Consecuentemente, las transfusiones de glóbulos rojos disminuyen HI porque hay un aumento tanto de las reservas de oxígeno y de la entrega de oxigeno al sistema respiratorio. Las reservas de oxigeno están aumentadas a través de un ascenso en el HTO. La entrega de oxígeno es entonces mejorada como resultado de un aumento en la presión parcial de oxígeno (Po2) por el cambio de disociación de la curva hacia la derecha, debido al aumento del cociente Hb adulta/ fetal después de una transfusión de glóbulos rojos. El efecto bolo de la expansión de volumen durante una transfusión puede tener también un papel; sin embargo, el efecto es transitorio.

SATURACIÓN DE OXIGENO DESEADA

La Spo2 deseada en UCINs individuales influencia la frecuencia de HI. Un análisis posterior de infantes enrolados en el Estudio de Surfactante Presión Positiva y Oxígeno mostró que los infantes randomizados a Spo2 más baja(85%-89%)tuvieron un aumento HI comparados con aquéllos con Spo2 deseada más alta (91%-95%) (8, 25).Los infantes del grupo más bajo tuvieron mayor incidencia tanto de eventos HI cortos o prolongados comparados con infantes del grupo de mayor saturación asignada. El aumento de HI fue más pronunciado durante el período postnatal temprano (<2 semanas después de nacer) quizás debido a la inhibición quimiorreceptora de respirar durante la transición de la vida intrauterina a la extrauterina. Además, la diferencia fue notada más tarde en el período postnatal (>8 semanas después de nacer) posiblemente debido a una Po2 basal alveolar baja en el grupo baja Spo2 que mostró causar desaturación temprana en presencia de apnea (16)

Otra posible explicación para el aumento de HI en el grupo de baja Spo2es la depresión ventilatoria hipóxica (descripta antes) que pueden desarrollarse a una Po2 arterial tan alta como 60-90 mmHg (7.9-11.9 kPa), resultando en respiración irregular y aumento de pausas

respiratorias en el grupo de Spo2 más bajo comparado con el grupo más alto. Estos hallazgos agregan debate a la más apropiada saturación blanco para infantes PT. Es crucial evitar la hiperoxemia inicial en el período postnatal temprano. Sin embargo, minimizar los episodios HI durante las semanas postnatales posteriores apuntando a una Spo2 basal levemente superior vale la pena investigarlo porque puede tener un impacto sobre HI y morbilidades asociadas.

MONITOREO

Documentar con precisión los eventos cardiorrespiratorios en el manejo día-a-día del paciente es un desafío, porque HI no es aparente clínicamente y por tanto, requiere registro fisiológico continuo para detección certera. Los infantes PT tienen en promedio 150 a 200 eventos severos HI por día durante los cuales la SpO2 cae por debajo del 80% y algunos tienen hasta 800 y 1000 eventos HI leves (SpO2 <90%) por día (1). Además, los cuidadores sub-registran el número de eventos comparados con registros objetivos automatizados. En un estudio, comparado con polisomnografía, el staff de enfermería registró menos del 30%-40% de eventos HI y bradicardia respectivamente. Cuanto más corto el evento, menos probable que sea detectado por por enfermería. Por ejemplo, los cuidadores al lado de la cama documentaron 35% y 29% de eventos HI que duraron más de 20 y 10 segundos respectivamente (26).

Los oxímetros de pulso son el estándar actual de cuidado para monitorear la oxigenación en la UCIN. Sin embargo, la programación del monitor, así como el tiempo promedio, afecta el número de eventos HI registrados (27). Los oxímetros de pulso promedian valores de varios latidos. Grupos de investigación que estudian HI usan oxímetros de pulso de alta resolución con 2 segundos de tiempo promedio para monitoreo continuo de SpO2. Los oximetros de pulso programados para tiempos más prolongados subestiman los eventos HI de corta duración y sobreestiman los de mayor duración. Este sería el resultado de varios eventos cortos que se reflejen como uno sólo prolongado. Los oxímetros de pulso clínicos son programados con tiempos de promedio más largos para disminuir la fatiga por alarma de los cuidadores junto a la cama. El tiempo promedio por default en los oxímetros de pulso clínicos varía entre 8 y 10 segundos pero puede ser tan largo como 16 segundos. Una opción para centros que desean tiempos promedios más cortos es establecer un tiempo de demora de alarma más largo (10-15 segundos) para reducir la fatiga por alarmas.

CONSECUENCIAS

Breves episodios de desaturaciones de oxígeno pueden parecer clínicamente insignificantes, pero estos episodios HI tienen un efecto acumulativo sobre la morbimortalidad (Fig. 4). Las preocupaciones acerca de la contribución significante de HI a las morbilidades neonatales son una observación relativamente nueva después del uso de oxímetros de pulso de alta resolución. Amplia evidencia de modelos animales muestra efecto significativo de HI sobre el déficit neurocognitivo, integridad neuronal disminuida, y aumento de inflamación. Ciclos repetitivos de HI y subsiguiente reoxigenación causan estrés oxidativo, producción de radicales libres, y la liberación de citokinas proinflamatorias (20). Experimentos en ratones han indicado que a exposición postnatal temprana a HI muestra evidencia bioquímica y por microscopía electrónica de deficitaria mielinización axonal y déficits neurofuncionales a largo plazo. Darnall et al mostraron que las crías de ratas expuestas a HI leve han aumentado los biomarcadores

inflamatorios sistémicos y cerebrales (ej, quemokina C-X-C ligando-I y IL-Iß) y disminución en biomarcadores neuroprotectores (ej, Tau) comparados con un grupo no expuesto. Además, la exposición leve HI dificultó la mielinización, causó injuria medular y axonal. Y aumentó el recambio de membrana (20). Julien et al usaron pletismografía de cuerpo entero para determinar patrones respiratorios en crías de ratas expuestas a HI crónica. Las crías de rata expuestas a HI temprana desde el primer día de nacimiento (PI) tuvieron un aumento de frecuencia de apneas en respuesta a la hipoxia posterior en el período postnatal (PIO) comparada con controles no expuestos (28).

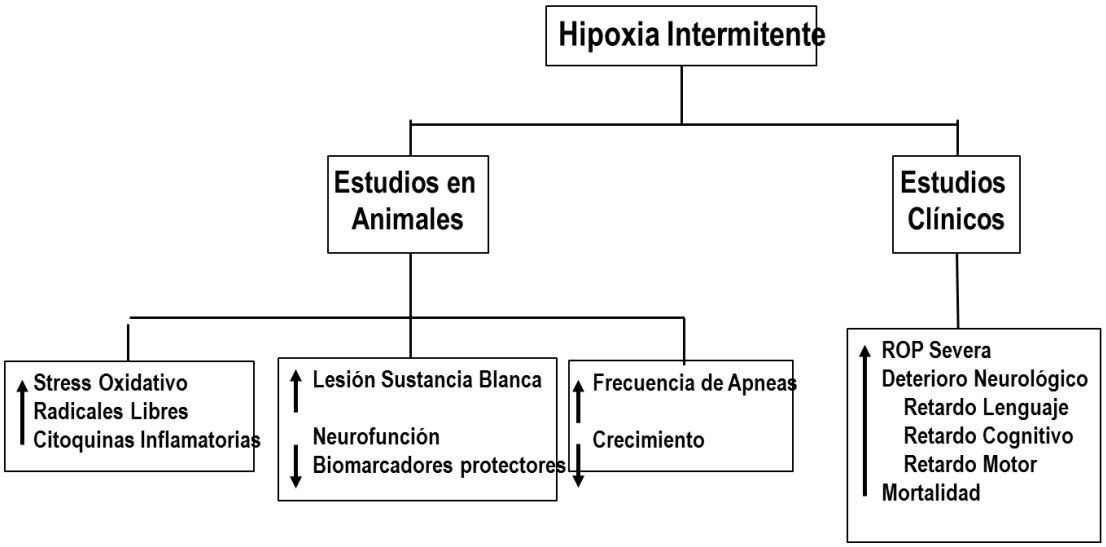

Figura 4. El aumento de la evidencia de estudios clínicos y en animales ha relacionado la HI hipoxemia intermitente con lesiones y resultados desfavorables.

Múltiples estudios animales han mostrado que HI es desfavorable para el crecimiento. Crías de ratas expuestas a HI durante la primera semana post-nacimiento (PI-7) exhibieron restricción de crecimiento comparado con controles expuestos a normoxia. Interesante, la restricción del crecimiento persistió hasta P21), mucho más allá del tiempo de exposición (29). Estos estudios pueden sugerir que los infantes PT con aumento de HI durante su estadía en UCIN están en riesgo aumentado de respiración alterada en el sueño y déficit de crecimiento durante la infancia. Schmid et al examinaron el efecto de HI y bradicardia sobre la oxigenación cerebral en 16 infantes EPT. La oxigenación cerebral disminuyó en presencia de HI, especialmente cuando ocurrió simultáneamente con eventos de bradicardia. Es de notar, sólo unos pocos infantes (25%) tuvieron oxigenación cerebral <60% con eventos HI severos (30). Estos hallazgos generan preguntas acerca de las características de los infantes en mayor riesgo para injuria en presencia de HI.

RETINOPATÍA DE LA PREMATUREZ

ROP, segunda causa más común de ceguera infantil en Estados Unidos, es un desorden proliferativo del desarrollo vascular que ocurre en la retina de los infantes PT. La patogénesis de ROP ha sido descripta para incluir dos fases secuenciales. En la primera fase, la hiperoxia lleva a la cesación del crecimiento de los vasos en el período postnatal temprano (nacimiento hasta >32-34 semanas PMA). El oxigeno suplementario suprime el factor de crecimiento endotelial

vascular (VEGF), que resulta en la cesación de crecimiento normal de vasos y regresión de los vasos existentes. La segunda fase es precipitada por el aumento de la demanda metabólica de la retina en desarrollo en la presencia de suplemento vascular comprometido. Esta fase comienza más tarde (>32-34 semanas PMA) y está asociada con un aumento de la expresión de VEGF en la retina causado por hipoxia relativa, que resulta en neovascularización patológica.

Pese a que la hiperoxia es la principal causa de ROP, estudios animales sugieren que las fluctuaciones en SpO2 llevan a ROP. Esta asociación también se ha visto en infantes PT usando oxímetros de pulso de alta resolución. Di Fiore et al mostraron una asociación entre HI crónica y ROP requiriendo cirugía láser (2). Después de ajustar para convariables confusoras, infantes con ROP que requirieron tratamiento láser tenían incrementada significativamente la frecuencia de eventos HI comparados con aquellos que no tenían ROP o no requirieron tratamiento. Infantes con ROP severa tuvieron eventos de HI más largo y más variables comparados con controles. Similarmente, en un análisis posterior del Estudio Canadiense del Oxígeno, Poets et al y Schmidt et al mostraron que el riesgo de ROP aumentó con el porcentaje de tiempo más elevado que los infantes experimentaron HI (3, 31). Fairchild et alno pudieron replicar estos resultados; sin embargo, los investigadores sólo consideraron eventos de HI precedidos por apnea y no emplearon oxímetros de pulso de alta resolución (tiempo promedio -2 segundos) (5).

DÉFICIT DEL NEURODESARROLLO Y MUERTE

Hay evidencia creciente asociando HI a déficit del neurodesarrollo (NDI) y mortalidad en infantes PT. NDI es usualmente definido como sobrevida con uno ó más de los siguientes: déficit motor o parálisis cerebral moderada a severa, retraso cognitivo, pérdidaauditiva severa, o ceguera. Janvier et al demostraron una correlación positiva entre el número de días con apnea/ bradicardia y NDI a los 3 años de edad en infantes PT con PN <1250 grs o EG <32 semanas (32). Esta asociación persistió después de corregir factores de riesgo, incluyendo esteroides postnatales, sexo, y duración de la ventilación asistida. En una cohorte de infantes de muy bajo PN, Pillekamp et al mostraron que tanto la apnea persistente como el aumento de apnea acumulado estuvieron asociados con muerte o déficit severo (Psychomotor Developmental Index/ Mental Developmental Index <69 documentado por escala Bayley de Desarrollo Infantil) a los 13 meses de EC (33). Luego de ajustar por variables sociales Greene et al mostraron que mayor frecuencia y severidad de eventos cardiorrespiratorios estuvieron asociados con peores resultados en lenguaje a los 20 meses de EC en una cohorte de infantes extremadadamente BP al nacer (34). Sin embargo, los estudios antes mencionados utilizaron eventos cardiorrespiratorios registrados en pie de cama por la enfermera, una limitación mayor porque los registros a pie de cama se correlacionan pobremente con el análisis objetivo digital.

En un análisis de 1035 infantes EPT, Poets et al mostraron una asociación entre eventos de HI prolongados y NDI a los 18 meses (3). Los autores también encontraron que HI estuvo asociada con muerte tardía en la misma población de pacientes. En una reciente publicación, Di Fiore et al examinaron la asociación entre patrones de oxigenación y sobrevida en 1054 infantes EP (35). Los infantes PEG fueron particularmente susceptibles porque ellos tenían un tiempo aumentado con hipoxemia y aumento de la incidencia de eventos HI. El aumento de HI en los primeros tres días de vida después del nacimiento estuvo asociado con sobrevida significativamente más baja a los 90 días en infantes PEG que en infantes con PN AEG. Sin

embargo, el hallazgo de una asociación entre HI y NDI/muerte en estos dos grandes estudios provino de un análisis posterior

CONCLUSIÓN

Los eventos HI son ubicuos en infantes PT. La frecuencia y duración de los eventos con frecuencia es subestimada y su significado no es apreciado por los cuidadores de salud. Factores asociados con la PT y la estadía en UCIN tales como inestabilidad respiratoria, enfermedad pulmonar, anemia, y SpO2 deseada más baja aumentan la frecuencia y severidad de HI en las poblaciones de pacientes más PT. Evidencia creciente tanto de modelos animales como de infantes PT muestra que HI está unida a pobres resultados en el corto y mediano plazo. Sin embargo, la mayoría de los estudios clínicos que utilizaron oxímetros de pulso de alta resolución no estuvieron diseñados primariamente para examinar las consecuencias de HI. Hay una necesidad urgente de estudios prospectivos para identificar infantes PT en mayor riesgo para aumento de déficit y mortalidad como resultado de HI.

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Intermittent Hypoxemia in Preterm Infants: Etiology and Clinical Relevance

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Education Gaps

The clinical relevance of intermittent hypoxemia (IH) is a relatively new observation with the advent of pulse oximeters. There is increasing evidence linking IH to poor outcomes in preterm infants.

Objectives After completing this article, readers should be able to

1. Describe the natural progression of intermittent hypoxemia (IH) in preterm infants.
2. Describe the main factors that place preterm infants at highest risk for IH.
3. Discuss the challenges in accurately documenting IH events for day-to-day patient care management in the NICU.
4. Discuss the mounting evidence linking IH to injury and poor outcomes.

Abstract

Intermittent hypoxemia (IH), episodic drops in hemoglobin oxygen saturation, is a common problem in preterm infants. The extent of IH is not apparent clinically because accurately documenting cardiorespiratory events for day-to-day patient care management is challenging. Multiple factors place preterm infants at high risk for increased IH. These factors include respiratory immaturity, lung disease, and anemia. Brief episodes of oxygen desaturation may seem clinically insignificant; however, these events may have a cumulative effect on neonatal outcomes. There is mounting evidence from both animal models and clinical studies suggesting that IH is associated with injury and poor outcomes such as increased inflammation, impaired growth, retinopathy of prematurity, and neurodevelopmental impairment. In this article, the author reviews the etiology and consequences of IH in preterm infants.

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ABBREVIATIONS

AOP	apnea of prematurity
FRC	functional residual capacity
GA	gestational age
IH	intermittent hypoxemia
IL	interleukin
NDI	neurodevelopmental impairment
P_{CO_2}	partial pressure of carbon dioxide
PMA	postmenstrual age
P_{O_2}	partial pressure of oxygen
ROP	retinopathy of prematurity
SGA	small for gestational age
S_{PO_2}	oxygen saturation
VEGF	vascular endothelial growth factor

INTRODUCTION

Intermittent hypoxemia (IH), generally defined as brief, episodic drops in hemoglobin oxygen saturation (S_{PO_2}), is a common disorder in preterm infants.

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All preterm infants are at risk for IH, with extremely preterm infants being at highest risk as a result of their extremely immature respiratory control and lung structure and function. Intermittent hypoxemia in preterm infants can persist beyond term postmenstrual age (PMA), even after perceived resolution of clinical symptoms and discharge from the NICU. The clinical relevance of IH is a relatively new observation with the advent of high-resolution pulse oximeters. Brief episodes of oxygen desaturation may seem clinically insignificant, but these IH episodes, occurring up to hundreds of times per day, have a cumulative effect on neonatal morbidity and mortality.

The specific definition and threshold below which IH becomes clinically significant are debatable; however, most consider an SpO_2 drop to less than 80% as substantial. Most experts measure IH at different SpO_2 thresholds to better assess the spectrum of the problem. (1)(2)(3)(4) In addition to the number of IH events, the percentage of time spent with SpO_2 below threshold (eg, SpO_2 <80%) is a valuable method to evaluate IH. The percentage of time with hypoxemia represents the cumulative IH events of short and long duration. IH should be differentiated from sustained hypoxemia because of their varying etiology and consequences. Most studies related to IH have set an upper limit for an IH event at 180 to 300 seconds. This article will review factors that influence IH and discuss the clinical relevance of IH in preterm infants.

NATURAL PROGRESSION

Gestational age (GA) is inversely related to the occurrence of apnea with resultant IH. The incidence of apnea and IH ranges from 50% in moderate preterm infants to virtually all (>97%) extremely preterm infants. In addition, there is an inverse correlation between GA at birth and PMA at which apnea, bradycardia, and oxygen desaturations resolve. (5)(6) Characteristics of IH change with advancing PMA. Prolonged IH events and events requiring stimulation resolve before shorter and self-resolving events. Infants born small for gestational age (SGA) are particularly prone to having increased IH compared with infants who are appropriate for gestational age.

The natural progression of IH event frequency in the early postnatal period is dynamic. (1)(2) There is a low frequency of IH during the first week after birth, followed by a progressive increase by weeks 2 to 3, with a peak around 4 to 5 weeks. Events then plateau/decrease during weeks 6 to 10 (Fig 1). The reasons leading to the rise in IH postnatally are poorly defined but IH likely occurs because of both developing lung disease and chemoreceptor dysregulation

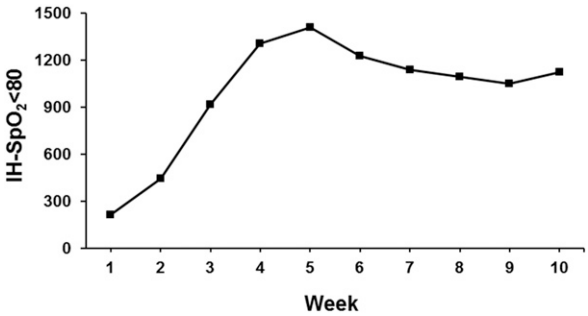

Figure 1. Natural progression of intermittent hypoxemia (IH) in preterm infants born at less than 30 weeks' gestation. The frequency of severe IH events (IH-oxygen saturation [SpO_2]<80%) is low during the first week after birth, increases during age 2 to 3 weeks, peaks at 1 month of age, and then reaches a plateau until 8 to 10 weeks after birth. This plot is from a cohort (N=88) of preterm infants prospectively recruited at our center and continuously monitored with high-resolution (2 second averaging time, 1-Hz sampling rate) pulse oximeters.

possibly resulting from inflammation and hypoxia. (7) One study showed that, although longer events decrease with advancing PMA, the number of severe events (lower nadir) initially increase before they start to resolve. (8)

FACTORS THAT INFLUENCE IH

Apnea is the main driver for IH in preterm infants. Apnea can be central, obstructive, or mixed. Central apnea is total cessation of inspiratory effort with a patent airway. In obstructive apnea, infants exhibit an inspiratory effort and chest wall motion, though nasal flow is absent because of an obstructed airway. Mixed apnea consists of respiratory effort against an obstructed upper airway, usually preceded or sometimes followed by a central respiratory pause. Although traditionally classified separately, central and obstructive apnea events likely form a continuum because purely central apnea has an obstructive component and vice versa. (9)(10)

The conventional definition of apnea of prematurity (AOP) is cessation of breathing for more than 15 to 20 seconds or more than 10 seconds when associated with a desaturation in oxygen ($Sp0_2$ <80%–85%) and/or bradycardia (heart rate <80 beats/min or ≤2/3 baseline). (11) This definition of apnea may not be applicable to the causality of IH in the current NICU population, especially in extreme preterm infants with lung disease, because oxygen desaturation events can often occur after very brief respiratory pauses, periodic breathing, or ineffective ventilation (Fig 2). Because it is not apnea that is relevant to the well-being of an infant, the focus should be on IH and bradycardia events—the end result of AOP. An intriguing finding is the close (few seconds) temporal relationship between apnea or respiratory pauses and IH events. The sequence of events is usually apnea, then IH, often followed by bradycardia.

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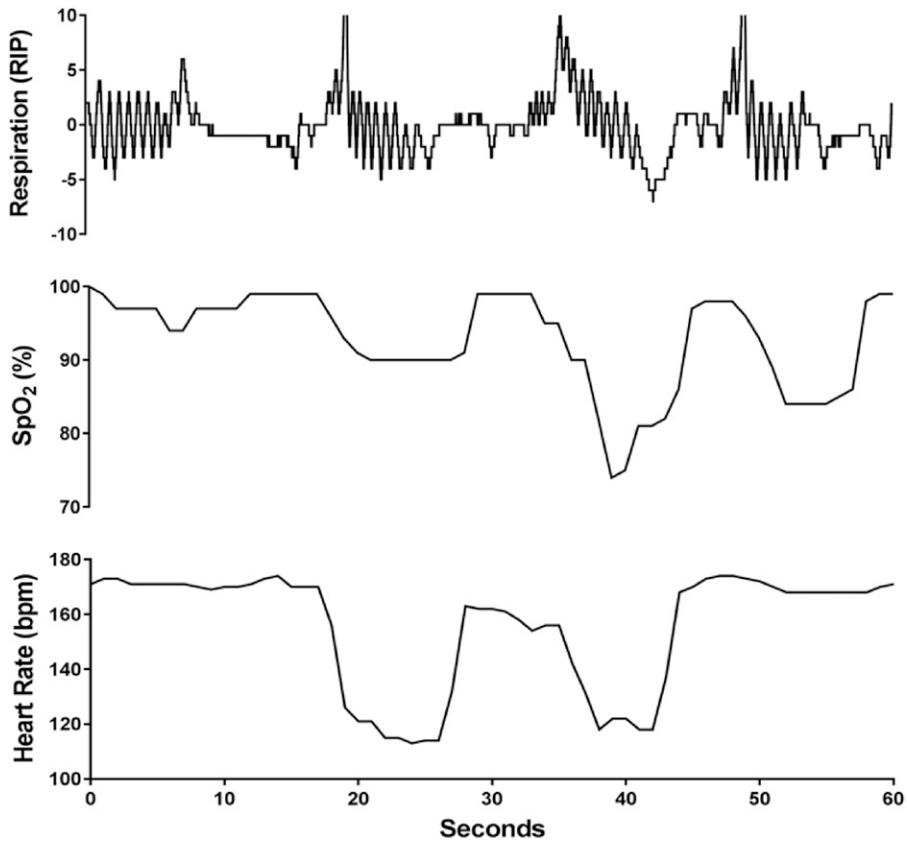

Figure 2. Example of intermittent hypoxemia (IH) from a polysomnography study performed on a preterm infant born at 26 weeks' gestational age at our center. Fluctuations in oxygen saturation occur after short respiratory pauses. Heart rate decelerations are noted simultaneously with IH events. Because of limited pulmonary reserves, even short breathing pauses can lead to severe oxygen desaturations. bpm=beats/min; RIP=respiratory inductance plethysmography; Spo_2=oxygen saturation

The etiology of bradycardia events in the setting of AOP is not completely understood. Apnea likely causes bradycardia as a result of cessation of lung inflation as the pulmonary inflation reflex increases heart rate. Hypoxemia likely causes bradycardia via stimulation of peripheral chemoreceptors. The presence of bradycardia is more prominent when preceded concurrently by both apnea and IH, likely because of the presence of both these mechanisms simultaneously. (10) Although bradycardia events are common in preterm infants, they do not seem to be of prognostic importance unless associated with hypoxemic events. (3)

THE "PERFECT STORM"

The combination of respiratory instability and lung disease/immaturity in preterm infants creates a "perfect storm," leading to an increased frequency of IH. (12) Multiple factors contribute to increased respiratory pauses and resultant IH in preterm infants. Preterm infants have upregulated inhibitory neurotransmitters and decreased central chemosensitivity compared with term infants. Changes in partial pressure of carbon dioxide (Pco_2) play a major role in respiratory drive. The hypercapneic ventilatory response is impaired in preterm infants with apnea, that is, the response to changes in Pco_2 is flat compared with controls. In addition, the apneic Pco_2 threshold is as little as 1 to 2 mm Hg (0.13–0.27 kPa) below eupneic threshold. The closer the eupneic threshold is to the apneic Pco_2 threshold, the greater the respiratory instability. Therefore, minor oscillations in ventilation induce apnea and subsequent IH. (7)(10)(13)

Hypoxemia also controls respiratory drive in preterm infants. In contrast to adults and children, preterm infants have a paradoxical ventilatory depression in response to hypoxia (ie, low tissue oxygenation) leading to a decreased respiratory drive. Instead of a rise in minute ventilation during hypoxemia, preterm infants (especially those <30 weeks' GA) have a reduction in minute ventilation mainly through decreased respiratory rate. Hypoxic ventilatory depression resolves around 35 weeks' PMA. (10)(13) The carotid body plays a large role in both maintaining baseline respiration and stimulating breathing and arousal during apnea. The hyperexcitable carotid bodies present in preterm

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infants overstimulate breathing, leading to hyperventilation and a decrease in circulating P_{CO_2} levels that approach the apneic threshold, thus resulting in apnea. Interestingly, fluctuations in oxygenation from IH alter chemoreceptor function, leading to further respiratory instability and subsequent IH. (14) Furthermore, preterm infants have an immature laryngeal chemoreflex, resulting in hypoxemia. The laryngeal chemoreflex evolves with advancing PMA from prolonged apnea and bradycardia to respiratory pause and cough. (15)

Preterm infants are born with immature lung structure and function. In addition to baseline lung immaturity, they develop lung injury from positive pressure ventilation and oxygen toxicity. Both lung immaturity and injury cause poor pulmonary reserves, leading to increased IH in the presence of apnea. There is an inverse relationship between functional residual capacity (FRC) and IH. The lower the FRC is at baseline, the more rapid is the oxygen desaturation. (16) Periodic apnea in preterm infants leads to a higher frequency of IH compared with isolated or dispersed apnea events. Oxygen saturation falls twice as fast during periodic apneas as that during isolated episodes. The rapid fall in Sp_{O_2} likely results from a progressive fall in lung volume and FRC during repeated apnea events. Hence, preterm infants with low baseline FRC and frequent apnea events have the perfect setup for increased IH frequency and severity (7)(10)(16) (Fig 3).

ROLE OF INFLAMMATION

Inflammation increases apnea events and subsequently IH. Hofstetter et al showed that systemic inflammation increased interleukin (IL)-1β, which binds to its receptors located on endothelial cells of the blood brain barrier. (17)(18) Activation of IL-1β receptors leads to increased prostaglandins in the respiratory control network in the brain, leading to respiratory depression/apnea and subsequent IH. In addition, systemic inflammation worsens lung disease and decreases lung reserves, leading to more episodes of IH in the presence of apnea. Interestingly, inflammation in the pulmonary system can be transmitted, likely through the vagal nerve, to the central respiratory network in the brain stem, leading to further respiratory instability/apnea. (19)

However, the relationship between inflammation and IH may be bidirectional. There is rising evidence to suggest that IH is proinflammatory. IH as a result of obstructive sleep apnea in children and adults is associated with increased levels of inflammatory biomarkers. There are no studies in preterm infants to support the proinflammatory nature of IH; however, there is increasing evidence from neonatal animal models. Newborn rat pups exposed to IH had increased serum inflammatory markers, such as interferon γ and IL-1β. (20) Chronic IH in rodent animal models also increased inflammation (eg, IL-1β, tumor necrosis factor α, and a 5-fold increase in IL-6) in the carotid body chemoreceptors, altering their function and subsequently affecting respiratory control and apnea. (14)(21)(22)(23) Because IH is proinflammatory itself, this may lead to a positive feedback loop. Apnea events cause IH and subsequent inflammation in the respiratory control network and peripheral chemoreceptors. The increased inflammation leads to a further cycle of increased apnea events and consequently higher frequency of IH (7) (Fig 3).

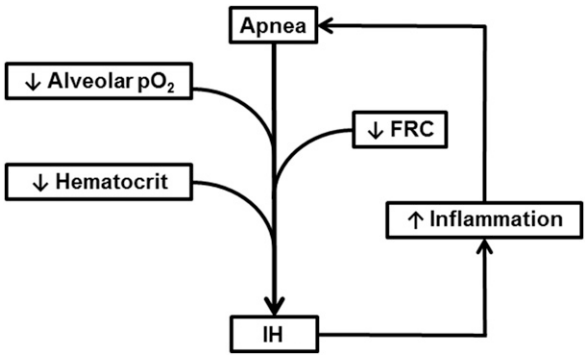

Figure 3. Factors that influence intermittent hypoxemia (IH) in preterm infants. Apnea/respiratory immaturity is the main driver for IH in preterm infants. Oxygen desaturations are further increased by: 1) decreased functional residual capacity (FRC) from lung immaturity and injury; 2) decreased alveolar partial pressure of oxygen (P_{O_2}) from low oxygen saturation target; and 3) decreased hematocrit due to prematurity and frequent blood sampling. Furthermore, the relationship between IH and inflammation is bidirectional, with inflammation worsening apnea and subsequently IH; in turn, IH increases inflammation, leading to further respiratory depression.

ANEMIA

Preterm infants with anemia are at increased risk for IH. As the hematocrit level decreases, the probability of apnea, bradycardia, and IH events increases. (24) In turn, red blood cell transfusions improve IH in preterm infants. (1) Changes in hemoglobin affect IH through 2 proposed mechanisms. The first suggests that infants with anemia have decreased oxygen stores, resulting in greater instability of oxygenation in the presence of apnea. This is consistent with an analysis showing that the rate of arterial oxygen desaturation during apnea increased with lower hemoglobin levels. (16)

The second mechanism relates to hypoxic ventilatory depression because of decreased oxygen delivery to the respiratory control network. Consequently, red blood cell transfusions decrease IH because there is improvement of both oxygen stores and oxygen delivery to the respiratory network. Oxygen stores are increased through a rise in

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hematocrit. Oxygen delivery is likely improved as a result of an increase in partial pressure of oxygen (Po_2) from shifting the oxygen dissociation curve to the right, because of the increase in adult-to-fetal hemoglobin ratio after a red blood cell transfusion. The bolus effect of volume expansion during a transfusion may play a role; however, the effect is transient.

TARGET OXYGEN SATURATION

The target Spo_2 in individual NICUs influences the frequency of IH. A post hoc analysis of infants enrolled in the Surfactant Positive Pressure and Oxygen Trial showed that infants randomized to the lower Spo_2 target (85%–89%) had increased IH compared with those with higher Spo_2 target (91%–95%). (8)(25) Infants in the lower target group had a greater incidence of both short and long IH events compared with infants in the higher Spo_2 target. The increased IH was most pronounced during the early postnatal period (<2 weeks after birth) likely because of peripheral chemoreceptor inhibition of breathing during the transition from intrauterine to extrauterine life. In addition, the difference was noted later in the postnatal period (>8 weeks after birth) likely because of a low baseline alveolar Po_2 in the low Spo_2 target group shown to cause early-onset desaturation in the presence of apnea. (16)

Another plausible explanation for increased IH in the group with a lower Spo_2 target is hypoxic ventilatory depression (described earlier) that may develop at an arterial Po_2 as high as 60 to 90 mm Hg (7.9–11.9 kPa), resulting in irregular breathing and increased respiratory pauses in the lower Spo_2 target group compared with the higher target. These findings add to the debate of the most appropriate Spo_2 target for preterm infants. Avoiding initial hyperoxemia in the early postnatal period is crucial. However, minimizing IH during the later postnatal weeks by targeting slightly higher baseline Spo_2 is worth investigation because it may have an impact on IH and associated morbidities.

MONITORING

Accurately documenting cardiorespiratory events for day-to-day patient care management is challenging, because the extent of IH is not apparent clinically and hence, requires continuous physiologic recording for accurate detection. Preterm infants have on average 150 to 200 severe IH events per day during which their SpO_2 drops below 80% and some have up to 800 to 1,000 mild IH events (SpO_2<90%) per day. (1) In addition, providers underrecognize the number of events compared with objective automated recordings. In one study, compared with polysomnography, nursing staff recorded less than 30% and 40% of IH and bradycardia events, respectively. The shorter the event, the less likely that it was recognized by nursing staff. For example, bedside providers documented 35% and 29% of IH events that lasted longer than 20 and 10 seconds, respectively. (26)

Pulse oximeters are the current standard of care for monitoring oxygenation in the NICU. However, the monitor settings, such as the averaging time, affects the number of IH events recorded. (27) Pulse oximeters average SpO_2 values over several heartbeats. Research groups who study IH use high-resolution pulse oximeters with 2-second averaging time for continuous SpO_2 monitoring. Pulse oximeters set to longer averaging times underestimate IH events of short duration and overestimate events of longer duration. This is likely as a result of several short events merged together as 1 prolonged event. Clinical pulse oximeters are set to longer averaging time to decrease alarm fatigue for bedside providers. The default averaging times in clinical pulse oximeters range between 8 and 10 seconds but can be as long as 16 seconds. An option for centers that wish to use shorter averaging time is setting a longer alarm delay time (10–15 seconds) to reduce alarm fatigue.

CONSEQUENCES

Brief episodes of oxygen desaturations may seem clinically insignificant, but these IH episodes have a cumulative effect on morbidity and mortality (Fig 4). Concerns about the significant contribution of IH to neonatal morbidities are a relatively new observation after the use of high-resolution pulse oximeters. Ample evidence from animal models shows a significant effect of IH on neurocognitive handicap, decreased neuronal integrity, and increased inflammation. Repetitive IH and subsequent reoxygenation cycles cause oxidative stress, free-radical production, and the release of proinflammatory cytokines. (20) Experiments in mice have indicated that early postnatal exposure to IH shows both biochemical and electron microscopic evidence for impaired axonal myelination and long-term neurofunctional deficits. Darnall et al showed that rat pups exposed to mild IH have increased systemic and brain inflammatory biomarkers (eg, C-X-C motif chemokine ligand-1 and IL-1β) and decrease in neuroprotective biomarkers (eg, Tau) compared with an unexposed group. In addition, mild IH exposure impaired myelination, caused medullary and axonal injury, and increased membrane turnover. (20) Julien et al used whole body plethysmography to assess breathing patterns in rat pups exposed to chronic IH. Rat pups exposed to IH early since the first day after birth (P1) had an increased apnea

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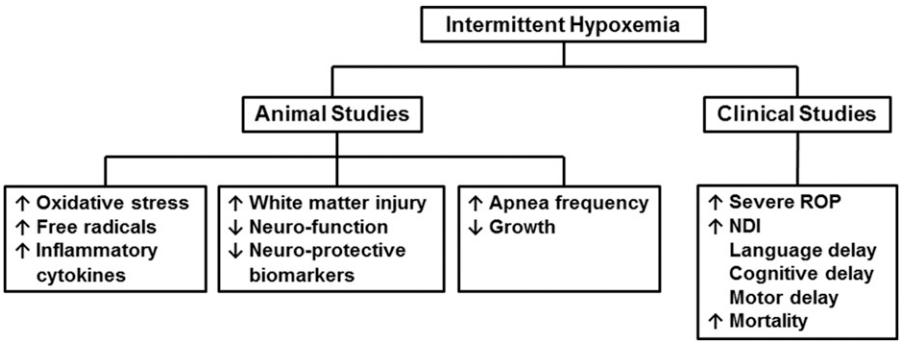

Figure 4. Increasing evidence from both animal and clinical studies have linked intermittent hypoxemia to injury and poor outcomes. NDI=neurodevelopmental impairment; ROP=retinopathy of prematurity.

frequency in response to hypoxia later in the postnatal period (P10) compared with unexposed controls. (28)

Multiple animal studies have showed that IH impairs growth. IH-exposed rat pups during the first week after birth (P1-7) exhibited growth restriction compared with normoxia-exposed controls. Interestingly, growth restriction persisted until P21, far beyond the exposure period. (29) These studies may suggest that preterm infants with increased IH during their NICU stay are at increased risk for sleep-disordered breathing and growth impairment during childhood. Schmid et al assessed the effect of IH and bradycardia on cerebral oxygenation in 16 extremely preterm infants. Cerebral oxygenation decreased in the presence of IH, especially when occurring simultaneously with bradycardia events. Interestingly, only a few infants (25%) had cerebral oxygenation less than 60% with severe IH events. (30) These findings raise questions about the characteristics of infants at highest risk for injury in the presence of IH.

RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP), the second most common cause of childhood blindness in the United States, is a developmental vascular proliferative disorder that occurs in the retina of preterm infants. The pathogenesis of ROP has been described to include 2 sequential phases. In the first phase, hyperoxia leads to vessel growth cessation in the early postnatal period (birth until >32–34 weeks' PMA). Supplemental oxygen suppresses vascular endothelial growth factor (VEGF), which results in the cessation of normal vessel growth and regression of existing vessels. The second phase is precipitated by the increasing metabolic demand of the developing retina in the presence of compromised vascular supply. This phase begins later (>32–34 weeks' PMA) and is associated with an increased VEGF expression in the retina caused by relative hypoxia, which results in pathologic neovascularization.

Although hyperoxia is the main cause of ROP, animal studies suggest that fluctuations in SpO_2 lead to ROP. This association has also been shown in preterm infants using high-resolution pulse oximeters. Di Fiore et al showed an association between chronic IH and ROP requiring laser surgery. (2) After adjusting for confounding covariates, infants with ROP requiring laser treatment had significantly increased frequency of IH events compared with those who had no ROP or did not require treatment. Infants with severe ROP had longer and more variable IH events compared with controls. Similarly, in a post hoc analysis of the Canadian Oxygen Trial, Poets et al and Schmidt et al showed that the risk of ROP increased with the higher percentage of time the infants experienced IH. (3)(31) Fairchild et al were unable to duplicate these results; however, the investigators only considered IH events preceded by apnea and did not use high-resolution (2-second averaging time) pulse oximeters. (5)

NEURODEVELOPMENTAL IMPAIRMENT AND DEATH

There is mounting evidence linking IH to long-term neurodevelopmental impairment (NDI) and mortality in preterm infants. NDI is usually defined as survival with 1 or more of the following: motor impairment or moderate or severe cerebral palsy, cognitive delay, severe hearing loss, or blindness. Janvier et al demonstrated a positive correlation between the number of days with apnea/bradycardia and NDI at 3 years of age in preterm infants with a birthweight less than 1,250 g or birth gestational age less than 32 weeks. (32) This association persisted after correcting for risk factors, including postnatal steroids, gender, and duration of assisted ventilation. In a cohort of very low birthweight infants, Pillekamp et al showed that both persistent apnea and increased cumulative apnea were associated with death or severe handicap (Psychomotor Development Index/Mental Development Index <69 as documented by the Bayley Scales of Infant Development) at 13

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months' corrected age. (33) After adjusting for social variables, [AQ1] Greene et al showed that greater frequency and severity of cardiorespiratory events were associated with worse language outcomes at 20 months' corrected age in a cohort of extremely low birthweight infants. (34) However, the aforementioned studies used cardiorespiratory events as recorded by the bedside nurse, a major limitation because bedside provider recordings correlate poorly with objective digital analyses.

In an analysis of 1,035 extremely preterm infants, Poets et al showed an association between prolonged IH events and NDI at age 18 months. (3) The authors also found that IH was associated with late death in the same patient population. In a recent publication, Di Fiore et al assessed the association between patterns of oxygenation and survival in 1,054 extremely preterm infants. (35) SGA infants were particularly susceptible because they had increased time with hypoxemia and an increased incidence of IH events. Increased IH in the first 3 days after birth was associated with significantly lower 90-day survival in SGA infants than in infants who are appropriate for gestational age. However, the finding of an association between IH and NDI/death in these 2 large studies was from post hoc analyses.

CONCLUSION

IH events are ubiquitous in preterm infants. The frequency and duration of events are often underestimated and their significance not appreciated by clinical providers. Factors associated with prematurity and NICU stay such as respiratory instability, lung disease, anemia, and lower Sp_{O_2} target increase the frequency and severity of IH in most preterm patient populations. Increasing evidence from both animal models and preterm infants shows that IH is linked to poor short- and long-term outcomes. However, most clinical studies that used high-resolution pulse oximeters were not primarily designed to assess the consequences of IH. There is an urgent need for prospective studies to identify preterm infants at highest risk for increased impairment and mortality as a result of IH.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathophysiology of apnea of prematurity.
- Know the risk factors for and pathophysiology of retinopathy of prematurity, and approaches to prevention.

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1. You are caring for a female infant born at 28 weeks' gestational age. She is now 4 weeks old and does not require respiratory support. However, she continues to have episodes of intermittent drops in oxygen saturation levels. Which of the following statements regarding oxygen desaturation events in preterm infants is correct?
   A. Regardless of gestational age at birth, intermittent desaturations should resolve at around 32 weeks' gestational age for preterm infants who do not have a congenital lung anomaly.
   B. Infants who are born small for gestational age are more likely to have episodes of intermittent hypoxemia.
   C. The period of 4 to 5 weeks after birth is the relative "honeymoon" stage for most preterm infants, when there should be little to no desaturation events.
   D. The phenomenon of intermittent hypoxemia events seen in preterm infants has largely been due to insensitive technology, and is now known to only occur in a small minority (<50%) of extremely preterm infants.
   E. In general, the severity of events is highest right after delivery, and then steadily declines as the infant gets older and bigger.
2. The 4-week-old 28-week gestational age infant is receiving full enteral feedings. She is in room air and having frequent events of intermittent hypoxemia daily. These are generally self-resolving and occur at various times in relationship to sleeping and feedings. Which of the following statements regarding factors that may be influencing these events is correct?
   A. Apnea is the main driver for intermittent hypoxemia in preterm infants.
   B. In this infant, any apnea that is leading to hypoxemia is likely to be purely central in nature.
   C. An instance of hypoxemia in this infant that is caused by apnea will likely only occur if apnea duration is at least 20 to 30 seconds.
   D. The typical sequence of events that precede these events is likely to be: apnea → bradycardia → hypoxemia.
   E. Apnea and intermittent hypoxemia in this infant at this age is not attributable to prematurity, and other etiologies should be investigated.
3. A 25-week gestational age male infant is now 7 weeks old. He was born to a woman who was diagnosed with chorioamnionitis before delivery. He was initially given surfactant after being placed on mechanical ventilation during the first day after birth. Nasal continuous positive airway pressure was discontinued at 6 weeks of age. He continues to receive oxygen via nasal cannula. His hematocrit is 35%. He has been having frequent intermittent hypoxemia events during the past week. He is receiving iron supplementation. Which of the following statements describes his current physiologic state appropriately?
   A. It is likely that periods of hypoxia (ie, low tissue oxygenation) may lead to decreased respiratory drive in this infant, with reduced respiratory rate during those episodes.
   B. After mechanical ventilation, preterm infants can develop higher functional residual capacity, which is associated with more rapid oxygen desaturation.
   C. Periodic apnea in this infant is not likely to have any effect on desaturation episodes.
   D. The history of chorioamnionitis is significant, because inflammation is likely to increase chemosensor receptivity, thereby reducing apnea and desaturation events, both immediately after delivery and in the convalescent period after discontinuing respiratory support.
   E. It is wise to avoid transfusion at this age, because it can increase both the development of necrotizing enterocolitis and the frequency of intermittent hypoxemia.

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4. Your quality team has noted that there is frustration about frequent alarms for intermittent hypoxemia in the unit. It is perceived that increased sensitivity of newly purchased monitors is picking up increasing numbers of false-positive signals. The team is considering lowering the alarm limits. Which of the following statements regarding oxygen saturation monitoring in preterm infants at risk of hypoxemia is correct?
   A. Infants who have relatively lower (85%–89%) oxygen saturation targets will have fewer intermittent hypoxemia events than infants who have higher targets.
   B. Infants at lower oxygen saturation targets have higher incidence of short intermittent hypoxemia events, but have decreased long hypoxemia events.
   C. In general, healthcare providers are very good at documenting what might be considered "real" events in regard to hypoxemia events that last more than 10 seconds, usually with more than 90% accuracy.
   D. Setting pulse oximeters to longer averaging times will overestimate the number of hypoxemia events, but underestimate events of longer duration.
   E. The impact of lower oxygen saturation targets on intermittent hypoxemia events is most pronounced during the early postnatal period, before age 2 weeks.
5. An infant born at 26 weeks' gestational age is now 5 weeks old, in room air without respiratory support, and having frequent intermittent hypoxemia events. The parents are worried about the potential consequences of these events on their neonate's prognosis. Which of the following statements most appropriately describes the consequences of these events for preterm infants?
   A. There has been no evidence in human studies to indicate that these events have any consequence for short- or long-term outcomes.
   B. Animal studies, including in rat pups and preterm pigs, have shown that intermittent hypoxemia during early development leads to increased rates of maturation of both brain and lung tissue when adequate nutrition is provided.
   C. Human and animal studies have shown that intermittent hypoxemia leads to increased insulin resistance and faster growth than in controls with more stable oxygenation.
   D. Several studies have shown an association of frequent intermittent hypoxemia events and more severe retinopathy of prematurity.
   E. In both crude and risk-adjusted analyses, intermittent hypoxemia is associated with increased risk of death in the initial hospitalization, but lower rates of later death and lower rates of neurodevelopmental impairment for survivors.

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